Organ and Tissue Transplantation
Series editor: Cataldo Doria

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Linda Bogar
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Contemporary Heart Transplantation

Springer

Organ and Tissue Transplantation

Series Editor

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Transplantation is the most regulated field in medicine and requires a detailed knowledge of the clinical as well as the non-clinical issues of a program to succeed in a highly competitive field. Organ and Tissue Transplantation is a series of seven volumes that will go over the science, the administrative and regulatory issues making a contemporary transplant program successful. The seven volumes will address separately the following: liver, kidney, pancreas, small bowel, heart, lung, and bone marrow transplantation. This series provides comprehensive reviews of the most crucial and provocative aspects of solid organ transplantation. It will be a unique source of information and guidance for the current generation of transplant surgeons that evolved from being pure clinicians into savvy administrators knowledgeable in every regulatory aspects governing transplantation. As a single transplant necessitates the effort of a large group of health care providers of different disciplines, the books in the series address the need and questions of everyone involved including surgeons, hepatologists, anesthesiologists, palliative care specialists, immunologists, infectious disease specialists, physiatrists, radiologists, scientists, transplant coordinators, financial specialists, epidemiologists, administrators, and attorneys. Volumes in the series contain chapters covering every single aspect of the surgical operation in the donors (live and cadaver: whole and split), as well as the recipients of transplants. The pre-operative work-up, as well as the post-operative immunosuppression management, and the treatment of recurrent diseases are addressed in detail. Single chapters are dedicated to controversial issues. The series goes beyond the analysis of the formal medical and surgical aspects of transplantation and introduces deep knowledge on key aspects of contemporary transplant programs, such as physical rehabilitation, palliative care, pregnancy, the multiple requirements of regulatory agencies ruling transplantation, quality measurements for transplant programs, finance, liability and the administration of an effective transplant program. The series analyzes and reviews medical as well as surgical issues related to transplantation in all its forms. Each book dedicates sections to every subspecialty collaborating in the success of transplantation. Differently from previously published books in this field the series dissects organizational issues that are vital to the good performance of transplant programs.

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Linda Bogar • April Stempien-Otero
Editors

Contemporary Heart Transplantation

With 74 Figures and 46 Tables

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About the Series Editor

Dr. Cataldo Doria graduated Magna cum Laude from University of Perugia, Italy, in 1990, where he was also resident in surgery from 1990 to 1995. He completed a research fellowship in small bowel transplantation at the University of Pittsburgh Transplantation Institute and a clinical fellowship in multi-organ transplantation at the Thomas E. Starzl Transplantation Institute of the University of Pittsburgh. Dr. Doria is Ph.D. in surgery biotechnology and transplant immunology and MBA.

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Prior to Jefferson, Dr. Doria was at the Mediterranean Institute for Transplantation and Advanced Specialized Therapies (IsMeTT–UPMC Italy) – a partnership between the University of Pittsburgh Medical Center and the Italian National Government– where he served as Chief of Abdominal Organ Transplant. He also served as Assistant Professor of Surgery at the University of Pittsburgh School of Medicine and at the Thomas E. Starzl Transplantation Institute, Children's Hospital of Pittsburgh, and the US Department of Veterans Affairs Medical Center of Pittsburgh, PA.

His research interest focuses primarily on cancer of the liver, pancreas, and bile duct. Dr. Doria's biography has been listed in Who's Who in Medicine and Healthcare, Who's Who in Finance and Industry, Who's Who in Science and Engineering, and Who's Who in America. Dr. Doria, in 2005, was named Honorary President of the Italian Association for Organ Donation of the Province of Taranto, Italy. In 2008, Dr. Doria was named "surgeon of the year" by the Mid-Atlantic Division of the American Liver Foundation. In 2009, he was the recipient of the Career Achievement Award by the International Association "Pugliesi nel Mondo." In 2010, Dr. Doria was awarded with the seal of University of Foggia, Italy. In 2012, he was named "Knight of the Italian Republic" by the President of the Italian Republic. In 2016, he was named Chairman, Board of Directors, American Liver Foundation, Mid-Atlantic Division. Dr. Doria has authored of 277 scientific publications and is a member of numerous professional and scientific societies where in the years covered several official positions. Most importantly, Dr. Doria has been, for the past 10 years, the leader of one of the most successful transplant institutes in North America and now leads one of the rising stars of cancer centers in the Northeastern United States. One of Dr. Doria's aims includes making Capital Health the most competitive and innovating cancer center on the East Coast of the United States.

About the Volume Editors

Linda Bogar Dr. Bogar earned her medical degree and completed her surgical and cardiothoracic transplant fellowships at Temple University in Philadelphia, PA. She later finished a cardiothoracic surgery residency at Thomas Jefferson University Hospital in Philadelphia, PA. Dr. Bogar has served on both regional and national committees for OPTN/UNOS and has published numerous publications.

Dr. Bogar brings 15 years of clinical and surgical experience besides expertise in complex and high-risk cardiac surgery along with a focus in heart and lung transplant and mechanical circulatory support. Dr. Bogar is currently practicing at AdventHealth Orlando as a cardiothoracic transplant surgeon. Her focus remains on heart and lung transplant, mechanical circulatory assist devices, and ECMO, along with high-risk coronary bypass surgery. Dr. Bogar is a current and active member of the Society of Thoracic Surgeons, the International Society of Heart and Lung Transplantation, and the American College of Cardiology.

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Dr. Stempien-Otero has been listed as Best Doctor in America for over a decade and has been appointed to major committees of the American Heart Association and United Network for Organ Sharing.

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Part I

Historical Background

History of Heart Transplant

1

Nina Badoe and Palak Shah

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Abstract

Cardiac transplantation represents the gold standard therapy for patients with advanced heart failure refractory to medical and device therapy. Decades of clinical and animal-based research laid the foundation for the first heart transplant performed on December 3, 1967, by Christiaan Barnard in Cape Town, South Africa. The initial enthusiasm for transplantation spread quickly and about 100 transplants were performed in the year that followed 1967. Early immunosuppressive regimens consisted of steroids and azathioprine. Early on, due to unthwarted and often undiagnosed rejection, 1-month mortality after cardiac transplant exceeded 50% and most centers abandoned the procedure by 1970. In 1972, Phillips Caves developed the technique for an endomyocardial biopsy and together with Margaret Billingham developed objective criteria for the histopathologic assessment of allograft rejection. Norman Shumway pioneered the use of a calcineurin inhibitor, cyclosporine as a more potent immunosuppressive agent to mitigate rejection after cardiac transplantation. With the successful incorporation of cyclosporine, short and intermediate-term survival improved dramatically and between 1980 and 1990, the

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number of heart transplants performed across the globe grew exponentially from 100 to 4,000 transplants annually.

Keywords

Heart failure · Cardiac transplantation · Cardiopulmonary bypass · Rejection · Immunosuppression

Introduction

The epidemic of heart failure continues to affect millions of patients worldwide. Despite considerable progress in reducing the incidence rates of coronary artery disease and case-fatality through management of blood pressure and dyslipidemia, similar trends have not been observed in heart failure. Further, as the patient population continues to age, the prevalence of heart failure continues to rise. Despite advances in medical and/or device therapy, survival for patients with heart failure still approximates 50% at 5 years (Benjamin et al. 2017). For patients with advanced heart failure, i.e., New York Heart Association Class IV symptomatology that is refractory to medical therapy, cardiac transplantation remains the treatment of choice. Beginning in the 1900s, over half a century of basic science research, surgical technique experimentation and medical forethought carried out by physicians and scientists worldwide culminated in making what was once an experimental surgery into what is now routine clinical practice in major medical centers across the globe. The International Society for Heart and Lung Transplantation (ISHLT) registry has reported 89,000 heart transplants worldwide since 1983 (Lund et al. 2016). It remains the gold standard for heart replacement therapy, albeit available to only 1–2% of patients who benefit from the treatment.

The Pre-clinical Era

Alexis Carrel, a French surgeon, was the first to perfect and describe vascular anastomosis techniques that did not result in thrombosis or failure and essentially establish the basic principles of vascular surgery which made whole organ transplantation possible. Carrel studied at the University of Lyon where he earned his medical degree in 1900. In 1902, Carrel in conjunction with an American physiologist Charles Claude Guthrie published their first landmark articles on vascular anastomosis, and the two are credited with developing the triangulation method of small vessel anastomosis and perfecting the everting anastomosis technique. Their experimental endeavors demonstrated for the first time the utilization of veins as a substitute for arteries. By replacing segments of the carotid artery with the jugular vein and using a vein as an arterial patch, it became evident that these vessels could tolerate arterial pressure without aneurysm formation. Carrel is also credited with the "Carrel patch technique" used in re-implantation of major vascular structures during organ transplantation. Not only a master of vascular surgical techniques his degree of experimental success should also be credited to his emphasis on rigid surgical asepsis (Flexner 1908; Carrel 1910, 2001; Lawrie 1987; Dente and Feliciano 2005; Sade 2005).

In 1905, Carrel and Guthrie published their first work in organ transplantation wherein they described auto-transplantation of a dog's kidney into the neck with vascular anastomoses to the carotid artery and external jugular vein. The ureter was implanted into the esophagus resulting in urine production. During this time, Carrel and Guthrie performed a series of animal experiments, both auto-transplantation and hetero-transplantation. In 1906, Carrel conducted additional work in blood vessel preservation demonstrating for the first time that blood vessels could be preserved with hypothermia (Carrel 1910, 2001).

In several of Carrel's publications, he recognized the difference in survival times between autografts and allografts in experimental animal models but unfortunately did not conceptualize rejection as a distinct entity from other graft-destroying processes. Carrel's groundbreaking research earned him the Nobel Prize in Medicine in 1912 "in recognition of his work on vascular sutures and the transplantation of blood vessels and organs" (Dente and Feliciano 2005).

The work of Carrel inspired research efforts implemented by physiologist Frank C. Mann in

both renal and cardiac transplantation through the 1920s and 1930s. In 1933, Mann and colleagues published an article entitled "Transplantation of the Intact Mammalian Heart" wherein they reported their work on canine heart transplantation. Without the use of hypothermia or cardiac bypass, denervated canine hearts were transplanted into the carotid circulation. In these studies, Mann emphasized the importance of restoring coronary artery circulation as soon as possible to reduce ischemic injury to the allograft, a critical element of heart transplantation today. Canine heart transplant subjects survived for up to 8 days. At autopsy, histological evaluation of the transplanted heart revealed a heart that was "completely infiltrated with lymphocytes, large mononuclear and polymorphonuclear cells" causing Mann and colleagues to postulate that "the failure of the homotransplanted heart to survive is not due to the technique of transplantation but to some biologic factor": essentially allograft rejection (Cooper 1968; Ventura and Muhammed 2001).

In 1937, Vladimir Demikhov, a Russian physiologist, designed a cardiac mechanical assist device which was the first to maintain circulation in animals with the heart excised. While the device was too large to fit inside the chest of his canine hosts, the device maintained cardiac function for approximately 5 h. Between 1946 and 1955, Demikhov conducted a series of experiments in which he attempted to transplant one canine heart into a different canine. His technique involved end to end anastomoses of the donor aorta, pulmonary artery, and vena cava to the corresponding recipient vessels. The donor pulmonary veins were joined together and attached to the left atrial appendage of the recipient thereby avoiding challenging pulmonary vein anastomosis. Survival times for his series of 22 canines in early experiments averaged between 11 and 15 h. This was the first evidence that a cardiac allograft could provide pumping function to a different recipient animal, i.e., orthotopic transplantation (Cooper 1968; Kirklin 2002). Wilford B. Neptune and colleagues pioneered the concept of cold preservation or organ hypothermia in 1953 (Neptune et al. 1953). The group performed successful canine heart and lung transplantation and subsequent return of circulation in the animal to the extent of the return of spontaneous respiration, return of reflexes, normal body temperature, and survival up to 6 h following surgery.

The next pivotal chapter in the history of heart transplantation can be attributed to the work of Dr. Norman Shumway, Dr. Richard Lower, and colleagues at Stanford (Figs. 1 and 2). Shumway and Lower were the first to propose adjuvant local hypothermia with cardiac anoxia revolutionizing cardiac surgery (Shumway et al. 1959). In this method, the body temperature was decreased to approximately 32 °C, and the pericardium was sutured to the surrounding muscular sternal edges creating a cradle or reservoir for continuous cold saline circulation around the heart. The aorta was clamped preventing coronary flow. After a specific period, coronary flow was restored, the heart was defibrillated with an electric shock, and in time the heart could maintain its own circulation independent of the bypass machine. Using this method and a bi-atrial surgical technique, the Stanford team completed their first successful

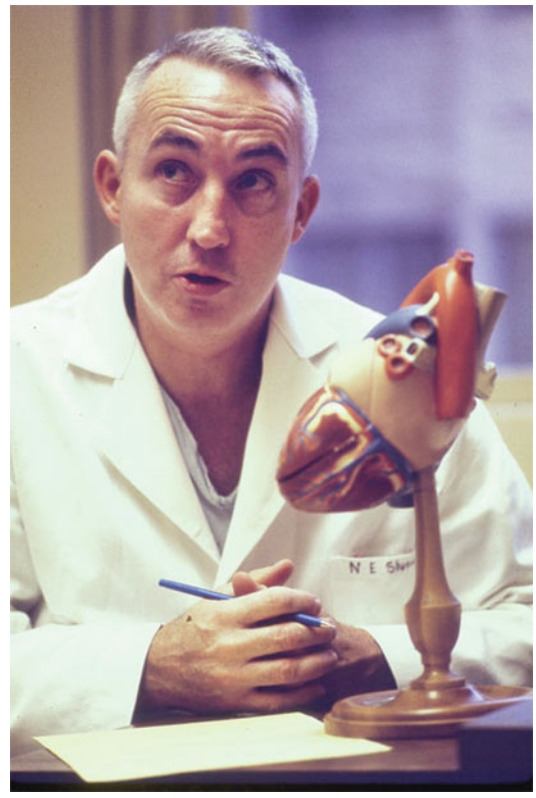

Fig. 1 Norman Shumway

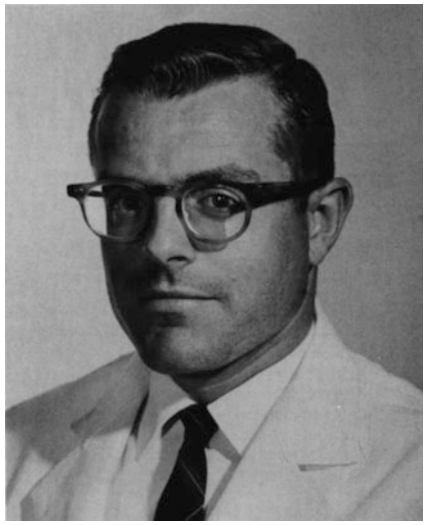

Fig. 2 Richard Lower

heart transplantation in a canine in December 1959 yielding the most impressive survival times to date – 8 days. Afterwards, 8 consecutive transplants were completed and the animals lived between 6 and 21 days. The transplanted dogs reportedly ate and exercised normally (Lower and Shumway 1960).

The theoretical explanation as to the variable lifespan of each animal was thought to be due to individual variation in immunologic response. Description of the postmortem gross examination of each heart revealed areas of myocardial ecchymosis, edema, fibrinous pericarditis, and generalized dilatation. Microscopic examination of sections demonstrated severe myocarditis, with massive round cell infiltration, patchy necrosis, interstitial hemorrhage, and associated regional lymphadenopathy. Shumway and Lower concluded that if the immunologic mechanisms of the host were prevented, destruction of the transplanted allograft would be prevented and it would continue to function adequately for the normal lifespan of the animal. By 1965, Lower and Shumway had extended graft survival to 250 days by using a combination of steroids, azathioprine, and 6-mercaptopurine. Immunosuppression was utilized to promote graft survival and electrocardiography served as a tool to help guide anti-rejection therapy. Ten years of animal experimentation led to the perfection of the pathologic, physiologic, and clinical events associated with orthotopic heart transplantation in animal models (Robbins 2000; Willis Hurst et al. 2000; Kirklin 2002; Pincock 2008).

Clinical Cardiac Transplantation: The Early Days of Heart Transplant in Humans

In 1963, James Hardy, a surgeon at the University of Mississippi, performed the first xenotransplantation into a human (Hardy 1999), Fig. 3. Hardy and colleagues began transplantation research in 1956 using canines, infant calves, and primates. Investigative efforts included trials of several operative techniques, storage, and preservation of harvested organs, evaluation of transplanted heart metabolism, and postoperative management. Hardy cited the operative techniques of Lower and Shumway as the most effective. Organ preservation was trialed with various hypothermic techniques including profound hypothermia via coronary artery perfusion and retrograde coronary sinus perfusion. Postoperative complications seen in canine experiments included bleeding, respiratory failure, arrhythmias, metabolic derangements, infection, and rejection. In 1963 following extensive experimentation and several hundred transplants, the university medical center and researchers decided to investigate orthotopic heart transplantation in a human. The donor heart was from a "young person who had died from brain hemorrhage or trauma" and the designated recipient was a patient near death with terminal myocardial disease.

The patient, a 68-year-old male named Boyd Rush, was found down in his home unresponsive. The patient had a past medical history of hypertensive cardiovascular disease and cardiomegaly. At the time of evaluation, the patient was in atrial fibrillation, cardiogenic shock requiring vasopressors, and acute respiratory failure. Rush's clinical status was described as "unequivocally critical" as a result of heart failure and his life expectancy was deemed to be within a matter of hours. The family

Fig. 3 James Hardy

was consented for cardiac transplantation as a last resort option. Rush's clinical situation deteriorated and the decision was made to proceed with transplantation of a primate heart instead of a human heart. The donor primate heart was preserved using cold oxygenated blood given retrograde through the coronary sinus. Following suturing of the atria, pulmonary artery, and aorta, the donor heart was rewarmed then defibrillated establishing normal sinus rhythm and cardiac output. The first human cardiac transplant had been executed and completed. The transplanted heart was described to have "vigorous contractions" and support a blood pressure ranging 60–90mmhg for approximately 60 min after the removal of bypass cannulas. Unfortunately, soon thereafter, the heart became increasingly unable to handle the venous return without periodic manual massage and the patient expired 90 min after the transplant had been completed. The short-lived success of Hardy and his team proved the technical feasibility of cardiac transplant in man.

Orthotopic Human Heart Transplantation

In his training years, Christiaan Barnard (Fig. 4) worked under the fellowship of Professor Owen Wangensteen and direct mentorship of cardiothoracic surgeons C. Walton Lillehei and Richard L. Varco at the University of Minneapolis in Minnesota. By his mentors, Barnard was described as an "outstanding cardiac surgeon and researcher."

Fig. 4 Christiaan Barnard

Barnard received instruction from these phenomenal surgeons who had successfully completed the first open heart surgery in 1952 and had utilized the newly invented helical reservoir pump oxygenator. Upon completion of his fellowship, Barnard returned to South Africa with a new skill set, a donated blood oxygenator, and a mission to establish a cardiac surgery program at Groote Schuur Hospital in Cape Town. In the years to follow, Barnard developed a high functioning cardiac surgery team with an expertise in valvular surgery and congenital heart defect correction. In 1967, Barnard returned to the United States, and under the mentorship of renal transplant surgeon David Hume at the Medical College of Virginia, learned the fundamentals of transplant immunosuppression. During his 3-month tenure, he also observed the canine orthotopic heart transplant surgical techniques of Richard Lower who had been recruited to the Medical College of Virginia after working with Shumway at Stanford

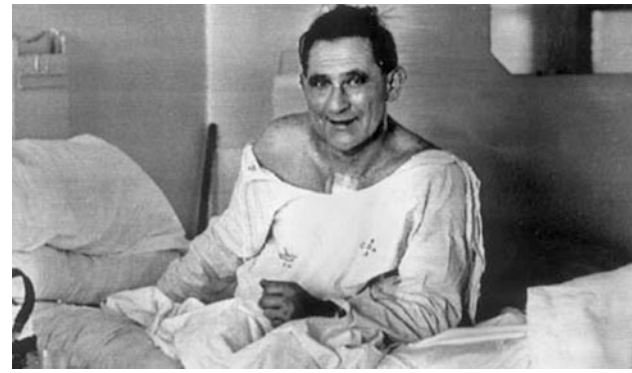

Fig. 5 Louis Washkansky. The first orthotopic human heart transplant recipient

University. Upon returning to South Africa, Barnard successfully completed the first successful single kidney transplant in Cape Town in October of 1967 allowing him to gain personal experience with transplant immunosuppressive therapy. With the culmination of years of experimental research, refining his surgical skill and clinical acumen, and establishing a high functioning surgical team, Christiaan Barnard was now ready to pursue human orthotopic heart transplantation (Cooper 2001; Cooper and Cooley 2001; Brink and Cooper 2005; Toledo-Pereyra 2010).

The first transplant recipient was 54-year-old Louis Washkansky, a diabetic smoker with coronary artery disease and peripheral vascular disease (Fig. 5). On the evening of December 2, 1967, he was taken to the operating room and the operation continued through the night; Washkansky received a heart from a 25-year-old female who was fatally injured in a motor vehicle accident. She was of the same blood type and a similar leukocyte antigen profile. Upon being pronounced dead by the medical examiner, the organ was harvested, and the first human to human cardiac transplantation was successfully completed by Christiaan Barnard and his team in Cape Town South Africa (Barnard 1967). Postoperative care concentrated on maintaining appropriate cardiac output, appropriate immune suppression, and infection prevention. Rejection was thwarted with the use of systemic steroids, local irradiation of the heart, and azathioprine. The patient's early recovery was excellent up until approximately the 12th postoperative day when his condition began to deteriorate. A chest x-ray at that time revealed pulmonary infiltrates. Washkansky was initially treated for acute rejection with augmentation of his immunosuppressive regiment but died on the 18th postoperative day. On autopsy, the heart had no evidence of rejection, but pulmonary evaluation revealed findings consistent with pneumonia.

Three days after Barnard's successful orthotopic heart transplantation, on December 6, 1967, the first heart transplant in the United States was completed by Dr. Adrian Kantrowitz at Maimonides Medical Center in Brooklyn New York (Kantrowitz 1998). The heart from an anencephalic 2-day-old newborn was transplanted into an 18-day-old infant who suffered from Ebstein's Anomaly. Conceptually the newborn infant would have an immature immune system that would adapt to the transplanted allograft without the need for immunosuppression. Postoperatively, the infant was reported to be progressing appropriately and was described to be moving all limbs. Unfortunately, metabolic and respiratory acidosis resulted in cardiac arrest and resuscitation efforts failed. The infant was declared dead a few hours after the operation. Autopsy revealed diffuse lung atelectasis. Gross examination of the heart was normal with no evidence of rejection.

In Barnard's second heart transplant attempt on January 2nd, 1968, he executed a modified surgical technique (Barnard 1969). The incision in the right atrium of the donor heart was extended from the inferior vena cava into the atrial appendage thereby avoiding the area of the sinus node at the

Fig. 6 Philip Blaiberg. Second heart transplant recipient worldwide

roof of the right atrium. The patient, Philip Blaiberg, was the first heart transplant recipient to leave the hospital. The account of his 19-month life after transplant was documented in his novel entitled "*Looking at My Heart"* (Fig. 6). Following his death, an autopsy revealed diffuse coronary artery disease. Between 1967 and 1973, Barnard's team performed 10 orthotopic heart transplants in an era of primitive immunosuppressive therapy and no means to screen or diagnose rejection (Barnard and Cooper 1981).

The fourth heart transplant globally was performed by Norman Shumway at Stanford University on January 6, 1968 (Fann and Baumgartner 2011). The recipient survived 15 days. In the United States, the first overwhelmingly successful heart transplant as measured by patient longevity was completed by Denton Cooley on May 2, 1968 at Baylor College of Medicine in Houston Texas. The patient, a 47-year-old male, received the heart of a 15-year-old girl and survived 205 days. By the end of 1968, 102 transplants were performed at 50 institutions in 17 countries worldwide. Initial enthusiasm for the procedure was blunted by the sobering reality of poor outcomes and limited intermediate-term survival. Of those patients transplanted in that first year, 54 patients (53%) survived to 1 month and 19 patients (19%) survived to 1 year. Given these grim outcomes, by 1970 all but a few centers had abandoned the procedure (Ventura and Muhammed 2001; Fann and Baumgartner 2011).

Understanding the Immune System and Allograft Monitoring

> . . .But it's what happens later with regard to the containment of rejection that makes the real difference. – Norman Shumway

Peter B. Medawar, an English Zoologist, during the early stages of the Second World War was tasked by the Medical Research Council of Britain to investigate why it is that skin taken from one human being would not form a permanent graft on the skin of another person (Billingham et al. 2010). In collaboration with surgeon Thomas Gibson in 1943, the two presented the theory of "active immunization" and immunological memory (Gibson and Medawar 1943). In both human studies and in rabbit models, Medawar's research identified that immune responses characterized by lymphocyte infiltration of the graft; those lymphocytes that were genetically dissimilar were responsible for rejection (Medawar 1944). Subsequent exposure to grafts from the same donor resulted in faster rejection times, demonstrating immunological memory. Additional work with monozygotic and dizygotic cattle demonstrated retention of skin graft with no rejection (Kirklin 2002).

Concurrent research by Sir Frank Mcfarlane Burnet in 1949 argued in favor of the phenomenon of immunological tolerance. Burnet hypothesized that if a foreign substance were introduced

into an embryonic animal before maturation of the immune system, the antigen would "trick" the body into accepting the relevant molecule as "self" rather than "not-self." As a result, no antibody would be formed, even when the antigen was reintroduced later in life. Medawar and Rupert Billingham confirmed this hypothesis by demonstrating that when injecting late-stage mouse embryos of an inbred strain with cell suspensions from another strain, test skin grafts placed on them as young adults were not rejected (Simpson 2015). This was interpreted as the recipient being rendered "fully tolerant" and accepting the foreign grafts as "self." In 1953, Medawar and Billingham published a landmark paper with this initial evidence in mice that demonstrated the concept of actively acquired immune tolerance (Billingham et al. 1953).

A key advance in the understanding of immunology in cardiac transplantation was the introduction of the endomyocardial biopsy technique established by Philip Caves and colleagues in 1972 at Stanford University (Caves et al. 1973). Transvenous biopsy of the endomyocardium allowed for the histological examination of myocardial tissue and the accurate assessment of a recipient's immune response to the donor heart. This paved the way for monitoring patients after transplant for allograft rejection and incorporating immunosuppressant treatment regimens to prevent rejection (Caves et al. 1974a). In a 1974 editorial, Caves et al. described the cardiac biopsy technique and protocol. He described the histological changes seen in the myocardium that typify rejection (Caves et al. 1974b). Stanford colleague Margaret Billingham established a four grade system to classify rejection and provided a basis for treatment (Billingham et al. 1973). Mild acute rejection was characterized by the presence of interstitial fibrinous exudate containing few lymphocytes, myocytes with myofibrillar separation, and myocardial edema. Moderate rejection was characterized by a significant increase in the number of lymphocytes and large mononuclear cells infiltrating the myocardium as well as significant myocardial edema. Severe acute rejection was characterized by profound interstitial cellular infiltrates with polymorphonuclear leukocytes and extravasated red blood cells (i.e., hemorrhage) in addition to the findings of moderate rejection. This allowed for standardization of the pathologic diagnosis of rejection. Endomyocardial biopsy quickly became the gold standard in diagnosing acute rejection episodes as the histopathologic evidence directly correlated with the clinical signs and symptoms of rejection (Singh and Taylor 2015).

Immunosuppression

As the first successful renal transplantation preceded cardiac transplantation by more than 10 years, researchers in that field had already been faced with the issues of allograft rejection. The practical wide-spread application of organ transplantation depended upon the development of pharmacologic immunosuppression. In the late 1950s, the immunosuppressive effects of total body irradiation were explored and used in early human renal transplantation. In 1960, methotrexate and cyclophosphamide were utilized to induce graft acceptance in experiments conducted by William E. Goodman and prednisone was utilized to treat acute rejection. Subsequent work identified the additive and synergistic effects of azathioprine and prednisone making this combination the mainstay of transplant immunosuppression in the early 1960s (Starzl et al. 1983; Müller-Ruchholtz 1999; Rapaport 1999).

The introduction of cyclosporine was a pivotal turning point in solid organ transplantation and patient survival (Colombo and Ammirati 2011). The immunosuppressive effects of cyclosporine A were first reported by J.F. Borel in 1976 (Borel et al. 1976). Cyclosporine, a fungal peptide, inhibits lymphocytes and was the first example of a new generation of immunosuppressive that forms the cornerstone of modern day immunosuppression – calcineurin inhibition (Watson and Dark 2012). In a 1978 publication, cyclosporine A was deemed to be a superior immunosuppressive drug in pigs with orthotopic cardiac allografts, claiming it to be sufficiently tolerated and powerful (Calne et al.

1978). Shumway and his team at Stanford University were the first to implement the use of cyclosporine as maintenance immunosuppressive therapy to prevent cardiac allograft rejection. Analysis of cyclosporine performance at Stanford between 1980 and 1993 showed a significant reduction in the rates of rejection and overall patient survival compared to previous drug regimens (Meine and Russell 2005). The success of cyclosporine and its utilization by Shumway and colleagues revived worldwide enthusiasm for cardiac transplantation. Before 1980, less than 100 heart transplants were being performed annually. However with the approval of cyclosporine, there was an exponential growth in cardiac transplantation growing to just over 4000 cases worldwide per year by 1990; a number that has remained unchanged for the past 25 years (Lund et al. 2016).

Conclusion

Orthotopic heart transplantation represents the scientific dedication of so many investigators and physicians for nearly a century to achieve the unachievable. Perseverance was necessary to develop the best surgical techniques, to identify best practices for organ preservation and cardiopulmonary bypass, and to detect allograft rejection and develop immunosuppression. This perseverance has allowed this therapy to be available to thousands of patients with advanced heart failure each year. Within medicine, the concept of removing a diseased organ and replacing it with a normally functioning organ that can be maintained over time is an outstanding accomplishment and is truly unparalleled.

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Part II

Preoperative Evaluation Process

Pathophysiology of Heart Failure

2

Deirdre M. Mooney and Amanda R. Vest

Contents

Abstract

Heart failure (HF) is a complex clinical syndrome that centers on the heart's impaired ability to support physiologic circulation. A wide range of etiologies can be responsible for HF, including but not limited to ischemic heart disease, valvular heart disease, infiltrative disease,

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restrictive physiology, genetic conditions, and idiopathic cardiomyopathy. The cardinal manifestations are dyspnea and fatigue. The syndrome of HF is a continuum of interrelated stages, starting from an asymptomatic with risk factors for HF or evidence of structural changes in the heart to debilitating functional limitations related to dyspnea and a high risk of sudden cardiac death. Guideline-directed medical therapy has most successfully improved morbidity and mortality in patients with reduced left ventricular ejection fraction, while therapy for patients with preserved ejection fraction largely focuses on symptomatic management. For patients with advanced HF who are refractory to conventional therapy, including oral agents, implantable electronic cardiac devices, and comprehensive care interventions, options may include inotropic therapy, mechanical circulatory support, cardiac transplantation, or transition to comfort-focused care.

Keywords

Heart failure · Cardiomyopathy · Stage D heart failure · Inotropic therapy · Mechanical circulatory support · Cardiac transplantation · Advanced care planning

List of Abbreviations

ABIM	American Board of Internal Medicine
ACCF	American College of Cardiology Foundation
ACE	Angiotensin-converting enzyme
ACP	Advanced care planning
AHA	American Heart Association
AHFTC	Advanced Heart Failure and Transplant Cardiology
ARB	Aldosterone receptor blocker
ARNI	Angiotensin receptor-neprilysin inhibitor
CAD	Coronary artery disease
cART	Combination antiretroviral therapy
CHD	Congenital heart disease
CMR	Cardiac magnetic resonance
CMY	Cardiomyopathy
DCM	Dilated cardiomyopathy
HF	Heart failure
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HFSA	Heart Failure Society of America
HFSS	Heart Failure Survival Score
HIV	Human immunodeficiency virus
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
ISHLT	International Society for Heart Lung Transplantation
LOE	Level of evidence
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MCS	Mechanical circulatory support
NYHA	New York Heart Association
PPCM	Peripartum cardiomyopathy
RAAS	Renin-angiotensin-aldosterone system
RHC	Right-heart catheterization
RV	Right ventricular
SCD	Sudden cardiac death
SHFM	Seattle Heart Failure Model
SNS	Sympathetic nervous system
TTR	Transthyretin
VADs	Ventricular assist devices

Introduction

Overview of Heart Failure

Heart failure (HF) is defined as a complex clinical syndrome of impaired ability of the heart to support physiologic circulation (e.g., fill or eject blood) that arises secondary to inherited or acquired abnormalities of cardiac structure and/or function (Libby 2008). Heart failure is a clinical diagnosis that is made based on a careful

history and physical examination, not on a single diagnostic test (Yancy et al. 2013). It may be the result of disorders involving the pericardium, myocardium, endocardium, heart valves, and great vessels or metabolic abnormalities. The cardinal manifestations are dyspnea and fatigue which commonly manifest through impaired exercise tolerance, decreasing functional status, and/or fluid retention. The most common etiology of HF symptoms is impaired left ventricular (LV) myocardial function. Heart failure is often dichotomized into patient with HF with reduced ejection fraction (HFrEF) and patients with HF with preserved ejection fraction (HFpEF). The cutoff for reduced left ventricular ejection fraction (LVEF) has varied over guidelines and trials with cut points commonly $\leq$35%, $<$40%, or $\leq$40%; however the 2013 ACCF/AHA HF Guideline endorsed the cut point of LVEF $\leq$40%. Patients with HFpEF are defined as those with LVEF $\geq$50%, with a "borderline" EF described in the LVEF 41–49% range. There is a subset of patients with HFpEF who had a history of HFrEF but have experienced recovery of myocardial systolic function, which may be clinically distinct from those with persistently preserved or reduced EF; however further research is needed to better characterize these patients. As described below, although the majority of heart transplantation candidates have HFrEF, there are rare situations where patients with a persevered ejection fraction may require transplantation.

The natural history of HF is generally a progressive, nonlinear decline in health-related quality of life as depicted in Fig. 1 (Allen et al. 2012). Progressive impairment in functional status, arrhythmias, and even sudden cardiac death (SCD) are not uncommon events over the course of HF. The syndrome of HF is viewed as a continuum comprised of interrelated stages (Yancy et al. 2013). The two most common classification systems routinely used in HF are the ACCF/AHA stages of HF and the New York Heart Association (NYHA) functional classification. These nomenclatures provide useful, complementary

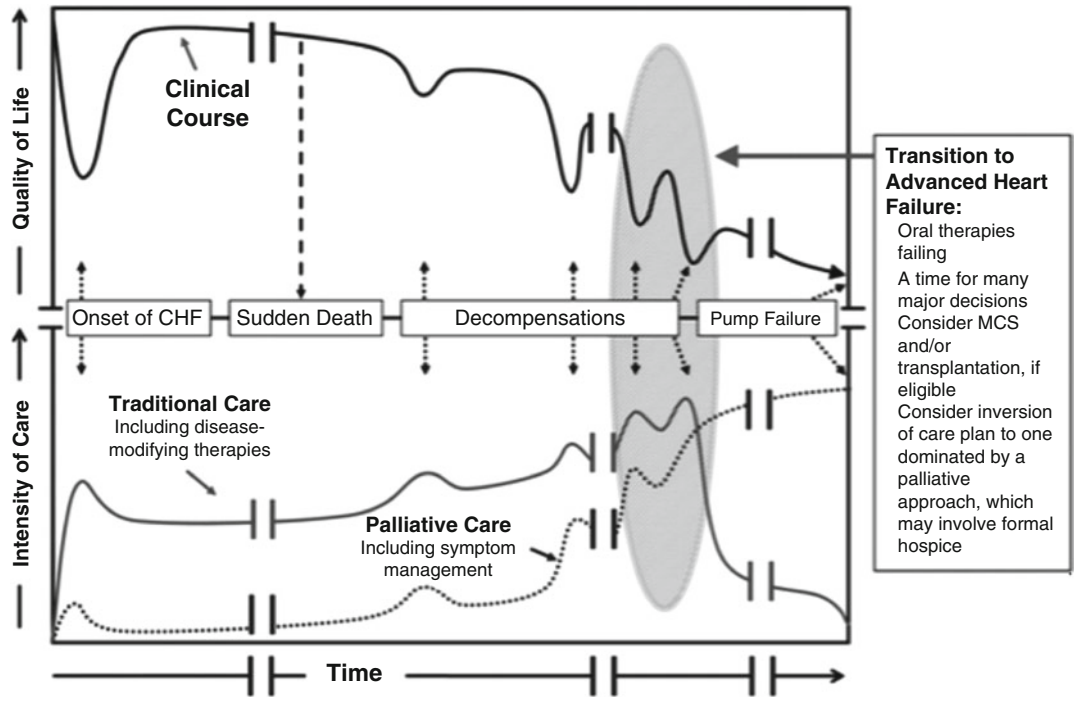

Fig. 1 Graphical representation of the clinical course of heart failure and intensities of medical therapies

information about the severity of HF. The ACCF/AHA stages emphasize the development and progression of disease, while NYHA class focuses on exercise capacity and symptomatic status. The ACCF/AHA stages progress from Stage A where a patient has no structural cardiac abnormalities or HF symptoms, to Stage B where this is structural heart disease but no signs or symptoms of HF, to Stage C structural heart disease with prior or current symptoms of HF, to Stage D when a patient has structural abnormalities and HF symptoms refractory to standard oral medications. Similarly, NYHA functional classification progress from Class 1, patients with no limitations of ordinary physical activity, to Class II, patients with slight limitation of physical activity who are comfortable at rest but have symptoms of HF with ordinary physical activity; Class III, patients with a marked limitation of physical activity such that less than ordinary activity causes symptoms of HF but whom are comfortable at rest; and Class IV, patients who are unable to carry on any physical activity without symptoms of HF and/or have symptoms of HF at rest. Patients with Stage D HF and either NYHA class III or IV functional status are typically the recipients of advanced therapies such as mechanical circulatory support (MCS) and cardiac transplantation.

A depiction of the clinical course of heart failure with associated types and intensities of available therapies. Black line: patients tend to follow a progressive, albeit nonlinear, decline in health-related quality of life as the disease progresses; this course can be interrupted by sudden cardiac death caused by arrhythmia or can end in a more gradual death caused by progressive pump failure. Gray line: at disease onset, multiple oral therapies are prescribed for cardiac dysfunction and/or treatment of comorbidities. As disease severity increases, the intensity of care may increase in parallel, with intensification of diuretics, addition of an implantable cardioverter defibrillator/cardiac resynchronization therapy for those eligible, and increasing interaction with the medical system through ambulatory visits and hospitalizations, until the time when standard therapies begin to fail (transition to advanced heart failure). Dotted line: palliative therapies to control symptoms, address quality of life, and enhance communication are relevant throughout the course of heart failure, not just in advanced disease; palliative therapies work hand in hand with traditional therapies designed to prolong survival. The critical transition into advanced heart failure from the medical perspective is often followed by a transition in goals of care from the patient and family perspective, wherein palliative therapies may become the dominant treatment paradigm (for the majority of patients in whom transplantation and mechanical circulatory support are not an option). Clinicians must recognize the transition to advanced heart failure so that therapeutic options can be considered in a timely fashion and patients are able to proactively match medical decisions to clinical realities. CHF indicates chronic heart failure; MCS, mechanical circulatory support. Borrowed from Decision making in advanced heart failure: a scientific statement from the American Heart Association (Allen et al. 2012). Original figure modified and reprinted with permission of the American Thoracic Society. Copyright © 2017 American Thoracic Society from Lanken et al.; An official American Thoracic Society clinical policy statement: palliative care for patients with respiratory diseases and critical illnesses. Am J Respir Crit Care Med. 2008;177:912–927.

The overall prevalence of HF ranges from 1% to 12% on studies in the United States and Europe, a wide range attributed to differences in ascertainment and adjustment (Roger 2013). The age-adjusted incidence has been increasing, particularly for men, older persons, and patients with hypertension and/or increased body mass index. The incidence of HF in the Unites States is quite high with an estimated lifetime risk of 20% for Americans 40 years of age or older and an estimated prevalence of 5.8 million persons in the Unites States already having clinically manifest HF. Incidence of HF was noted to be higher in blacks than in whites in both the Atherosclerosis Risk in Communities study and the Multi-Ethnic Study of Atherosclerosis; however the difference was attenuated after adjustment for atherosclerotic

risk factors and socioeconomic variables. Despite the progress in treatment and management, absolute mortality rates remain high for HF with approximately 50% of patients dying within 5 years of diagnosis, and progression in HF stages is also associated with reduced 5-year survival (Yancy et al. 2013). Heart failure is a clinical and public health problem of staggering proportions with estimated costs of HF care in the Unites States exceeding $30 billion in 2013 due to direct healthcare services, medications, and lost productivity.

The progression of systolic HF pathophysiology is driven by dysfunction of the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system (SNS) (Lang and Struthers 2013). The circulating RAAS is designed to acutely maintain circulating volume, normotension, and electrolyte homeostasis, but chronic overactivity in the setting of HF leads to progression of the HF syndrome. Liver-derived angiotensinogen is activated by renin secreted from the kidneys and converted into angiotensin I. Angiotensin I is converted by angiotensin converting enzyme (ACE) into angiotensin II, which acts on angiotensin 1 receptors to promote aldosterone secretion, sodium, and water retention and vasoconstriction. Long-term RAAS stimulation is associated with myocardial remodeling and renal dysfunction. Similarly, in response to physiological and pathophysiological stresses, catecholamine release and stimulation of the adrenoceptors of the SNS are increased. Although the SNS response is acutely beneficial in augmenting cardiac output, long-term sympathetic stimulation is maladaptive and contributes to myocardial remodeling and mortality. Specifically, desensitization and downregulation of myocardial beta-adrenoceptor density in the myocardium contribute toward progressive failure of the heart. Myocardial remodeling is defined as the structural alteration in the dimension, shape, and mass of the heart in response to hemodynamic load and cardiac injury (Kramer et al. 2010). Remodeling may be described as physiologic or pathologic and adaptive or maladaptive. It is strongly associated with neurohumoral activation and generally accepted as a key determinant of prognosis in HFrEF. Patients with marked ventricular remodeling, such as increased left ventricular end-diastolic volume and ventricular sphericity, also demonstrate progressive worsening of systolic function. A major goal of chronic systolic HF management is neurohumoral antagonism to improve the structure and function of the myocardium, as well as to alleviate symptoms and achieve improved survival. To date, almost all drug and device therapies that have been associated with improved mortality in HFrEF also induce reverse (favorable) ventricular remodeling with reductions in LV volumes.

General Management of Chronic Heart Failure

The initial diagnostic evaluation for heart failure is well covered in the 2013 ACCF/AHA Heart Failure Guideline, which also provides extensive guidance on medical and device therapy management (Yancy et al. 2013). Management of HFpEF predominantly focuses on symptoms and underlying risk factors and comorbidities due to difficulties demonstrating improvement in morbidity or morality with HFpEF interventions. Unlike HFpEF, management of HFrEF has been driven by successful trials demonstrating significant improvement in morbidity and mortality with guideline-directed medical therapy (GDMT) and implantable electronic cardiac devices. However, even successful HF therapies generally may only slow disease progression (Allen et al. 2012), and even HF patients who experience recovery of myocardial dysfunction have residual hospitalization and mortality risks. As the severity of HFrEF advances, standard therapies may no longer be efficacious, and consideration of advanced therapies such as cardiac transplantation, mechanical circulatory support (MCS), or transition to palliative focused care paradigm may be necessary (Allen et al. 2012).

The GDMT for patients with HF is thoroughly addressed in the 2013 ACCF/AHA Guidelines and 2016 Focused Update (Yancy et al. 2013, 2016). In patients with Stage A heart failure, care should be focused on optimizing risk

factors, particularly with respect to elevated blood pressure, dyslipidemia, vascular disease, obesity, diabetes mellitus, sleep disorders, tobacco use, and toxin exposure, including specific cardiotoxic chemotherapy regimens (Yancy et al. 2013). The goal for patients with Stage A HF is to lead a heart-healthy lifestyle and prevent the development of structural heart abnormalities, coronary disease, and/or vascular disease. For patients with Stage B HF, risk factor optimization is still the primary recommendation, with a goal of preventing further cardiac remodeling and the development of HF symptoms. There is a potential role for angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), specific beta-blockers, and/or statins and a role for avoiding non-dihydropyridine calcium channel blockers with negative chronotropic effects. In addition, there is a Class IIb, level of evidence (LOE) B recommendation for implantable cardiac defibrillator (ICD) placement in patients with an asymptotic ischemic cardiomyopathy (CMY) with sustained severe LV systolic dysfunction (e.g., LVEF $\leq$30%) 40 days post-MI despite appropriate medical therapy and an expectation of survival with a good functional status for over 1 year.

The main goals for a patient with Stage C HF, regardless of LVEF, are to control symptoms, improve health-related quality of life, and prevent morbidity and mortality, particularly with respect to HF decompensations and hospitalizations. A patient with Stage C HF should receive specific education to facilitate self-care, including how to monitor and control symptoms and weight fluctuations, restrict sodium and fluid intake, take medications as prescribed, and continue being physically active. The basic pharmacologic armamentarium for HFrEF includes an ACE inhibitor, ARB or ARNI, and an evidence-based beta-blocker, unless intolerant (Class I, LOE A) (Yancy et al. 2013, 2016). Additional therapies include diuretics for patients with volume overload (e.g., NYHA class II–IV), combination of hydralazine and nitrates for persistently symptomatic African Americans with NYHA class III–IV, aldosterone antagonists for patients with NYHA class III–V with an estimated glomerular filtration rate $>$ 30 ml/min and no issues with hyperkalemia (K+ $<$5.0 mEq/dl), and digoxin for patients with HFrEF and recurrent hospitalizations for acute decompensated HF without known contraindications to digoxin. In 2016, the ACCF, AHA, and HFSA published a focused update on the pharmacological treatment of HFrEF which included utilizing an angiotensin receptor-neprilysin inhibitor (ARNI) as a first-line therapy with evidence-based beta-blockers as an alternative to ACE inhibitors or ARBs (Class I, LOE B-R), as well as promoting switching to an ARNI in patients already tolerating an ACE inhibitor or ARB (Yancy et al. 2016). The same update provided a Class IIa LOE B-R recommendation to initiate a sinoatrial node modulator (e.g., ivabradine) for patients with symptomatic stable chronic HFrEF who were tolerating GDMT, including a beta-blocker at maximum tolerated dose, who were in sinus rhythm with a heart rate of 70 bpm or greater at rest. Omega-3 fatty acids received a Class IIa, LOE C recommendation for patients with HFpEF or HFrEF and NYHA II–IV symptoms. The GDMT of patients with Stage C HFpEF remains limited to general blood pressure control, diuretics for symptomatic hypervolemia, and consideration of revascularization for patients with angina or ischemia associated with worsening HF symptoms. There are three class I device-based recommendations for Stage C HFrEF, including an ICD for primary prevention of SCD in patients with ischemic heart disease at least 40 days post-MI or patients with nonischemic dilated cardiomyopathy (DCM), who have NYHA II or III symptoms on chronic GDMT with a reasonable expectation to live more than 1 year. For patients with ischemia-related HF but only NYHA class I symptoms who are at least 40 days post-MI with an LVEF of 30% or less despite GDMT, with a reasonable expectation to live 1 year or more, an ICD is recommended. Cardiac resynchronization therapy (CRT) is indicated for patients in sinus rhythm with a left bundle branch block (LBBB) with QRS duration $\geq$150 ms, LVEF $\leq$35%, and NYHA class II, III, or ambulatory IV symptoms on GDMT.

A small percentage of patients with chronic HF progress to stage D HF, also known as “advanced

HF," "end-stage HF," or "refractory HF" (Yancy et al. 2013). In 2015, James Fang et al. proposed that stage D advanced HF be defined by "the presence of progressive and/or persistent severe signs and symptoms of heart failure despite optimized medical, surgical, and device therapy" and that "...the progressive decline should be primarily driven by the heart failure syndrome" (Fang et al. 2015). Goals of care can vary widely for a patient with Stage D HF but often include controlling symptoms, improving health-related quality of life, reducing HF hospitalizations, and establishing end-of-life goals. It is imperative to ensure that the diagnosis of Stage D HF is correct and there are no remediable etiologies or alternative explanations as these are the patients in whom specialized advanced HF treatment strategies may need to be discussed, including mechanical circulatory support (MCS), continuous inotropic infusions, cardiac transplantation, innovative or experimental procedures, and/or end-of-life care such as hospice. Per the ACCF/AHA guidelines, advanced HF is a clinical diagnosis; however objective criteria for the diagnosis have been developed by the European Society of Cardiology, and a stratification system was developed by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) (Metra et al. 2007; Stevenson et al. 2009).

Pathological Basis of Heart Failure

Classification of Cardiomyopathies

The classification of cardiomyopathies is a challenging process. There are benefits to favoring anatomic designations (e.g., hypertrophic, dilated) as well as functional designations (e.g., restrictive, constrictive) or even etiologic designations (e.g., ischemic, infiltrative, genetic, idiopathic, etc.) (Yancy et al. 2013). Rather than attempting to redefine classification strategies for cardiomyopathies, the 2013 ACCF/AHA Heart Failure Guideline stated the goal of helping clinicians target the appropriate diagnostic and therapeutic strategies for preventing the development and/or progression of HF and subdivided the causes of CMY into the following categories: dilated, familiar/genetic, endocrinologic and metabolic (e.g., obesity, diabetes, thyroid, acromegaly, growth hormone deficiency), toxin-induced (e.g., alcohol, cocaine, cardiotoxic cancer therapy-induced, myocardial toxins, nutritional), tachycardia-induced, myocarditis and inflammation (myocarditis, acquired immunodeficiency syndrome, Chagas), noninfectious inflammation-induced (e.g., hypersensitivity myocarditis, rheumatologic/connective tissue disease), peripartum, iron overload, amyloidosis, cardiac sarcoidosis, and stress (i.e., takotsubo).

Dilated Cardiomyopathy

The term DCM is commonly used to describe patients with LV dilation and depressed myocardial contractility, occurring in the absence of abnormal loading conditions. DCM can be an early or late result of a large heterogeneous mixture of myocardial disorders, including both ischemic and nonischemic processes. The incidence and prognosis of DCM varies which may reflect confounding due to differing etiologies. However, approximately one quarter of patients with a DCM and recent onset of HF symptoms may improve within a short period of time, regardless of the use of GDMT; however patients with >3 months of HF symptoms who present with severe decompensation and marked LV dilatation generally have a lower chance of recovery. It is estimated that 20–35% of patients with idiopathic DCM have a familial CMY, (defined as two closely related family members meeting criteria for idiopathic DCM), although advances in the genetic screening may reveal this to be an underestimate in the future.

Ischemic Cardiomyopathy

Patients with a CMY originating from an ischemic etiology may present in many ways, including end-stage systolic dysfunction due to multivessel coronary artery disease (CAD)

without reasonable surgical and/or percutaneous revascularization options resulting in chronic infarction or advanced HFpEF from recurrent ischemia and stunning. Additionally, patients with advanced ischemic CMY may suffer from debilitating refractory angina or refractory ventricular tachycardia nonresponsive to antiarrthymic therapy, implantable cardiac device optimization, myocardial ablation techniques, and/or stellate ganglion blocks. Refractory angina without potential medical or surgical therapeutic options and recurrent life-threatening LV arrhythmias despite an ICD, antiarrhythmic therapy, or catheter-based ablation are both indications for cardiac transplantation (Jessup et al. 2009). Unfortunately, patients with refractory angina or VT who are listed for cardiac transplantation are likely to be listed as the lowest acuity, UNOS Status 2, and thus much less likely to be transplanted. Criteria for Status 1a or 1b is heavily weight by use of MCS, inotropic support, and invasive hemodynamic monitoring, and there is little demonstrated efficacy for MCS to suppress refractory angina or VT, and continuous inotropic support may exacerbate both.

Endocrinologic and Metabolic Causes of CMY

The list of nonischemic etiologies of CMY continues to expand as diagnostic testing such as high-throughput sequencing and genotypic, as well as phenomapping algorithms, improve (Yancy et al. 2013; Shah et al. 2015). Both obesity and diabetes mellitus have been shown to be independent risk factors for a significant future risk of developing HF even after controlling for other established risk factors. The precise mechanisms causing obesity-related HF are not known but have been postulated to be due to systemic metabolic dysfunction promoted by the secretion of adipokines and inflammatory proteins from hormonally active visceral adipose tissue, in addition to changes in myocardial substrate utilization and myocardial lipid accumulation (Vest and Young 2014). While weight loss is usually advised for HF patients with severe obesity, an obesity survival paradox has been observed in retrospective cohorts, and there are no large prospective studies of safety or efficacy of weight loss interventions in obesity CMY. The optimal treatment strategy in patients with diabetes mellitus and HF is controversial. There is a U-shaped association between mortality and hemoglobin A1C in these patients, and many common diabetes medications have evidence of harm in HF populations. In particular, thiazolidinediones should be avoided in patients with NYHA class II–IV HF due to associated fluid retention.

The association between hyperthyroidism and DCM is not well understood and may reflect issues with persistent sinus tachycardia or atrial fibrillation with rapid ventricular response more than the specific state of hyperthyroidism. Hypothyroidism has been associated with abnormalities in cardiac systolic and diastolic performance, although patients with myxedema do not usually have a CMY. Low cardiac output may result from bradycardia, decreased ventricular filling, reduced cardiac contractility, and diminished myocardial work. Both deficiency and excess of growth hormone in patients with impaired cardiovascular function have been associated with reduced life expectancy. Multiple histopathologic changes can be seen in the CMY associated with acromegaly, including myocardial hypertrophy with interstitial fibrosis, lympho-mononuclear infiltration, myocyte necrosis, and biventricular concentric hypertrophy.

Toxin-Associated CMY

Multiple toxins are associated with the development of a CMY. One of the most important and potentially reversible causes of a DCM is chronic alcoholism (Yancy et al. 2013). Alcoholic CMY is classically associated with biventricular dysfunction and dilatation in the absence of other known causes of myocardial disease. Patients have classically been heavy consumers of alcohol for >10 years; it is particularly prevalent in those consuming >90 g of alcohol per day (approximately 7–8 standard drinks per day) for over 5 years. The concept of

an alcoholic CMY is paradoxical given the evidence that support mild to moderate alcohol consumption may be protective against the development of HF and other cardiovascular diseases (Yancy et al. 2013); however multiple mechanisms have been implicated in mediating the adverse myocardial effects of ethanol, including the generation of oxidative stress, apoptotic cell death, impaired mitochondrial bioenergetics/stress, derangements in fatty acid metabolism and transport, and accelerated protein catabolism (Piano and Phillips 2014). The highly varied relationship between alcohol consumption, development of alcohol-related CMY, and severity of HF symptoms may reflect variations in individual's drinking patterns (particularly duration), genetic susceptibility, nutritional factors, ethnicity, and sex.

Cocaine is well known to cause irreversible structural changes on the brain, heart, lung, liver, and kidney (Riezzo et al. 2012). Cocaine has multiple cardiotoxic effects, including coronary artery vasoconstriction, accelerated atherosclerotic plaque formation, vascular thrombosis, myocarditis, ventricular hypertrophy, arrhythmogenesis, DCM, and HF. Some of these effects are attributed to its powerful stimulation of the sympathetic nervous system, e.g., inhibiting catecholamine reuptake, stimulating central sympathetic outflow, and increasing the sensitivity of adrenergic nerve endings to norepinephrine, while others are due to blocking of myocardial potassium channels, enhancing the function of calcium channels, and inhibiting the flow of sodium during depolarization. In a study of 30 consecutive asymptomatic subjects with regular cocaine use but no history of cardiovascular disease evaluated 48 hrs after the withdrawal of cocaine, a high prevalence of evidence of cardiac damage was found by cardiac magnetic resonance imaging (83%), as well as abnormalities on resting ECG (50%) and echocardiography (12%) (Aquaro et al. 2011). Despite the known benefits of beta-blockers in HF, CAD, and arrhythmias, prior studies have suggested they may precipitate coronary vasoconstriction due to unopposed α-receptor stimulation and have active metabolites for days (Finkel and Marhefka 2011). However, there are multiple case reports of patients receiving beta-blockers with cocaine in their system without known sequelae and possible benefit; thus the safety and efficacy of beta-blocker use in patients with cocaine use is not known (Finkel and Marhefka 2011).

Multiple pharmacologic agents have been strongly associated with cardiotoxic effects, particularly certain cytotoxic antineoplastic drugs such as anthracyclines, trastuzumab, high-dose cyclophosphamide, taxiods, mitomycin-C, 5-fluorouracil, and interferon therapy (Yancy et al. 2013). Other medications that have also been implicated as myocardial toxins include ephedra, cobalt, anabolic steroids, chloroquine, hydroxychloroquine, clozapine, amphetamine, methylphenidate, and catecholamines. There is hope for a possible cardioprotective role for iron-chelating agents such as dexrazoxane to prevent the generation of oxygen free radicals; however this is still being studied in conjunction with chemotherapy agents.

Specific primary and secondary nutritional deficiencies have been associated with the development of CMY, including thiamine deficiency, selenium deficiency, and L-carnitine deficiency.

Infiltrative and Deposition CMY

Iron overload CMY is due to increased deposition of iron in the heart, usually associated with primary hemochromatosis or diseases associated with lifetime transfusion requirements such as beta-thalassemia major. Historically, cardiac failure has been one of the most frequent causes of death with these genetic disorders; however chelation therapy and gene therapy may significantly improve morbidity and mortality.

Amyloidosis can be a localized or systemic disease due to the deposition of proteins with unstable tertiary structures that form insoluble amyloid fibrils (Maurer et al. 2017). Over 30 proteins can form amyloid fibrils, but 5 proteins are more commonly associated with cardiac infiltration. These proteins may result from primary or AL amyloidosis (monoclonal kappa or lambda

light chains), secondary amyloidosis (protein A), familial transthyretin (TTR), amyloidosis (mutant transthyretin), wild-type TTR amyloidosis (wild-type transthyretin), or dialysis-associated amyloidosis (beta-2-microglobulin). Primary AL amyloidosis is uncommon with an estimated prevalence of 8–12 per million, with approximately 10,000 affected individuals in the United States, of which 30–50% have cardiac involvement. TTR amyloidosis is much more common but may be overlooked clinically. Autopsy data has demonstrated TTR amyloid deposits in myocardium in 25% of adults over the age of 80 years and 32% of those with HFpEF over the age of 75 years. Diagnosis may be an incidental finding based on imaging or due to rapidly progressive HF symptoms. The key to improving prognosis in cardiac amyloidosis is reduction of the precursor proteins that forms amyloid fibrils. For AL cardiac amyloidosis, this can be achieved with combination chemotherapy, while orthotopic liver transplantation can be considered to remove the hepatic source of genetically variant TTR proteins, either alone or in combination with cardiac transplant, for selected patients with TTR amyloidosis. Unfortunately, the diagnosis is often late which limits treatment options and efficacy. Current management of TTR amyloidosis is limited; however there are multiple therapies in late-phase clinical trials such as TTR stabilizers, TTR silencers, and antifibrillar therapies. High-risk features associated with <6 month median survival include ventricular septal thickness $>$ 15 mm, LVEF$<$40%, and presence of HF symptoms. Biomarkers such as BNP and cardiac troponin have been reported to predict response, progression of disease, and survival.

Sarcoidosis is a multisystem granulomatous disease of unknown etiology, and the prevalence of isolated or concomitant cardiac sarcoidosis ranges from 5% to 40%. Cardiac sarcoidosis can present with conduction abnormalities, ventricular arrhythmias, and heart failure or be clinically silent (Birnie and Nery et al. 2016). Cardiac sarcoidosis may present as asymptomatic LV dysfunction, HF, atrioventricular block, atrial or ventricular arrhythmia, or SCD. Cardiac involvement can be seen as patch areas of inflammation and fibrosis by CMR and cardiac position emission tomographic scanning. Observational studies and case reports suggest early use of high-dose steroid therapy may halt or reverse cardiac damage, although immunosuppressives are unlikely to be beneficial once significant myocardial scarring and remodeling has occurred. Patients with cardiac sarcoidosis and evidence of ventricular tachyarrhythmias may benefit from a primary prevention ICD. Two recent studies looked at the role of advanced imaging in cardiac sarcoidosis with respect to predicting all-cause mortality and arrhythmogenic events. Late gadolinium enhancement on CMR imaging suggests myocardial scar and was associated with increased odds of both all-cause mortality and arrhythmogenic events in patients with known or suspected cardiac sarcoidosis in both studies, while abnormal fluorodeoxyglucose positron emission tomography, suggestive of myocardial inflammation, did not correlate (Bravo et al. 2017; Coleman et al. 2017).

Electrophysiology-Related CMY

Tachycardia-induced CMY is a common reversible cause of HF associated with LV myocardial dysfunction (Yancy et al. 2013). The underlying mechanism for tachycardia-induced CMY is not fully understood, but there is a close correlation between duration and rate of the tachyarrhythmia. Control of ventricular rate is critical for treatment, and there can be near universal reversibility with restoration of normal rate and rhythm. Additional rhythm-related HF issues can be seen with any ventricular pacing at high rates and with right ventricular pacing in particular. The use of CRT can alleviate HF associated with intrinsic or right ventricular induced conduction delays.

Peripartum Cardiomyopathy

Peripartum CMY (PPCM) is a well-established complication of pregnancy, a process in which LV dysfunction occurs during the last trimester of pregnancy or in the early puerperium, usually

within the last month of pregnancy or first 5 months post-delivery (Sliwa et al. 2010). As shortness of breath and ankle swelling are common in the peripartum period, a high index of suspicion is necessary to make the diagnosis. More than half of patients recover completely, while greater abnormalities of LVEF and LV diameter at the time of diagnosis are associated with lower likelihood of recovery and greater morbidity and mortality (McNamara et al. 2015). The pathophysiology of PPCM is still under investigation but likely includes immune, oxidative, and inflammatory mechanisms. There is a proposed etiologic role for a cleaved anti-angiogenic and proapoptotic 16 kDa form of the nursing hormone prolactin (Hilfiker-Kleiner et al. 2007). Risk factors for PPCM include advanced maternal age, multiparity, African descent, twin pregnancy, pregnancy-induced hypertension, and protracted tocolysis. A large ongoing prospective, international, multicenter, observational registry is being organized by the European Society of Cardiology with 500 patients enrolled from 43 countries between August 1, 2012, and March 1, 2016 (Sliwa et al. 2017). Despite marked sociodemographic differences in these first 500 patients, obstetric history and clinical presentation were remarkably similar among PPCM patients, and depending on region, 10–27% had a preexisting diagnosis of prior PPCM. One third presented prepartum, while most others presented within the first month postpartum. The large majority had symptomatic HF 1 month after diagnosis (92.3% in non-ESC vs. 81.3% in ESC, $P < 0.001$) and/or embolic events (6.8%). Current therapies for chronic PPCM are similar to those general HF with attention paid to concern about antenatal transmission. Trials are currently investigating the role for novel therapies such as bromocriptine, pentoxifylline, and immune modulators. In the PPCM registry, medication use included diuretics (83.6%), ACE inhibitors (78.8%), beta-blockers (79.9%), and bromocriptine (21.2%), with significant differences noted between ESC and non-ESC countries ($P < 0.001$). In the same registry, patients who had full recovery of LVEF before a subsequent pregnancy experienced lower mortality and better cardiac function at follow-up (Hilfiker-Kleiner et al. 2017). Also, it appeared that the addition of bromocriptine (which inhibits prolactin release) to standard therapy for HF immediately after delivery was safe and associated with a better outcome in African and Caucasian patients with a subsequent pregnancy after PPCM.

Inflammatory Cardiomyopathies

Myocardial inflammation may explain approximately 10% of initially unexplained CMY and may be due to acute or chronic infections, toxins, medications, or systemic diseases, such as autoimmune and rheumatologic disorders (Yancy et al. 2013). The presentation of an inflammatory CMY can range from an acute fulminant onset to a subacute insidious onset. Prognosis is varied and paradoxically may be best in those who present with acute fulminant myocarditis who often have spontaneous complete resolution, while a subacute presentation may be more likely to result in a DCM. Giant cell myocarditis is a rare form of an inflammatory CMY that is characterized by fulminant HF, refractory ventricular arrhythmias, and a poor prognosis. Consideration for early utilization of advanced HF therapies, including immunosuppression, MCS, and transplantation may be warranted. In other cases, the role of immunosuppressive therapy is controversial.

Rheumatological disease can be associated with a number of cardiac abnormalities. Cardiac involvement of systemic lupus erythematous is likely related to myocardial fibrosis and can result in pericarditis, pericardial effusions, conduction abnormalities, and rarely a DCM. Scleroderma can also be a rare cause of DCM or HFpEF, while cardiac involvement with rheumatoid arthritis is more commonly manifested as myocarditis and/or pericarditis due to microvasculitis and microcirculatory disturbances. In addition, there is controversy regarding the risks and benefits of immune-modulating medications used for the rheumatologic disorders, such as etanercept, infliximab, and adalimumab, as some reports suggest an association with incident or worsening HF (Jain and Singh 2013).

Chronic Chagas disease is endemic to Central and South America but becoming a more prevalent condition in North America. Cardiac changes associated with chronic *Trypanosoma cruzi* infection includes biventricular cavity enlargement, thinning or thickening of ventricular walls, apical aneurysms, mural thrombi, and conduction disease including right bundle branch block, left anterior fascicular block, and complete atrioventricular block.

Human immunodeficiency virus (HIV) is associated with a wide range of structural and arrhythmic complications likely due to abnormal inflammatory processes, opportunistic infections, and drug toxicities (Manga et al. 2017). HIV-associated heart disease may involve the pericardium, myocardium, valves, and any vasculature. HIV-associated cardiomyopathies can present with focal myocarditis, subclinical LV or RV dysfunction, or symptomatic DCM with HFrEF and may or may not be associated with concurrent atherosclerotic heart disease. Improved access to combination antiretroviral therapy (cART) is associated with a decreased prevalence of HIV-associated CMY. As per the 2016 International Society of Heart and Lung Transplantation (ISHLT) updated heart transplantation listing criteria, select patients with HIV may be eligible for transplantation (Mehra et al. 2016).

Hypersensitivity myocarditis is a specific allergic reaction involving the myocardium that is characterized by peripheral eosinophilia and a perivascular infiltration of the myocardium by eosinophils, lymphocytes, and histiocytes. The drug is usually the offending agent, most commonly sulfonamides, penicillins, methyldopa, amphotericin B, streptomycin, phenytoin, isoniazid, tetanus toxoid, hydrochlorothiazide, dobutamine, and chlorthalidone. While many patients do not appear clinically ill, there is the risk of SCD, presumably secondary to an arrhythmia. Resolution of the inflammation upon withdrawal of the offending agent is common.

Stress cardiomyopathy, also known as takotsubo syndrome, is an important common cause of acute LV dysfunction, often with marked reduction of LVEF, occurring in the absence of significant CAD and often associated with acute emotional or physical stress (Yancy et al. 2013). Multiple diagnostic criteria have been proposed, including those by the Mayo Clinic (modified in 2008), the Japanese Takotsubo Cardiomyopathy Group, the Gothenburg Group, the Takotsubo Italian Network, and the European Society of Cardiology. The classic presentation is often a mimic of ST-elevation myocardial infarction with chest discomfort, ST-T ischemic changes, elevated cardiac markers, normal or non-flow limiting coronary artery lesions, and transient LV wall motion abnormalities typically involving the apex with preserved basal contractility (Lyon et al. 2016). The most common LV wall motion abnormality described is apical ballooning with a hyperdynamic basal segment that bears the resemblance of a traditional Japanese octopus trap (takotsubo); however multiple variants exist**.** The rise in cardiac enzymes is often low to moderate which is often discrepant with the large amount of dysfunctional myocardium and ECG changes. It can be challenging to distinguish takotsubo syndrome from acute infective myocarditis due to the occasional presence of myocardial edema and inflammation in an anatomical distribution. While stress CMY predominantly affects post-menopausal women (~90%), it occurs in men and younger women as well. The ESC position statement on takotsubo draws a distinction between primary and secondary syndromes. With primary takotsubo, the acute cardiac symptoms are the primary reason for seeking care and are often associated with a clearly stressful trigger (~70%), while secondary takotsubo syndrome is more common in patients already hospitalized for another reason and may be associated with a sudden activation of the sympathetic nervous system or a rise in catecholamines due to a complication of a separate primary condition or its treatment. A few potential triggers for secondary takotsubo include pheochromocytoma, thyrotoxicosis, neurologic emergencies, acute massive pulmonary embolism, and attempted suicide. The leading hypothesis is that the syndrome is due to acute catecholaminergic myocardial stunning. Recovery can vary and may not be complete; however the LVEF usually recovers by 12 weeks, while ECG changes and BNP levels may take 6–12 months to recover.

Genetic Cardiomyopathies

Hypertrophic CMY is one of the most common known genetic cardiovascular diseases with a diverse clinical presentation (Gersh et al. 2011). The prevalence of the classic phenotype is estimated to be 1 in 500 (0.2%) of the general population throughout the world. The disease is characterized by unexplained LV hypertrophy associated with nondilated LV chamber in the absence of another explanation, although any degree of wall thickness is compatible with the presence of the HCM genetic substrate. A maximal LV wall thickness of $\geq$15 mm by echocardiography is common, but a diagnosis can be made with thinner walls (13–14 mm) in the presence of other compelling information. As genetic testing advances and more disease-causing sarcomere mutations are known, a group of patients has emerged who have a positive family history of hypertrophic CMY and causative genetic mutation but no evidence of the disease phenotype (i.e., LV hypertrophy); these patients are often labeled as "genotype positive/phenotype negative" or "subclinical HCM." Most individuals with hypertrophic CMY usually have normal or hyperdynamic wall motion and LVEF, with a normal life expectancy with minimal to no disability or need for major therapeutic interventions. The most common complications include unpredictable ventricular tachyarrhythmias, atrial fibrillation with increased risk of systemic thromboembolism, and HF. Many HCM patients with advanced HF symptoms have a preserved EF, although a minority do progress to an end-stage CMY characterized by LV remodeling and systolic dysfunction. In a small percentage of HCM patients, advanced HF therapies may need to be considered, although without significant LV dilatation, LVADs may not be an option due to safety concerns about placing an inflow cannula in a small LV cavity.

Arrhythmogenic CMY is defined by progressive fibrofatty replacement of the ventricular myocardium associated patchy fibrosis, inflammation, myocyte death, wall thinning, and aneurysm formation (Cahill et al. 2013). Arrhythmogenic CMY has predominantly been considered a disease of the right ventricle (arrhythmogenic right ventricular cardiomyopathy, ARVC), but left and biventricular involvement is increasingly recognized. Clinical manifestations include malignant arrhythmias, HF, and SCD. Prevalence is estimated to be somewhere between 1 in 1000 and 5000. It is often familial although the inheritance is not well understood as penetrance is low and a genetic mutation is only identified in approximately 50% of patients.

Left ventricular noncompaction CMY (LVNC) is a clinical entity that is increasingly recognized; however it is unclear if it is sporadic or familial and whether it is a distinct CMY or a phenotypic variant of hypertrophic and/or dilated CMY (Cahill et al. 2013). It is characterized by persisting noncompaction from the embryological stage, although cases of LV noncompaction CMY have been made in patients with previously normal-appearing myocardium. It is associated with HF, thromboembolism, arrhythmias, or SCD. Cardiomyopathy may also occur as a component of systemic mitochondrial disease. The mitochondrial CMY phenotype is heterogeneous, but very early presentation is classic, often in utero or infancy. Other genetic CMY are known or suspected, such as with neurodegenerative diseases, Friedreich's ataxia, or inborn errors of metabolism, such as Pompe disease.

Adult Congenital Heart Disease

Congenital heart disease (CHD) is one of the most common congenital abnormalities; the estimated prevalence of moderate or severe CHD is 6 per 1,000 births (19 per 1,000 if bicuspid aortic valves are included) (Benziger et al. 2015). Innovation and advancement of the medical and surgical therapies available for patients with congenital heart disease (CHD) has improved the survival of children and adolescents with CHD such that the number of adults living with CHD in the United States has surpassed the number of children with CHD (Marelli et al. 2014). Adults with a history of corrected or uncorrected CHD may ultimately develop clinical HF, and a modest proportion of candidates for heart transplantation

include children with CHD or adult survivors of CHD (Mehra et al. 2016). Bridging children and adults with CHD to a successful transplantation in a timely manner can be quite challenging due to a myriad of issues, including pulmonary arterial hypertension, sensitization from prior transfusions, hostile chests from multiple prior surgeries, unique and challenging anatomy, and nontraditional advanced HF symptoms that are less responsive to current therapies (e.g., failing Fontan circulation). For CHD patients with pulmonary hypertension that does not respond to conventional medical therapy, the role of VADs and total artificial hearts is under investigation, and heart or heart-lung (block) transplantation remains a potential therapeutic option (Roth and Aboulhosn 2016).

Advanced Heart Failure Management

Prognosis in Heart Failure

Survival is not the only outcome of importance to patients with chronic disease. As illustrated in Fig. 2, patient-centric outcomes vary based on the relative values individuals assign to elements of various domains such as the economic impact of the disease, the social impact of the disease, time utilization, and the personal experience of living and dying. The initial diagnosis of heart failure is associated with significant uncertainty about the future with respect to symptom burden, progression of functional impairment, and life expectancy (Upshaw et al. 2016). Risk prediction and prognostic models can set up the foundation for treatment planning and shared decision-making. One of the most widely used is the Seattle Heart Failure Model (SHFM), which is publically available and provides individualized estimated of mean survival at 1, 2, and 5 years (Levy et al. 2006). The SHFM has a moderate predictive, and discriminatory value with an area under the receiver operating characteristic curve for 1-year prognosis is typically $\leq$0.73. Another commonly used model is the Heart Failure Survival Score (HFSS) which stratifies patients with HFrEF into low-, medium-, and high-risk subgroups. In 2011, the accuracy of the HFSS for assessing risk in contemporary patients stratified by the presence of ICD and/or CRT therapy was assessed in comparison to peak VO_2 (Goda et al. 2011a, b). Using the area under the receiver operating characteristic curve, the HFSS performed better than the peak VO_2 at 1 year in the total cohort (0.72 vs. 0.65; $p < 0.001$) and at 1 year in the device subgroup (0.69 vs. 0.65; $p < 0.001$).

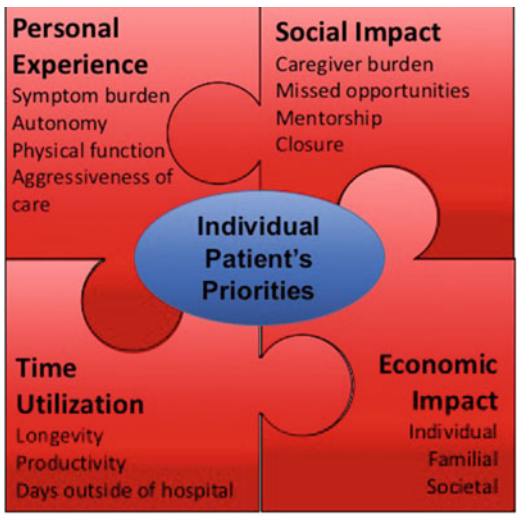

Fig. 2 Patient-centric outcomes comprise multiple domains, including the overall personal experience, opportunity for time utilization, social impact of disease, and economic impact of disease. The importance of each domain and the various subcomponents will vary for each individual. (Adapted from Allen et al. 2012)

The ISHLT Listing Criteria for Heart Transplantation provides a Class IIb LOE C recommendation that HF prognosis scores should be performed along with CPET to determine prognosis and guide listing for transplantation for ambulatory patients, with an estimated 1-year survival of <80% as calculated by the SHFM or an HFSS in the high−/medium-risk range (Mehra et al. 2016).

The opportunity to discriminate between high-risk and low-risk ambulatory patients with HF can help healthcare providers direct costly disease management services to higher-risk patients (Upshaw et al. 2016). Recognizing some of the limitations of existing models which focus on single-state prediction (e.g., mortality alone, HF hospitalization alone, or a composite of death or hospitalization), as well as the limited

attention to ambulatory HF patients in models and the use of patient cohorts from over two decades ago when limited GDMT was available, Upshaw et al. developed a multistate model for ambulatory HF patients (NYHA II–III) to predict HF hospitalization and all-cause mortality as the primary outcomes of interest using more contemporary derivation and validation cohorts of ambulatory patients with HFrEF (Upshaw et al. 2016).

While there is clear utility for risk scores to assist clinicians with therapeutic decisions, particularly around mechanical circulatory support (MCS) and listing for heart transplantation, there was previously little in the literature regarding the patient perspective of receiving risk communication information from clinicians (Narayan et al. 2017). Using qualitative methods with in-depth semi-structured interviews, Narayan et al. recently explored the perspectives of patients with HF regarding the conveyance of individualized SHFM survival estimates. The majority of patients were interested in their individualized prognostic survival estimates (17/24); however 29% (7/24) declined to see their prognostic information. Patients who accepted the information generally reported valuing the receipt of estimated prognosis, demonstrated an understanding of the nature of the information, and found the information to provide clarity, control, and hope rather than invoking confusion or anxiety. Of patients who did not wish to view the information, common reasons included the belief that the information would not apply to them, a lack of faith in physician predictions, and skepticism about the predictive capability of statistical models without perceived important personal attributes, such as willpower and ability to defy the odds, in the model. A common criticism of disease-specific predictive models, including the SHFM, is that they perform well on the population level but have limitations on the individual level with respect to accuracy, and it is not clear if survival is the most relevant outcome from a patient perspective (Nassif et al. 2017). An additional issue is that models are considered most useful when they are actionable, so a potential role for risk models could be to help patients understand the potential impact of treatment options and lifestyle changes.

Patient Evaluation with Advanced Heart Failure

The majority of patients with HF can be well managed by general internists or cardiologists; however the continued rise in advanced HF prevalence, technological advances in diagnostic modalities, and expanding array of treatment options, including electrophysiologic and hemodynamic support devices, complex percutaneous and surgical procedures, and cardiac transplantation, created a need for expert HF consultants (Konstam et al. 2009). The Heart Failure Society of America (HFSA) called for the creation of an Advanced Heart Failure and Transplant Cardiology (AHFTC) subspecialty. In September 2008, the American Board of Medical Specialties approved a proposal from the American Board of Internal Medicine (ABIM), which originated in the HFSA and was endorsed by the ACCF, to establish an AHFTC subspecialty training program governed by the ACGME and board certification through the ABIM starting in 2010.

Patients with advanced (Stage D) heart failure face a high symptom burden, often with debilitating symptoms, markedly impaired functional status, and recurrent episodes of decompensation and hospitalization. Identification of patients in Stage D is a clinically important task because treatments are inherently limited, morbidity is typically progressive, and survival is often short. Identifying the point when medical and device therapies have failed an individual patient is challenging; however a formal assessment including signs, symptoms, hemodynamics, exercise testing, biomarkers, and risk prediction models can be useful. In addition to a systematic evaluation of indications, contraindications, clinical status, and comorbidities, management of Stage D patients also involves incorporating the patient's wishes for survival versus quality of life (Fang et al. 2015). At this point, cardiologists need to discuss the possible role for disease-exchanging therapies such as cardiac transplantation and durable MCS versus a transition to focusing more on palliation of symptoms (Allen et al. 2012). It is important to recognize that survival may not be the only relevant outcome for individual patients when discussing prognosis and the patient may need to

reflect on other domains. Other common domains include the direct and indirect costs and burdens of care, which include lost opportunities for the patient and caregivers, as well as the impact on the patient's quality of life with respect to symptoms, physical functionality, mental status, emotional well-being, and social life.

The evaluation of candidates for cardiac transplantation is a complex, multidisciplinary evaluation process outlined in the 2016 ISHLT Listing Criteria for Heart Transplantation (Mehra et al. 2016). One of the fundamental aspects of assessing the role for listing patients for transplants is a formal assessment of functional capacity with an eye toward risk stratification and clarification of key limitations to patients' exercise capacity. Cardiopulmonary exercise testing (CPET) is used to precisely define a patient's maximum exercise capacity through measurement of peak oxygen uptake (VO_2); however this information needs to be used in conjunction with clinical assessment, and listing patients solely based on peak VO_2 is not recommended (Malhotra et al. 2016). A maximal CPET is defined as attaining a respiratory exchange ratio (RER) > 1.05 and anaerobic threshold on optimal pharmacologic therapy; peak VO2 has been used to inform patient selection for advanced HF interventions such as heart transplantation and ventricular assist devices. Based on trial data over the years, ISHLT Listing Criteria suggest a cutoff of peak $VO_2 \leq 14$ ml/kg/min for patients on a beta-blocker or a peak $VO_2 \leq 12$ ml/kg/min for patients intolerant of a beta-blocker. For women and patients under the age of 50 years, assessing the percent of predicted peak VO_2 can also guide listing decisions, as can a lean body mass-adjusted peak VO_2 for patients with a body mass index >30 kg/m^2. For patients unable to complete a maximal CPET, the oxygen uptake and ventilatory patterns and functional status observed during a submaximal test can still provide prognostic information. Right-heart catheterization is another fundamental aspect of evaluating a patient for transplant candidacy at baseline and periodically while listed, not only to guide clinical management but also to assess for the presence and reversibility of pulmonary hypertension (Francis et al. 2010). A CPET can be integrated with concurrent invasive hemodynamic monitoring and/or cardiac imaging to more comprehensively characterize a patient's multisystem reserve capacity (Malhotra et al. 2016). A multivariable analysis by Kato et al. revealed that high B-type natriuretic peptide (BNP) and low-peak VO2 were independently associated with death, heart transplantation, or ventricular assist device (VAD) requirements (Kato 2013). In particular, a BNP cutoff of 506 in patients with a peak VO2 of 10–14 mL/min/kg was demonstrated to help further risk stratify patients.

Indications for Mechanical Circulatory Support

As the number of patients with advanced HF is unresponsive to guideline-directed conventional medical therapy, demand for advanced HF therapies has grown in parallel (Miller and Guglin 2013). Advanced HF treatment options include inotropic therapy, mechanical circulatory support (MCS), heart transplantation, or transition to comfort-focused care. The number of heart transplants has been fairly stable for years at 4,500 per year worldwide and 2,200 per year in the United States, limited for many reasons, most notably suitable donor organ availability and geographic restraints. Inotropic therapy and MCS can both be done as a bridge to transplantation, as palliative or destination therapies, or as a bridge to consideration for transplantation. Unfortunately, despite improved hemodynamics, positive inotropic agents have not demonstrated improved outcomes in outpatient or inpatient HF settings and still have poor 1-year outcomes (Yancy et al. 2013). The use of MCS is increasing for management of patients with advanced stage D HFrEF refractory to optimal GDMT and cardiac device interventions. Ventricular assist devices (VADs) are MCS devices that can be utilized for short-term (hours to days) management of acute decompensated hemodynamically unstable HFrEF refractory to inotropic support, as well as long term (months to years) for patients with chronic Stage D HFrEF. Due to continued improvements in MCS device technology, prior limitations to implantation such as small body size, advanced age, body mass

index, prior sternotomies, significant lung disease, and certain other comorbidities are becoming less prohibitive (Miller and Guglin 2013). The ISHLT 32nd Official Adult Heart Transplantation Report indicated that the use of MCS as defined by LVAD, RVAD, TAH, and ECMO at time of transplant for adult heart recipients has been increasing from 22.2% during 1992–2003, to 26.0% during 2004–2008, to 43.0% from 2009 to 2014 (Lund et al. 2015). A look at the more recent years on data provided by the ISHLT, use of MCS as a bridge occurred in <20% of adult heart transplants in 2000, 22–29% from 2001 to 2008, and for 2013 and 2014 in 50–51% (ISHLT). United Network for Organ Sharing (UNOS) data also confirms a rise in the ongoing use of a VAD as a bridge to transplantation; in 2016, 29.5% of cardiac transplants (942 of 3191) were supported by a VAD, an increase from 25.9% in 2015 (728 of 2804) (OPTN).

While there are dedicated published guidelines regarding patient selection for heart transplantation which are endorsed by most societies in the field (i.e., the 2016 ISHLT Listing Criteria for Heart Transplantation), there is less guidance on patient selection for inotropic support and/or MCS (Miller and Guglin 2013). The 2013 ACCF/AHA 2013 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult provides two recommendations on non-short-term use of inotropic therapy. There is a Class IIa, LOE B recommendation that "Continuous intravenous inotropic support is reasonable as 'bridge therapy' in patients with stage D HF refractory to GDMT and device therapy who are eligible for and awaiting MCS or cardiac transplantation," and a Class IIb LOE B recommendation that "Long-term, continuous intravenous inotropic support may be considered as palliative therapy for symptom control in select patients with stage D HF despite optimal GDMT and device therapy who are not eligible for either MCS or cardiac transplantation." The same guidelines provide three Class IIa LOE B recommendations on MCS:

1. "MCS is beneficial in carefully selected patients with stage D HFrEF in whom definitive management (e.g., cardiac transplantation) or cardiac recovery is anticipated or planned
2. Nondurable MCS, including the use of percutaneous and extracorporeal ventricular assist devices (VADs), is reasonable as a 'bridge to recovery' or 'bridge to decision' for carefully selected patients with HFrEF with acute, profound hemodynamic compromise.
3. Durable MCS is reasonable to prolong survival for carefully selected patients with stage D HFrEF."

Durable ventricular assist devices are able to correct insufficient cardiac output by shunting blood from the left ventricle to the aorta, which can provide significant improvement in functional status and symptoms but may not be sufficient to overcome refractory angina or ventricular tachycardia.

Indications for Heart Transplantation

Despite the challenges associated with post-transplant management, cardiac transplantation is still the gold standard for the treatment of refractory end-stage HF due to significant improvements in patients' functional status and health-related quality of life (Yancy et al. 2013). The ACCF/AHA strongly endorses that carefully selected patients with Stage D HF despite GDMT, device, and surgical management should be evaluated for heart transplantation (Class Ia, LOE C recommendation). Indications for heart transplantation can be summarized as refractory HF despite optimal medical and device therapy, manifesting as intractable angina, recurrent refractory decompensated HF, or intractable ventricular arrhythmias (Kittleson and Kobashigawa 2014). Angina alone is often not considered an indication for transplantation in the absence of heart failure, as it is not clear if the survival of such patients is improved with heart transplantation. Common clinical indicators of Stage D HFrEF include deteriorations in renal and/or hepatic function, diuretic refractoriness, persistent hyponatremia, intolerance of neurohumoral

antagonism due to renal dysfunction or hypotension, recurrent HF hospitalizations, worsening pulmonary hypertension, NYHA class III–IV symptoms, inability to complete activities of daily living, and/or a hemodynamic requirement for inotropic therapy. Neither the 2013 ACCF/AHA Guideline for the Management of Heart Failure nor the 2017 ACC/AHA/HFSA Focused Update of these guidelines provide Class 1 recommendations on the use of non-short-term (e.g., prolonged) use of inotropic therapy and MCS for Stage D HF.

Advanced Care Planning in Advanced Heart Failure

While heart disease remains the leading cause of death worldwide, progress with advanced care planning (ACP) in advanced HF has been hindered by patient and provider underestimation of poor prognosis, clinicians' lack of communication training, and clinicians' uncertainty about the trajectory of heart failure (El-Jawahri et al. 2016). In patients with advanced HF, it is difficult to know when the opportune time is to broach discussions about care preferences and future care options due to prognostic uncertainty and the potential use of multiple advanced therapies (Miller and Guglin 2013). It is increasingly recognized that there may be an opportunity to deliver more effective patient-centered care through the earlier introduction of palliative care, concurrent to traditional medical therapy, for patients with advanced HF. An analysis of the impact of a video decision support tool and patient checklist on ACP for hospitalized patients with established advanced HF who viewed a video reviewing ACP was more informed, more likely to select a focus on comfort, and less likely to desire CPR/intubation compared with patients receiving verbal information only (El-Jawahri et al. 2016). Additional interesting findings included improved concordance of clinicians' and patients' preferences for CPR and intubation in the video-assisted intervention arm ($\kappa = 0.13$ for CPR and $\kappa = 0.14$ for MV) than in the verbal control arm ($\kappa = -0.05$ for CPR and $\kappa = 0.06$ for MV) and that participants randomized to the video-assisted intervention arm were more likely to report goals-of-care conversations with healthcare providers compared with verbal control participants at 1 month (40% vs. 6%, respectively, $P < 0.001$) and 3 months (61% vs. 15%, respectively, $P < 0.001$).

Conclusion

Heart failure is a complex clinical syndrome driven by the heart's inability to fully support the demands of living that progresses across multiple stages in a nonlinear fashion, often starting with an asymptomatic or preclinical state. Guideline-directed medical therapy has most successfully improved morbidity and mortality in patients with reduced left ventricular ejection fraction, while therapy for patients with preserved ejection fraction largely focuses on symptomatic management unless there is a treatable underlying etiology. The pathophysiology of HF is highly varied with some cardiomyopathies more responsive to therapies than others. The majority of patients develop a dilated hypocontractile left ventricular as the common end point which has driven most of the science behind medical and device therapies; however, a smaller proportion of patients with advanced HF have a phenotype other than a dilated cardiomyopathy and can be more challenging to support to transplantation. For patients with advanced HF who are refractory to conventional therapy, including oral agents, implantable electronic cardiac devices, and comprehensive care interventions, options may include inotropic therapy, mechanical circulatory support, cardiac transplantation, or transition to comfort-focused care.

Cross-References

▶ Contraindications to Heart Transplantation
▶ Current Listing System
▶ History of Heart Transplant

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Contraindications to Heart Transplantation

3

Nael Hawwa and David O. Taylor

Contents

Abstract

The criteria for heart transplantation are evolving, and higher-risk patients are being transplanted with reasonable outcomes. Previously established contraindications may be less absolute and more flexible than initially proposed. When assessing whether a certain patient-related factor is prohibitive, the stagnant donor pool should be taken into consideration.

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We must remain an advocate for the individual patient while factoring in the ethical dimension of organ supply and demand. The current trend of using marginal donors for higher-risk patients solves part of this ethical dilemma. As such, the contraindications discussed must be viewed in this broader context and may at times be dynamic.

Keywords

Pulmonary hypertension · Hepatitis · Malignancy · Obesity · Chronic kidney disease · Congestive hepatopathy · Peripheral arterial disease · Cerebrovascular disease · Amyloidosis · Sarcoidosis · SIPAT score

Introduction

The criteria for heart transplantation are evolving, and higher-risk patients are being transplanted with reasonable outcomes. Previously established contraindications may be less absolute and more flexible than initially proposed. When assessing whether a certain patient-related factor is prohibitive, the stagnant donor pool should be taken into consideration. We must remain an advocate for the individual patient while factoring in the ethical dimension of organ supply and demand. The current trend of using marginal donors for higher-risk patients solves part of this ethical dilemma. As such, the contraindications discussed must be viewed in this broader context and may at times be dynamic. The criteria referred to in this chapter are based on the International Society for Heart and Lung Transplantation (ISHLT) 2016 guidelines (Mehra et al. 2016).

The contraindications detailed in this chapter include factors that (1) directly impact the donor organ including pulmonary hypertension; (2) relate to the immunosuppressed state including malignancy, infection, and psychosocial issues that may determine immunosuppressant compliance; and (3) influence the overall survival of the recipient including systemic diseases and age.

Pulmonary Hypertension

The right ventricle is an afterload-sensitive chamber that cannot acutely compensate for sudden rises in pulmonary pressures. This scenario is observed when transplanting a healthy heart into a recipient with pre-existing pulmonary hypertension (PH). The resulting acute right ventricular failure of the donor heart significantly contributes to postoperative morbidity and mortality. The most important hemodynamic parameter used to assess candidacy for heart transplantation is the pulmonary vascular resistance (PVR) as calculated by the following equation:

$$\mathrm{PVR} = (\mathrm{mPAP} - \mathrm{PCWP})/\mathrm{CO}$$

PVR: pulmonary vascular resistance (Woods units)
mPAP: mean pulmonary arterial pressure (mmHg)
PCWP: pulmonary capillary wedge pressure (mmHg)
CO: cardiac output (L/min)

Hemodynamic measurement is fraught with potential errors that can have implications when assessing patients for heart transplantation. Therefore the assessment must be performed in a deliberate and methodical manner. Factors to take into account are the zero reference level at the mid-thorax, measuring pressures at end-expiration while avoiding Valsalva and avoiding extremes of sedation or anxiety. The PCWP is an integral part of the calculations used in PH and its accuracy is of paramount importance. In addition to the above factors, careful attention should be paid to evaluating the waveform of the PCWP, as severe diastolic dysfunction or functional mitral regurgitation, entities commonly seen in this population, can cause pronounced V waves. A direct measurement of the left ventricular end-diastolic pressure may sometimes be performed if there is concern regarding the accuracy of the PCWP.

Patients with left heart disease commonly develop “passive” pulmonary venous

hypertension. With time, the unhalted progression will result in neurohormonal-mediated changes and structural remodeling of the pulmonary vasculature. This leads to an elevated pulmonary arterial pressure out of proportion to the left-sided filling pressure, i.e., a high transpulmonary gradient (mPAP-PCWP). Initially this process may be "reactive" and reversible but eventually becomes "fixed." Patients who demonstrate reversible PH have good outcomes following heart transplantation, similar to those without pre-transplant PH. Reversibility has been defined as a reduction in PVR to < 2.5, without excessive hypotension. These points highlight the importance of right heart catheterization, which should be performed prior to listing candidates, as well as periodically as they await transplantation. For those with elevated pulmonary pressures, an attempt should be made to demonstrate reversibility. This can be performed as an acute vasodilator challenge in the catheterization laboratory. Various medications can be used including inhaled nitric oxide, which lacks some of the systemic effects seen with intravenous prostacyclin or adenosine. The expected effect is usually within minutes. Acute vasodilator testing should be reserved for those without a significant component of pulmonary venous hypertension. For those who do not respond to this challenge, or those with elevated left-sided filling pressures, certain medications and interventions should be used to assess for reversibility.

Commonly used medications to reverse pulmonary pressures include diuretics, afterload reducing agents such as sodium nitroprusside, and inotropes, especially milrinone with its pulmonary vasodilating properties. For those who fail such measures, the advent of mechanical circulatory support has introduced a new dimension and broadened our understanding of PH in the heart failure population. Chronically, the aggressive unloading of the left ventricle that is provided by the left ventricular assist device (LVAD) has been shown to reduce PVR to levels that make heart transplantation permissible. As such, some patients with significant PH can have an LVAD implanted as "destination therapy," but their status switched to "bridge to transplant" at a later date (Salzberg et al. 2005; Zimpfer et al. 2007; Torre-Amione et al. 2010; Mikus et al. 2011). Although a broad armamentarium of medications exist for managing patients with pulmonary arterial hypertension, these medications have not been approved for use in left heart disease. One concern of using such medications in this population is the potential to worsen left-sided filling pressures due to increased flow across the pulmonary vascular bed. This may result in adverse outcomes as was seen with the use of epoprostenol in patients with left heart disease (Califf et al. 1997). Current data does not support the routine use of oral medications that target the nitric oxide pathway in group 2 PH, although they may have a more selective role, including use as an add-on strategy in LVAD patients (Tedford et al. 2008; LaRue et al. 2015). Future direction will be guided by ongoing clinical trials in this field. An irreversible elevation of PVR >5 Woods units and an elevated transpulmonary gradient >15 mmHg are considered contraindications to isolated heart transplantation. Heart-lung transplantation can be considered in such cases as well as in patients with end-stage cardiomyopathy and severe parenchymal lung disease.

Malignancy

The development of potent immunosuppressant medications over the last few decades has revolutionized the field of transplantation by reducing allograft rejection and early graft failure, making transplantation a viable option. While shifting the tide away from allograft rejection, immunosuppression has led to a rise in other complications including malignancy and infection. Malignancy remains an important cause of death following transplantation and is one of the limiting factors in long-term survival. This includes skin cancers and lymphoproliferative disorders that arise de novo, as well as recurrence or metastases in those with a known history of malignancy. This latter group includes the subset of patients with chemotherapy-induced cardiomyopathy.

Contributing factors of the immunosuppressed state include reduced cancer immunosurveillance, activation of oncogenic viruses such as Epstein-Barr virus, and the direct pro-oncogenic properties of immunosuppressants. The duration and intensity of immunosuppression impact malignancy, and efforts to mitigate the consequences of posttransplant malignancy involve a reduction in immunosuppression. It should be noted that the mammalian target of rapamycin (mTOR) inhibitors uniquely possesses both immunosuppressive and antineoplastic properties. Data suggests that they may have a benefit in reducing malignancy, especially skin-related (Geissler 2015).

Active malignancy is understandably an absolute contraindication to heart transplantation. The decision process in those with a history of malignancy is more complex. Collaboration with an oncologist is of paramount importance in such cases, and factors to consider include the risk of tumor recurrence and duration of remission. Some advocate a 5-year remission period before considering transplantation, although the most recent ISHLT 2016 guidelines recommend against defining an arbitrary time period, but rather dealing with the issue on a case-by-case basis. Interestingly, data shows that the higher rates of posttransplant malignancy that occur in those with prior malignancy are not necessarily a recurrence of the original malignancy.

Primary cardiac sarcoma presents a unique, albeit rare situation. Surgical resection with the goal of obtaining microscopically negative margins provides the best outcome in a disease with overall poor prognosis. However, given its aggressive nature, the radical resection required is not always anatomically feasible. There are multiple reports of heart transplantation being performed as a treatment for cardiac sarcoma. Unfortunately outcomes are dismal, mainly attributable to a high rate of distant metastases post-transplantation, limiting survival to less than a few years. This risk is more prominent with certain histologic subtypes such as angiosarcoma and higher-grade tumors. Therefore, a more selective approach to non-resectable primary cardiac sarcoma is warranted, acknowledging that even then the outcomes remain inferior to that of heart transplantation for cardiomyopathy (Jimenez Mazuecos et al. 2003; Uberfuhr et al. 2002).

Infection

Active infection especially when systemic is a contraindication to heart transplantation given the potential for worsening and dissemination with immunosuppression. Therefore, every effort should be made to eradicate the infection prior to transplantation. One notable exception is LVAD infection. Although this frequently starts as a localized superficial infection at the driveline site, it may progress to an abscess of the pocket site or bacteremia. Such infections are difficult to eradicate with conservative measures including antibiotic therapy or incision and drainage, due to formation of biofilms on the prosthetic material. Pump removal is rarely a feasible option given the underlying cardiac function, and pump exchange leaves behind residual foreign material. Heart transplantation remains a viable option to provide source control by completely removing all foreign materials. The current allocation system assigns patients with deep or systemic LVAD infection Status 1A for listing. In a large analysis of the United Network of Organ Sharing (UNOS) database that studied the posttransplant outcomes of those with LVAD-related complications, infection was the only complication to adversely impact survival (Healy et al. 2013). This may be a result of the associated rise in panel reactive antibodies (PRA) and allosensitization, with its long-term effects on graft survival due to chronic rejection. Moreover, infection may necessitate a reduction in immunosuppressive medication in the immediate posttransplant period especially if there is evidence of systemic infection. However, other studies show similar posttransplantation outcomes to those without LVAD infection (Sinha et al. 2000; Schulman et al. 2009; Tong et al. 2015). Despite a theoretical risk of fulminant infection with initiation of immunosuppressive medication, the available data does not demonstrate this, likely a result of selection bias. Patients with overwhelming sepsis and those with multi-organ dysfunction are unlikely to be transplanted

and included in these analyses. Thus, in selected patients with LVAD infection, heart transplantation remains the preferred treatment. Careful attention should be given to monitoring PRA, controlling the infection in the pretransplant period, and adjusting immunosuppressive medications as deemed necessary.

The advent of anti-retroviral therapies (ART) has changed the outlook of patients with human immunodeficiency virus (HIV), such that it is no longer considered an absolute contraindication to heart transplantation. The fear of administering immunosuppressive medications to patients with a baseline progressive immunosuppressed disease state was rational. However, in the era of ART, the spectrum of mortality has changed in HIV patients, evolving from opportunistic infections to common chronic conditions seen in the general population, including cardiac disease. The data on outcomes following heart transplantation in HIV patients is limited to a few case reports and series, but suggests that the HIV viral load remains low with good intermediate-term outcomes (Aguero et al. 2016). The ISHLT 2016 guidelines define important selection criteria for HIV patients, including lack of opportunistic infections, undetectable viral load, and a CD4 count >200 cells/μl for at least 3 months on a regimen of ART. An additional concern is management of immunosuppressive medications in patients on ART, and close collaboration with an infectious disease specialist is essential. Combination ART using at least three medications is standard of care in HIV therapy. The various classes have different interactions, but the most commonly described is the inhibition of cytochrome P450 3A4, an enzyme involved in the metabolism of calcineurin inhibitors. Thus calcineurin inhibitors must be administered at lower doses with close monitoring of levels. A newer class of ART, the integrase inhibitors, may have less potential for interactions.

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infection are only considered absolute contraindications in the setting of acute infection or with resultant advanced cirrhosis or hepatocellular carcinoma. Patients with prior resolved HBV or HCV infection can proceed with heart transplantation. Chronic HBV as defined by HBV surface antigen positive, or chronic HCV infection as defined by HCV RNA PCR positive, can be considered for heart transplantation. Ideally patients should be on treatment with adequate virologic response and absence of histologic evidence of cirrhosis. Intermediate-term safety had been established in small case reports, and our perspective on HCV in patients being considered for advanced heart failure therapies continues to change with the evolution and development of direct antiviral agents (Lin et al. 2012; Belga and Doucette 2016). Compared to the historical alternatives of interferon (IFN) and ribavirin, these novel medications have superior efficacy with higher rates of sustained virologic response and improved tolerability especially in patients with heart failure. Use of IFN-based therapy has classically been considered a contraindication in advanced heart failure due to the concern for potential arrhythmia and cardiotoxicity. Similarly, use of IFN carries a risk of graft rejection, whereas the direct antiviral agents may be safe in the posttransplant setting based on extrapolation from the liver transplant data. This would allow the safe management of posttransplant HCV, although in the current era, IFN-free regimens have led to high pretransplant cure rates.

Age

An aging population has fueled the heart failure epidemic, resulting in older patients being referred for heart transplantation. This has necessitated the need to redefine historical age limits. Age should not be viewed as an isolated factor that precludes a patient from heart transplantation. Patients above the age of 60 years and carefully selected patients older than 70 years can be transplanted with good long-term outcomes. The physiologic age becomes more important in this scenario, with close attention given to comorbidities, prior open-heart surgery, and frailty. Although there is no standardized method of evaluating or defining frailty, important measures to consider include presence of cardiac cachexia, gait speed, level of physical activity, and grip strength.

In the largest study of data provided by UNOS, 332 patients age 70–79 years were compared to 5,807 patients age 60–69 years. The elderly group had a median survival of 8.5 years, although this was slightly inferior to the 9.8-year median survival of the younger group. Age was a multivariate predictor of death in this study. Notably the elderly group had a lower incidence of rejection consistent with the decline in immune function with age, providing a paradoxical benefit (Goldstein et al. 2012). Some single-center experiences suggest outcomes in those age 70 years and older to be similar to those that are younger (Daneshvar et al. 2011). This may be related to a higher level of selection bias in such studies and the fact that some programs do not use an alternate allocation system. Although such a system provides elderly patients easier access to marginal donors, theoretically avoiding competition with younger recipients, the outcomes are expectedly further reduced. The current ISHLT guidelines do not support the routine use of an alternative allocation system. The consideration of heart transplantation in elderly recipients must be weighed in the context of a limited donor pool, as well as the advances and development of newer generation mechanical circulatory support devices.

Obesity

Obesity is associated with cardiac disease, serving as an independent risk factor for coronary artery disease and increasing risk of heart failure. Interestingly an obesity paradox exists in heart failure, where obese patients may have better outcomes. The data on weight loss and its impact is less clear. Ultimately heart transplantation outcomes are inferior in obese recipients, possibly a result of posttransplant cardiovascular complications including hypertension and hyperlipidemia and increased incidence of rejection. The previous 2006 ISHLT guidelines suggested achieving a BMI <30 kg/m^2 pretransplant. However, subsequent studies did not reveal an excess in morbidity and mortality in the BMI 30–35 kg/m^2 group, leading to a change in the cutoff to 35 kg/m^2 (Macha et al. 2009, Russo et al. 2010).

In those with more severe degrees of obesity, LVAD has been considered an option to help with weight loss and improve candidacy for heart transplantation. In an analysis on the impact of LVAD on obesity in 3,856 patients from the UNOS database, the group with BMI >35 kg/m^2 had increased risk of complications requiring a status upgrade, including thromboembolism and infection. Additionally this group had decreased posttransplantation survival. Importantly, only a minority of obese patients in this study achieved significant weight loss (Clerkin et al. 2016). Further strategies that may provide superior results include implanting an LVAD along with performing bariatric surgery. Laparoscopic sleeve gastrectomy is more favorable compared to gastric bypass, as the latter has more association with malabsorption, which may interfere with immunosuppressant medications, and has higher incidence of marginal ulcers, which may lead to complications in the setting of anticoagulation. A few case reports have demonstrated successful weight loss of a considerable degree and bridge to transplantation (Shah et al. 2015).

Diabetes Mellitus

Diabetes and its ensuing complications contribute to poor prognosis following heart transplantation. Such complications include renal disease, peripheral arterial disease (PAD), and cerebrovascular disease (CVD). A large analysis of over 20,000 heart transplant recipients demonstrated the inferior survival of diabetic heart transplant recipients but also showed no significant survival difference in diabetics without complications compared to nondiabetics (Russo et al. 2006). Therefore, heart transplantation can be performed in diabetics without end-organ damage (with the exception of nonproliferative retinopathy), with adequate glycemic control ($HbA_{1c} < 7.5\%$). Special attention should be given to corticosteroid dosing and duration posttransplantation to improve metabolic control and reduce complications including infection.

Renal Disease

Chronic kidney disease (CKD) is a commonly encountered comorbidity in heart failure. Hemodynamic abnormalities of reduced renal arterial flow and renal venous congestion lead to cardiorenal syndrome. Additionally intrinsic renal disease may be present, especially in those with underlying conditions such as diabetes and hypertension. CKD increases morbidity and mortality following transplantation, influences selection of immunosuppressant medications especially calcineurin inhibitors, and limits the ability to routinely assess for cardiac allograft vasculopathy with coronary angiography.

In evaluating CKD patients for heart transplantation, it is important to perform a thorough workup to determine the degree of reversibility as well as the cause of their renal dysfunction. This will identify those that may benefit from heart transplantation alone. Renal dysfunction related to hemodynamic disturbances is likely reversible especially in its earlier stages. Intrinsic causes of renal disease should be excluded by performing urinalysis to assess for proteinuria and hematuria, ultrasonography to assess for kidney size, and renal biopsy if the etiology remains unclear. Assessing individual trends and patterns of serum creatinine also provides useful information, although even long-term elevations may be reversible.

An estimated glomerular filtration rate (eGFR) of less than 30 ml/min/1.73 m^2 that is deemed irreversible is considered a relative contraindication for heart transplantation alone. In such patients, combined heart-kidney transplantation is an option. Between January 1988 and October 2016, 1,281 heart-kidney transplants have been reported by UNOS (almost 2% of the total heart transplants in that period). Using a single donor reduces the antigenic exposure of the recipient, and combined heart-kidney transplant recipients actually experience less allograft rejection than single-organ recipients due to mechanisms that are not fully understood. Non-randomized data suggests performing a staged procedure: Heart transplantation is followed by a brief period of hours to allow hemodynamic stabilization before performing the kidney transplantation (Ruzza et al. 2013). Despite longer cold ischemic time to the renal allograft, the approach is favorable as a consequence of protecting the kidney from hemodynamic insults seen with cardiopulmonary bypass and high-dose vasoactive medications. An additional strategy is heart transplantation followed by living donor kidney transplantation, which partially circumvents issues related to waiting time. Regardless of the strategy, postoperative management must focus on minimizing nephrotoxic exposure. Induction therapy with anti-lymphocyte antibodies allows delay in initiating calcineurin inhibitors during the initial vulnerable postoperative period. Some institutions propose the use of calcineurin-sparing agents, specifically the mTOR inhibitors, although long-term data from randomized studies on the safety of such an approach is lacking.

Liver Disease

Liver disease may be seen in patients with advanced heart failure as a result of passive hepatic congestion, ischemic insult from malperfusion, or concomitant infection with hepatitis. Cardiac cirrhosis may be seen in any form of cardiomyopathy, but occurs at disproportionately higher rates in the congenital heart disease population who have Fontan circulation. Abnormal levels of transaminases, bilirubin, and albumin are usually the first indicator of congestive hepatopathy. However, laboratory disturbances may be lacking in some patients, and radiographic screening with ultrasonography is necessary. Concerning biochemical or sonographic findings usually warrants a liver biopsy. Microscopic examination is important as it allows characterization of the degree of hepatic fibrosis. Additionally, the histologic pattern helps differentiate cardiac cirrhosis from other forms of cirrhosis. The former lacks bridging fibrosis between adjacent portal areas.

Liver cirrhosis is considered a relative contraindication to heart transplantation alone as such patients have higher morbidity and mortality, especially in the immediate postoperative period.

This is especially true if it is performed indiscriminately. However, in very carefully selected patients such as those with preserved synthetic function and a Child-Pugh score of A, with lower Model for End-stage Liver Disease (MELD) score, and without the complications of portal hypertension, heart transplantation may be successfully performed. There has been a shift in our understanding of cirrhosis, which was traditionally considered an irreversible process. Reports have demonstrated regression of hepatic fibrosis when the underlying cause has been addressed. In the case of cardiac cirrhosis, heart transplantation treats the underlying chronic hepatic venous congestion. Experience with heart-liver transplantation is not as extensive as heart-kidney transplantation. Between January 1988 and October 2016, 208 heart-liver transplants have been reported by UNOS (<1% of the total heart transplants in that period), largely limited to a few experienced centers. Reports from such institutions suggest survival similar to isolated transplantation (Cannon et al. 2012). Additionally it appears that due to immunologic mechanisms of tolerance that are not fully understood, risk of rejection in dual transplantation is lower, resulting in improved graft survival. Regarding surgical technique, the sequence is usually heart followed by liver transplantation as the heart is more sensitive to ischemic time, and liver transplantation is associated with severe blood loss and massive transfusion and resultant hemodynamic disturbances. However, in rare instances, the reverse order has been performed with liver before heart transplantation. This has been utilized in patients with particularly high donor-specific antibodies, as the liver graft may provide tolerance to the subsequently implanted cardiac allograft.

Cerebrovascular Disease and Peripheral Arterial Disease

Identifying factors associated with stroke post-transplantation is of paramount importance given its detrimental impact on level of functioning and survival. Severe symptomatic CVD defined as those with prior transient ischemic attack or stroke is considered a contraindication for heart transplantation as it increases the risk of stroke. This was demonstrated in a large analysis of the UNOS database, which compared 1,078 patients with symptomatic CVD to 16,765 patients without. Those with symptomatic CVD had higher rates of stroke and increased risk of functional decline. Although the increased mortality was negated when adjusted for confounding factors, it should be noted that these factors including hypertension, diabetes, and renal disease are common comorbidities observed in patients with CVD (Patlolla et al. 2011). Therefore, presence of CVD represents a higher-risk substrate. It is unclear from the available data whether this risk is modifiable by revascularization.

PAD resulting in lifestyle-limiting claudication that is not amenable to revascularization is considered a relative contraindication for heart transplantation, as it limits recovery and rehabilitation. Similar to CVD, PAD is strongly associated with the presence of atherosclerotic risk factors that impact survival. However based on analysis of the UNOS database, unlike CVD, PAD is an independent risk factor for mortality following heart transplantation (Silva Enciso et al. 2014).

Amyloidosis

Cardiac amyloidosis is an infiltrative disease resulting from extracellular deposition of protein fibrils in the myocardium. These proteins are derived from monoclonal immunoglobulin light chains in AL amyloidosis or transthyretin (TTR) protein in ATTR amyloidosis. The latter can be a mutant protein in familial ATTR or a nonmutant protein in wild-type (senile) ATTR. Management of cardiac amyloidosis poses a challenge, as the resultant restrictive cardiomyopathy is less responsive to standard heart failure medications, which at times may be harmful. Moreover, the use of LVAD is limited by the small left ventricular dimensions that usually characterize the disease. Even in the later "burned-out" stage, biventricular failure is a common manifestation that also limits the use of LVAD. Historically the survival of

amyloidosis patients (predominantly AL) undergoing heart transplantation had been poor, likely a result of disease recurrence in the allograft or progression in systemic involvement. In the modern era, and with better understanding of the disease process, heart transplantation offers much improved long-term survival (Davis et al. 2015).

The evolution in management of AL amyloidosis has resulted in effective therapeutic strategies (Sperry et al. 2016). In the absence of prohibitive systemic involvement, and when aggressive management of AL amyloidosis is pursued, outcomes of patients with AL amyloidosis undergoing heart transplantation may be comparable to those undergoing transplantation for other causes. This usually involves bortezomib-based chemotherapy regimens, as well as autologous stem cell transplant following heart transplantation, and requires close collaboration with an oncology team at specialized centers.

In familial ATTR, the liver produces a mutant TTR protein. Liver transplantation is therefore seen as a means to suppress its production preventing further disease progression and has been used for manifestations of peripheral neuropathy as well as cardiomyopathy. Cases of simultaneous heart-liver transplantation for familial ATTR have been reported with good outcomes. However, heart transplantation alone has been successfully performed for both subtypes of ATTR. Given the slow progression of disease, cardiac allograft involvement with ATTR is less likely to manifest before the recipient reaches median survival. Therefore, isolated heart transplantation may be considered especially in older individuals and those with senile ATTR. It should also be noted that in recent years several medications have been investigated for use in ATTR, including those that decrease production, as well as stabilize the TTR molecule.

Sarcoidosis

Sarcoidosis is a systemic inflammatory disorder characterized by noncaseating granulomas. Cardiac involvement is becoming increasingly recognized and may range from subclinical to manifestations of conduction abnormalities, tachyarrhythmia, and cardiomyopathy. Cardiac involvement does not necessarily correlate with involvement of other organs including the lungs. Rigorous data on medical management of cardiac sarcoidosis is lacking, although patients are frequently treated with corticosteroids and steroid-sparing immunosuppressant medications. In those that develop a severe cardiomyopathy, the concern with heart transplantation is disease recurrence in the allograft or systemic involvement of other organs. At times the diagnosis of cardiac sarcoidosis is first made following heart transplantation during histologic examination of the explanted recipient heart. Multiple reports, mostly single-center, have demonstrated good outcomes similar to heart transplant recipients without sarcoidosis (Zaidi et al. 2007; Perkel et al. 2013). The risk of disease recurrence appears to be reduced by maintaining patients on corticosteroids. Thus in the absence of significant extracardiac involvement, heart transplantation is a reasonable option with extra attention to immunosuppression, as well as close surveillance for posttransplant recurrence.

Psychosocial

The psychological burden of end-stage heart failure and transplantation is immense. Patients experience symptoms of shortness of breath and diminished quality of life. The debilitating nature of heart failure requires family members to assume the caregiver responsibility, putting strain on family relationships. Posttransplantation the patient deals with a new array of issues, including complications such as graft rejection, infection, malignancy, and medication side effects such as those of corticosteroids. The financial burden includes aspects beyond insurance coverage such as the frequent pre- and posttransplant follow-up and its associated travel-related expenses, as well as time required off work for both patient and family members. As a result of these multiple stressors, conditions such as depression and anxiety are commonly seen.

Pretransplant psychosocial factors influence posttransplant outcomes, both psychological and medical. Data has demonstrated that these factors correlate with medication noncompliance, rejection, and mortality. Factors associated with noncompliance include young age, lower education level, psychiatric disorders including depression, lack of social support, and substance abuse. Although medical criteria for transplant listing are relatively defined, psychosocial factors are prone to a significant degree of subjectivity. The importance of establishing a more standardized approach to psychosocial evaluation of the potential transplant recipient has led to the development of formal tools of assessment, including the Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT) tool (Maldonado et al. 2012). SIPAT covers four domains, including patient readiness, social support system, psychological stability and conditions, and substance abuse. The 4 domains include a total 18 risk factors predictive of patient compliance and posttransplant graft survival. These factors differ in their degree of predicting outcomes and are thus weighted accordingly in the scoring system. The SIPAT score has been shown to possess excellent reproducibility, making it an ideal means of comprehensive psychosocial assessment. Those with scores of 40–69 are considered poor candidates who require interventions to address their risks before proceeding with transplantation. Those with scores >70 are considered too high risk to recommend transplantation. In this setting, the transplant social worker is an integral part of the evaluation. Some patients may be well known to the transplant program, having followed for years with a cardiomyopathy. Others may present acutely, making the assessment less straightforward.

Smoking impacts prognosis following transplantation leading to early postoperative pulmonary complications and increasing the risk for cardiac allograft vasculopathy and malignancy, most commonly lung and skin cancer (Sanchez-Lazaro et al. 2007; Botha et al. 2008). Additionally, smoking relapse following transplantation may be as high as 25% and has been shown to negatively impact survival. The guidelines place a relative contraindication to active smoking, with most programs requiring a 6-month nicotine and tobacco-free period before listing. Random and periodic screening for nicotine use is standard for those on the transplant waiting list. Cotinine, the metabolite of nicotine, is commonly tested for. It has a longer half-life than nicotine and higher concentrations. Various cutoffs are used to differentiate active tobacco users from passive exposure and those who are abstinent or nontobacco users. Urine cotinine levels are higher than serum levels and can take many weeks to drop to the level of a nontobacco user. Similarly active drug and alcohol abuse are contraindications to heart transplantation. Ideally patients should demonstrate 24 months of abstinence, and aggressive counseling and rehabilitation should be provided.

Conclusion

Prior publications on heart transplant eligibility have typically listed “absolute” and “relative” contraindications. Using an “all or none” concept is dated and no longer appropriate. As an example, “Program X” may deny transplantation to a 29-year-old woman with a BMI of 37 due to the BMI cutoff of 35, yet accept a 65-year-old man who has previously undergone an LVAD and has CKD due to the lack of “absolute contraindications,” despite the latter case being much higher risk. Therefore, a comprehensive risk assessment of both favorable and detrimental patient factors in a weighted fashion is essential and is the preferred process for heart transplant centers today.

Cross-References

- ▶ Complications of Immunosuppression
- ▶ Malignancy After Transplant
- ▶ Psychosocial Considerations of Heart Transplant: Keeping Apace with the Revolution in Cardiac Care

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4 Psychosocial Considerations of Heart Transplant: Keeping Apace with the Revolution in Cardiac Care

Elizabeth D. Morris

Contents

Abstract

The cardiac transplant social worker assumes a complex role on a transplant team: assessor, fixer, ethical conscience of the team, resource expert, ambassador to other consultative teams, and is one of the central figures to the patient and family as they move through all phases of care. The function of the cardiac transplant social worker has evolved in similar parallel fashion as has cardiac transplantation itself. Once tasked with responsibilities that included supporting patients and their families while patients waited in hospital for organs to become available, social workers now work with patients and families who, for the most part, wait at home, often for years, on left ventricular assist devices (LVAD) as a prelude to transplant. The steps between listing and transplant have elongated as has the need for critical assessment tools and skills in an ever changing and revolutionary cardiac landscape.

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Social workers in cardiac transplant have been called upon to acquire different skill sets to incorporate the cataclysmic changes in cardiac care. Developing a psychosocial assessment tool is the foundation of performing a comprehensive, thorough, and detailed evaluation of the transplant candidate and LVAD candidate and should incorporate guidelines from UNOS, CMS, and JCAHO. Assessing health literacy is crucial to ascertaining a patient and family's ability to understand, comply, and execute required care. Including the palliative care team at consistent intervals is imperative. Collective team agreement on absolute contraindications to listing and/or implanting is crucial to a shared vision of candidacy.

Keywords

Cardiac transplant social worker · LVAD (left ventricular assist device) · Psychosocial assessment · Health literacy · Substance abuse disorder · SIPAT · Contraindications · Scoring tool · Caregivers · Palliative care · Psychosocial presentation · Retransplantation

Introduction

The role of the cardiac transplant social worker has evolved in similar parallel fashion as has cardiac transplantation itself. Once tasked with responsibilities that included supporting patients and their families while patients waited in hospital for organs to become available, social workers now work with patients and families who, for the most part, wait at home, often for years, on left ventricular assist devices (LVAD) as a prelude to transplant. Once teams struggled to apply the concepts of distributional justice to initial transplants and retransplants; now VAD "change outs" are considered equally seriously. The steps between listing and transplant have elongated as has the need for critical assessment tools and skills in an ever changing and revolutionary cardiac landscape. Social workers in cardiac transplant have been called upon to acquire flexible and emerging skill sets to incorporate the cataclysmic changes in cardiac care.

The Center for Medicare and Medicaid has mandated that transplant programs have social work membership to the multidisciplinary committee (CMS 2007). Often the social worker is the only nonmedical individual on a team made up entirely of medical professionals. This can make psychosocial input seem like an afterthought in comparison to the often-compelling medical needs of the patient under consideration. Yet the medical success of the patient often depends on the ability to adhere to medical instruction and support from the "family"/network in which the patient sits among many other factors. For anyone who has been on the receiving end of the long stare and deafening silence which follows the delivery of psychosocial concerns, it can be an uncomfortable and unpopular position to take on a transplant team. Often viewed as a "soft science," transplant social work has fought hard to gain and maintain a seat at the table.

This chapter seeks to examine the psychosocial assessment tool for both LVADs and cardiac transplant; how they are similar, how they differ, and the nexus of the two. Steps to engage the team in collectively identifying absolute contraindications versus relative contraindications as programmatic policy (to avoid the pitfalls of subjectivity) will be explored. Study will be given to the assessment tool as a potential roadmap for the partnership between the patient and team. The critical role that health literacy plays in assessing any patient will be incorporated into all aspects of social work intervention. In addition, the concepts of distributional justice in combination with balancing beneficence and nonmaleficence will be approached through the lens of the social worker's role on the heart transplant team. Finally, we will discuss the role of the social worker after LVAD implantation and cardiac transplantation.

Why Evaluate Patients from a Psychosocial Standpoint?

The rate of organ donation has increased by 20% over the past 5 years according to the United Network for Organ Sharing (UNOS). After

many years of stagnant numbers, the recent increase can be attributed to:

> . . .medical characteristics or a medical history that, prior years, may have been considered less often by clinicians. These include people who donated after circulatory death, as well as donors who died of drug intoxication or those identified as having some increased risk for blood borne disease. (UNOS January 2017)

In cardiac transplant, there is no living donor option, nor is donation after circulatory death (DCD) utilized as frequently in procuring hearts as it is in other organ donation scenarios. A brief explanation is offered as to why:

> The use of an ex-situ transportable cardiac perfusion platform together with modified cardioplegia, supplemented with post conditioning agents, had allowed three centers to report successful transplantation of distantly procured human DCD hearts. . .In the face of continued and significant donor organ shortage and inevitable wait list attrition, the rejection of suitable donor DCD hearts, in jurisdictions permitting this donation pathway, is increasingly hard to justify. (Dhital et al. 2017)

In his book *When Breath Becomes Air*, Paul Kalanithi writes:

> Science is based on reproducibility and manufactured objectivity. As strong as that makes its ability to generate claims about matter and energy it also makes scientific knowledge inapplicable to the existential, visceral nature of human life, which is unique and subjective and unpredictable. (Kalanithi 2016)

Transplant social workers often find themselves in a position where they are concurrently being asked to assess, alter, and predict the candidate's behavior. The psychosocial evaluation is both an opportunity to survey the candidate's network of support, history of adherence/understanding of past medical conditions or situations, and to identify the gaps in the existing structure. Once the gaps have been identified, the social worker must mobilize support, or advocate on the patients' behalf towards corrective action. Before presenting the patient to the transplant committee, the social worker must make sure that all potential moveable obstacles have been eliminated or adjusted to ensure that candidates are not eliminated inappropriately. Fitting referrals, often to psychiatry and insurance coordinators, can be part and parcel of many psychosocial evaluations. Despite the best psychosocial tools, care coordination, and supportive interventions, the transplant psychosocial evaluation is not a predictive tool, nor should a medical team expect that the assessment will bear out the best candidates.

Distributional Justice

> Being a gatekeeper necessitates difficult decisions. Using one's moral imagination or the principles of distributive justice and the maximum strategy does not in any way dictate what clinical decision one should make. Better ethics is about having better justifications for decisions; it is not about always agreeing or there being only one correct answer, especially when the benefits and harms are finely balanced. What a consideration of moral distance and distributive justice offers clinicians is an ethical framework that moves any debate regarding resource allocation away from emotion and toward rationality. (Shaw and Gardiner 2014)

Decision-making around organ transplant candidacy is not for the faltering. The decisions are weighty and lifesaving or life costing. The "team" decision process can offer individual members of a team, who differ in opinion, the safety of the balance of the views of the others. Many times, someone on the team will state how "nice" the patient may be or what a wonderful family they may have. At times, perhaps the patient was known to the practice for many years. It can be extremely difficult to say either "yes" or "no" to listing when the psychosocial evaluation leans against candidacy. Maintaining objectivity is of paramount importance and a monumental task. In regions where there is a saturation of transplant centers, the pressure to list can be ever greater as the program fears "losing" the patient to another, less discerning center. Transplant teams look to medical ethics to guide their ability to list the candidates they believe will best care for the organ as well as who may benefit most from a longevity standpoint.

Historically, there have been some shared standards between and among centers designed in

large part to provide some basic structure to transplant eligibility:

- Many transplant centers will not accept people without insurance.
- Transplant teams rarely consider anyone over 75 years of age.
- Some centers exclude patients with moderate mental retardation, mental health challenges, HIV, a history of addiction, or a long criminal record.
- Though American transplant centers can list foreigners, they can make up no more than 5% of any center's list. Most non–U.S. citizens listed have substantial financial resources and pay in cash.
- Some transplant programs will admit undocumented immigrants, but most of those are children. Some transplant centers have caused controversy by refusing to retransplant organs in undocumented immigrants whose initial organs, received at the same hospital during childhood, have failed.
- Some hospitals do not accept persons who use marijuana, including medical marijuana (Caplan 2008).

Balancing nonmaleficence and beneficence is the charge of all transplant teams while remaining cognizant of the need to transplant patients to stay in existence. UNOS (the United Network for Organ Sharing) has requirements for the number of transplants a center must perform in a rolling statistical period as well as survival outcomes. The combination of the team's attempt to list patients and the UNOS requirements can bridle errant listing practices.

The advancements in heart failure medications, interventional procedures, and most certainly LVADs has kicked the can down the road with regards to difficult patient selection. Likewise, LVADs have also allowed patients who demonstrated behaviors that prevent listing to course correct with the time the LVAD can buy them. With all interventions, this too is not without risk; another surgery and wait time can only add to the risk for the patient. Teams must be careful to not use LVADSs as a bail out for difficult decision-making or difficult patients. Equally, transplants cannot be sought to salvage poor LVAD outcomes.

This discussion demonstrates in part why the psychosocial portion of transplant candidacy is crucial; it adds to the depth and breadth of the discussion and the preparation for successful outcomes. While medical knowledge of cardiac transplantation and circulatory devices are a distinctive advantage, it is not the focus of the social worker's role. The aptitude to engage with families and the medical team, awareness of the patient and family's understanding of what is expected in cardiac transplant or LVAD therapy, knowledge of resources and entitlement programs, and a keen ability to articulate issues are basic components of the transplant social workers skill set. Most teams rely on their social workers to present the psychosocial facts and interpret them, despite what can often seem like dismissiveness or outright objection to the contribution of potentially tarnishing information.

The Heart Transplant Psychosocial Evaluation

Developing a psychosocial assessment tool is the foundation of performing a comprehensive, thorough, and detailed evaluation of the transplant candidate. A solid psychosocial assessment should incorporate guidelines from UNOS (united network of organ sharing), CMS (Center for Medicare and Medicaid Services), and JCAHO (Joint Commission on Accreditation of Hospital Organization). Many cardiac transplant centers' psychosocial evaluations cover in large part the following areas: cognitive evaluation; screening for psychiatric illness; evaluate for history of alcohol, tobacco, and or substance abuse; evaluate history of compliance with medical therapies; evaluate history of compliance with medical therapies and recommendations; evaluate psychosocial obstacles that would limit chance of successful outcome; assess level of family/caregiver support and presence of caregiver burden; and verify adequate level of health insurance/ability to obtain it and maintain it (Petty and Bauman 2015).

More recently, many transplant social workers have added a thorough evaluation using the DSM V guidelines for substance abuse disorder including alcohol as well as thoughtfully posed questions about literacy and health literacy. The goal of this enhancement is an increase in the accuracy of the assessment and to accommodate for differences which could impact the interpretation of candidacy. Most centers now realize the value of the AUDIT (alcohol use disorders identification test) tool (NIH 2001) to standardize what is agreed upon as *use* versus *abuse*. In addition, there is great value to pay special attention to all aspects of diversity and to ensure that the candidate's identified gender is asked as well as couching relationship status as "partnered" first instead of "married." Establishing rapport with the patient and family is as important as information gathering; the relationship developed with the patient will likely last the life of the patient thus the approach and sensitivity to information gathering is a crucial part of the process.

A comprehensive assessment tool is one way to gather information for candidacy as well as to be able to have a source of information about the patient and family structure as patients move through listing, delayed listing, LVAD implantation, total artificial heart implantation, and possibly transplantation. There is no clear instruction on the time intervals of psychosocial reevaluation, and therefore many centers will combine it with the medical reevaluation for completion of the process (generally on an annual basis). What has been lacking for many years was a way to capture the patient's candidacy consistently for transplant from a psychosocial standpoint. In 1993, the first widely known attempt at providing a scale for transplantability was developed, the TERS.

> The Transplant Evaluation Rating Scale (TERS) classifies patients' level of adjustment in 10 aspects of psychosocial functioning that are thought to be important in adjusting to transplantation. On the basis of pretransplant psychiatric consultations, 35 liver transplant recipients received retrospective TERS ratings. Results showed significant correlations between TERS scores and visual analogue scale ratings of five outcome variables at 1-3 years posttransplant. Significant interrater reliability was also found. The TERS represents a promising instrument for transplant candidate selection as well as a valuable tool for further research. (Twillman 1993)

Often the same or a similar tool can be used for an LVAD or total artificial heart (TAH) patient. There are several tools available, most notable the Stanford Integrated Psychosocial Assessment (SIPAT). "The SIPAT is a comprehensive screening tool to assist in the psychosocial assessment of organ transplant candidates. Its strengths include the standardization of the evaluation, and its ability to identify subjects who are at risk for negative outcomes after the transplant, for the development of interventions directed at improving the patient's candidacy. Our goal is that the SIPAT, in addition to a set of agreed upon minimal psychosocial listing criteria, would be used in combination with organ-specific medical listing criteria to establish standardized criteria for the selection of transplant recipients." (Maldonado 2012). A copy of the SIPAT can be obtained by contacting the author of the SIPAT.

The LVAD evaluation has to this point predominantly emulated the heart transplant evaluation with a few subtle differences. "Psychosocial predictors of LVAD outcomes have not been standardized. There is limited data on objective psychosocial predictors of LVAD outcomes. The SIPAT (Stanford Integrated Psychosocial Assessment for Transplant) scale has been validated in organ transplant evaluation and patient selection." (Maldonado 2012). However, there are many differences, especially in the role of ultimate physical independence which transplant affords and which the LVAD may not. As LVAD technology changes, the LVAD evaluation may need to change in tandem to acknowledge the advances in the technology. A 2016 study in the Journal of Cardiac Failure concluded that "The SIPAT score may not be sensitive enough for psychosocial risk assessment of LVAD patients" (Tsarova 2016).

While the SIPAT is a promising pretransplant/pre-LVAD evaluation tool and lends itself well to an electronic medical record (EMR), its predictive strength in determining successful transplant outcomes is debatable. As Khaled Housseini writes "Human behavior is messy and unpredictable

and unconcerned with convenient symmetries" (Hosseini, 2013). After all, there is not an even playing field when it comes to patients who require care, and such high levels of care. In addition, the tool is quite lengthy and gets into areas which may be better served by the social worker referring to psychiatry or psychology.

A limitation of the SIPAT can be that it tends to read as a checklist with the goal of data collection for the ultimate tabulation of the score. The psychosocial evaluation is an art, like the way physicians amass information by engaging with the patient. A very different answer can be accrued simply in the way it is posed, and the space allowed for response. Perhaps an answer to a SIPAT question may lead to another question that is not on the SIPAT but is born from the experience of the social worker's experience working with patients and families. The responses given are generally given with a context, which is the value of having an experienced transplant social worker assess a patient and family system. The risk of standardizing an assessment tool is to think that the numeric score produced is the gestalt of the patient and situation. Social workers are the translators, advocates, and detectives when it comes to making sense of the psychosocial information. As transplant programs expand and the use of electronic medical records is the norm, transplant social workers must find a way to still have the opportunity for narrative and prose not otherwise captured by the standardized tool.

A possibility to consider is for a transplant program to develop their own tool based on their specific program's philosophies and contraindications (absolute and relative), keeping the TERS or the SIPAT as the framework. Does the program even believe a scoring tool is necessary? If so, for what reasons? Some programs have piloted a scoring tool and followed their listings for 6 months to determine efficacy or increased versus decreased listings. The goal would be to create an adaptable psychosocial tool that can be developed with team input, transplant social worker experience, and a consistent objective method by which to categorize, guide, plan, and advocate for candidates. When a patient is evidently a candidate with all the required components and features for an anticipated successful outcome, that is simple. It is far more complicated when a patient is not able to be listed but has the potential to work toward psychosocial candidacy while the medical issues do not wait.

Health Literacy as It Impacts Psychosocial Evaluation

What has become increasingly clear over the past several years is the significant role that health literacy plays in a patient and family's ability to understand, comply, and execute required care. This would be especially true for chronic conditions such as LVADs or cardiac transplant, and in many cases, both.

> Low health literacy was shown to be associated with poor health outcomes, higher mortality rates, and greater health disparity. Lee and colleague studied the link between health literacy, self-care activities, and quality of lifelong type 2 diabetes patients from out-patients clinics. It suggested that health literacy was recommended in clinical practice for enhancing self-care activities and could improve health-related quality of life in patients. Therefore, it was important to identify patients at different levels of health literacy and provide adequate and effective interventions such as tailored counseling, improved provider–patient interactions, organizing information by patient preference using plain language and visual items. (Duong 2017)

Table 1 (Abel 2015) lists several questions that can assist in ascertaining the patient's overall health literacy in an objective manner.

Many times, members of the team will think and say, "the patient just doesn't *get* it" and make a referral to psychiatry or request a neurocognitive exam. It is highly likely that the patient has arrived at the point of needing transplant secondary to lack of comprehension of their heart disease, and the medical information they have received. The above 8 questions are key to determining the patients' health literacy in advance of the psychosocial evaluation for heart transplant or LVAD. The 5 minutes required by the social worker to ask these questions of the patients can put the findings of the psychosocial assessment into a context, as well as illuminate areas where patients

Table 1 Health literacy among young adults: a short survey tool for public health and health promotion research

HL1	How well do you understand instruction leaflets for medication	Very bad = 1; bad = 2; moderate = 3; good = 4; very good = 5; I do not make use of this kind of information = 0[a]
HL2	How well do you understand information brochures on health issues	Very bad = 1; bad = 2; moderate = 3; good = 4; very good = 5; I do not make use of this kind of information = 0[a]
HL3	When I have questions on diseases or complaints, I know where I can find information on these issues	Disagree strongly = 1; disagree = 2; agree = 3; agree strongly = 4; I do not have experience with these issues = 0[a]
HL4	When I want to do something for my health without being sick, I know where I can find information on these issues	Disagree strongly = 1; disagree = 2; agree = 3; agree strongly = 4; I have not been interested in these issues = 0[a]
HL5	How often were you able to help your family members or a friend if they had questions concerning health issues	Never = 1; seldom = 2; sometimes = 3; often = 4; always = 5; there have never been any questions = 0[a]
HL6	When you came up with questions concerning health issues, how often were you able to get information and advice from others (family and friends)	Never = 1; seldom = 2; sometimes = 3; often = 4; always = 5; there have never been any questions = 0[a]
HL7	How well are you doing in choosing the advices and offers that fit with you the most	Very bad = 1; bad = 2; moderate = 3; good = 4; very good = 5; I have not been interested in these issues = 0[a]
HL8	Regarding information on health on the internet, I'm able to determine which sources are of high and which of poor quality	Disagree strongly = 1; disagree = 2; agree = 3; agree strongly = 4; I do not have experience with these issues = 0[a]

[a]Answers external to the ordinal scales were seen as difficult to interpret due to ambiguity. Such responses were scored 0 points

may require additional education and support versus a referral to psychiatry.

Far and above the marketing department of the institution ensuring that their patient education material is presented in an attractive layout, a program should absolutely consider having their materials assessed for readability. Likewise, any psychosocial assessment tools should also be examined for accessibility to a general population and/or an aging population.

> The average US resident reads at an 8thgrade level, and the average Medicare beneficiary reads at a 5thgrade level. These statistics have implications for patients, including their ability to understand common medical terms. In a study of 249 adults at a metropolitan Emergency Department, investigators found that nearly 80% could not correctly state that "hemorrhage" meant "bleeding", "myocardial infarction" meant "heart attack", or that "fractured" meant "broken". This is despite the fact that greater than 50% of surveyed patients had a college education. (Stosell 2012)

For a rapid estimation of the materials with which your center is providing information to patients, Google has now added a search filter for "reading level" in the advanced search page. The standard method used by Google is called the "Flesch/FleschKincaid readability test."

LVADS and the LVAD Psychosocial Evaluation

A left ventricular assist device (LVAD) is a type of mechanical circulatory support that is implanted to restore the physiologic function of the damaged left ventricle in patients with stage D HF. Currently, there are two approved long-term indications: LVAD as a bridge to transplant (BTT) and LVAD as destination therapy (DT). LVAD-DT is a permanent alternative for stage D HF patients who are not transplant candidates. Once implanted, the majority of these patients will live with and die with this device in place. The main goals of destination therapy are to improve the daily function and health-related quality of life, and to improve survival compared to patients who receive optimal medical management. Studies have shown a 68% survival rate with an LVAD at 1 year and a 58% increase in survival at 2 years compared to those who are

> managed medically. Based on the current evidence, quality of life also improves post-implant. Once FDA approval, there has been an exponential increase in the use of LVAD-DT with a tenfold increase from 2006–2010.The implantation of LVADs will continue to increase with improvements in technology, scarcity of donor hearts, and the aging population. (Kitko 2013)

The introduction of the LVAD from an in-hospital device as a bridge to transplant to an FDA-approved device for use as an outpatient while waiting for transplant, or as a destination therapy, engages the social worker in a different way than in transplant. Specifically, the support system will be required for a longer period and will require more training. Assessing the caregiver's health literacy could also contribute valuably to the longevity of both patient and caregiver's endurance.

That same study concluded that "Caregivers were able to adapt and develop effective strategies to incorporate the demands of caring for a spouse with an LVAD-DT, but the role remained challenging. The findings underscore the need for continued research that may be translated into effective interventions to support patient and caregivers as they live through this end-of-life trajectory." (Kitko 2013). By extension, the support system will need ongoing support thus extending the role and reach of the social worker beyond sustaining the patient.

It is important to point out the differences between the LVAD psychosocial assessment and the transplant assessment, though there is significant overlap. As previously mentioned, the caregiver involvement will be more long term in the LVAD cohort. The wound care, battery requirements, potential for infection, and frequent blood tests to prevent blood clots cannot be underestimated. Many patients have been in heart failure for years and may have some permanent cognitive delay requiring unending supervision, albeit at varying levels. In addition, many LVAD patients cannot return to work as easily if at all, as can a heart transplant recipient; thus evaluating employment, income, and insurance is just as crucial if not more so than in transplant. Similarly, a thorough exploration for a backup layer of support should be undertaken in the event the planned support person becomes unexpectedly ill or the relationship deteriorates.

It is extremely important to take note that LVAD patients have an ability to terminate their life most immediately and directly. In the days and weeks which follow an LVAD implant, patients can confront medical setbacks and pain which could lead to "buyer's remorse." As medical professionals and those familiar with the often-undulating course that post-LVAD implantation can take, a thorough discussion should take place ahead of time to establish the parameters the team and family desire to establish. In a 2013 article, Morris and Shore (Morris 2013) strive to balance the patient's right to self-determination with what they know as the potential medical and emotional challenges after an LVAD implant. They posit that in general, a minimum of 90 days should be the baseline before which end-of-life discussions should be entertained while input and consultation from psychosocial support teams should be maximized during this time. As always, establishing a baseline trust with patients and families is critical to the process; at decision points along the way that trust will be invoked and relied upon heavily.

The role of caregivers for LVAD patients has recently gained quite a bit of attention as a sizeable cohort of long-term and destination therapy patients have allowed for study of this group. Destination therapy (DT) patients are those patients who are considered not eligible to proceed to transplant. The psychosocial support required for the caregiver in any chronic condition should not be overlooked and is nowhere more evident than with a DT patient's family. The learning curve, as with anything new and technologic, can be steep and thus the social worker can lean on questions which flesh out trends to evaluate caregiver adaptability. This distinct difference in LVAD versus transplant is one of the areas where the psychosocial assessment needs to specifically be adjusted. In one study, it was noted that throughout the process of caregiving, preimplant through postimplant, all caregivers discussed their ability to adapt within the role as a caregiver. Adaptation as a caregiver occurred

through three distinct time frames following the progression of the patient's HF and subsequent LVAD implantation: caring for a spouse with HF, decision for LVAD implantation made, and caring for a spouse with the LVAD-DT (Kitko 2013). The adaptability of long-term caregiving can be difficult to assess in a tool such as the SIPAT which examines a moment in time. Specifically asking about other times in the family's history where they can describe how they adjusted to something new, different, or even traumatic can help ascertain the possibility of both strengths and areas of vulnerability and can serve as a reference point going forward.

LVAD programs will need to decide collectively how and for how long, caregiver support will be required. Often checking in with other programs of similar size and experience can be helpful. A minimum of 12 weeks of 24-hour care coverage from time of discharge was one experience in Philadelphia in the early 2000s (as compared to only 6 weeks for transplants). This time frame was based on the collective input of the multidisciplinary group considering healing, cognitive status, general age of the patient, and learning the device care. It was often challenging for patients and families to come up with the duration of coverage; thus the role of the social worker was to assist in mobilizing family and community support to assist in the family's coordination of that care.

An excellent addition to a roadmap for psychosocial support for LVAD patients is a social work led and facilitated support group. On line support groups and forums are an excellent resource for patients and families who live a distance from the hospital or who are unable to drive. So often the caregiver's needs are placed after the patient's which can affect the caregiver's mood. In addition, the need to take time off from work can negatively impact the family system and put the caregiver's job in jeopardy. Many caregivers report feelings of isolation, thus the support group, in whatever forum, was an opportunity to exchange concerns, tips, triumphs, and even clothing adjustment ideas. The importance of the caregiver's role cannot be undervalued.

> A striking finding from our study is that the risk of death was 3.1× more likely among patients who live alone compared with those who did not live alone. This suggests that having a caregiver present and available is strongly associated with mortality. Further supporting the interpretation, we also found that the risk of death for an LVAD patient was significantly lower among those who had at least 1 adult child living close by (defined as ≤50 miles). Theorizing why we found these associations, it could be that these better mortality risks are related to adherence to medical regimens and self-efficacy (the latter being a person's ability to complete a skill successfully and confidently). In the absence of caregivers who can routinely assist and monitor patients (and other caregivers to provide backup support if the primary caregiver is unavailable), mortality risks may increase because patient self-efficacy lowers in the absence of support. Specific examples include patients not taking Coumadin without reminders from caregivers, resulting in thrombosis or stroke and patients not properly adhering to hygienic practices for dressing changes or cleaning drivelines without caregiver assistance, either because of patients' cognitive detriments or because of physical limitations. There is some support for hygienic practices influencing mortality because our previous work demonstrated that persistent bloodstream infections (related to driveline infections) strongly correlated with mortality and risks of stroke. It may also be the case that without support, patients may become burned out or are otherwise so burdened that they cannot fully contribute. (Bruce 2017)

The role of the palliative care team is newer to LVAD programs, but the late to arrive addition to the LVAD evaluation process makes it no less important. In fact, in October 2014 CMS mandated that all VAD implanting centers have palliative care as part of their interdisciplinary team. The timing of the placement of the consult can be tricky: it should already be decided if the patient is an LVAD candidate by the medical team so that the consult is in sync with what is being offered. The palliative care team typically needs to respond to consults within 24 hours of receiving them, thus mastering the flow of the consult should be discussed ahead of time. Without a doubt, the emergent LVAD implants will have to have a collateral palliative care consult protocol which should be established well ahead of time by the program.

The process for a palliative care consult ideally flows as illustrated at University Hospitals Case Medical Centers:

- Heart failure (HF) places palliative care (PC) consult.
- Psychosocial assessment completed by HF team prior to PC consult.
- PC consult ideally completed prior to candidacy discussion.
- PC meets patient to introduce role and preparedness planning process.
- Follow-up meetings planned if needed.
- The following quality of life issues related to VAD are discussed:
  - Hemodialysis.
  - ICH/embolic stroke.
  - LVAD failure.
  - LVAD infection/need for long-term antibiotics.
  - Artificial nutrition and hydration.
  - Mechanical ventilation (short vs. long term).
  - Caregiver burden (Cohen 2015).

As in hospitals, inquiring as to a Living Will/Advance Directive and Health Care Proxy is of paramount importance and should be imbedded into the psychosocial evaluation. This information can be exceedingly helpful to the palliative care team as they interview and connect with families embarking on LVAD implantation. The palliative care consult in conjunction with the patient's AD can serve as a record for their initial wishes at the start of treatment. For many patients and families, it can be difficult to see how far a patient has strayed from their initial ideals on quality of life and end-of-life care issues. Likewise, complications at the time of implant or at any point along the LVAD trajectory can be immediately contextualized if the patient and family's philosophical roadmap has been concretized.

So much of the palliative care discussion at the time of LVAD implant has to do with the approach, both with the team as well as the patient. Despite the 2014 CMS recognition and mandate to include the consult, many team members find the timing discordant to the message they are trying to impart to the patient. That message is one of hope and rebirth while the PC consult may be viewed as serving to undermine or contradict the goal of the program. That is why it is highly recommended to have ideologic covenant between your VAD and transplant team and the palliative care program that in fact the message is unified and comprehensive. The presence and input of a palliative care representative at your selection criteria meeting is crucial to round out the total patient experience. Moreover, many programs have found it useful to have a revisit every 6 month to see if the patient's wishes have changed over time. This can prove extremely useful should a patient's health status decline, an established relationship with the PC team has been forged already.

Perhaps the most useful and user-friendly AD tool for this particular patient population is The Five Wishes. This tool is available through the Aging with Dignity Program (www.agigwithdignity.org). The Five Wishes provokes the following questions:

- Who you want to make health care decisions for you when you can't make them.
- The kind of medical treatment you want or don't want.
- How comfortable you want to be.
- How you want people to treat you.
- What you want your loved ones to know.

The Five wishes can also be completed on line through Aging with Dignity. In this way, should families be physically apart the document can be readily accessed in times if immediate need or medical crisis. The tool is also available in Spanish.

In an ideal world, a palliative care consult would be beneficial both for patients listed for transplant in the absence of LVAD implantation as well as those who undergo LVAD implant as either destination therapy, potential heart transplant candidacy at some point, or a listed patient. Most programs do not have the capacity to accommodate the volume of such an ambitious agenda but the value of the role of the palliative care team is inestimable. If possible, the

palliative care team should be present at the selection team meeting.

Selection Committee Procedure and Presentation

The goal of every LVAD and transplant program is to implant and list/transplant patients to improve as many lives as possible. Social workers share this attitude despite having different and less binary measures. Collective team agreement on absolute contraindications to listing and/or implanting is crucial at the start of tenure with your team. Without those established standards, the ability to discuss a patient's candidacy and the proposed intervention will be unfocused. Preparing ahead of time what should be conveyed will help a busy team with limited time understand the psychosocial clearance, concerns, or contraindications to moving forward. Should the social worker anticipate not being able to "clear" a patient, it is advisable to reach out to the physician or physician extender ahead of time to share what is expected to be presented. If steps towards candidacy are needed, then a clear, measurable time frame should be outlined with team feedback as goals are met or unmet. Finally, a succinct, cogent, and well verbalized psychosocial presentation is imperative to best advocate for the patient, program, and all others who wait on a heart transplant list or LVAD implant date.

It may be helpful to standardize the psychosocial presentation, so the team can follow the cadence and rhythm of that assessment. As an example, social workers may want to begin with the patient's family constellation, history of self-care, current insurance, and any contributory psychiatric or substance abuse-related issues. This could be followed by the patient and family's desire to proceed with transplant/implant and finally the social worker's input. If the patient has steps which need to be completed, those should be outlined with a clear follow-up time frame and documentation. If the patient is not a candidate based on programmatic absolute contraindications, that should be stated as well. Below are some examples of a concise presentation.

1. Mr. Z is a married man with two adult children who reside nearby and are supportive and involved. He has been followed closely by his local physicians for many years and demonstrates adherence to the prescribed medical plan. He is currently covered by his wife's insurance plan and will have Medicare in 3 months. He and his family deny a history of mental health issues or substance abuse-related issues. Patient and family look to transplant to improve his quality of life and he hopes to return to work when medically cleared. Psychosocially cleared for transplant/VAD; reevaluate in one year.
2. Mr. Z is recently separated from his wife but has a daughter who has been involved in his care intermittently. He is, for the most part, compliant with medications and appointments but often does not have a ride to the pharmacy. He is covered under COBRA which will end 2 months before he becomes Medicare eligible. After 30 years of smoking two packs per day, he stopped smoking 3 months ago. Finally, he reports a history of sporadic depressive episodes for which he did not receive treatment, but these episodes did not interfere with his overall health or adherence. He is psychosocially cleared but with a plan for random urine nicotine checks and the need for his daughter to accompany him for the first six visits while listed for transplant/post-VAD implant. Transportation needs to be secured and a financial coordinator obtained to develop a plan for the transition from COBRA to Medicare with prescription plan in place. Reevaluate in one year or sooner if there is a deterioration of the psychosocial situation.
3. Mr. Z lives alone but came for his transplant/LVAD evaluation with a neighbor who is willing to help. He has been newly diagnosed with heart failure though he had symptoms for years but no insurance to seek medical care. He continues to smoke but has cut back to a half pack per day. He reports that smoking cannabis has helped his anxiety a great deal since he completed a dual diagnosis treatment program for bipolar disease and heroin abuse 20 years prior. He has not had any psychiatric follow-up

since his discharge from the program. Patient is not cleared for transplant until he has been evaluated by psychiatry and has stopped smoking both cigarettes and cannabis. He should be reevaluated for listing for transplant in 3 months but a vigorous discussion about LVAD candidacy should be entertained.

The medical contraindications for smoking are clear. A study first published in 2016 looked at smoking and mortality while listed for transplant.

> During the study period (April 2005 to March 2010), 14% of those who never smoked died, 18% among former smokers died, and almost half (42%) died among those who reported smoking at time of wait listing. Multivariate Cox regression models controlling for age, sex, and disease severity revealed smoking at time of listing was associated with significantly higher risk of mortality compared to never smoking (hazard ratio [HR] = 3.43; P = .03). The relationship between smoking and mortality risk appeared to follow a dose-dependent pattern: adjusted HRs were 1.80 for those who quit ≤1 year ago, 1.25 for those who quit >1 to 10 years ago, and 0.90 for those quit >10 years ago, compared to never smokers. Smoking at time of listing may increase risk of mortality during the waiting period, indicating the need for improved strategies to achieve smoking cessation as early as possible in the course of heart transplant. (Gali 2016)

The rate of cancer increase after immunosuppression is also indisputable. "Hard core" drug use and abuse such as cocaine, heroin, opioids, and similarly classified drugs is consistently an absolute contraindication for listing for transplant. Less clear is what role, if any cannabis, plays both medically and psychologically often rendering marijuana a relative contraindication to listing for transplant.

Although cannabis use remains illegal under federal law, at the time of the writing of this chapter, 24 states have passed laws which legalize marijuana use for medical or recreational use. This places transplant programs in a difficult position in terms of deciding if marijuana use is a relative or absolute contraindication to listing for transplant. Arguments can be made on either side and without a doubt the personal opinions of team members can play a role in this determination, much the way alcohol use can also be perceived relationally. In fact, "several states have passed legislation prohibiting marijuana-using patients from being denied transplant listing based on their use of the substance" (Neyer 2016). That study, conducted in 2016, surveyed transplant providers and concluded that "The majority of heart and lung transplant providers in our study sample support the listing of patients who use medical marijuana for transplant after a period of abstinence. Communication and collaboration between the medical community and legislative groups about marijuana use in transplant candidates is needed to ensure the best patient outcomes with the use of scarce donor organs" (Neyer 2016). From a social work perspective, a detailed substance use/abuse history might be helpful in determining if the cannabis use is a maladaptive behavior which could be replaced by a better strategy (psychiatric treatment, medication, or an alternative methodology). In addition, there remains the concern that the relaxing effects of cannabis could contribute to lack of initiative in medication adherence, ultimately contributing to potential noncompliance.

Ultimately, each team will decide what are their criteria medically and psychosocially, and where the two meet. It cannot be stated enough how important it is to visit and revisit these criteria, as team members change, as laws change, and as the transplant climate in your community changes. As much as it goes against the social work grain, the reality is that competitive markets where there are many transplant centers from which to choose can liberalize listing criteria from center to center. More data will be needed, especially in an area so under studied as cannabis use, for teams to make a best practices decision.

Alcohol use and abuse is another area that is often quite controversial. To avoid controversy and subjective input, a constant definition should be sought and utilized consistently. According to the National Institute on Alcohol Abuse and Alcoholism, drinking levels are defined as:

Moderate alcohol consumption:

According to the *"Dietary Guidelines for Americans 2015-2020," U.S. Department of Health and Human Services and U.S. Department of Agriculture*, moderate drinking is up to one

drink per day for women and up to two drinks per day for men.

Binge drinking:

NIAAA defines binge drinking as a pattern of drinking that brings blood alcohol concentration (BAC) levels to 0.08 g/dL. This typically occurs after four drinks for women and five drinks for men—In about 2 hours.

The Substance Abuse and Mental Health Services Administration (SAMHSA), which conducts the annual National Survey on drug use and health (NSDUH), defines binge drinking as five or more alcoholic drinks for males or four or more alcoholic drinks for females on the same occasion (i.e., at the same time or within a couple of hours of each other) on at least 1 www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/moderate-binge-drinkingday in the past month.

Heavy alcohol use:

SAMHSA defines heavy alcohol use as binge drinking on 5 or more days in the past month.

NIAAA's Definition of Drinking at Low Risk for Developing Alcohol Use Disorder (AUD):

For women, low-risk drinking is defined as no more than 3 drinks on any single day and no more than 7 drinks per week. For men, it is defined as no more than 4 drinks on any single day and no more than 14 drinks per week. NIAAA research shows that only about 2 in 100 people who drink within these limits have AUD (NIH 2015).

Organizing the Family Meeting

Whether performing an inpatient of outpatient transplant or LVAD evaluation, gathering the support team that will assist the patient throughout the many steps in their journey is a critical first step in even establishing candidacy to move forward with the evaluation phase. The inability to accrue a base group of individuals is a telling sign. Without being considered insensitive to work and family obligations, the patient must be able to mobilize support. In addition to be a litmus test for the patient, those who plan to commit to an individual must be made aware of what they can expect and what will be expected of them. It can be helpful to have a document summarizing the responsibilities of the support structure at each phase of the process so families can refer back as they move through the process. Similarly, creating a document which specifically outlines the support people within the patients' family can help the team recall and refer to what has been agreed upon and adjust accordingly.

Retransplantation and LVAD Exchange

Approaching the concept of retransplantation is extremely complicated. Clearly, the dearth of available organs for so many who need them is the foundation of the struggle in considering retransplantation. Teams all over the world confront this issue especially when a patient was transplanted as a child and has reached adulthood and needs retransplantation. From a psychosocial evaluation standpoint, most of the guess work is eliminated with retransplantation consideration; compliance has either been demonstrated or not, family support over time has declared itself, and the patients desire to reinvest in the transplant process is evident by virtue of their consideration of moving forward with reevaluation. What can get complicated is the ensuing discussion if a patient's obstacle to relisting is founded upon psychosocial indications-how the team interprets those issues can get sticky. For example, supposing a patient was noncompliant with medications because they lost their insurance? On the surface, this can seem like a punishing reason not to relist. From a psychosocial standpoint, the questions that need to be asked fall into the realm of what created the inability for the patient to reach out to the transplant center for guidance and resources? What happened to the support system that had been in place? Was isolation a contributing factor? There is tremendous reluctance to proceed with retransplant if the afore mentioned issues contributed to the loss of the organ.

Consideration for LVAD exchange is less complicated but should none the less be approached with similar serious consideration as retransplantation, especially if medication noncompliance was a contributing factor. Likewise, device-related noncompliance (such as driveline infection due to lack of support or carelessness with equipment) should be factored in. Though not short in supply such as an organ, an LVAD remains a costly intervention and relies heavily on a support network. Obtaining input from those who are involved with either an LVAD or transplant patient can help explain or fill in vital information when considering either LVAD exchange or retransplantation.

Helping families feel comfortable in sharing their knowledge of the patient's situation without creating an environment where they feel contributory to the denial of care is very important. The finesse required to engage the family to reveal the truth about the reasons for device failure or allograft dysfunction may require widening their perspective on the shortage of organs and the continued risk to the patient, among many other possible approaches. Helping families and the team decipher what types of interventions may help with candidacy is a role that the social worker can assume. Conversely, social work is equally obligated to the awareness of organ shortage, human behavior, and distributional justice. Requesting a palliative care consult as well can be extremely helpful in retransplantation or LVAD exchange conversations for the family, patient, and team.

Maintaining Social Work Relevancy in Cardiac Transplantation

It is imperative that social workers be at the forefront of policy changes in all areas to be the best advocates for patients, families, the transplant team, and donor families. There are many opportunities for heart transplant social workers to continue to be relevant to the process including attending the UNOS region meetings in whichever region they work. The agenda can often seem very medical but there are policies which are discussed as well as those which can be read on line in advance of approval to be considered. The regional meetings are also wonderful opportunities to network with others in the region and bring awareness and recollection that singularity in transplantation in nonexistent.

In regions across the country there are transplant centers who exists with blocks of one another. In Philadelphia alone (UNOS Region 2), there were at least five fully functioning cardiac transplant centers at one time. This seeming deluge of centers, each vying for the same limited number of organs had the potential to lead to psychosocial secrecy. Instead, The Delaware Valley of Transplant Social Workers was formed and remains operational to this day. The goal of the group was to meet every other month and share information through organized guest speakers as well as to formally present difficult cases for collegial input and to bring awareness to the commonality of some of the challenges patients and centers face. In addition to the acquisition of knowledge germane to our unique group was the sequela of the opportunity to obtain information when a patient transferred care to the other's center. The group often invited transplant financial coordinators to join so that changes in Medicare and Medicaid coverage could be shared with all centers. More recently, the group was besieged with the contests that undocumented patients often face when requiring transplants which then called upon the invitation for community legal services to speak to the group.

There has been much discussion of late in all work sectors about work/life balance, self-care, and similar such concepts. In all professions, we grapple to attain that coveted nirvana. Social work in cardiac transplant is not for the faint of heart; the vicissitudes of the journey of transplantation calls upon the ability to stay the course through the heights of the incredible victories and be stalwart during the darker and less successful outcomes. Undoubtedly, there is vicarious trauma associated with our profession and while there is no magic bullet to avoid such exposure, hopefully some of the suggestions within the chapter can assuage the full impact of the by-product of such courageous work.

Conclusion

The cardiac transplant social worker assumes a complex role on a transplant team: assessor, fixer, ethical conscience of the team, resource expert, ambassador to other consultative teams, and is one of the central figures to the patient and family as they move through all phases of care. The ability to have longevity with the family and in the field is dependent upon the relationships formed with colleagues, patients, and caregivers. As social workers, we are privileged to work with expert transplant teams and patients alike, who each demonstrate bravery in the field and personal courage to pursue life altering medical care, respectively. No chapter would be complete if not to mention the pioneers of transplant surgery, donor families, and those patients and families who joined in that initial and continued leaps of faith with each new disruptive medical innovation. As social workers, we honor their valor by committing to judge candidacy without being judgmental, to guide without being directive, to be knowledgeable without arrogance, and to walk alongside with strength and humility for the miracle of transplant.

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Part III

Mechanical Support of the Pretransplant Patient

Extracorporeal Membrane Oxygenation

5

Elizabeth S. Pocock, Farzad Najam, and Gurusher Panjrath

Contents

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Abstract

Extracorporeal Membrane Oxygenation (ECMO) is a mode of mechanical cardiopulmonary support that is a direct extension of cardiopulmonary bypass (CPB) and provides temporary support for patients with cardiac and pulmonary failure. Because of the ease of institution, ECMO can be started emergently and can provide almost immediate cardiopulmonary support for patients in hemodynamically unstable clinical conditions. Though ECMO and extracorporeal life support (ECLS) circuits are simple in principle, ECMO circuitry has seen tremendous innovation in the past few decades. ECMO can be modulated in multiple configurations to provide cardiac and pulmonary support and to suit the specific needs of

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patients in many clinical conditions. This chapter included discussion on the historical inception of ECMO, expansion in scope, the indications, and clinical conditions it is used for and its role as a bridge to heart and lung transplantation in selected patients.

Keywords

Extracorporeal Membrane Oxygenation (ECMO) · Cardiogenic shock · Veno-arterial · ECMO · Cardiac Transplantation

Introduction

ECMO is an extracorporeal circulatory support system that provides hemodynamic and pulmonary support to patients who are critically ill. ECMO is a direct extension of CPB but can provide longer duration of artificial support than CPB. With miniaturization of ECMO circuit, patients can now be supported in various clinical situations. With the advent of ECMO in the 1970s, indications for ECLS and ECMO support have broadened to provide circulatory and pulmonary support for both pediatric and adult critically ill patients. ECMO had been mostly applied to pediatric patients as initially the results with ECMO support in the adult patients were fraught with a very high incidence of complications and mortality. With an improvement in blood pumps, extracorporeal blood tubing, available oxygenators and experience, complications on ECMO have declined and an improvement of survival has been observed. Because of this, there has been a positive trend towards using ECMO in various clinical conditions as a support modality. Early institution and modifications of techniques have led to better outcomes for a cohort of patients with life-threatening illnesses.

History of ECMO

John Gibbon reported the use of the heart lung machine that he and his wife developed and used on a cat to occlude the pulmonary artery and sustain circulation for more than 30 min. Gibbon later reported his four cardiac surgical cases that he used the heart lung machine on and his case studies were published in *Minnesota Medicine* in 1954. (Gibbon 1954) In 1965, Rashkind et al. reported the use of a bubble oxygenator in a neonate with respiratory failure. (Rashkind et al. 1965) The use of membrane oxygenator was reported by Dorson et al in 1969. (Dorson et al. 1969) In 1972, Hill and colleagues used long term extracorporeal support on a 24-year-old man who sustained multiple injuries from blunt trauma and developed respiratory failure. Veno-arterial support was used with peripheral cannulation. The patient recovered and Hill et al concluded that respiratory failure may be reversible if the patient received adequate gas exchange through extracorporeal circulatory support[5]. Kolobow[6] reported using extracorporeal membrane circulation for removal of Carbon Dioxide (CO_2). In 1976, Bartlett and colleagues reported using prolonged extracorporeal membrane oxygenation (ECMO) in the treatment of 13 infants (including 9 neonates). Four patients survived. Cases that were successfully treated included postoperative cardiac failure, infant respiratory distress syndrome, massive meconium aspiration, and persistent fetal circulation.

In 1974, the United States National Institutes of Health sponsored the first randomized controlled trial of ECMO versus conventional mechanical ventilatory therapy for the management and treatment of acute severe respiratory failure. Ninety patients were selected based on criteria for severe acute respiratory failure. Forty-eight patients were treated with conventional mechanical ventilation and 42 patients were managed with conventional mechanical ventilation supplemented with ECMO. Only four patients in each group survived, resulting in a high mortality of 90%. (Zapol et al. 1979) Lewandowski reported a survival rate of 89% in patients with acute respiratory syndrome (ARDS) treated with mechanical ventilation with clinical algorithm and without ECMO and 55% in patients with ARDS treated with ECMO. (Lewandowski et al. 1997) Mols reported a survival rate of 55% in patients with ARDS who were treated with ECMO. (Mols et al. 2000) Smedira and

colleagues reported the Cleveland Clinic experience with ECMO in patients with cardiac failure. (Smedira et al. 2001) Two hundred and two adults patients with cardiac failure were supported with ECMO. Survival at 3 days, 30 days, and 5 years was 76%, 38%, and 24%, respectively. Forty-eight patients were bridged to transplantation.

Conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR) was a multi-institutional, randomized controlled trial of ECMO for the management of ARDS that was conducted in the United Kingdom. One hundred and eighty patients were enrolled and randomly selected for treatment with ECMO or conventional ventilation. Sixty eight (75%) patients actually received ECMO; 63% (57/90) of patients allocated to consideration for treatment by ECMO survived to 6 months without disability compared with 47% (41/87) of those allocated to conventional management (relative risk 0.69; 95% CI 0.05–0.97, $p = 0.03$).

Components and Cannulation for ECMO

ECMO comprises of pumps, blood tubing, and oxygenators, with direct cannulation of blood vessels for venous drainage and venous or arterial return of oxygenated blood, hence providing pulmonary or hemodynamic support.

The modern ECMO circuits are simpler, portable, and compact (Figs. 1 and 2). Roller and centrifugal pumps are the main types of pumps used as blood pumps in ECMO. Most of the modern configurations of ECMO involve centrifugal pumps. A standard ECMO circuit includes a mechanical blood pump, gas exchange device (oxygenator), and a heat exchanger. ECMO circuits can also have various monitoring devices as well. Current ECMO circuits have improved biocompatibility and have heparin bonded tubing, hence reducing the need for higher levels of anticoagulation. The oxygenators can last longer than the oxygenators used in the cardiopulmonary bypass circuits used in the operating room for the performance of cardiac surgical operations.

Fig. 1 Centrifugal pump with heparin bonded circuit for ECMO. The design is simple and portable. (Courtesy Farzad Najam, MD)

Centrifugal pumps operate by converting rotational kinetic energy to hydrodynamic energy. A centrifugal pump consists of housing with a tapered shape and the blood is accelerated by the impellar. The impellar rotates in the case filled with blood and the centrifugal force that is generated pushes the blood out of the pump into the outlet tubing. (Khodeli et al. 2016) There are a large number of varied centrifugal pumps available that can be configured to be used for ECMO. The most common pumps used in clinical practice for ECMO are Tandem Heart™ (Tandem Life, Pittsburgh, Pennsylvania, USA), Rotaflow (Maquet, Rastatt, Germany), Thoratec CentriMag (Thoratec Corporation, Pleasanton, California, USA).

Membrane oxygenators have provided the necessary innovation for ECMO. Membrane oxygenators utilize a hydrophobic gas permeable membrane to allow gas exchange. Membrane oxygenators provide a true barrier between blood and gas and gas exchange takes place because of diffusion across the membrane. Most membrane oxygenators have micropores. The micropores provide conduits that give sufficient diffusion capability to the membrane for both

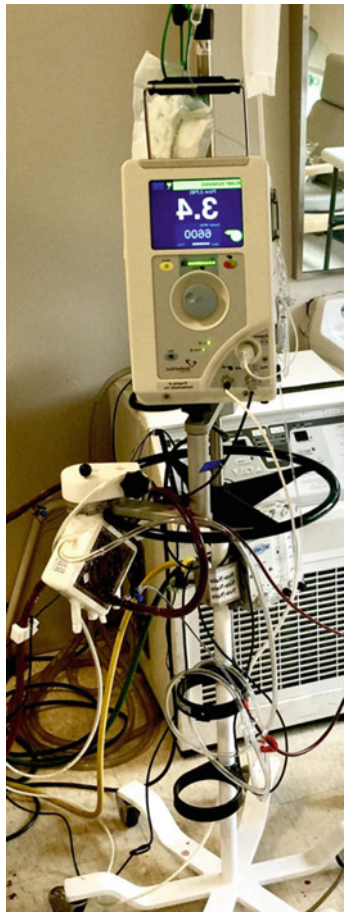

Fig. 2 Portable and simplified ECMO circuit and controller. (Courtesy Farzad Najam, MD)

oxygen and carbon dioxide exchange. Polymethyl pentene hollow-fiber oxygenators are suitable for longer term ECMO as they have lower rates of hemolysis, better durability with lower pressure differential, and less plasma leakage. (Horton et al. 2004) These oxygenators also limit the inflammatory response and decrease transfusion requirements. (Peek et al. 2002) Usually 100% oxygen is introduced into the gas phase of the membrane using a blender and the sweep is used to control the level of CO_2. A number of commercially available membrane oxygenators in commercial use include the Quadrox-iD (Maquet, Rastatt, Germany) (Fig. 3), Hilite LT (Medos, Stolberg, Germany), Lilliput 2 (Sorin, Mirandola Modena, Italy), and the Biocube (Nipro, Osaka, Japan).

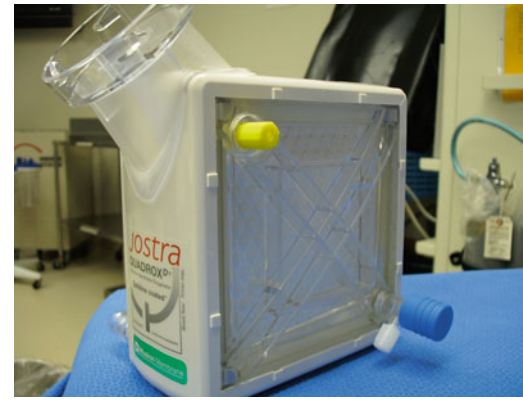

Fig. 3 Diffusion Membrane Oxygenator. (Courtesy Farzad Najam, MD)

Cannulae provide the drainage and return conduits for ECMO. Cannulae determine the flow dynamics of ECMO as the size and length of the cannulae govern drainage and flow rates. In adults, venous cannulae between 19 and 25Fr and arterial cannulae between 15 and 19Fr for veno-arterial ECMO cannulation are commonly used. Cannulation for VA ECMO is usually done percutaneously via femoral vein and artery. Increasingly, centers perform ECMO cannulations percutaneously, at the bedside, in the intensive care unit. Cut-down for femoral vessels can also be done, in cases when percutaneous cannulation is either not possible or difficult. Seldinger technique is used to access the femoral vein and then to advance the venous cannula into the right atrium. The same technique is used to access femoral artery for arterial cannulation. Ultrasound guidance is recommended for safe access to peripheral vessels. (Seto et al. 2010) A smaller antergrade distal perfusion cannula is also added to prevent limb ischemia. Figure 4 shows the configuration of a femoral arterial cannula and a smaller distal perfusion cannula with the femoral cut-down technique. Figure 5 shows the same configuration with the percutaneous technique. Subclavian and axillary artery cannulation with a synthetic graft can be utilized for arterial cannulation for VA ECMO with the advantage of avoiding lower extremity ischemia (Fig. 6). (Javidfar et al. 2012; Hysi et al. 2014) Central cannulation, most commonly for postcardiotomy

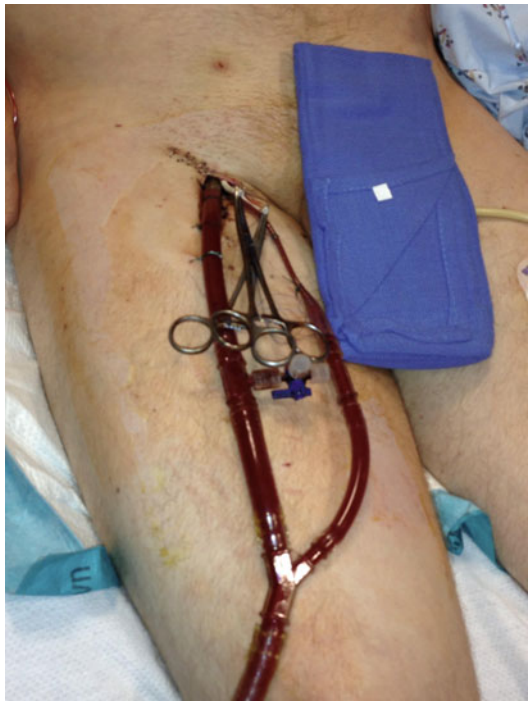

Fig. 4 Femoral arterial cannulation with the cut-down technique with a distal pediatric cannula for limb perfusion. (Courtesy Farzad Najam, MD)

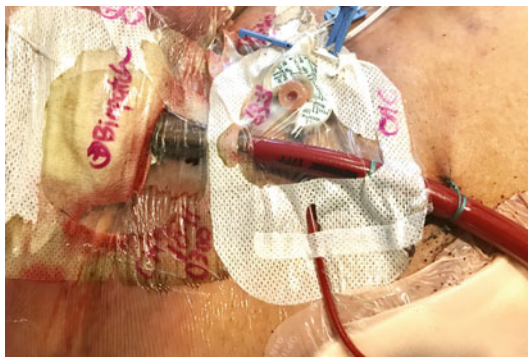

Fig. 5 Femoral cannulation with percutaneous technique and 7 Fr Sheath in the Superficial femoral artery for distal limb perfusion. (Courtesy Farzad Najam, MD)

cardiogenic shock, requires full sternotomy and open chest but provides excellent drainage and ante-grade flow. (Pavlushkov et al. 2017) To prevent left ventricular distension which may be associated with peripheral VA ECMO, a left ventricular vent via either the right superior pulmonary vein or left ventricular apex can be added

Fig. 6 Right Subclavian artery cannulation using a synthetic graft. (Courtesy Farzad Najam, MD)

(Fig. 7). With increasing use of axillary flow pumps such as Impella 2.5, CP or 5.0 (Abiomed, MA), percutaneous options to decongest the left ventricle are now available.

Cannulation for VV-ECMO can either be performed via femoral veins or right internal jugular vein. One large bore (19–25Fr) venous cannula is inserted via femoral vein and is placed in the right atrium for return of oxygenated blood. Venous drainage is established with another venous cannula inserted via femoral vein and is placed in the inferior vena cava.

Alternatively, single site double lumen cannulation for VV-ECMO can be performed via the right internal jugular vein (RIJ) utilizing a double lumen bicaval cannula (AVALON ELITE® Bi-Caval Dual Lumen Catheter, Maquet, Rastatt, Germany) (Fig. 8). This cannula has proximal, middle, and distal ports. The distal port located at the tip of the cannula is positioned just below atrial-IVC junction (Fig. 9). Both the distal and the proximal port drain the blood from IVC and SVC, respectively. The middle port rests in the

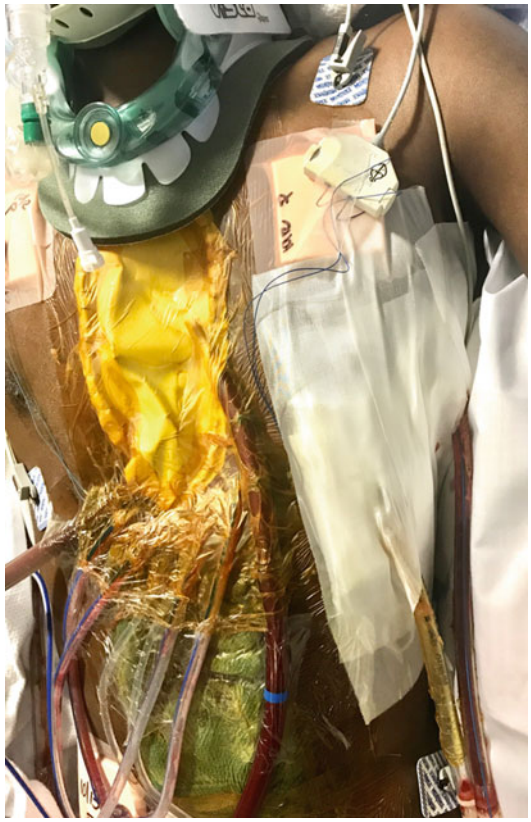

Fig. 7 Open Chest central cannulation VA ECMO with a vent in the left ventricular apex. (Courtesy Farzad Najam, MD)

Fig. 8 Single site double lumen cannula inserted via the right internal jugular vein. (Courtesy Farzad Najam, MD)

RA and faces the tricuspid valve. This port returns oxygenated blood from the ECMO circuit to the right ventricle. The advantage of single site RIJ vein cannulation is that the patients can be taken off mechanical ventilation and sedation. This also allows early mobilization and rehabilitation. Figure 10 shows a patient with VV ECMO with single site double lumen catheter breathing spontaneously and Fig. 11 shows a patient on ECMO ambulating with physical therapy.

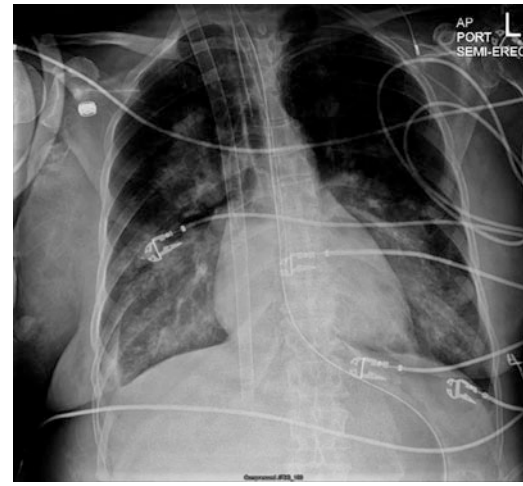

Fig. 9 Chest roentgenogram showing the tip of the double lumen cannula in the inferior vena cava. (Courtesy Farzad Najam, MD)

Right ventricular assist device ECMO (RVAD-ECMO) cannulation is performed for right ventricular support. This type of support can be provided with central cannulation with right atrial and pulmonary arterial cannulation or percutaneous peripheral cannulation with a single site double lumen cannula (Protek Duo^{TM}, Tandem Life, Pittsburgh, Pennsylvania, USA) (Fig. 12). This cannula drains the blood from the failing right ventricle and then the blood is circulated in the extracorporeal circuit and is returned to the main pulmonary artery via the same cannula but a different lumen. Percutaneous RVAD ECMO cannulation allows for right ventricular rest with the possibility of extracorporeal oxygenation and weaning off mechanical ventilation. The patients can be mobilized and rehabilitated at the same time.

BiVAD cannulation is used to provide chamber specific biventricular support with an addition of an oxygenator in patients who are initially stabilized with central VA ECMO for postcardiotomy

Fig. 10 Patient on VV ECMO without mechanical ventilation. (Courtesy Farzad Najam, MD)

cardiac failure. The cannulation requires a venous drainage cannula in the right atrium with a return cannula in the pulmonary artery for RVAD support and in parallel a venous drainage cannula in the left ventricle (via right superior pulmonary vein or left ventricular apex) and return cannula in the aorta. Cannulae used for this type of configuration are the same as for central VA ECMO. With this type of biventricular support, patient's lungs are supported and when the right ventricle recovers, the patient can be bridged to a long term implantable LVAD.

ECMO as a Bridge to Myocardial Recovery, Decision, and Implantable Ventricular Support

Refractory cardiogenic shock (CS) carries a very high mortality despite the availability of pharmacologic support, intra-aortic balloon pump (IABP), and mechanical ventilation. (Carnendran et al. 2001) In the acute setting, VA ECMO can provide circulatory support with the possibility of reversal of hemodynamic collapse and end-organ mal-perfusion and hence prevention of multiorgan failure. (Hata et al. 2000; Kihara et al. 2002; Doll et al. 2004; Murashita et al. 2004) VA ECMO can be instituted for both postcardiotomy cardiac failure and intrinsic CS. (Bowen et al. 2001) VA ECMO can be initiated emergently even with on-going cardiopulmonary resuscitation (CPR) via percutaneous femoral cannulation and can provide both cardiac and pulmonary support in CS. For patients with postcardiotomy cardiac failure, the existing cannulae used for cardiopulmonary bypass (CPB) can be converted easily to VA ECMO. For patients who developed intrinsic CS, VA ECMO can be utilized without the need for a sternotomy. ECMO support can be divided among various strategies: i. Bridge to Decision, ii. Bridge to Recovery, and iii. Bridge to Durable Ventricular Assist Device or Transplantation.

ECMO for Bridge to Recovery for CS is commonly used. (Smedira et al. 2001; Alozie et al. 2014) Smedira et al. reviewed retrospective data of 202 patients who were supported with ECMO after cardiac failure between 1992 and July 1, 1999, at the Cleveland Clinic Foundation, Cleveland, Ohio. Patients supported with ECMO ranged in age from 18 to 82 years (mean, 55 ± 14 years) and 145 (72%) were men. Of the 202 patients, 107 had undergone cardiotomy. Seventy-one patients were weaned off ECMO with the intent to survival. Patients were more likely to be weaned if IABP was used in conjunction with ECMO. Survival after being weaned from ECMO was 72%, 52%, 43%, and 40% at

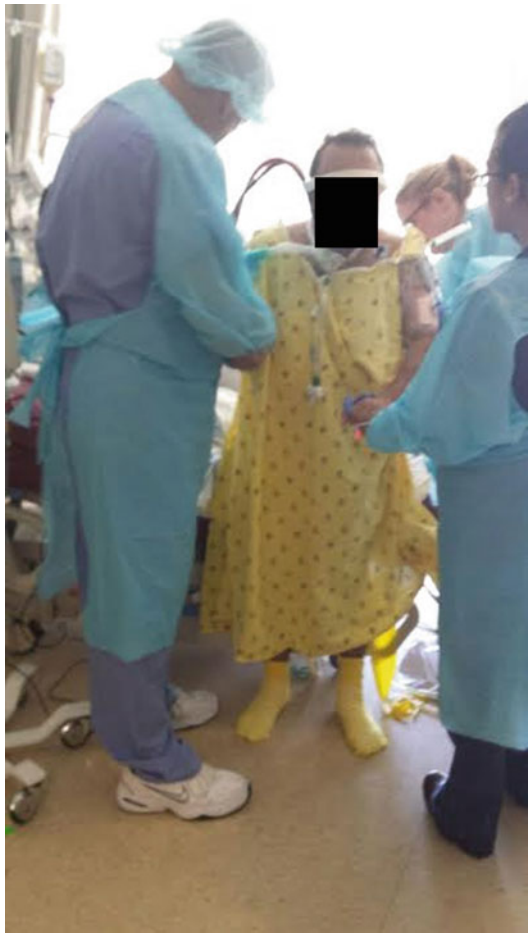

Fig. 11 Patient on VV ECMO ambulating with the help of physical therapists. (Courtesy Farzad Najam, MD)

7 days, 30 days, 1 year, and 5 years, respectively (Fig. 13). Sheu and colleagues reported on 334patients with cardiogenic shock who underwent primary percutaneous coronary intervention (PCI) for acute ST segment elevation myocardial infarction. They found a 33% absolute risk reduction and a 45.8% relative risk reduction for 30 day mortality in the 46 patients who underwent ECMO support. (Sheu et al. 2010) Importantly, when the patients with profound cardiogenic shock were excluded, no significant difference in 30-day mortality was noted between the two groups (26.1% [30 of 115] vs. 21.9% [48 of 219], $p = 0.392$). This suggests that ECMO may offer benefit in reducing 30-day mortality for patients with profound CS.

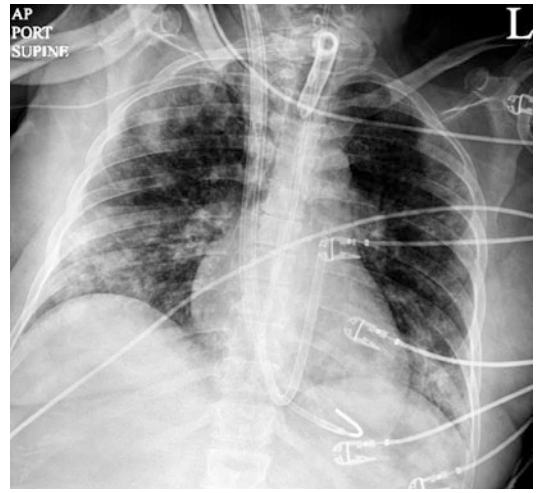

Fig. 12 Tip of RVAD cannula in the main pulmonary artery. (Courtesy Farzad Najam, MD)

ECMO as a Bridge to Decision

Often, during acute failure and rapid progression to profound cardiogenic shock, there may be lack of knowledge of patients' co-morbidities, healthcare beliefs, and wishes. In addition, the etiology of the rapid or progressive hemodynamic collapse may not be clear. Moreover, as multiple end organ injury often accompanies hemodynamics collapse, it is difficult to ascertain if the end organ dysfunction is reversible or permanent. In these scenarios, ECMO provides immediate hemodynamic stability and the opportunity to ascertain reversibility of end organ function and other patient-related factors prior to making decision on long term strategy.

Russo and colleagues used VA ECMO as a mechanical circulatory support device in an effort to use it as a bridge to decision in patients with CS. (Russo et al. 2010a) VA ECMO was implanted peripherally in 8 patients and centrally in 7 patients. Mean veno-arterial extracorporeal membrane oxygenation duration was 11.5 + 8.1 days (range, 1–30). Eighty percent of the patients were either weaned off ECMO or were bridged to a long term left ventricular assist device or transplantation. In their experience, VA ECMO allowed for the hemodynamics to be stabilized in patients with

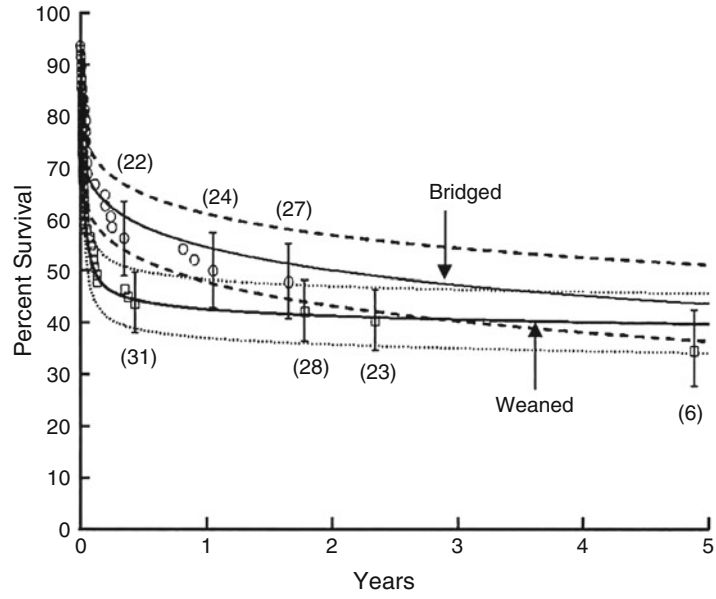

Fig. 13 Survival after discontinuing ECMO stratified according to the outcome of ECMO: bridged or weaned. (Reprinted from Smedira, N.G., Moazami, N., Golding, C.M., McCarthy, P.M., Apperson-Hansen, C., Blackstone, E.H. et al, **Clinical experience with 202 adults receiving extracorporeal membrane oxygenation for cardiac failure: survival at five years.** J Thorac Cardiovasc Surg. 2001;122:92–102 with permission from Elsevier)

cardiopulmonary collapse, allowing time to further evaluate patients for myocardial recovery or candidacy for a long-term device or cardiac transplantation.

In acute clinical situations, CS provides many challenges. Adequate assessment of patients before a definitive decision can be made in terms of the most appropriate form of mechanical support is difficult. In such circumstance, ECMO has the advantage of the ease of insertion and initiation without the need for this to be done in the operating room. It stabilizes hemodynamics and possibly promotes myocardial recovery. It also leaves the patient's chest untouched, making future left ventricular assist device (LVAD) implantation and cardiac transplantation more feasible. John et al focused on rapid stabilization of unstable patients in refractory CS with VA ECMO to allow time for the patients' organs to be perfused and for meaningful neurological recovery. (John et al. 2007) This led to a more comprehensive evaluation of their patients for implantable long term mechanical support. This strategy also allowed a thorough assessment of cost-benefit analysis of implanting an expensive long-term device in the patients. Though implantable LVADs have greatly improved survival in patients with CS, there are many patients who remain very high-risk candidates for LVAD implantation. (Frazier et al. 1994, 1995; Oz et al. 1995a, b, 1997) For such patients, rapid institution of ECMO in patients with hemodynamic instability provides an opportunity for risk stratification and prognostication for LVAD implantation, hence optimizing survival and utilization of resources. (Pagani et al. 1999)

ECMO as a Bridge to Ventricular Assist Device (VAD)

ECMO is an effective technique to provide mechanical circulatory support to critically ill patients and can provide time for a bridge to decision or for appropriate patients who are not able to be weaned off ECMO, patients can be bridged to an implantable long term VAD.

Though ECMO can provide emergent circulatory support, it does carry its risk of complications such a bleeding and stroke and the duration of support is limited. Hence, in patients who cannot be weaned off successfully, ECMO provides a bridge to bridge for patients in CS. Pagani et al reviewed data on 33 adult patients who were supported with ECMO for primary cardiac failure. (Pagani et al. 2001) The etiology of cardiac failure

was nonischemic in 30% (10 of 33 patients), ischemic in 58% (19 of 33 patients), and post-cardiotomy failure to wean in 12% (4 of 33 patients). Mean duration of ECMO support was 65 h (range 0 to 369 h; mean ± SD 94 ± 91). Overall, 36% of patients (12 of 33) survived to hospital discharge. Ten patients were bridged to an LVAD. Six patients underwent transplantation and were discharged, two were alive and well on LVAD support awaiting transplantation at home, and two patients died after LVAD implant. Patients surviving ECLS to LVAD implant, 1-year actuarial survival were 80 ± 12% (mean ± SE). In a cohort of high-risk patients undergoing LVAD implantation, survival after ECMO was not different as compared with patients undergoing initial LVAD implantation or LVAD implantation after extracorporeal VAD. In contrast McCarthy and colleagues showed that ECMO before LVAD implantation was a risk factor for death. (McCarthy et al. 1998; Pagani et al. 1999, 2000).

Schibilsky et al also showed an improvement in the INTERMACS level to INTERMACS III temporary cardiac support (TCS). (Schibilsky et al. 2017) Fifteen patients were studied in a retrospective manner at a single center who were treated with ECMO for CS prior to LVAD implantation. Improvement to INTERMACS III was successful in 93.3% of patients. End-organ function also recovered during the phase when the patients were supported with ECMO improved significantly. Survival rates were also found to be comparable to those seen in patients in INTERMACS III TO IV.

In summary, the strategy of initial ECMO implantation for CS offers immediate hemodynamic and circulatory support to patients who otherwise would not have been considered candidates for implantable LVAD. Initial insertion of ECMO stabilizes these patients and then later a decision or evaluation for an implantable LVAD can be taken in due course. Patients who do not survive ECMO would not likely have survived LVAD implantation. Thus, initial support with ECMO improves resource utilization and improves overall LVAD survival. (Pagani et al. 2001)

ECMO as a Bridge to Cardiac Transplantation

Heart transplantation remains the most effective long term therapy for patients with end-stage heart failure. (Fang et al. 2015) Mechanical circulatory support (MCS) devices including ECMO are increasingly used to support transplant eligible patients with end-stage heart failure. As has been established, ECMO provides emergent and immediate cardiorespiratory support in an acute clinical condition in patients with CS. ECMO can provide a bridge to decision, a bridge to bridge, or in patients who do not recover myocardial function and who are candidates, a bridge to cardiac transplantation. Apart from CS, ECMO finds utility in supporting patients with heart failure phenotypes where durable LVAD or inotropes may not be suitable. Patients with hypertrophic cardiomyopathy, arrhythmogenic ventricular dysplasia, restrictive cardiomyopathy, or those with recurrent or refractory rejection post-transplantation may require hemodynamic support most aptly provided by ECMO.

ECMO utilization has been recently effected by changes in the UNOS allocation system driven by persistent high waitlist mortality. (Prieto et al. 2014) (Zaroff et al. 2002; Johnson et al. 2010) In 1988, the United Network for Organ Sharing (UNOS)/the Organ Procurement and Transplantation Network (OPTN) introduced the two-tiered system for allocation of cardiac transplantation. This system took into account urgency, waiting time, geography, and blood type. In June of 1988, UNOS/OPTN created a three-tiered system for organ sharing. In 2016, the UNOS/OPTN Board of Directors approved a major update of the system used to allocate hearts for adult transplant candidates nationwide, creating six new medical urgency status levels to replace the three-tiered system that prioritized adult cardiac transplantation candidates. (Meyer et al. 2015) This policy change was in part driven by the increased use of VADs and ECMO in support of patients with heart failure. Status 1 includes patients on ECMO and non-dischargeable right ventricular and bi-ventricular assist devices and MCS with life-threatening ventricular arrhythmias.

Success of ECMO as bridge to transplant is dependent on multiple factors. Renal failure was a variable associated with poor outcomes and elevated creatinine was an independent marker for increased mortality. Fifty percentage of the patients were able to be weaned from ECMO, transitioned to LVAD, or underwent heart transplantation. Of the 13 patients who were transplanted, one-year survival was 51%. Patients supported with ECMO waiting for cardiac transplantation have a lower one-year overall survival rate (52.2%) compared with patients who were not supported with ECMO (75.5%), ($p < 0.01$) but cardiac transplantation has been associated with a lower risk of mortality (hazard ratio, 0.44; 95% confidence interval, 0.2–0.9). Barth and colleagues retrospectively evaluated 242 patients placed on femoral VA ECMO from 2004 to 2009. Ninety patients were able to be weaned from ECMO. Eight patients were transplanted with high-urgency prioritization. There were no deaths after transplant with a mean follow-up of 2 years, compared to 25% 1 year mortality in patients undergoing urgent transplant without an ECMO bridge during the same time period in France. Patients to be listed for high-urgency transplant needed to be unable to be weaned from ECMO after 4 days. Chung et al evaluated the risk factors for unsuccessful bridge to cardiac transplantation with ECMO. (Chung et al. 2010) Higher sequential organ failure assessment (SOFA) scores, older age (>50 years), pre-ECMO CPR, and ischemic cardiomyopathy were predictors of unsuccessful bridging. Their patients were evaluated earlier for LVAD and transplant. The evaluation was initiated if the patient failed to show improvement 2 days after ECMO initiation. Seventy patients were considered for bridging to LVAD or transplant. If not accepted for either of those two options, the outcomes were not favorable. Of those accepted for VAD or transplant, 44% of the patients were successfully bridged. Eight of sixteen patients bridged to VAD died. Of the remaining eight VAD patients, these were all transplanted and survived to leave the hospital.

In recent times, there has been an increase in patients undergoing cardiac transplant directly from ECMO. Figure 14 shows the trend of an increasing number of patients who are supported with ECMO before cardiac transplantation is performed. Zalawadiya and colleagues reported that though there has been an increase in the number of patients awaiting cardiac

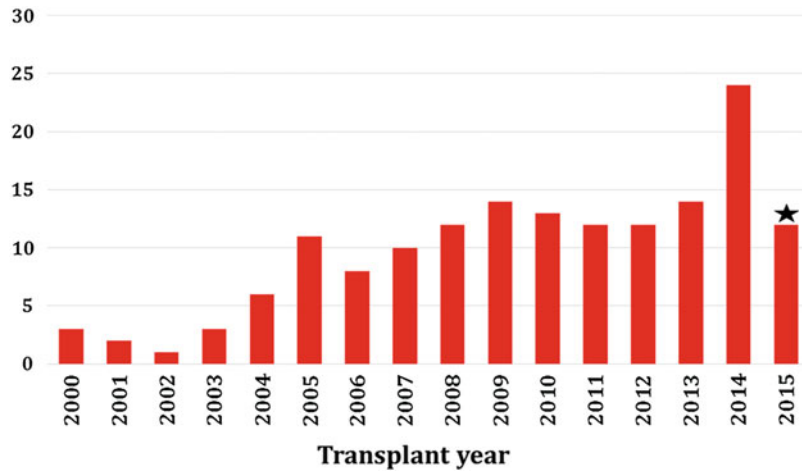

Fig. 14 Number of heart transplant recipients with extracorporeal membrane oxygenation support listed at the time of transplantation. ★The number of patients for the year 2015 is limited for transplants until June 2015 and follow-up through September 2015. (Reprinted from Zalawadiya S, Fudim M, Bhat G, Cotts W, Lindenfeld J, Extracorporeal membrane oxygenation support and post-heart transplant outcomes among United States adults. J Heart Lung Transplant 2017;36:77–81 with permission from Elsevier)

transplantation being supported with ECMO, mortality of patients remained high. (Zalawadiya et al. 2017) Sixty one percent of the patients died within 30 days with graft failure as the cause of death in 30.2% of the patients. Survival at 1 year was 57.8%. The patients who survived 30 days, long-term survival were acceptable, at 82.3% at 1 year and 76.2% at 5 years; multiorgan failure (27%) was the major cause of death among these patients. There was no difference in survival after cardiac transplantation after ECMO support and transplant era and patients with renal insufficiency and mechanical ventilation had a significantly increased risk of post-transplant mortality (Fig. 15).

Primary graft dysfunction (PGD) and cardiogenic shock is the main etiology of mortality after cardiac transplantation. PGD can complicate cardiac transplantation in 2.3 to 28% of cases. (Ibrahim et al. 2007; Russo et al. 2010b) PGD can

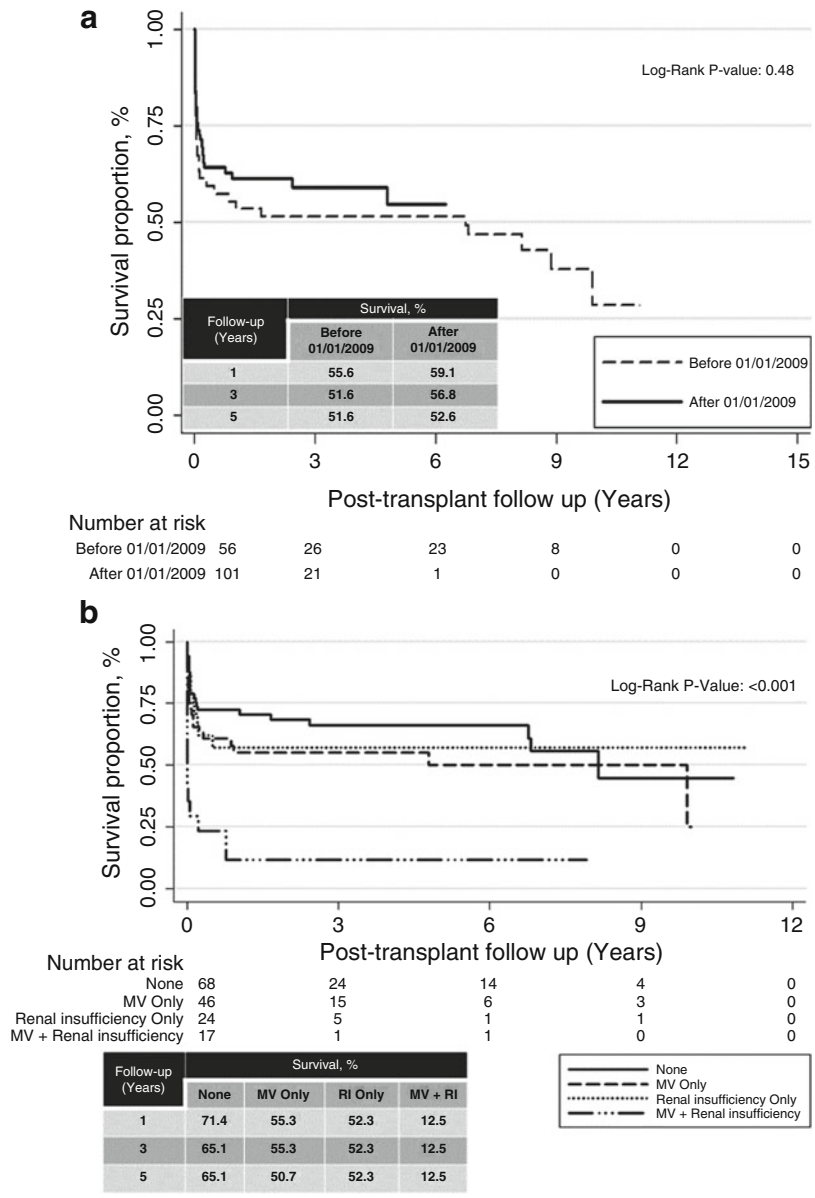

Fig. 15 Post-transplant survival among adults supported by extracorporeal membrane oxygenation (ECMO). (A) Survival by transplant era. (B) Post-transplant survival across categories of renal insufficiency (RI), defined as estimated glomerular filtration rate < 45 ml/min/1.73 m^2 or on dialysis, and mechanical ventilation (MV). Those with both MV and RI had significantly poor survival compared with other categories. LV, left ventricle; MCS, mechanical circulatory support. (Reprinted from Zalawadiya S, Fudim M, Bhat G, Cotts W, Lindenfeld J, Extracorporeal membrane oxygenation support and post-heart transplant outcomes among United States adults. J Heart Lung Transplant 2017;36:77–81 with permission from Elsevier)

manifest as failure to wean from cardiopulmonary bypass after transplantation and severe hemodynamic instability in the immediate postoperative period with severe cardiac dysfunction. ECMO support was reported by Lima and colleagues in eleven of seventy-one patients (15.5%) of patients who received orthotopic cardiac transplantation. (Lima et al. 2015) The average duration of support with ECMO was 76 ± 47.4 h (range 32 to 144 h). Nine (81.8%) patients were successfully weaned and two patients did not survive to hospital discharge. Other centers have shown successful support with ECMO for PGD. ECMO support was also shown to be a viable option for adult heart transplant recipients with severe rejection and refractory cardiogenic shock. (D'Alessandro et al. 2010; Kittleson et al. 2011; Listijono et al. 2011) Marasco et al. reported an 87% success rate of weaning from ECMO and a 74.3% survival rate of discharge from the hospital in patients who developed PGD and cardiogenic shock after orthotopic, heterotopic and heart lung transplantation requiring ECMO support. (Marasco et al. 2010) There were no significant differences in wean rates or complications between central and peripheral ECMO. Comparison of survival in the ECMO patients to the non-PGD patients showed a significantly worse survival in the ECMO group ($p = 0.007$). When those patients who died in the first 30 days were excluded, there was no difference in overall survival between groups ($p = 0.73$).

Complications of ECMO

Despite the utility of ECMO in stabilizing patients who are hemodynamically unstable and in clinical conditions where ECMO can provide a valuable bridge to decision, long term ventricular support and transplant, mortality on ECMO remains significant. (Aubron et al. 2013) Complications and survival after ECMO depend on the disease process and indications for which ECMO is instituted. Extracorporeal cardiopulmonary resuscitation (ECPR) carries the worst prognosis. (Makdisi and Wang 2015) Complications on ECMO are frequent. (Zangrillo et al. 2013) Major complications can be categorized as related to (1) ECMO insertion, (2) anticoagulation, and (3) organ dysfunction.

Initiation of ECMO requires proper placement of ECMO cannulae. Cannula insertion-related complications are a result of vessel injury and distal limb ischemia. (Rupprecht et al. 2015) Femoral vessel injuries are more common with VA ECMO than VV ECMO. (Bisdas et al. 2011) The incidence of lower extremity ischemia has been reported to be 16.9% (12.5% to 22.6%); fasciotomy or compartment syndrome, 10.3% (7.3% to 14.5%); and lower extremity amputation, 4.7% (2.3% to 9.3%) in a meta-analysis of patients undergoing ECMO. (Cheng et al. 2014) Vascular complications on ECMO have been found to be an independent risk factor for mortality. (Tanaka et al. 2016) Ultrasound guided femoral vessel access can reduce the incidence of serious femoral vessel injury during percutaneous insertion of cannulae for ECMO. (Benassi et al. 2014) Vascular calcifications and previous vascular surgery can make peripheral percutaneous cannulation difficult or impossible. Distal limb perfusion can be compromised with peripheral cannulation leading to limb ischemia. The authors have, in their own institution, reverted to the use of smaller arterial cannulae (15–17 Fr) to avoid completely obstructing the distal femoral vessel. Smaller cannulae have been shown to provide comparable hemodynamic support. (Takayama et al. 2015) Finally, distal limb perfusion with a small distal cannula can prevent limb ischemia. (Avalli et al. 2016)

Bleeding is a common complication occurring in 30–60% of patients undergoing ECMO and is independently related to in-hospital mortality. (Brogan et al. 2009)(Aubron et al. 2013) Bleeding is related to heparin effect or overdose, coagulopathy, thrombocytopenia, platelet dysfunction, acquired von Willebrand syndrome, and hyperfibrinolysis. (Avalli et al. 2016)

The most common sources of bleeding were found to be ECMO cannula (37%), hemothorax or cardiac tamponade (17%), ear–nose and throat (16%), and intracranial hemorrhage (2.2%). Higher activated partial thromboplastin time (aPTT), higher APACHE III score, and postsurgical ECMO have a significant association with the risk of bleeding. Kasirajan and colleagues found a high

correlation between thrombocytopenia and the risk of intracranial hemorrhage. (Kasirajan et al. 1999) Acquired Von-Willebrand syndrome has been reported in patients on ECMO and can increase bleeding tendencies in these patients. (Heilmann et al. 2012) Careful monitoring of coagulopathy with a laboratory protocol using antifactor Xa assays, thromboelastography, and antithrombin measurements has been shown to decrease blood transfusion requirements and bleeding complications. (Northrop et al. 2015)

Renal failure is a common complication in patients on ECMO. The incidence of acute kidney injury (AKI) in patients on ECMO for respiratory failure has been shown to be around 78%and 81% for patients on ECMO for postcardiotomy cardiac failure. Patients who develop AKI on ECMO also have higher mortality rates (78% in patients with AKI versus 20% in non-AKI patients).

Other complications that can affect patients on ECMO are bacterial pneumonia (33%), oxygenator dysfunction requiring replacement (29%), sepsis (26%), hemolysis (18%), liver dysfunction (16%), venous thrombosis (10%), central nervous system complications (8%), gastrointestinal bleeding (7%), aspiration pneumonia (5%), and disseminated intravascular coagulation (5%). (Zangrillo et al. 2013)

Ethical Considerations in ECMO

As increasing number of patients get supported on ECMO towards bridge to transplant or other outcomes, it raises ethical challenges which are unique and need to be addressed. Key issues are (i) engagement and education of patient and family members in a timely fashion, (ii) buy in from bedside care givers and addressing the needs and expectations of healthcare teams participating in the care of the patient, and (iii) perception about ECMO in general and resource utilization for public health officials. Hospitals need to formulate specific policies and procedures for situations such as futility and withdrawal in line with local and state laws. Early counseling and engagement of patient and family members with palliative care teams should be considered.

Conclusion

ECMO is beneficial when utilized early in cardiogenic shock and is combined with early crossover to another form of mechanical support or transplant. With the miniaturization of the circuits and with technological advances in oxygenators, ECMO has seen an increase in utilization. Indications for extracorporeal life support have increased and patients can now be stabilized with the help of ECMO with the intent of recovery, bridge to decision and bridge to organ transplantation. ECMO has also created an ecosystem where satellite hospitals that do not have capabilities of advanced circulatory support can utilize ECMO as a stabilizing modality to then transfer patients to tertiary care hospitals where more advanced techniques can be offered.

Though ECMO provides support for patients with cardiac dysfunction who are awaiting cardiac transplantation, no survival benefit is shown to exist with support with ECMO. However, waitlist mortality for cardiac transplantation also remains high. The optimal modality and protocols to support patients with nonsurvivable acute decompensation of heart failure while waiting cardiac transplantation remain in flux. Despite limitations, ECMO, because of the ease of implantation, remains at the forefront of ECLS for cardiogenic shock awaiting cardiac transplant and primary graft dysfunction.

Cross-Reference

- ▶ Cardiac Allograft Rejection
- ▶ Current Listing System
- ▶ Recent Changes and Future Challenges in the Heart Allocation System

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Ventricular Assist Device as Bridge-to-Transplant

6

Vidang Nguyen and Song Li

Contents

Abstract

Due to the limited donor supply and long wait times for heart transplantation, the use of a ventricular assist device as a bridge to heart transplantation is increasing. With the development of the continuous flow device, there has been improved mechanical durability with a resultant decrease in waitlist mortality for patient who are waiting for heart transplantation. When selecting patients for potential assist device therapy, it is important to consider heart failure severity for timing of device implantation, right ventricular function, and ability to tolerate anticoagulation.

Keywords

Bridge-to-transplantation · heart transplantation · left ventricular assist device

Introduction

Heart transplantation has long been considered the ultimate long-term therapy for refractory (American College of Cardiology/American Heart Association (ACC/AHA)) stage D heart

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failure (HF). However, since transplant wait time can be long and unpredictable, ventricular assist devices (VADs) have been widely used to help appropriate patients stay alive and active on the transplant list until a suitable donor heart can be identified. This strategy has commonly been termed bridge-to-transplant (BTT). VADs can also be implanted in patients with temporary and potentially reversible contraindications to transplant with intention of eventual listing, a strategy termed bridge-to-candidacy (BTC).

Despite a slight increase in the number of heart transplants in recent years (2015 to 2017), the number of suitable donor hearts remains inadequate to meet the demand. New active listings for heart transplant have increased 49% between 2006 and 2017 and the number of candidates on the waiting list has increased by 119% (Colvin et al. 2019). The median waiting time for heart transplant, as a result, has nearly doubled from 4.0 months in 2006–2007 to 7.9 months in 2016–2017. With lengthening transplant wait time, VAD implantation as BTT has become increasingly necessary. The proportion of patients on the transplant waiting list with a VAD has increased from 9.1% in 2006 to 32.6% in 2017, and among those transplanted in 2017, 49.4% had a VAD prior to transplant (Colvin et al. 2019).

The Ventricular Assist Device

The VAD field has progressed tremendously in recent years so that VAD therapy on its own significantly improves end stage HF patients' survival and quality of life. In addition, patients on the transplant waiting list with VADs are less likely to be delisted for being too ill compared to those without durable devices (Cogswell et al. 2018). The implantation of VADs significantly increased after the commercialization of the continuous flow (CF) HeartMate II (Thoratec Corp, Pleasanton, CA) VAD with much improved mechanical durability compared to earlier pulsatile devices. With the third generation centrifugal flow VADs, the HeartWare HVAD (Medtronic, Framingham, MA) and the HeartMate 3 (Abbott, Chicago, IL), mechanical durability and VAD thrombosis risk have further improved (Rogers et al. 2017; Mehra et al. 2019). According to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), the 1-year survival rate for CF-VAD is now 81% and patients' perception of health, as measured by EQ. 5D visual analog scale, on average improves from 35 out of 100 before VAD to 71 1 year after VAD implantation (Kirklin et al. 2017). Furthermore, patient satisfaction rate with VAD is high and steady at around 81% from 3 months to 2 years after VAD implantation (Kirklin et al. 2017).

Outcomes of VAD as BTT

The strategy of VAD as BTT has become more successful with iterative improvement in VAD technology and medical management. Waitlist mortality for patients with VADs have declined significantly from 47.8 to 11.8 deaths per 100 waitlist-years, nearly identical to patients without VADs (Colvin et al. 2019). Among BTT VAD patients in the INTERMACS registry from 2015 to 2016, 88% were alive and 34% were transplanted at 1 year (Kirklin et al. 2017). A recent clinical trial of BTT/BTC patients implanted with the HVAD showed similar results with a 20% transplant rate at 6 months and an impressively high 87% Kaplan-Meier survival rate at 2 years with very low rates of complications such as stroke (Fig. 1) (McGee et al. 2019; Khush et al. 2018). These results show that with appropriate patient selection and post implantation care, VAD as BTT can achieve very favorable outcomes even with extended transplant wait time. However, with implantation of VAD as BTT, lower waitlist mortality has occurred at the expense of reducing the likelihood of transplantation. Therefore, the circumstances of the individual patients and regional elements must be taken

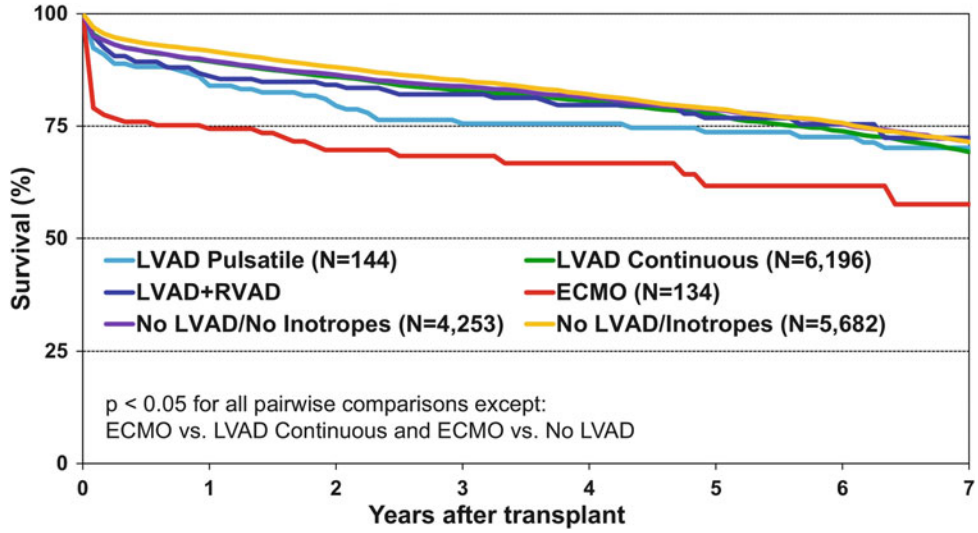

Fig. 1 Kaplan-Meier curve showing posttransplant survival by type of pretransplant mechanical circulatory support. Data includes adult heart transplantation between January 2009 and June 2016. *ECMO* extracorporeal membrane oxygenation, *LVAD* left ventricular assist device, *RVAD* right ventricular assist device. Previously published by Khush et al. (2018). (Reprinted from The Journal of Heart and LUng Transplantation, Vol 37/Issue 10, Khush et al., The International Thoracic Organ Transplant Registry of the International Society for Heart and Lung Transplantation: Thirty-fifth Adult Heart Transplantation Report—2018; Focus Theme: Multiorgan Transplantation, Pages 1155–1168., Copyright (2018), with permission from Elsevier)

into consideration when deciding to implant a patient with VAD (Truby et al. 2018; Nguyen et al. 2016).

Predictors of Outcomes after BTT VAD

Few studies have examined the predictors of short- and long-term outcomes after VAD implantation in the current continuous flow device era. A review of patients implanted with HeartMate II and HVAD as BTT showed that the only independent predictors for 90-day mortality were elevated central venous pressure $>$ 18 mmHg and age $>$ 45 years old (Sabashnikov et al. 2014). Another retrospective analysis of both BTT and destination therapy (DT) VAD patients showed that 1-year survival could be predicted using a model including age, creatinine, total bilirubin, body mass index, and severity of RV dysfunction and aortic insufficiency on echocardiogram (Birati et al. 2018). However, when applied to an external validation cohort, the model's discriminative power was only modest.

Management of Patients on BTT VAD

While careful patient selection and optimizing clinical status prior to VAD implantation might improve post-VAD survival, there is a rapidly expanding evidence basis that meticulous medical management of VAD patients after implantation can improve outcomes. For example, stroke is the number one cause of death in VAD patients and frequently a barrier to future heart transplantation (Kirklin et al. 2017). The ENDURANCE Supplemental trial showed that a blood pressure management protocol targeting a mean arterial pressure (MAP) of less than 85 mmHg significantly reduced stroke, especially hemorrhagic stroke, rates (Milano et al. 2018). It has also been shown in CF-VAD patients that Doppler opening pressure is a highly accurate estimate of MAP and should be used as the default noninvasive BP

measurement method (Li et al. 2019). In addition, in the course of the HeartWare ADVANCE BTT + CAP trial, a protocol change requiring high-dose aspirin 325 mg daily and an INR goal range of 2.0–3.0 reduced ischemic stroke rate without increasing hemorrhagic stroke rate (Slaughter et al. 2013). Therefore, discovering and implementing beneficial medical management strategies post VAD implantation is crucial to improving survival to transplant rate in BTT VAD patients.

Patient Selection

Patient selection is key to a successful transplant outcome after BTT VAD implantation. VADs are most commonly used in men and those with blood group O due to a longer wait time for heart transplantation (Ciarka et al. 2017). On the flipside, CF-VADs remain clinically underutilized in women, who experience a higher waitlist mortality and lower transplant rate (DeFilippis et al. 2019). Additionally, unique anatomies and hemodynamics in congenital heart disease patients have limited the benefits of VAD as BTT with significantly increased waitlist mortality in those with a VAD (Krishnamurthy et al. 2016; Blume et al. 2018; Gelow et al. 2013). The key to successful VAD utilization in this unique patient population is early implementation and thoughtful patient selection (Serfas et al. 2018; VanderPluym et al. 2018). In addition to meeting common requirements for heart transplant listing, below we review the unique considerations for VAD implantation as BTT.

HF Disease Severity

Traditionally, end-stage HF patients on the heart transplant list who are "too sick" to continue waiting for an available donor heart are considered for VAD implantation as BTT. These patients are generally of INTERMACS profile 1–3 at time of VAD implantation (Kirklin et al. 2017). However, several factors favor BTT VAD decision in patients with less severe disease. First, significant advancement in VAD design and VAD management has continually improved patient survival to the point that short-and mid-term survival post VAD is nearly equal to post heart transplantation (Mehra et al. 2019; McGee et al. 2019). Second, it has been shown that heart transplant outcomes in patients bridged with VAD are equivalent to patients not bridged with VAD, possibly due to improved end-organ function and functional status, and longer duration of support does not adversely affect transplant outcome (John et al. 2010; Seco et al. 2017; Williams et al. 2011). On the other hand, INTERMACS registry data clearly show that patients who are sicker at the time of VAD implantation have worse outcomes. Patients with INTERMACS profile 1, 2/3, and 4–7 have 1-year survival of 74%, 82%, and 84%, respectively (Kirklin et al. 2017). Furthermore, post-transplant outcomes in VAD patients are superior when compared to other forms of mechanical support such as extracorporeal membrane oxygenation (ECMO). In fact, VAD remains an effective bridging strategy when implemented after ECMO with a similar survival to those who were implanted with VAD without ECMO (Pagani et al. 2000). From 2008 to 2016, there has been a steady decrease in the proportion of VAD implantation in INTERMACS profile 2 patients (41–34%) and a steady increase in profile 3 patients (25–38%) (Kirklin et al. 2017). Whether it would be beneficial to consider BTT VAD even earlier in INTERMACS profile 4 (resting symptoms) patients remains to be seen. Given the above considerations and the lengthening transplant wait time, it is not surprising that we have seen a trend towards a greater proportion of patients transplanted with VAD bridging and a shift towards implanting VAD in less sick patients.

Another key issue of utilizing the LVAD as a bridge to transplantation is to get to the heart transplant prior to the onset of device-related complications, such as infection, bleeding, or thromboembolic events as described (Steffen et al. 2017; Wever-Pinzon et al. 2013; Dardas 2018). With the newly implemented heart allocation system in October of 2018, patients with durable LVADs are experiencing longer wait times,

which therefore increases the risk of developing a complication. The longer the wait time for transplantation, the more likely the patient is to be upgraded to a higher listing status due to device complication (Uriel et al. 2013). Wait times for LVAD patients vary significantly depending on the center transplant rate, regional donor availability, patient blood type, and body size, and thus, it is important to take these factors into consideration when deciding to pursue LVAD implantation as a bridge to transplant (Nguyen et al. 2016). Although device-related complications significantly increase waitlist mortality, there is no impact of posttransplant survival (Chauhan et al. 2017a; Healy et al. 2013).

Right Ventricular Function

It is important to carefully evaluate the right ventricular function when considering a patient for left ventricular assist device (LVAD). LVADs do not support the right heart circulation and in some cases may actually precipitate right ventricular failure (RVF) by (Colvin et al. 2019) altering the contractility of the intraventricular septum which contributes ~30% of RV stroke volume, (Cogswell et al. 2018) increasing venous return to the right ventricle, and (Rogers et al. 2017) arterial-ventricular uncoupling between the RV and pulmonary vasculature. Depending on its definition, RVF complicates 5–35% of LVAD implantations and may be more frequent in nonischemic cardiomyopathy and in patients with longer history of HF (Kormos et al. 2010; Bellavia et al. 2017). Compared to LVAD patients without RVF, those with RVF have significantly higher mortality, longer length of stay, higher risk of bleeding, diuretic resistance, renal failure, and worsening nutritional status in part due to congestive hepatopathy and nephropathy (Patlolla et al. 2013; Lampert and Teuteberg 2015). The evidence that use of pulmonary vasodilators in RV failure is beneficial remains sparse and few therapies have been found to be effective in RVF (Sparrow et al. 2018; Kalogeropoulos et al. 2011). In the consideration for BTT therapy, it is important to note that RVF is one of the greatest risk factors for mortality after transplant. Patient who required a right ventricular assist device prior to transplant have an increased posttransplant mortality (Taghavi et al. 2016). Even in the absence of RV dysfunction at the time of implantation, late RV failure development still correlates with poor posttransplant outcomes (Takeda et al. 2015).

To estimate potential candidates' risk of developing RVF post LVAD implantation, a large number of studies have attempted to identify clinical predictors and develop risk models. These predictors and risk models are summarized in two recent review articles and a meta-analysis (Bellavia et al. 2017; Lampert and Teuteberg 2015; Turner 2019). However, the clinical application of these risk models has been limited for several reasons. First, many studies are small single-center cohorts with different definitions of RVH. Second, most early studies were done in patients with pulsatile LVADs that are no longer applicable to the current era of continuous flow VADs. Third, the predictive power of the published models remains very modest. Six RVF risk models were systemically evaluated in an external validation cohort of CF LVADs using two representative sets of RVF definitions and the models' c-statistics ranged from 0.50 to 0.62, barely better than random guessing (Kalogeropoulos et al. 2015). Routine echocardiographic assessment is important for ongoing surveillance of the RV function during the time of LVAD support, including strain and RV to left ventricular diameter ratio (Grant et al. 2012; Vivo et al. 2013). However, a recent meta-analysis has concluded that, at present, while a number of clinical, hemodynamic, and echocardiographic variables are statistically associated with RVF after LVAD, no single variable is able to predict RVF with clinically acceptable accuracy (Bellavia et al. 2017). Thus, patient selection to avoid RVF post LVAD continues to be challenging.

Anticoagulation

Early LVAD models were designed to mimic the human heart with pulsatile blood flow, but due to a high rate of mechanical failures, newer VADs provide continuous flow with fewer possible

points of failure and greater durability. However, the continuous flow comes at a cost of the ongoing loss of von Willebrand Factor (vWF), which is thought to be due to excessive cleavage of the large vWF multimers by ADAMTS-13 in the CF-VAD circulation (Nascimbene et al. 2016; Meyer et al. 2010). Elevated tumor necrosis factor-α levels in CF-VAD patients have also been shown to induce pericyte apoptosis, tissue factor expression, and vascular instability (Tabit et al. 2018). These patients are therefore prone to hemostatic complications, most notably gastrointestinal bleeding from arteriovenous malformations (Kirklin et al. 2017). Contributing factors to high incident of bleeding in LVAD patients include concurrent hemolysis, abnormal platelet activation, and decreased pulsatility (Shah et al. 2017). Therapeutic anticoagulation can exacerbate the coagulopathy caused by VADs but is necessary to prevent VAD thrombosis and thromboembolic complications. Other pharmacotherapies are being used in attempt to minimize risk of bleeding, however the supporting data remains sparse (Sieg et al. 2017). It is therefore important to ensure that potential candidates of VAD therapy are capable of adhering to warfarin treatment and maintaining International Normalized Ratio in the therapeutic range. VAD patients who develop a thromboembolic event have a significantly elevated mortality, especially when managed conservatively without pump exchange (Wever-Pinzon et al. 2016).

Other Factors for Consideration

VADs can increase the risk of allo-sensitization, which occurs in more than one fifth of VAD patients who are waiting for heart transplantation (Grosman-Rimon et al. 2019). This observation may account for the finding that duration of CF-VAD therapy correlates with the incidence of acute rejection prior to discharge (Chauhan et al. 2017b). Although allo-sensitization raises the risk of both cellular- and antibody-mediated rejection after transplant, several studies suggest that clinical outcomes are not affected (Ko et al. 2016; Shankar et al. 2013; Joyce et al. 2005; Fraser et al. 2019). In severe cases of rejection, plasmapheresis and intravenous immunoglobulin can be considered (Massad et al. 1997; Dowling et al. 1998). VAD therapy as BTT may be indicated prior to heart transplant in candidates with prohibitive pulmonary hypertension due to long-standing left heart failure (Atluri et al. 2013; Mikus et al. 2011). Left ventricular unloading can potentially reverse some degree of fixed pulmonary hypertension with comparable post-transplant outcomes as those without pulmonary hypertension; however, only third of patients with elevated pulmonary vascular resistance (PVR) actually normalize their PVR prior to transplant (Al-Kindi et al. 2017; Moayedifar et al. 2018). RVF as a result of pulmonary hypertension has a significantly elevated posttransplant mortality (Schumer et al. 2018).

Conclusion

The use of VADs as BTT has increased over time since its introduction over 15 years ago with favorable outcomes and a concurrent decrease in waitlist mortality. It should be considered for patients who are expected to have a prolonged waiting time for heart transplantation and in candidates who are becoming too sick to continue waiting. However, sicker patients tend to do worse after VAD implantation so potential candidates should be considered prior to the decline of end-organ dysfunction. RVF is one of the leading causes of mortality both after LVAD implantation and after heart transplantation, so the right heart function should be thoroughly assessed when selecting patients for LVAD as BTT. Potential downsides to the use of VADs include the requirement for therapeutic anticoagulation and the risk of strokes, gastrointestinal bleeding, and infections.

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Part IV

Organ Allocation

Current Listing System

7

Deirdre M. Mooney and Marwa Sabe

Contents

Abstract

The United Network of Organ Sharing (UNOS) is the Organ Procurement and Transplantation Network (OPTN) that oversees heart transplantation in the United States. In 2016, a 10-year update to the 2006 International Listing Criteria for Heart Transplantation was published by the International Society for Heart and Lung Transplantation (ISHLT). Criteria were revised to reflect advances in the management of advanced heart failure patients, incorporate evidence from interval landmark trials, and specifically address patients with congenital heart disease, restrictive or infiltrative cardiomyopathy, and chronic infectious disease. Notable updates include frailty assessment, use of mechanical circulatory support as a bridge for candidacy, prioritization of highly sensitized patients, retransplantation for severe chronic allograft vasculopathy, removal of allocation algorithms that allowed for prioritization of higher-status

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patients within larger geographic areas, lower suggested cutoff values for minimal estimated glomerular filtration rate, assessment of the adequacy of social support in potential transplant candidates, and the role of heart failure prognosis scores in ambulatory patients. Three sections provide guidance on patients that may be less responsive to traditional pharmacologic and device-based therapies and/or have unique challenges with respect to support prior to transplant and posttransplant management. The OPTN policy on allocation of donor hearts was most recently revised in 2018.

Keywords

Listing criteria for heart transplantation · Heart transplant candidate · International Society for Heart and Lung Transplantation (ISHLT) · Advanced heart failure · United Network for Organ Sharing (UNOS) · Organ Procurement and Transplantation Network (OPTN) · Adult heart status · Mechanical circulatory support

List of Abbreviations

AHS	Adult heart status
CMS	Centers for Medicare and Medicaid Services
DSA	Donor-specific area
OPO	Organ procurement organization

Introduction

When a patient develops irreversible dysfunction of an organ, transplantation may be considered. The United Network for Organ Sharing (UNOS) is responsible for managing the national transplant waiting list for the United States and Puerto Rico, the matching of donors to recipients, and maintaining the database that tracks all organ transplant data (History of UNOS 2017). Patients with end-stage heart failure considering a heart transplant need to be evaluated and approved by an accredited cardiac transplant hospital in order to be formally listed with UNOS for potential transplantation. Each adult heart transplant candidate is assigned a status that reflects the candidate's medical urgency for transplant based on estimated wait-list mortality. Organs are allocated according to wait-list status utilizing a geographic algorithm which was last updated in 2018.

At the 24th Bethesda Conference in 1993, task forces created documents which provided directions toward maximizing the life-saving potential of heart transplantations and provided guidelines for heart transplant candidacy (Mudge et al. 1993). The first International Society of Heart and Lung Transplantation (ISHLT) guidelines were published in 2006 and were subsequently followed by three focused updates addressing evolving areas of importance such as congenital heart disease, restrictive cardiomyopathy, and infectious diseases (Mehra et al. 2006). In 2016, the prior ISHLT guidelines and focused updates were reviewed and revised to include evidence from interval landmark trials and other advances in the management of advanced heart failure patients, resulting in a 10-year update of the ISHLT Listing Criteria for Heart Transplantation (Mehra et al. 2016). Many of the 2006 guidelines recommendations were continued in 2016 without significant change. Notable updates included sections on frailty scores, mechanical circulatory support (MCS) as a bridge for candidacy, highly sensitized patients, severe chronic allograft vasculopathy, the removal of allocation algorithms that allowed for prioritization of higher-status patients within larger geographic areas, a lower suggested cutoff for prohibitive estimated glomerular filtration rate, clarifications on the impact of cardiac resynchronization devices on cardiopulmonary stress testing, assessment of the adequacy of social support in potential transplant candidates, and the role of heart failure prognosis scores in ambulatory patients.

Organ Procurement and Transplantation Network

In 1984, the US Congress passed the National Organ Transplant Act which called for a national network to coordinate the allocation of organs for transplant and collect clinical data about organ donors, transplant candidates, and transplant recipients (United States. Congress. House.

Committee on Energy and Commerce. Subcommittee on Health and the Environment. 1984). The United Network for Organ Sharing (UNOS) was incorporated as a private, nonprofit organization in March 1984 and was awarded the initial contract in 1986 to manage the national organ transplant system for the United States. In 2000, the United States Department of Health and Human Services (US DHHS) implemented a final rule establishing a regulatory framework for the structure and operations of the Organ Procurement and Transplantation Network (OPTN) (About the OPTN 2017). UNOS serves as the OPTN under contract with the Health Resources and Services Administration of the US DHHS.

Overview of the 2016 International Society for Heart Lung Transplantation Listing Criteria for Heart Transplantation

The 2016 ISHLT listing criteria guidance document is broken into five major sections (Mehra et al. 2016). The first section discusses general considerations of listing patients for heart transplantation and encompasses a formal review and revision of the 2006 guidelines. These revisions are summarized in Table 1. The subsequent three sections focus on the unique aspects of managing patients with restrictive and infiltrative cardiomyopathies, chronic infectious disease, and congenital heart disease. The final section is a brief commentary on marijuana and heart transplantation.

Breakdown of the 2016 ISHLT Listing Criteria

Cardiopulmonary exercise testing (CPET) has been used for decades to guide prognosis and heart transplant listing criteria in ambulatory heart failure patients; however it is continually emphasized that CPET variables should not be the sole criterion for heart transplant listing. Peak VO_2 should only be assessed on a maximal CPET, which is defined as one with a respiratory exchange ratio (RER) >1.05 and achievement of an anaerobic threshold on optimal tolerated pharmacologic therapy. The cutoff for peak VO_2 to guide listing in patients on a beta-blocker should be ≤12 ml/kg/min or ≤14 ml/kg/min in patients intolerant of a beta-blocker (Mancini et al. 1991; Peterson et al. 2003). As an alternative option for women and younger adults (<50 years), the percent of predicted (≤50%) peak Vo_2 can be used. In obese patients, those with a body mass index >30 kg/m^2 and a lean body mass-adjusted peak VO_2 <19 ml/kg/min can be considered. For patients who are unable to complete a maximal CPET, use of ventilation equivalent of carbon dioxide (VE/VCO2) slope of >35 can be considered a determinant for listing based on evidence that the lowest VE/VCO2 ratio is additive to the prognostic power of conventional CPET variables (Myers et al. 2009; Arena et al. 2004).

Heart failure prognosis scores in conjunction with CPET should be performed to determine prognosis and guide listing in ambulatory patients, but also should not be the sole criterion for listing a patient. The recommended prognostic models include the Seattle Heart Failure Model and Heart Failure Survival Score.

Right heart catheterization (RHC) is recommended on all adult candidates prior to listing for cardiac transplantation and should be periodically repeated until transplantation. The specific recommendation to repeat RHC every 3–6 months was removed as it was felt that programs should individualize the timing based on the individual. More frequent RHC is recommended in patients with reversible pulmonary hypertension or worsening heart failure symptoms, and less frequent RHC may be considered in patients with durable left ventricular assist devices (LVADs) as a bridge to transplant (Houston et al. 2015). To clarify reversibility of elevated pulmonary pressures, an acute vasodilator challenge using agents such as intravenous nitroprusside, inhaled nitric oxide, or intravenous milrinone is recommended for patients with elevated pulmonary artery systolic pressures (≥50 mmHg) and either elevated transpulmonary gradient (≥15) or pulmonary vascular resistance (>3 Wood units) in the setting of normal systolic

Table 1 Review of changes to ISHLT heart transplant listing guidelines

Section	Change	2016 guidelines	2006 guidelines
1.1. Cardiopulmonary stress testing to guide transplant listing	New: Clarification provided that the use of CRT therapy should not impact peak VO_2 interpretation for listing	The presence of a CRT device does not alter the current peak VO_2 cutoff recommendations (Class I, LOE: B)	n/a
1.2. Use of heart failure prognosis scores	Update: Change in recommendation to routinely incorporate HF prognosis scores to determine prognosis and guide listing in ambulatory patients rather than use in circumstances of ambiguity	Heart failure prognosis scores should be performed along with cardiopulmonary exercise test to determine prognosis and guide listing for transplantation for ambulatory patients. An estimated 1-year survival as calculated by the Seattle Heart Failure Model (SHFM) of 80% or a Heart Failure Survival Score (HFSS) in the high-/medium-risk range should be considered as reasonable cut points for listing (Class IIb, LOE: C)	In circumstances of ambiguity (e.g., peak VO_2 $\leq$12 and $\leq$14 ml/kg/ml) a Heart Failure Survival Score (HFSS) may be considered, and it may add discriminatory value to determining prognosis and guide listing for transplantation for ambulatory patients (Class IIb, LOE: C)
1.2. Use of heart failure prognosis scores	New: Statement added that listing patients solely due to poor prognosis score(s) is not appropriate	Listing patients solely on the criteria of heart failure survival prognostic scores should not be performed (Class III, LOE: C)	n/a
1.3. Role of diagnostic right-heart catheterization	Update: Clarification that RHC should be repeated periodically in adults, but no longer specifies a timeline for this reassessment	Right-heart catheterization (RHC) should be performed on all adult candidates in preparation for listing for cardiac transplantation and periodically until transplantation (Class 1, LOE: C)	Right-heart catheterization (RHC) should be performed on all candidates in preparation for listing for cardiac transplantation and annually until transplantation (Class 1, LOE: C)
1.3. Role of diagnostic right-heart catheterization	New: Clarification that routine surveillance RHC is not appropriate in children	Periodic RHC is not advocated for routine surveillance in children (Class III, LOE: C)	n/a
1.3. Role of diagnostic right-heart catheterization	Update: Recommendation regarding patients with irreversible pulmonary hypertension, strengthened and updated, stating that for those who become supported by an LVAD, the lack of reversibility should be reconfirmed 3–6 months post-implantation of the LVAD. Recommendation strengthen increased from IIb to IIA	If medical therapy fails to achieve acceptable hemodynamics and if the left ventricle cannot be effectively unloaded with mechanical adjuncts, including an intra-aortic balloon pump (IABP) and/or left ventricular assist device (LVAD), it is reasonable to conclude that the pulmonary hypertension is irreversible. After LVAD, reevaluation of hemodynamics should be done after 3–6 months to ascertain reversibility of pulmonary hypertension (Class IIA, LOE: C)	If medical therapy fails to achieve acceptable hemodynamics, and if the left ventricle cannot be effectively unloaded with mechanical adjuncts, including an intra-aortic balloon pump (IABP) and/or left ventricular assist device (LVAD), it is reasonable to conclude that the pulmonary hypertension is irreversible (Class IIb, LOE: C)

(continued)

Table 1 (continued)

Section	Change	2016 guidelines	2006 guidelines
1.4.1. Age, obesity, and cancer	Update: Removal of reference to "alternate-type program" for older candidates	Carefully selected patients >70 years of age may be considered for cardiac transplantation (Class IIb, LOE: C)	Carefully selected patients >70 years of age may be considered for cardiac transplantation. For centers considering these patients, the use of an alternate-type program (i.e., use of older donors) may be pursued (Class IIb, LOE: C)
1.4.1. Age, obesity, and cancer	Update: The recommended upper limit of acceptable BMI for listing patients increased from 30 to 35 kg/m^2, as well as removal of percent ideal body weight guidelines	Pretransplant body mass index (BMI) >35 kg/m^2 is associated with a worse outcome after cardiac transplantation. For such obese patients, it is reasonable to recommend weight loss to achieve a BMI of ≤35 kg/m^2 before listing for cardiac transplantation (Class IIa, LOE: C)	Overall, pretransplant BMI >30 kg/m^2 or percent ideal body weight (PIBW) >140% is associated with poor outcome after cardiac transplantation. For obese patients, it is reasonable to recommend weight loss to achieve a BMI of <30 kg/m^2 or percent BMI of <140% of target before listing for cardiac transplantation (Class IIa, LOE: C)
1.4.2. Diabetes, renal dysfunction, and peripheral vascular disease	Update: Addition of a second unit of measurement for glycosolated hemoblobin for assessing persistent glycemic control of diabetes, with clarification that HbA1C >58 mmol/mol or >7.5% be a relative contraindication to listing	Diabetes with end-organ damage (other than non-proliferative retinopathy) or persistent poor glycemic control (glycosylated hemoglobin [HbA1c] 7.5% or 58 mmol/mol) despite optimal effort is a relative contraindication for transplant (Class IIa, LOE: C)	Diabetes with end-organ damage other than non-proliferative retinopathy or poor glycemic control (glycosylated hemoglobin [HbA1c] 7.5%) despite optimal effort is a relative contraindication for transplant (Class IIa, LOE: C)
1.4.2. Diabetes, renal dysfunction, and peripheral vascular disease	Update: Lower limit for acceptable eGFR for listing lowered from 40 ml/min/1.73 m^2 to 30 ml/min/1.73 m^2	Renal function should be assessed using estimated glomerular filtration rate (eGFR) or creatinine clearance under optimal medical therapy. Evidence of abnormal renal function should prompt further investigation, including renal ultrasonography, estimation of proteinuria, and evaluation for renal arterial disease, to exclude intrinsic renal disease. It is reasonable to consider the presence of irreversible renal dysfunction (eGFR <30 ml/min/1.73 m^2) as a relative contraindication for heart transplantation alone (Class IIa, LOE: C)	Renal function should be assessed using estimated glomerular filtration rate (eGFR) or creatinine clearance under optimal medical therapy. Evidence of abnormal renal function should prompt further investigation, including renal ultrasonography, estimation for proteinuria, and evaluation for renal arterial disease, to exclude intrinsic renal disease. It is reasonable to consider the presence of irreversible renal dysfunction (eGFR <40 ml/min/1.73 m^2) as a relative contraindication for heart transplantation alone (Class IIa, LOE: C)

(continued)

Table 1 (continued)

Section	Change	2016 guidelines	2006 guidelines
1.4.2. Diabetes, renal dysfunction, and peripheral vascular disease	Update: Change to state that clinically severe symptomatic cerebrovascular disease may be considered a contraindication to transplantation without the additional requirement that it "... is not amenable to revascularization"	Clinically severe symptomatic cerebrovascular disease may be considered a contraindication to transplantation. Peripheral vascular disease may be considered a relative contraindication for transplantation when its presence limits rehabilitation and revascularization is not a viable option (Class IIb, LOE: C)	Clinically severe symptomatic cerebrovascular disease, which is not amenable to revascularization, may be considered a contraindication to transplantation. Peripheral vascular disease may be considered as a relative contraindication for transplantation when its presence limits rehabilitation and revascularization is not a viable option (Class IIb, LOE: C)
1.4.3. Assessment of frailty	NEW: Addition of a subsection that highlights the importance of evaluating frailty in potential transplant candidates	Assessment of frailty (3 of 5 possible symptoms, including unintentional weight loss of $\geq$10 pounds within the past year, muscle loss, fatigue, slow walking speed, and low levels of physical activity) could be considered when assessing candidacy (Class IIb, LOE: C)	n/a
1.4.4. Mechanical circulatory support for bridge to candidacy	New: Addition of a subsection that highlights the role for using mechanical circulatory support as a bridge to candidacy for patients with potentially reversible or treatable comorbidities	Use of mechanical circulatory support should be considered for patients with potentially reversible or treatable comorbidities, such as cancer, obesity, renal failure, tobacco use, and pharmacologically irreversible pulmonary hypertension, with subsequent reevaluation to establish candidacy (Class IIb, LOE: C)	n/a
1.5.3. Psychosocial evaluation	New: Additional clause stating that inadequate social support for outpatient compliance may be regarded as a relative contraindication to listing, added to section addressing severe cognitive-behavioral disabilities or dementia	Any patient for whom social supports are deemed insufficient to achieve compliant care in the outpatient setting may be regarded as having a relative contraindication to transplant (Class IIa, LOE: C)	n/a
1.5.3. Psychosocial evaluation	Update: Clarification provided as to the rational behind the recommendation not to list patients with severe	The benefit of heart transplantation in patients with severe cognitive-behavioral disabilities or dementia (e.g., self-injurious	Mental retardation or dementia may be regarded as a relative contraindication to transplantation (Class IIa, LOE: C)

(continued)

Table 1 (continued)

Section	Change	2016 guidelines	2006 guidelines
	cognitive-behavioral disabilities or dementia	behavior, inability to ever understand and cooperate with medical care) has not been established and has the potential for harm, and, therefore, heart transplantation cannot be recommended for this subgroup of patients (Class IIa, LOE: C)	
1.7. Dynamic listing and new donor allocation algorithms	Update: Recommendation added to monitor heart failure survival prognostic scores in addition to the previously recommended monitoring of cardiopulmonary exercise testing at 3–6 month intervals for outpatient, ambulatory, non-inotropic therapy-dependent transplant candidates	Listed patients in an outpatient, ambulatory, non-inotropic therapy- dependent state should be continually evaluated for maximal pharmacologic and device therapy, including implantable cardioverter defibrillator (ICD) or biventricular pacing, when appropriate. Such patients must be reevaluated at 3- to 6-month intervals with cardiopulmonary exercise testing and heart failure survival prognostic scores to assess their response to therapy and, if they have improved significantly, should be considered for delisting (Class I, LOE: C)	Listed patients who are in an outpatient ambulatory non-inotropic therapy-dependent state should be continually evaluated for maximal pharmacologic and device therapy, including implantable cardioverter defibrillator (ICD) or biventricular pacing, when appropriate. Such patients must be reevaluated at 3- to 6-month intervals with cardiopulmonary exercise testing to assess their response to therapy, and if they have improved significantly, they may be candidates for delisting (Class I, LOE: C)
1.7. Dynamic listing and new donor allocation algorithms	Deletion: Clause calling for alternate allocation algorithm that prioritizes higher-status patients within larger geographic areas removed from guidelines	n/a	Redesigned allocation algorithms should be considered that allow for the prioritization of higher-status patients within larger geographic areas (within accepted safe ischemic time limitations). This practice may reduce deaths on the waiting list by both providing more hearts in a timely fashion to the higher acuity population (Class I, LOE: C)
1.7. Dynamic listing and new donor allocation algorithms	New: Addition of a subsection that states higher prioritization may be appropriate for certain highly sensitized patients	Higher prioritization for highly sensitized patients may be considered due to difficulty obtaining a donor, causing excessive waiting times and an increase in waiting list mortality (Class IIb, LOE: C)	n/a

(continued)

Table 1 (continued)

Section	Change	2016 guidelines	2006 guidelines
1.8. Retransplantation	New: Addition of a subsection that states that listing for retransplantation may be appropriate in patients with refractory cardiac allograft dysfunction due to CAV, in the absence of ongoing rejection	Retransplantation is indicated for those patients who develop significant CAV with refractory cardiac allograft dysfunction, without evidence of ongoing rejection (Class IIa, LOE: C)	n/a

LOE level of evidence, *CRT* cardiac resynchronization therapy, *RHC* right heart catheterization, *LVAD* left ventricular assist device, *IABP* intra-aortic balloon pump, *BMI* body mass index, *HbA1c* glycosylated hemoglobin, *PIBW* percent ideal body weight, *eGFR* estimated glomerular filtration rate, *ICD* implantable cardioverter defibrillator

arterial blood pressure (>85 mmHg). If an acute vasodilator challenge is unsuccessful, hospitalization for continued monitoring and an attempt to optimize with diuretics, inotropes, and vasoactive agents are recommended, possibly with the addition of an intra-aortic balloon pump and/or left ventricular assist device if additional unloading is necessary. In children, periodic RHC is not advocated for routine surveillance (Class III, Level of Evidence: C).

Several specific comorbidities have been identified as having significant implications for heart transplant listing, including advanced age, obesity, malignancy, diabetes, renal dysfunction, peripheral vascular disease, frailty, tobacco use, illicit substance abuse, and psychosocial limitations. With respect to age, patients should be considered for cardiac transplantation if they are ≤70 years of age, while carefully selected patients >70 years of age may be considered. The caveat in the 2006 listing criteria that suggested the option of an alternate-type program (i.e., use of older donors) was removed in the 2016 update as it was felt to be unnecessary and confusing. The recommendation for a formal assessment of frailty was included in the 2016 criteria as a potential consideration when assessing candidacy. It was considered an evolving metric as some measures of frailty may be responsive to advanced heart failure therapies, while others are not, and received a Class IIb, Level of Evidence C strength recommendation.

In the 2016 guidelines, a target BMI <35 kg/m^2 for listing was recommended, which was less restrictive than the recommended target of a BMI <30 kg/m^2 from the 2006 guidelines. This change was supported by evidence that having a BMI >35 kg/m^2 has been associated with longer wait time, decreased likelihood of finding a suitable donor, and possible increased posttransplant morbidity and mortality (Mehra et al. 2016; Weiss et al. 2009; Russo et al. 2010). The guidelines recommend that obese patients be counseled on weight loss to achieve a BMI <35 kg/m^2 prior to being listing (Mehra et al. 2016).

The presence of additional end-stage disease processes or significant medical conditions is often considered relative contraindications for isolated heart transplant listing. Diabetes mellitus is considered a relative contraindication for transplant if, despite optimal effort, there is persistent poor glycemic control (HbA1C >7.5% or 58 mmol/mol) or evidence of end-organ damage other than non-proliferative retinopathy. The presence of irreversible renal dysfunction (eGFR <30 ml/min/1.73 m^2) is a relative contraindication for heart transplantation alone, although a combined heart/kidney transplantation may be considered. Cerebrovascular disease may be considered a contraindication to transplantation if clinically severe and symptomatic. Peripheral vascular disease may be considered a relative contraindication for transplantation when its presence limits rehabilitation and revascularization is not a viable option.

Patients with a history of neoplasm should be evaluated in collaboration with oncology specialists and can be considered for listing for heart transplantation when tumor recurrence is low based on tumor type, response to therapy,

and negative metastatic work-up. No arbitrary time period for observation is recommended given the diverse range of neoplasms.

For patients being considered for heart transplant listing with potentially treatable or reversible comorbidities, consideration of the use of MCS is recommended as a potential bridge to candidacy. Potential opportunities for MCS with subsequent reevaluation to establish candidacy could include patients with nonfatal cancer diagnoses, obesity, tobacco use, moderate renal failure, and pharmacologically irreversible pulmonary hypertension.

Behavioral and psychosocial health have a significant impact on transplant candidacy and outcomes. Active tobacco smoking is considered a relative contraindication to transplantation as active tobacco smoking during the previous 6 months is a risk factor for poor outcomes after transplantation (Corbett et al. 2012; Khanna et al. 2009). Posttransplant smoking is also associated with worse outcomes, including higher odds of having new posttransplant cardiovascular disease, nonskin malignancies, shorter survival time, and increased mortality (Duerinckx et al. 2016). Active substance abuse, including alcohol, is considered an absolute contraindication to listing (Class III, Level of Evidence C), and a structured rehabilitative program may be considered in those with a recent (24-month) history of alcohol abuse. A formal psychosocial assessment should be performed before listing any candidate for transplantation, including an assessment of the patient's ability to give informed consent and comply with instructions, as well as assessment the support systems in place at home or in the community. As per the 2016 guidelines, heart transplantation is still not recommended for patients with severe cognitive-behavioral disabilities or dementia due to a lack of demonstrated benefit and risk for potential harm (Mehra et al. 2016). Additionally, patients for whom social supports are deemed insufficient to achieve compliant outpatient care may be considered as having a relative contraindication to transplant.

In the 2006 ISHLT listing criteria, Table 3 showed a "Recommended Schedule for Heart Transplant Evaluation." In the 2016 updated guidelines, this is referred to as a screening grid for pretransplant evaluation, and no changes were recommended; however it was anticipated that transplant programs may need to update their grids based on the new general and special considerations in the 2016 listing criteria.

Additionally, it was specified that ambulatory outpatients who are not dependent on inotropic therapy should be serially evaluated for maximal pharmacologic and device therapy options and undergo periodic reevaluations at 3- to 6-month intervals with CPETs and heart failure survival prognostic scores to assess for interval improvement meriting consideration of delisting. Reallocation algorithms that allowed for prioritization of higher-status patients within larger geographic areas were removed from the listing criteria in 2016. However, consideration was added to afford higher prioritization for highly sensitized patients due to difficulty obtaining a donor, causing excessive waiting times and an increase in waiting list mortality. Retransplantation was also clarified as appropriate for patients with significant chronic allograft vasculopathy without evidence of ongoing rejection.

Special Considerations in the 2016 ISHLT Listing Criteria

Three sections of the 2016 ISHLT Listing Criteria for Heart Transplantation address specific cohorts of patients with advanced heart failure who have phenotypes that may be less responsive to traditional pharmacologic and device-based therapies and/or pose unique challenges for bridging to transplant and posttransplant management.

Section II of the 2016 ISHLT OHT Listing Criteria Guideline discusses patients with restrictive, infiltrative, hypertrophic, or arrhythmogenic right ventricular dysplasia cardiomyopathy. These patients express a phenotype that is usually not characterized by LV dilation and hypokinesis and thus may be less responsive to traditional interventions, including possible intolerance of vasodilator therapies and diuretic adjustments (Yancy et al. 2013). This population is also felt to be

difficult to treat with an LVAD due to cavity size and/or biventricular disease processes (Patel et al. 2017; Topilsky et al. 2011). Small LV cavity size may increase the risk of contact between inflow cannulas and the ventricular septum, leading to focal irritation of the septum which is a nidus for life-threatening ventricular arrhythmias or thrombus formation, as well as result in partial or complete obstruction of the inflow cannula causing submaximal support. If MCS is pursued, partial myomectomies to augment cavity size or a total artificial heart may be appropriate in some cases. Inotropes seldom provide significant symptomatic relief and may result in problematic arrhythmias and/or left ventricular outflow tract obstruction (Nicholls 2014). No medical or device therapy has been proven to improve outcomes in RCM, and symptomatic therapy is often of limited efficacy. If no treatable etiology is identified, heart transplantation may be the sole therapeutic option available to improve prognosis and symptoms. In cases of cardiac amyloidosis, guidelines specifically state that extracardiac organs must be carefully evaluated for involvement of amyloid prior to considering heart transplantation. Concern was high that restrictive, infiltrative, hypertrophic, and arrhythmogenic phenotypes were associated with increased morbidity and mortality with the prior listing criteria due to limited advanced therapy options for supporting patients with lethal dysthymias and non-dilated ventricles leading to low priority status and long wait times. The 2018 update of Policy 6, the allocation of hearts and heart-lungs, attempted to address these concerns with multiple options for higher status for patients not supported by inotropes or durable MCS, including the option for listing as an outpatient at status 4 if one of six criteria is met.

Screening and management of advanced heart failure patients with certain chronic or latent infectious diseases is covered in Section III of the guidelines, specifically human immunodeficiency viral (HIV) infection, Chagas disease, tuberculosis, and hepatitis B and C viral (HBV and HCV) infections. As of 2016, patients with HIV infection, HBV, HCV, Chagas disease, or latent tuberculosis may be considered as potential candidates, provided there is demonstrated clinical stability and adherence to specified patient management principles. Selected HIV-positive candidates may be considered for heart transplantation if they have no active or prior opportunistic infections, are clinically stable, are compliant on combination antiretroviral therapy (cART) for >3 months, have undetectable HIV RNA, and have CD4 counts 4200 cells/μl for >3 months.

Due to migration and travel, Chagas disease is now a worldwide health problem. Heart transplantation is the recommended therapy for heart failure related to Chagas disease, despite the elevated risk of reactivation posttransplantation (18–22%). Universal screening for *Trypanosoma cruzi* infection should be performed in all heart transplant candidates with significant exposure to Latin America through birth or travel as close monitoring for reactivation posttransplantation may be necessary.

Universal screening for latent tuberculosis infection (LTBI) is recommended for all heart transplant candidates to minimize the risk of reactivation posttransplantation, which is associated with significant challenges in management as well as high mortality (Subramanian et al. 2013). Patients with confirmed LTBI should be treated for 6–9 months; however the guidelines specify that this treatment should not interfere with the timing of transplantation.

Vaccination and/or revaccination are suggested before heart transplantation if candidates lack evidence of seroprotection for vaccine preventable diseases on screening serology. Heart transplant candidates should be screened for chronic or resolved HBV and HCV infections. Owing to differential therapeutic responses, determination of HCV genotype is recommended. If resolved or prior inactive HBV or HCV infection is confirmed, serial monitoring at 3-month intervals while listed is recommended, as well as repeat screening at the time of transplantation. In patients with chronic HCV or HBV infection, clinical, radiologic, or biochemical signs of cirrhosis, portal hypertension, or hepatocellular carcinoma are contraindications to heart transplantation.

Advanced heart failure in patients with congenital heart disease (CHD) is addressed in Section IV of the 2016 guidelines. Patients with CHD

may require transplantation in the absence of overt heart failure due to unique anatomic and physiologic issues such as failing Fontan circulation. Bridging these candidates to transplantation can be challenging, and timely transplantation can be challenged by sensitization. Patients with "hemodynamically significant" CHD can be listed as an outpatient at status 4 as per the 2018 updated UNOS policy. Clear delineation of intrathoracic anatomy within the chest can identify aortopulmonary collaterals in patients with single ventricle physiology which may need to be addressed prior to transplantation, and anatomic details may aid in planning bypass cannulation and surgical strategies.

Marijuana

The last section of the 2016 guidelines is Section V, which briefly reviews the use of marijuana and eligibility for heart transplantation. Marijuana use is identified as a highly controversial area with little evidence to guide decision-making. No recommendations by the ISHLT are provided; however the guidelines advise caution in considering the listing of candidates unable to give up the use of cannabis or those with heavy use which has impaired cognitive ability and could lead to challenges with medication adherence, infectious complications, and/or interactions with immune suppression.

Heart Transplant Allocation System

Donor heart management is coordinated by UNOS and local OPTN, and donor hearts are offered to listed heart transplant candidates based on medical urgency, blood type compatibility, and geographic sharing. Potential candidates are assigned a status that reflects their medical urgency and appropriateness for transplantation. In 2016, the Thoracic Organ Transplantation Committee of the Organ Procurement and Transplantation Network (OPTN) proposed modifications to the heart allocation system to improve stratification of candidates ("Adult Heart Allocation Changes 2016"). The last revisions had been in 2006, and multiple concerns were raised, including frequent use of exemption requests for uplisting, grouping of candidates with disparate estimated wait-list mortality together in the same status, and potential inequalities in allocation related to the geographic sharing scheme. After community-wide discussion and debate, the system was updated in 2018 with the expectation and goal of improving overall wait-list morality rates and transplant rates for the most medically urgent candidates without negatively impacting overall posttransplant mortality rates or wait-list mortality rates for candidates in lower urgency statuses. Notable changes included increased wait-list statuses to more accurately stratify heart transplant candidates based on estimated wait-list mortality (Fig. 1) and a redesign of the organ distribution scheme to provide the most medically urgent candidates access to donors from a broader geographic area.

In the new (current) system, candidates who are at least 18 years of age can be assigned to an adult heart status (AHS) ranging from 1 to 6 for highest to lowest estimated risk for wait-list mortality, with multiple different clinical scenarios to qualify for each status (Organ Procurement and Transplantation Network Policies 2019). Listing statuses are temporary with varied duration and renewal requirements. Listed candidates who are temporarily not appropriate for heart transplant are listed as status 7. Changes in listing status are to be reported and/or requested from the OPTN. Heart candidates less than 18 years of age at the time of registration may be assigned pediatric status 1A, pediatric status 1B, pediatric status 2, or inactive status. Candidates listed as pediatric remain eligible for pediatric status regardless of age until removed from the waiting list.

Adult candidates may satisfy the requirements to be listed as status 1 if supported by veno-extracorporeal membrane oxygenation (VA ECMO) or a non-dischargeable, surgically implanted, non-endovascular biventricular support device. Criteria for status 2 ranges from support by various MCS systems including but not limited to total artificial heart, biventricular assist devices,

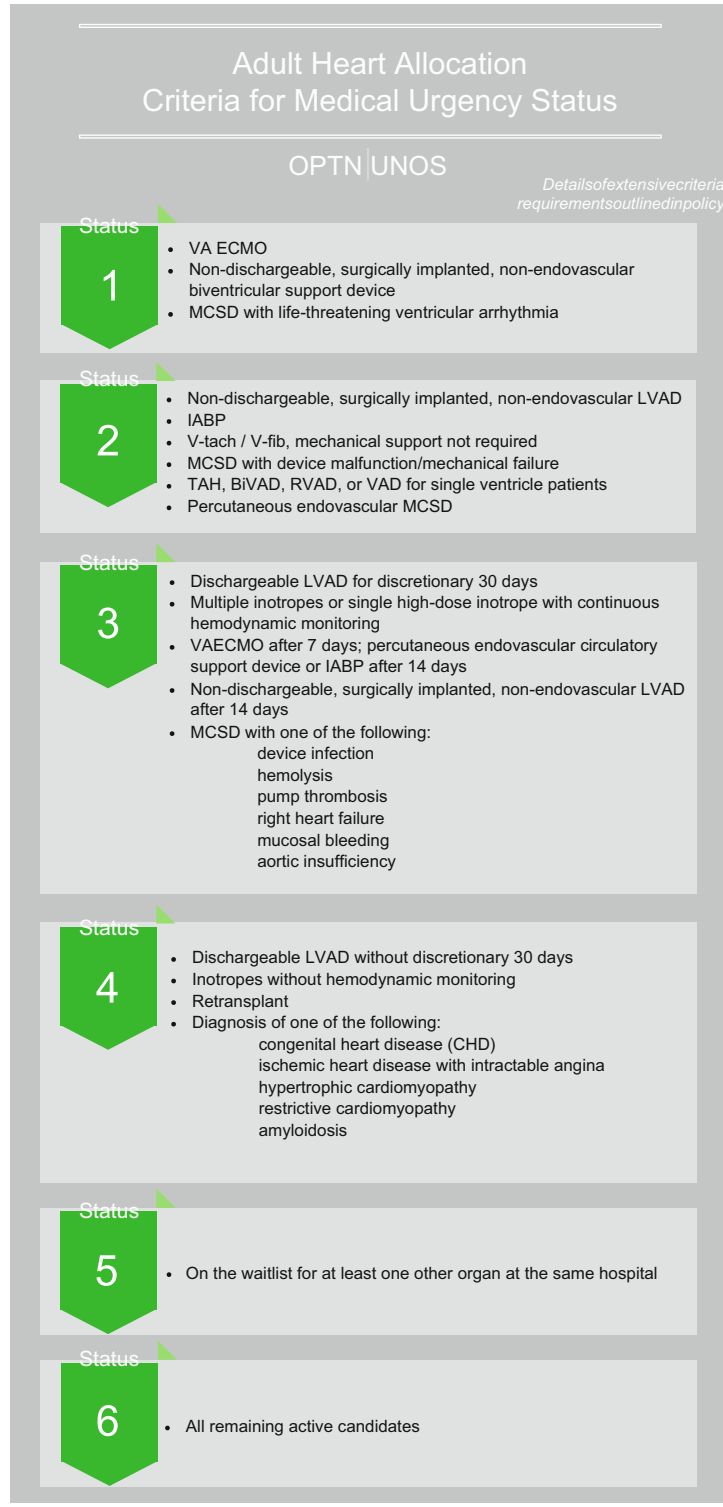

Fig. 1 Adult Heart Allocation Criteria for Medical Urgency. An infographic overview of the status criteria for the UNOS adult heart and heart-lung allocation system. (Organ Procurement and Transplantation Network Policies 2019)

Table 2 OPTN allocation zones: Five concentric bands or zones of geographical areas are used in the allocation of thoracic organs

DSA	The geographic area designated by the Centers for Medicare and Medicaid Services (CMS) that is served by one organ procurement organization (OPO), one or more transplant hospitals, and one or more donor hospitals
Zone A	Includes all transplant hospitals within 500 nautical miles of the donor hospital but outside of the donor hospital's DSA
Zone B	All transplant hospitals within 1000 nautical miles of the donor hospital but outside of Zone A and the donor hospital's DSA
Zone C	All transplant hospitals within 1500 nautical miles of the donor hospital but outside of Zone B and the donor hospital's DSA
Zone D	All transplant hospitals within 2500 nautical miles of the donor hospital but outside of Zone B and the donor hospital's DSA
Zone E	All transplant hospitals more than 2500 nautical miles from the donor hospital

This table defines the geographical system utilized for distribution of solid organs for transplantation. (Borrowed from the OPTN Policies, Effective Date: 3/30/2017, Section "Administrative Rules and Definitions") (Organ Procurement and Transplantation Network Policies 2019)

intra-aortic balloon pump (IABP), and an MCSD with high risk for life-threatening malfunctioning or the presence of recurrent or sustained ventricular tachycardia or fibrillation. Requirements for AHS 3 include but are not limited to support by a high-dose inotrope, multiple inotropes, an MCSD with complication, prolonged VA ECMO or IABP, and a subset of MCSD. Eligibility for AHS 4 includes support by inotropes without daily hemodynamic monitoring or LVAD, history of prior cardiac transplant, or a high-risk phenotype not easily supported by MCSD or inotropes. Candidates are listed for AHS 5 if they are listed for more than one organ at the same hospital, and AHS 6 includes all other remaining active candidates.

When compared to the prior UNOS status categories, the current statuses 1–3 were the previous 1A status, status 4 was the previous 1B or 2 status, and statuses 5–6 were the previous status 2. The new criteria do increase the status ranking of patients with restrictive and congenital cardiomyopathy (previously status 2 if ambulatory without inotropes). Patients with durable LVADs again have 30 discretionary time as status 3 (previously 1A), and the previous exception criteria for LVADs as status 1A are more restrictive in allowing patients to move up to a status 3.

Within each heart status and geographical zone classification, hearts are first allocated to primary blood type candidates then to secondary blood type candidates in a sequential order reflecting acuity of listing and geographical proximity within predefined regions, further stratified by wait-list time (Tables 2 and 3) (Organ Procurement and Transplantation Network Policies 2019). The OPTN contractor will only offer organs from deceased donors with mismatched antigens equal to or less than the maximum specified by a transplant program. Wait-list time is calculated by status and time accrued at a status; time accrued at one status does not transfer or get lost with status upgrades or downgrades.

Conclusion

UNOS is the OPTN that manages the heart transplantation matching and allocation system for the United States and Puerto Rico (Organ Procurement and Transplantation Network Policies 2019). The ISHLT published updated International Listing Criteria for Heart Transplantation, which were revised from the 2006 guidelines to reflect progress in the management of advanced heart failure patients and specifically address evolving areas of importance including congenital heart disease, restrictive cardiomyopathy, and chronic infectious diseases, such as HIV (Mehra et al. 2006, 2016). Many prior recommendations were continued without significant change; however notable updates include recommendations on frailty assessment, use of

Table 3 OPTN adult heart allocation: Overview of the allocation sequence for offering of hearts from deceased donors of at least 18 years of age

Allocation order	Candidates' listing region	Candidate criteria
1	OPO's DSA	Adult or pediatric status 1A and primary blood type match with the donor
2	OPO's DSA	Adult or pediatric status 1A and secondary blood type match with the donor
3	OPO's DSA	Adult or pediatric status 1B and primary blood type match with the donor
4	OPO's DSA	Adult or pediatric status 1B and secondary blood type match with the donor
5	Zone A	Adult or pediatric status 1A and primary blood type match with the donor
6	Zone A	Adult or pediatric status 1A and secondary blood type match with the donor
7	Zone A	Adult or pediatric status 1B and primary blood type match with the donor
8	Zone A	Adult or pediatric status 1B and secondary blood type match with the donor
9	OPO's DSA	Adult or pediatric status 2 and primary blood type match with the donor
10	OPO's DSA	Adult or pediatric status 2 and secondary blood type match with the donor
11	Zone B	Adult or pediatric status 1A and primary blood type match with the donor
12	Zone B	Adult or pediatric status 1A and secondary blood type match with the donor
13	Zone B	Adult or pediatric status 1B and primary blood type match with the donor
14	Zone B	Adult or pediatric status 1B and secondary blood type match with the donor
15	Zone A	Adult or pediatric status 2 and primary blood type match with the donor
16	Zone A	Adult or pediatric status 2 and secondary blood type match with the donor

This table is an abbreviated overview of the algorithm for allocation of hearts from deceased donors at least 18 years old. The full version of all 36 options is available in the (OPTN Policies, Effective Date: 3/30/2017 in the Section "Allocation of Hearts and Heart-Lungs") (Organ Procurement and Transplantation Network Policies 2019)

mechanical circulatory support as a bridge for candidacy, prioritization of highly sensitized patients, retransplantation for severe chronic allograft vasculopathy, removal of allocation algorithms that allowed for prioritization of higher-status patients within larger geographic areas, lower suggested cutoff for minimal estimated glomerular filtration rate, assessment of the adequacy of social support in potential transplant candidates, and the role of heart failure prognosis scores in ambulatory patients. The US adult heart allocation system was updated in 2018 with increased stratification of patients based on estimated wait-list mortality and changes designed to enhance access to donor heart offers to those with the highest wait-list mortality in a broader geographic area.

Cross-References

- ▶ Contraindications to Heart Transplantation
- ▶ History of Heart Transplant
- ▶ Matching Donor to Recipient

- Psychosocial Considerations of Heart Transplant: Keeping Apace with the Revolution in Cardiac Care
- Recent Changes and Future Challenges in the Heart Allocation System

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Recent Changes and Future Challenges in the Heart Allocation System

8

Louis H. Stein and Scott C. Silvestry

Contents

Abstract

The limited number of donor hearts is one of the greatest and persistent challenges to heart transplantation. Allocation of this precious resource requires the integration of objective data, clinical intuition, and moral fairness. Institution of an allocation system by UNOS has provided important structure to the allocation methodology. The system must be periodically reviewed and reorganized to ensure it is reflective of current patient disease and clinical practice and builds upon the knowledge of previous paradigms. Since the establishment of the 2006 allocation system, not only has there been a dramatic increase in the number of heart transplant candidates but also a dramatic increase in the number of patients qualifying as high-priority candidates. To address these changes, UNOS Thoracic Organ Transplantation Committee was tasked with providing a revised allocation system. The resulting system aims to improve waitlist mortality and posttransplant outcomes by better prioritizing the highest acuity patients while improving the geographic distribution of organ offers.

Keywords

Allocation · Adult congenital heart disease · Donor service area (DSA) · Exception rule · Mechanical circulatory support (MCS) · LVAD · Scientific Registry of Transplant Recipients · Status · Thoracic Organ Transplantation Committee · Thoracic surgery allocation modeling · UNOS

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Introduction

> "Indeed it has been said that democracy is the worst form of Government except for all those other forms that have been tried from time to time…" Winston Churchill to the House of Commons, November 11, 1947

Since the inception of heart transplantation, the donor graft has been considered a sacred resource. The comparative rarity of donor grafts compared to the number of eligible recipients emphasizes the need for a system which can optimize the utility of each graft while being fair and just to potential recipients. The goal of heart allocation policy has remained to provide appropriate organs to those patients who were the "best" candidates with the shortest expected survival given geographic constraints. The US heat allocation system has evolved from its formal inception as a basic two-tiered, local plus three-zone system in 1989 to a three-tiered urgency-based heart allocation system in 1998 (OPTN/UNOS Thoracic Organ Transplantation Committee 2016; Moazami et al. 2011; Meyer et al. 2015). Further modification occurred in 2006, integrating pediatric allocation and refining geographic ordering of heart offers. In this system, potential organ recipients were categorized as 1A, 1B, or 2 from most to least clinically urgent. Many legacy rules in the current system remain from the initial agreements of the small group of initial US heart transplant centers that were assigned without clinical data or physiologic basis but rather "because they sounded good" (O. Frazier, personal communication). In the decade since the last modification to the allocation system, the management and spectrum of potential heart transplant recipients has changed dramatically. As a result, Status 1A has become crowded and the differences in urgency between patients have become obscured.

In 2006, 1203 patients were listed for transplant rising to 3008 by 2015 (OPTN/UNOS Thoracic Organ Transplantation Committee 2016). In the same period, Status 1A patients increased from 5% to 13% of all patients listed. Sixty-seven percent of those who received transplants in 2015 were Status 1A. Despite this, those listed as 1A were three times more likely to die while on the transplant waiting list. These data point to a top-heavy prioritization scheme, with Status 1A representing a heterogeneous group. Finer granularity was needed to better represent the diversity of the Status 1A patient population.

Mechanical circulatory support (MCS) technology has dramatically expanded as well with markedly improved survival since prioritization was first assigned in the late 1980s (Coke and Edwards 2004). As a result, patients with end-stage heart failure have markedly changed: MCS-supported patients encompass a spectrum ranging from deteriorating CHF to acute cardiogenic shock while utilizing a larger range of percutaneous and implantable devices. In the setting of a strain on the 1A classification, a "one-size-fits-all" approach to listing MCS patients was no longer appropriate.

The 2006 modifications to the US heart allocation system integrated pediatric allocation maintaining a pediatric preference and addressed urgency, geography, and ABO compatibility. These changes included urgency and geographic ordering to integrate regional ordering and preferential pediatric allocation. After initial offers to waiting list candidates in local or donor service area (DSA) served by an organ procurement organization (OPO), offers then progressed to successive 500 mile geographic zones. Preference was given to ABO-identical and then ABO-compatible recipients within each status category, and allocation proceeded to candidates eligible to receive a heart from any blood type donor after allocation to all compatible blood types. Importantly, patients with restrictive diseases such as amyloidosis or those adults with congenital heart disease relied on prioritization based on "exception criteria." For a given patient, a transplant center must elect to request for an exception from a given region through a review board. This mechanism created the potential for regional variability in patient status due to regional practices and organ availability with resultant unequal access to transplantation.

A criticism of the 2006 policy between patient prioritization and geographic proximity was that the allocation rule was inconsistent with the UNOS mandate that access to organs "shall not be based on the candidate's place of residence or place of listing …" (42 CFR 121.8). By first

offering hearts to waiting list candidates listed as Status 1A and 1B at transplant hospitals within the DSA and then broadened to waiting list candidates in status listed 1A or 1B in surrounding zones (A and B), geographically close, high-acuity patients may have very different access and outcomes.

In 2016 the UNOS Thoracic Organ Transplantation Committee proposed changes to this allocation system, which were subsequently ratified. The protocol prompting each of these concerns will be reviewed along with the relevant data. Finally, the revised policy will be presented to address these potential issues.

Reassessment of the Prioritization Algorithm

Throughout the 1990s, UNOS utilized a two-tiered system in to classify heart transplant recipients (Moazami et al. 2011). Patients necessitating ICU care with inotropic infusions, those with MCS or IABP, were considered the highest priority, Status 1, while the remainder were listed as Status 2. In 1999, the system was reappraised to include a Status 1A, 1B, and 2. In that era, mortality following LVAD implant reached 5–10% per week (Moazami et al. 2011). Therefore, patients could be listed as 1A with $\leq$30 days of LVAD support. Alternatively, patients with >30 days of support and a device-related complication could also be listed as 1A. This policy was subsequently revised in 2002 to permit listing any LVAD patient for 30 days once the treating physician determined they were "clinically stable." Criteria for listing patients as 1A just prior to the most recent change are listed in Table 1.

Over time, Status 1A has become a multifarious group. From the perspective of waitlist mortality, the indications for Status 1A have become increasingly disparate (Fig. 1) ranging from 1500 deaths per 100 patient year for patients on ECMO to 5 deaths per 100 patient year for candidates with select post-LVAD complications.

Status 1B was created for waiting list candidates with less urgent need for cardiac transplantation such as candidates stably waiting at home or in the hospital requiring intravenous inotrope or LVAD support. Active patients who were stable at home on oral medications were listed as Status 2 (Table 1).

As would be expected in as system prioritizing the most urgent patients, Status 1A has received the majority of heart transplants on an annual basis since 1998 (Fig. 2). Despite this persistent trend, the distribution of the medical urgency has radically changed over nearly a decade. According to the Scientific Registry of Transplant Recipients (SRTR), the number (%) of Status 1A listed for transplant has gone from 660 (34.8% of the waitlist) to 1190 (58.4% of the waitlist). In the same time period, the Status 1B has gone from 723 (38.8% of the waitlist) to 743 (3.5% of the waitlist) and Status 2 from 509 (26.9%) to 102 (5.0% of the waitlist) (Scientific Registry of Transplant Recipients 2016).

Evolution of Status 1A: The Impact of the Evolution of Mechanical Circulatory Support

In 2006, 8.9% of candidates were registered with MCS criteria. By 2015, MCS patients increased to 24.4% (OPTN/UNOS Thoracic Organ Transplantation Committee 2016). MCS has concurrently expanded to distinct applications, with a wide

Table 1 Indications for listing status prior to 2017

Status	Criteria
1A	1. Continuous hemodynamic monitoring in the setting of either: Infusion of a single high-dose intravenous inotrope Multiple intravenous inotropes 2. Mechanical circulatory support with either: Total artificial heart (TAH) Intra-aortic balloon pump (IABP) Extracorporeal mechanical oxygenation (ECMO) Mechanical ventilation 3. A ventricular assist device (VAD) for a discretionary 30-day period 4. A device-related complication 5. An approved exception
1B	1. VAD 2. Continuous infusion of inotropes
C	1. Patients stable on home oral medication

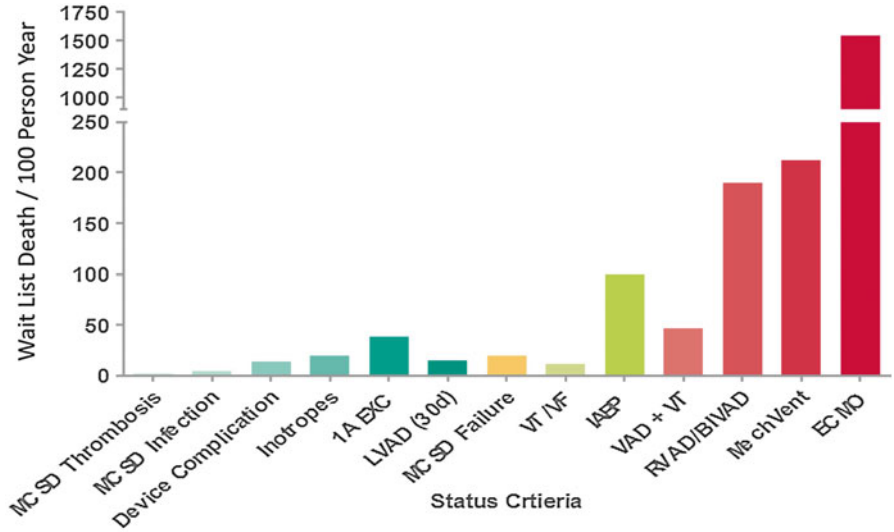

Fig. 1 Waitlist mortality vs Status 1A indication. (Figure courtesy of Ryan R. Davies, MD, UT Southwestern Medical Center)

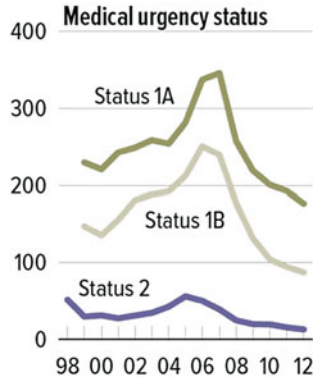

Fig. 2 Number of heart transplants/100 patient year vs patient year. (Figure courtesy of the scientific registry of transplant recipients, 2012)

range of expected mortality. Patients with RVAD support experience a log10 higher mortality on the wait list compared to those with LVAD. The increased use of MCS has also resulted in a similarly complex array of complications. Clearly, the MCS per se is no longer suitable as a dichotomous gage for acuity and transplant listing.

Exception Rule

The 2006 paradigm for heart allocations focuses primarily on patients with systolic dysfunction who are amenable to long-term MCS. A growing component of the heart transplant candidate population includes patients, such as those with lethal arrhythmia or heart failure with preserved ejection fraction (HFpEF) who do not fit this clinical picture (Reddy and Borlaug 2016). Most of these patients necessitate applying administrative exception for listing represents a growing component of the transplant candidate cohort. Applications for exception have grown in all clinical status since 2005 (Fig. 3).

Patients requiring exceptions to the group requiring exceptions is a heterogeneous group. The most common exceptions for Status 1A were as follows: (1) candidate is experiencing ventricular tachycardia or ventricular fibrillation; (2) candidate does not have intravenous access for inotropes or cannot tolerate a pulmonary artery catheter; and (3) congenital heart, while the most common exceptions for listing as Status 1B were as follows: (1) candidate is experiencing ventricular tachycardia or ventricular fibrillation; (2) congenital heart disease diagnosis; and (3) candidate requires a re-transplant. These six criteria comprise over half of those listed for exception.

These patients are inherently susceptible to regional variability as their institution must first elect to apply for exception, which must be

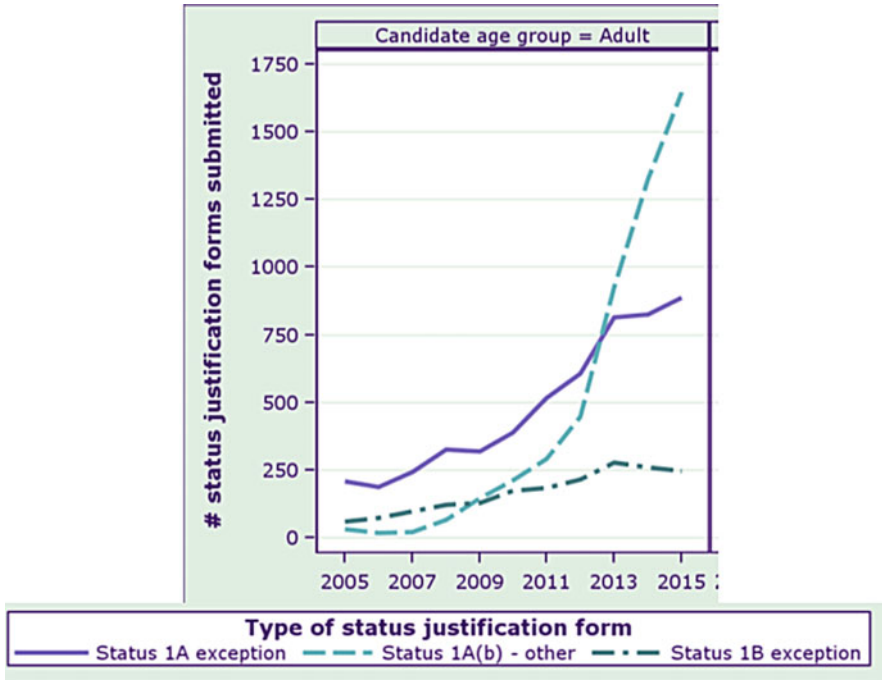

Fig. 3 Number of applications for exception vs year of application. (Figure courtesy of the scientific registry of transplant recipients, 2012)

approved by the regional. Therefore, they were considered to ensure they not become marginalized in a new system.

Equality in Geographic Distribution

The geographic allocation of donor hearts is based on the donor location and associated donation-specific area (DSA). The Centers for Medicare and Medicaid Services (CMS) established 58 DSA, which are served by an OPO and at least 1 transplanting hospital. Subsequent concentric geographic tiers outside of the DSA are based on geographic zones which increase in 500 mile increments. The first 500 miles surrounding the donor center, exclusive of the DSA, is termed Zone A. The first 1,000 miles, exclusive of the DSA and Zone A, comprises Zone B. Zone C comprises the first 1,500 miles surrounding donor hospital outside of the DSA and Zone B. These iterations are repeated though Zone E, which includes all transplant hospitals more than 2,500 miles from the donor hospital exclusive of the DSA and prior zones.

The system in established in 2006 balanced medical acuity with geographic proximity by first allocating Status 1A and B to transplant centers within donor hospital's DSA. Offers were then extended to Status 1A and B within Zone A. The organ was then offered to Status 2 within the DSA before extending offers to the Status 1A and B patients within Zone B. This can potentially be problematic in areas with dense concentrations of heart transplant centers. A high-acuity patient at a hospital designated as Zone A, although only 25 miles away from the donor institution, could be listed to receive an offer after less acute patients within the DSA (OPTN/UNOS Thoracic Organ Transplantation Committee 2016).

The Problem

All factors considered, the heart transplant waiting list reflected changes in the management of heart failure. A new system was needed to ensure a balanced offering of a donor heart to patient as wide as geographic area as possible, finding those patients who are most acute in the

current areas perspective. The number of exception requests for previous Status 1A scenarios underscored the need for further discrimination of the more acutely ill patients. The evaluation of medical and device therapy for heart failure has led to a proliferation of treatment strategies. Because of this variation, choices in treatment vary between institution and region. To aid in leveling the playing field, universally accepted, objective clinical data needed to be incorporated to level the playing field.

The New System

In an effort to meet the specific needs of heart transplant candidates, a new prioritization system that could provide more granularity and accuracy in representing their relative acuity in the current era. A "straw man" model was developed based on the analysis of waitlist and posttransplant mortality data, with significant emphasis on candidates listed as Status 1A as well as those who required exceptions for listing (Meyer et al. 2015). One source of concern in designing a fair S the improvements and expanded use of LVAD therapy since the creation of the 2006 model (Moazami et al. 2011). Patients supported with continuous flow LVAD (cfLVAD) demonstrated a mortality closer to Status 2 patients than those at Status 1A or B (such as those requiring inotropic therapy) (Wever-Pinzon et al. 2013). Conversely, mortality has remained high among patients with biventricular support or LVAD complications (Wever-Pinzon et al. 2013; Meyer et al. 2015; Moazami et al. 2011). Taken together, the stable LVAD population was given a lower status with in the high-acuity tiers. The SRTR utilized thoracic surgery allocation modeling (TSAM) to determine the effects of these changes on the newly proposed status system (Meyer et al. 2015). This modeling analysis did not suggest a change in waitlist deaths or transplants (Meyer et al. 2015).

The resulting new system includes six statuses, with an emphasis on subdividing Status 1 to better reflect the candidate's relative urgency as reflected by waitlist mortality data. Status 1A candidates were re-stratified into Status 1–3. Status 4 is roughly equivalent to Status 1B, with the addition of patients who would require exception status to apply for transplantation. The new status policy is presented in Table 2 with its equivalent 2006 status.

The geographic distribution of organs was restructured to provide higher-acuity patients over a wider region. In the revised system, offers would be made to Status 1 patients with in the DSA and Zone followed by Zone B. Status 2 patients would then be extended the offer. These changes strike a necessary balance between broadened access to a precious resource and availability to closer patients of lesser acuity (OPTN/UNOS Thoracic Organ Transplantation Committee 2016).

Unmet Challenges

In spite of its changes and hoped for benefits, the upcoming allocation system does not address several significant challenges in cardiac transplantation. Highly sensitized patients present a potentially vulnerable cohort. It is clear that patients with a high PRA require a broader donor pool. The 2006 allocation system did provide some provision to out of sequence prioritization for patients with high PRA. Unfortunately, little can be concluded regarding the impact of sensitization on overall survival as few centers have reported PRA data. Despite multiple attempts to provide appropriate priority for highly sensitized patients, sufficient data did not exist within the SRTR to develop appropriate offsets.

The prioritization of patients with adult congenital heart disease (ACHD) represents several challenges for allocation. The 2006 typically necessitated application for an exception for optimal prioritization. The natural history is a spectrum of complex cardiac disease and establishing consistent criteria that are comparable to other cardiac diseases in waiting list mortality.

Current practice of combined organ transplant involving heart-lung or heart-other is inconsistent at best. Patients for combined organ would be listed at a minimum as Status 5, but the majority of patients would qualify for higher status. The actual allocation of combined thoracic/thoracic-abdominal organs is inconsistently applied and varies from OPO to OPO despite policies aiming to clarify this

Table 2 2017 Prioritization status policy for heart transplant candidates

Corresponding 2006 status	Status (2016 criteria)	Indications
1A	1	ECMO[1] Non-dischargeable VAD[2] MCS with life-threatening ventricular arrhythmia[2]
1A	2	Non-dischargeable LVAD[2] Percutaneous endovascular LVAD[2] IABP[2] VT/VF without MCS[2] MCS with mechanical failure[2] Dischargeable BiVAD/RVAD/TAH[2]
1A	3	Dischargeable LVAD[3] High-dose inotrope/multiple inotropes requiring monitoring[2] MCS with hemolysis[2], pump thrombosis[2], RV failure[2], Infection[6], mucosal bleeding [7], aortic insufficiency[8] ECMO[4] Non-dischargeable LVAD[5] Percutaneous endovascular LVAD[5] IABP[5]
1B	4	Congenital heart disease[8] Hypertrophic cardiomyopathy[8] Restrictive cardiomyopathy[8] Dischargeable LVAD[8] Inotropes without monitoring[8] Intractable angina[8] Re-transplant[8]
1B	5	Multi-organ transplant[9]
2	6	All others[9]

1. Renewable 7 days, 2. Renewable 14 days, 3. Discretionary 30 days, 4. If Status 1 not renewed, 5. If status 2 not renewed, 6. 14 days of clinical evidence of drive line infection, 42 days if bacteremia requiring antibiotic, 90 days if device pocket infection or recurrent bacteremia, 7. 14 days if two hospitalizations in 6 months, 90 days if 3 times in past 6 months, 8. Renewable 90 days, 9. 180 days

practice. Current efforts within the transplant community seek to standardize these practices.

Lastly, while geographic disparities exist, the exact unit of correction is unclear. Equal 500 mile circles do not yield equal access to potential organ offers. Should geography be indexed to population? Should the number of transplant centers encompassed by these widening circles be factored into this algorithm? Further, all organ procurement organizations do not perform equally, with regional, cultural, and religious differences contributing to willingness to donate as well as inherent differences in OPO practices and efficiencies. Should geography be indexed to create equal access in potential organ offers? Lastly organ acceptance varies greatly from program to program (Khush et al. 2015). By offering wider circles of potential organ offers, is the new system incentivizing conservative acceptance practices instead of remedying geographic disparities in heart transplantation for acutely ill patients?

Remaining Concerns

Treating an acutely ill patient with temporary circulatory support may be appropriate and necessary. As the clinical condition evolves, therapeutic choices change, and medical decisions at a given center reflect program tools, skills, experience, and risk profile. Comparing and assessing the transplant need of a patient on ECMO with a patient with a total artificial heart/durable biventricular support is exceedingly difficult, given the initial condition may have been cardiogenic shock for both patients. Similar patients may be treated differently in centers with

implications for transplant access that is the result of the center choices not patient acuity – a difference that is hard to incorporate into allocation policy.

Therapeutic escalation has been a concern with the current system and will likely continue to be a concern with new allocation systems. Despite stricter requirements for data and verification, no system will be able to prevent behavior aimed at simply improving the chances of heart transplantation by choosing one therapy over another. Whether the utilization of temporary mechanical support in clinical scenarios that previously were treated with medical bridging (inotropes) or durable mechanical circulatory support will be preferentially treated with short term support is up to the provider. Patients have always been free to seek dual listing and evaluation at centers with higher rates of transplantation. Lastly, patients desire transplantation directly in most cases. Programs that aim to deliver this goal utilizing the new allocation system may make choices for temporary support that offer higher likelihood of achieving this goal to meet this patient preference without the use of durable support.

In game theory, behaviors that result in stable equilibriums in game that remove another player's ability to worsen the other player's outcomes are Nash equilibriums. In transplantation, regional Nash equilibriums evolve over time in clinical practice. In the upcoming allocation system, practice patterns will likely shift due to the impact of neighboring geographic practice patterns with greater geographic sharing leading to national shifts in practice patterns.

Conclusion

The current UNOS allocation system dates from 2006 and reflects the practice of heart failure before the explosion of mechanical circulatory support and advances in acute circulatory support technology. The upcoming allocation systems focuses on current waiting list mortality rates for specific conditions and patients grouped according to the therapies they are receiving and enhances regional sharing to allow acutely ill patients greater access to organ offers. The upcoming allocation system has attempted to address the lack of discrimination of the upper waiting list status, as well as geographic access problems noted in the current system. The redesign of UNOS allocation status aims to reduce waiting list mortality rates by allocating organs to the most critically ill candidates, rectify issues with specific patient groups, and incorporate broader geographic sharing to optimize access and limit regional disparities while keeping post-transplant survival (within each status) comparable to the current system. This system will transition during the latter part of 2018. Future allocation systems will likely evolve toward a global heart allocation score weighting the impact of waiting list mortality risk, remaining barriers to transplantation such as sensitization and posttransplant benefit. To paraphrase Dr. Norman Shumway, the perfect heart allocation score is the future of heart transplantation and always will be.

Cross-References

- ▶ Chronic Rejection
- ▶ History of Heart Transplant
- ▶ Regulatory Agencies

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Matching Donor to Recipient

9

Molly Schultheis and Margarita Camacho

Contents

Abstract

Considering the exponential increase in organ demand with a stable donor supply, cardiac donor management and selection is of utmost importance. The criteria for an acceptable donor have changed dramatically over the last 40 years and transplant teams are accepting older patients, longer ischemic times, donor substance abuse, and sometimes donor infection. Expanding the donor pool to the "increased risk" donors has enforced a more complex balance of donor and recipient components. A risk benefit ratio is commonly explored to provide the best donor to the more stable patient and accept an increased-risk donor in the patient with a shorter life expectancy. Patients with more urgent status designation include those on veno-arterial extra-corporeal membrane oxygenation (VA ECMO), with surgically implanted ventricular-assist devices and nondischargeable status or life

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threatening ventricular arrhythmias. Recently, use of VA ECMO as a bridge to heart transplant has expanded moving patients to the top of the waiting list. The intricacy of this risk-benefit balance will be highlighted in this chapter to provide optimal cardiac transplant outcomes to as many patients as possible and use all resources to their full potential.

Keywords

Match · Donor · Criteria · Selection · Recipient · Heart · Transplant

Introduction

Since the first cardiac transplant was performed in 1967, the introduction and improvement of immunosuppressive drugs have contributed to increased success worldwide (John et al. 2000). Currently, more than 2300 cardiac transplants are performed in the United States annually. Additionally, ventricular assist devices have been established as a viable option for heart failure patients as a bridge to transplant (BTT). These accomplishments have led to a longer waiting list of recipients for cardiac transplant; however, the organ donor supply is consistent. Considering this challenge, donor selection must be performed methodically in order to achieve a favorable prognosis. The selection criteria have broadened due to increased demand for donor hearts. Now included for consideration and evaluation are hearts that are older, unstable, and susceptible to longer ischemic times (Brock et al. 2001). Using such donor hearts necessitates assessing the risk/benefit ratio associated with the cardiac transplant operation and postoperative outcomes versus the mortality and morbidity risk of the recipient remaining on the waiting list (John et al., "Donor management. . ." 2004).

Donor Selection Overview

Heart failure patients are eligible to become transplant candidates when they meet the criteria outlined by the United Network for Organ Sharing (UNOS). The preliminary donor assessment is performed to determine a potential donor match. The initial evaluation includes confirmation and mechanism of brain death, consent for donation, ABO type and screen, and geographic location (Kilic et al. 2014). Ideally, the cardiac donor will not have the following: penetrating cardiac trauma, known cardiac disease, prolonged cardiac arrest (>15 min), human immunodeficiency virus, or an extra cranial malignancy (Edwards et al. 2005). However, recent experience has shown that a prolonged history of cardiac arrest, up to 1 h, may not exclude young donors under the age of 30. Often with hormone therapy, such as T4 (levothyroxine) infusion, the ejection fraction (EF) of such donor hearts has improved from below 30–40% to above 55%.

ABO Compatibility and Panel Reactive Antibodies

When selecting a donor recipient match, ABO blood group compatibility is the essential first consideration. Conversely, the Rhesus blood group does not have to match. When compared to ABO-identical grafts (i.e., A-recipient with A-donor), ABO-compatible (i.e., A-recipient with O-donor) adult hearts do not result in unfavorable outcomes for graft survival and incidence of acute rejection (Jawitz et al. 2013).

All recipients on the waiting list are tested for panel reactive antibody (PRA)), which is repeated monthly. When there is a > 10% reactivity to the testing panel, a prospective cross-match will be requested at the time of provisional donation. Some recipients with <10% reactivity may still require cross-match due to history of pregnancy, exposure to blood products, or previous surgery. If a recipient has >10% reactivity and the donor hospital distance is too far for a prospective cross-match, a "virtual cross-match" can be performed by comparing the recipients HLA antibody

specificity profile to the HLA type of the potential donor.

Donor Assessment Studies

Electrocardiogram (EKG), cardiac enzymes, echocardiogram, and often coronary catheterization will be necessary for cardiac donor evaluation. The quality of the study and interpretation can differ between institutions. It is recommended the transplant program evaluate the donor EKGs, TTE/TEEs, and request repeat examinations as needed.

A 12-lead EKG must be performed on all donors. Abnormal EKG rhythms such as bundle branch block or ST wave changes are common findings leading to declination of a donor heart (Khasati et al. 2007). However, abnormal EKG findings are often a result of brain death catecholamine surges which are uninhibited by central vagal input. This sympathetic response is known to cause acute myocardial dysfunction. Appropriate hemodynamic management can improve EKG and echocardiographic findings (Allan et al. 2014).

Cardiac enzymes should be measured on all donors since sustained elevation suggests severe myocardial injury. An initial rise in cardiac enzymes may be due to CPR-induced myocardial trauma. Transient elevations may be due to hypoxic injury to other organs. It is therefore important to correlate abnormal enzyme values with EKG, echocardiogram and, in some cases, cardiac catheterization (Cooper et al. 2007). A donor heart should not be accepted without resolution of abnormal cardiac enzymes.

It is important that the initial echocardiogram, whether transthoracic (TTE) or trans esophageal (TEE) is performed after conventional management has taken place. The volume status should be adjusted to a CVP 6–10 mmHg, the pH 7.4–7.45, Hgb >10 g/dL, and MAP>60. While an initial TTE can be used to screen for abnormalities such as poor EF, substantial left ventricular hypertrophy (LVH), and aortic insufficiency, a TEE may also be required to assess the other valves, particularly mitral, and rule out congenital lesions and regional wall abnormalities. If the EF is <45%, this may be due to catecholamine depletion after initial surge leading to severely reduced vascular resistance and myocardial shock (Kilic et al. 2014) A trial of hormonal resuscitation and evaluation with placement of a pulmonary artery catheter for hemodynamic management may help improve the EF and result in a suitable donor heart.

Coronary angiography is usually required for donors over the age of 40. It is beneficial to request catheterization in patients over the age of 30–35 years when there is history of significant hypertension, smoking, diabetes, cocaine use, or regional wall motion abnormalities on echocardiogram. If coronary catheterization is not available in the donor institution, a CT angiogram can be performed. Direct coronary palpation for evaluation during procurement is not reliable, as ostial lesions cannot be evaluated.

There should be no evidence of active infection (i.e., fever, leukocytosis, chest x-ray suggesting pneumonia, positive blood cultures). Historically, an acceptable donor must have negative serologies including Hepatitis C antibody, Hepatitis B surface antigen, HIV, and HTLV 1 & 2.

In order to expand the donor pool, Hepatitis C virus Antibody (HCVAb) positive donor hearts have recently been used for transplant to consenting recipients. Donors who have positive HCVAb undergo Nucleic Acid Testing (NAT) to test for acute HCV infection. Both HCVAb +/NAT- and HCVAb +/NAT+ donors have been used for transplant. The recipients of the HCVAb+/NAT- hearts have not shown to develop a detectable HCV viral load up to 6 months postoperatively (Patel et al. 2018). Those patients receiving HCVAb+/NAT+ hearts who acquire HCV post-heart transplant subsequently undergo direct-acting antiviral therapies (DAAs) to cure the transmitted HCV. This has been suggested as a potential approach to safely broaden the donor pool (Schlendorf et al. 2018).

Donor/Recipient Match: Standard Parameters

Gender

Recently data has shown a significantly worse outcome in donor-recipient gender mismatch. More specifically, male recipients of female hearts have the poorest long-term outcomes on a multivariate analysis (Peled et al. 2017). The International Society for Heart and Lung Transplant data for female allograft allocation to a male recipient did not affect 1-year survival but was associated with higher 5-year mortality (Costanzo et al. 2010). In addition, female recipients, regardless of donor gender, have a significantly higher risk of rejection and renal dysfunction at 1 year (Stehlik et al. 2011). Gender matching has been recommended as recent literature has shown an impact on major outcomes following heart transplant. However, many successful institutions do not use gender mismatch alone as a predictor of rejection or survival outcomes. It is recommended to place a greater emphasis on the importance of size matching.

Size

Guidelines from ISHLT are primarily based on expert opinion and it is recommend that the heart from a donor weighing <70% of the intended recipient's body weight should not be accepted (Costanzo et al. 2010). However, expert opinions also state that body weight alone does not correlate well with true adult cardiac size on echocardiogram and should not be used as an exclusion criterion for a donor heart (Chan et al. 1991). In an attempt to expand the appropriate donor pool, rather than rely on a strict weight difference requirement, an alternative approach can be used for evaluation.

With respect to weight difference, if there is greater than 30% discrepancy, it is recommended to perform specific LVEDD measurements via TEE. In general, when matching female donors to male recipients, female donors can be accepted with LVEDD >3.8 for recipients with normal pulmonary pressures, and LVEDD >4.2 for recipients with moderately elevated pulmonary pressures.

With respect to height differences, donors who are up to 6 inches shorter may be accepted for a recipient with no prior cardiac operations. For those recipients who have had prior sternotomies and possible significant scarring that may result in shortened/contractured great vessel cuffs, the donor should be no more than 4–5 inches shorter than the intended recipient. When evaluating a donor who is >3–4 inches taller than a recipient, a CT scan can be used to measure and compare the longitudinal axis distance from pulmonary valve to the diaphragmatic edge of the right ventricle.

Recent findings suggest that predicted heart mass (PHM), which is the sum of predicted right and left ventricular mass, may provide better size matching in cardiac transplantation than total body weight (TBW). Analysis confirmed that undersizing donor hearts by PHM, but not by TBW, was predictive of moderate to severe primary graft dysfunction and 90-day post-heart transplant mortality (Gong et al. 2018; Kransdorf et al. 2017). Most programs will not accept an undersized heart with a donor to recipient ratio less than 0.8–0.85 using this formula.

Age and Ischemic Time

Multiple publications have concluded that age is not an independent variable affecting postoperative survival (Schüler et al. 1989; Alexander and Vaughn 1991; Tenderich et al. 1998). The donor age requirement varies between institutions; reasonable donor criteria includes age less than 55 years. It is recommended to exert caution with regard to ischemic time when considering an older (>40yo) donor heart. In younger donors (<40yo), it is reasonable to allow for an ischemic time greater than 4 h. In contrast, if the donor heart is older, it is appropriate to ensure an ischemic time of less than 4–1/2 hours.

Cardiac and Vasoactive Medications

Donors commonly require vasoactive and/or inotropic agents for hemodynamic stability after brain death. Inotropes have been associated with direct cardiac toxicity. A recent retrospective analysis evaluated 233 donor-recipient matches and the effects of various inotropes on myocardial necrosis and clinical outcomes. Results demonstrated that high-dose dopamine appears to have a higher tendency to result in post-transplant myonecrosis; however, there is no impact on clinical outcomes (Nixon et al. 2012).

The hormonal changes after brain stem death frequently include decreases in the level of cortisol, insulin, thyroxine (T_4), and tri-iodothyronine (T_3). The donor should receive steroids, insulin, levothyroxine, and vasopressors in order to maintain stability and end-organ profusion.

At the time of procurement, donors are commonly on vasopressin for brain death-related diabetes insipidus (Capatina et al. 2015). If dopamine is required for circulatory stability, doses less than 5 μg/kg/min are recommended. Hypervolemic donors may exhibit cardiac edema, evident at the time of procurement by a hypokinetic right ventricle. In these situations, the anesthesiologist can administer furosemide and possibly start low dose dobutamine for support. However, a donor that becomes inotrope-dependent to maintain hemodynamic stability, or whose right ventricle does not recover after attempts at diuresis, will be deemed unsuitable.

Substance Abuse

It has become more common to find a history of prior substance abuse in an adult cardiac donor. Donors over the age of 35 with a significant history of cigarette smoking are at greater risk of having coronary artery disease, and therefore performing a cardiac catheterization is recommended. Donor alcoholism raises concern for future alcoholic myotoxicity; when alcoholic donor transplantation outcomes were analyzed, a possible correlation was found with early graft rejection and death (Houyel et al. 1992; Freimark et al. 1996). The ISHLT guidelines state "...the use of hearts from donors with a history of alcohol abuse remains uncertain, but it should probably be considered unwise." (ISHLT 2010). However, a 2015 meta-analysis found no difference in mortality and graft dysfunction between alcoholic and non-alcoholic donors (Jacob et al. 2015). It is reasonable to accept alcoholic donors with normal echocardiograms but coronary catheterization should be performed for donors over 35 years of age.

A history of intravenous or recreational drug abuse will classify the donor as "increased risk" and the recipient is required to be made fully aware and sign a written consent to continue with transplantation. Nonintravenous cocaine use has not shown to contribute to increased morbidity, mortality, or myocardial ischemia (Freimark et al. 1994).

Recipient Comorbidities and Condition at the Time of Transplant

Recent ISHLT guidelines for heart transplant listing carefully analyze obesity, diabetes, renal function, cerebral disease, and peripheral vascular disease. Body mass index (BMI) >35 kg/m^2 is associated with a worse outcome and weight loss is recommended before listing. Diabetes with end-organ damage or HbA1c >7.5% is a relative contraindication for transplant. Insulin-diabetic patients with no evidence of significant end-organ involvement can be listed as long as they are well-controlled with a HbA1c < 7.5%. Irreversible renal dysfunction (eGFR <30 ml/min/1.73 m^2) is a relative contraindication for heart transplant alone. An evaluation by the renal transplant team is recommended in order to consider listing the recipient for heart-kidney transplant. Clinically, severe symptomatic cerebrovascular disease should be considered a contraindication to transplantation unless the neurological issues are reversible. Recent institutional experience includes patients on temporary mechanical support, in-house, status post-

CVA, with eventual successful transplantation 4–6 weeks later. Peripheral vascular disease may be considered a relative contraindication for transplantation when its presence limits rehabilitation or limits peripheral cannulation for cardiopulmonary bypass in redo sternotomy recipients (Mehra et al. 2016) With all stated recommendations Class IIa-b, Level of evidence C, recipient physicians are left with many "borderline" heart failure patients with comorbidities who are reasonable to consider for heart transplantation with acceptable outcomes. As is usually the case, decisions are made on a case-by-case basis. Most importantly, a potential recipient cannot be listed for heart transplant without control of any of the aforementioned comorbidities.

Many aspects of heart transplantation are changing. In the recent years, older patients are being considered for heart transplantation and the number of complex congenital heart disease (CHD) patients benefitting from heart transplant is growing (Ventura and Muhammed 2001). Additionally, there is a significant increase in recipients with previous open-heart surgeries, transplants, and mechanical circulatory support (MCS) devices as bridge to transplant (Taylor et al. 2007). This changing population creates new challenges for the transplant physicians. For example, the risk of having preformed antibodies (PRA) directed against the donor heart may increase the risk of antibody-mediated rejection and allograft vasculopathy (Kerman 2007; Valantine 2004). Plasmapheresis, intravenous immunoglobulin (IVIG), and rituximab have been used to decrease the PRA prior to transplantation with varying degrees of success (Velez and Johnson 2009). The congenital heart disease patients tend to have more complex anatomy and are also at an increased risk of perioperative bleeding and mortality because of previous operations (Hosseinpour et al. 2006). It is imperative to evaluate congenital heart disease anatomy preoperatively with TEE, contrast CT scan of the chest, catheterizations and/or angiograms in order to plan the surgical approach.

Conclusion

The incidence of heart failure is increasing, patients are living longer, and more ventricular assist devices are being placed for BTT. The UNOS waiting list continues to grow with a steady donor pool; subsequently, transplant teams are left with the formidable mission of matching as many recipient patients on the waiting list as possible with suitable donor hearts.

When an initial donor offer had been made, the recipient surgeon and cardiologist need to consider all donor and recipient inpatient studies, age, ischemic time, size, location, and specific characteristics. Most cases are not simple and the risk/benefit ratio must be carefully assessed for the proposed heart transplant procedure and potential postoperative outcomes.

Cross-References

- ▶ Chronic Rejection
- ▶ Contemporary Survival in Heart Transplantation
- ▶ Contraindications to Heart Transplantation
- ▶ Donor Operation and Organ Preservation
- ▶ Ex Vivo Perfusion
- ▶ History of Heart Transplant
- ▶ Recent Changes and Future Challenges in the Heart Allocation System

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Part V

Organ Procurement

Donor Operation and Organ Preservation

10

Gurpreet Sodhi and Ramesh Singh

Contents

Abstract

Orthotopic heart transplantation is an effective and definitive treatment option for advanced heart failure patients. Since the first human heart transplant, major advances have occurred in the field of heart transplantation, including new surgical strategies. There continues to be an increasing donor shortage for patients on the heart transplant waiting list. Providers need to fully understand the process of retrieving a heart from a donor and appreciate the importance of preserving the donor heart during transport. In the current chapter, the authors will review in detail a standard operative procedure during organ procurement. Important steps the organ procurement team needs to perform will be highlighted to ensure the donor heart is satisfactory for excision and transport to the recipient. Equally important, a standard method to preserve the donor heart will be described, and alternative strategies that are being studied in clinical trials will be discussed. It is imperative to maximally preserve the structure and function of the donor heart as this translates into excellent clinical

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outcomes for the recipient. Low morbidity and mortality rates of heart transplant recipients are dependent on the swift and precise actions of the donor procurement and recipient teams.

Keywords

Orthotopic heart transplantation · Donor operation · Organ procurement · Donor organ preservation · Bicaval technique · Biatrial technique · Ischemic time · Organ Care System · Hypothermic storage · Crystalloid preservation solutions

Introduction

In the United States, advanced heart failure is an epidemic with an estimated 500,000 patients having refractory stage D heart failure symptoms (Mancini and Naka 2015). Advanced heart failure is associated with a high mortality rate and poor quality of life. Heart transplantation has developed into an effective treatment option for these patients, with median survival of 10–15 years (Lund et al. 2013). Since the first human heart transplant, the field of heart transplantation has advanced tremendously in many aspects. Unfortunately, there continues to be an increasing donor shortage and many advanced heart failure patients are dying on the waitlist. Even today, the donor pool has not expanded rapidly enough to meet the rising demand for cardiac allografts. In this chapter, the organ procurement process, including newer donor heart preservation strategies, will be described. The operation to obtain the donor heart will be outlined in detail. At the same time, the newer surgical techniques used during the donor operation will be highlighted.

History of Heart Transplantation

The first successful human-to-human heart transplantation was performed by Christiaan Barnard in South Africa on December 3, 1967, which was 7 years after Shumway and Lower's orthotopic heart transplantation using a canine model (Allen et al. 2012). Not only did this historical event receive endless media coverage and publication in the *South African Medical Journal*, but it also laid the foundation for heart transplantation to become a feasible option for end-stage heart disease. His first heart transplant patient survived only few weeks, but 4 of his first 10 patients survived for more than 1 year. For the next 15 years, Barnard and his team continued to make significant contributions to organ transplantation, including heterotopic heart transplantation, preservation of the donor heart, and insight into the metabolic effects of brain death (Brink and Hassoulas 2009).

During that decade, several key figures attempted to make significant contributions and achieve similar success. In the 1960s and 1970s, only dedicated centers around the world continued clinical and research work in the field. Since Barnard's groundbreaking achievement, many heart centers started their own heart transplant programs but high mortality rates led to a standstill in transplant activities during that decade. Shumway and his Stanford colleagues' efforts shaped the field of heart transplantation and allowed a reemergence of the field. Shumway remained steadfast in believing good results of heart transplantation, and ultimately his group gained recognition for the most heart transplantations worldwide in the 1970s (Schmitto et al. 2008).

By the mid-1960s, many physicians in the field of heart transplantation gathered considerable knowledge and learned from the previous work from pioneers such as Demikhov (1965), Carrel and Guthrie (Cooper 1968), and Stansel and Terino (1965). Physicians adopted the basic principles of heterotopic heart transplantation, cardio-pulmonary bypass, hypothermia, and preservation of the donor heart. Physicians also expanded on the concept of brain death and when brain death laws were enacted in 1981 the field of transplantation grew due to the better acceptance of organ donation in brain death. Although Christiaan Barnard's first successful human-to-

human heart transplantation was a remarkable achievement and laid the foundation for the field, earlier experiences from pioneers should be recognized. Nevertheless, Christiaan Barnard has been credited for the first successful human-to-human heart transplantation, and his work still echoes today, allowing heart transplantation to a viable treatment for advanced heart failure patients.

Epidemiology

The annual data report of organ donation and transplant by UNOS (United Network for Organ Sharing)/OPTN (Organ Procurement and Transplantation Network), which was updated March 2016, reports on the average 2500–3000 new patients are listed for heart transplant each year, and approximately 4000 patients total are on the heart transplant waiting list. There is equal number of patients added to the heart transplant waiting list as the number of patients removed from the list. The majority of the adult patients on the heart transplant waiting list are 50–64 years-old, Caucasian, blood type O, and suffer from advanced heart failure due to coronary artery disease or a specific type of cardiomyopathy. On the average, they spend 1–2 years on the waiting list, with a majority of the patients on the list less than 1 year. Most patients who have median wait times of 10 months are either status 1 or have a VAD (ventricular assist device). Approximately 2% per year are listed for combined heart-lung transplant.

The total number of heart transplants in the Unites States has been steadily above 2000 every year since 2000, and 4000 worldwide. Approximately, 1.7–2% per year receives a combined heart-lung transplant, and 3–4% per year receive their second heart transplant. Most of the heart donors are very young (15–34 year-old) white non-Hispanic males. The most common causes of death among the deceased heart donors are head trauma, anoxia, or a cerebrovascular accident ("Annual Report" 2016).

Donor Operation

When Christiaan Barnard in South Africa performed the first orthotopic heart transplant in 1967 (Allen et al. 2012), the technique he employed utilized a biatrial anastomotic technique. This is the technique developed by Norman Shumway and Richard Lower (Lower and Shumway 1960). This elegant and efficient method was successfully used for over 20 years worldwide and avoided the technical difficulty of separate caval and pulmonary vein anastomoses. This approach entails a simple anastomosis of both atria at midlevel and also of the pulmonary artery and aorta above the valves. This method retained the left and right atria of both the donor and the recipient (Lower et al. 1961). It was clear this was a quick and effective strategy that avoided potential complications of venous thrombosis and stenosis (Cass and Brock 1959; Barnard 1968). Unfortunately, long suture lines on the right atria also led to sinus node dysfunction and tachyarrhythmias. Barnard et al. recognized this issue and modified the surgical strategy. Instead of a posterior incision in the right atrium from the inferior vena cava (IVC) to the superior vena cava (SVC), which would increase the risk of sinus node dysfunction, Barnard and his Stanford colleagues would avoid the sinus node area. They would ligate the donor SVC 1–2 cm above its entrance into the right atrium and open the right atrium by an incision that extended from the IVC up the lateral aspect of the atrium into the right atrial appendage (Barnard 1968) (Fig. 1a). However, having large atrial cavities resulted in the loss of atrial geometry and anatomy, which led to several postoperative complications including mitral and tricuspid regurgitation, atrial septal aneurysms, and atrial thrombus formation.

Due to these postoperative complications, alternative anastomotic techniques were developed over the past several decades in an attempt to maintain the normal shape of the atria. One such method was the bicaval technique, which was widely and rapidly adopted and has become the most frequently used technique at present (Sarsam et al. 1993). Webb et al. are recognized as the first to

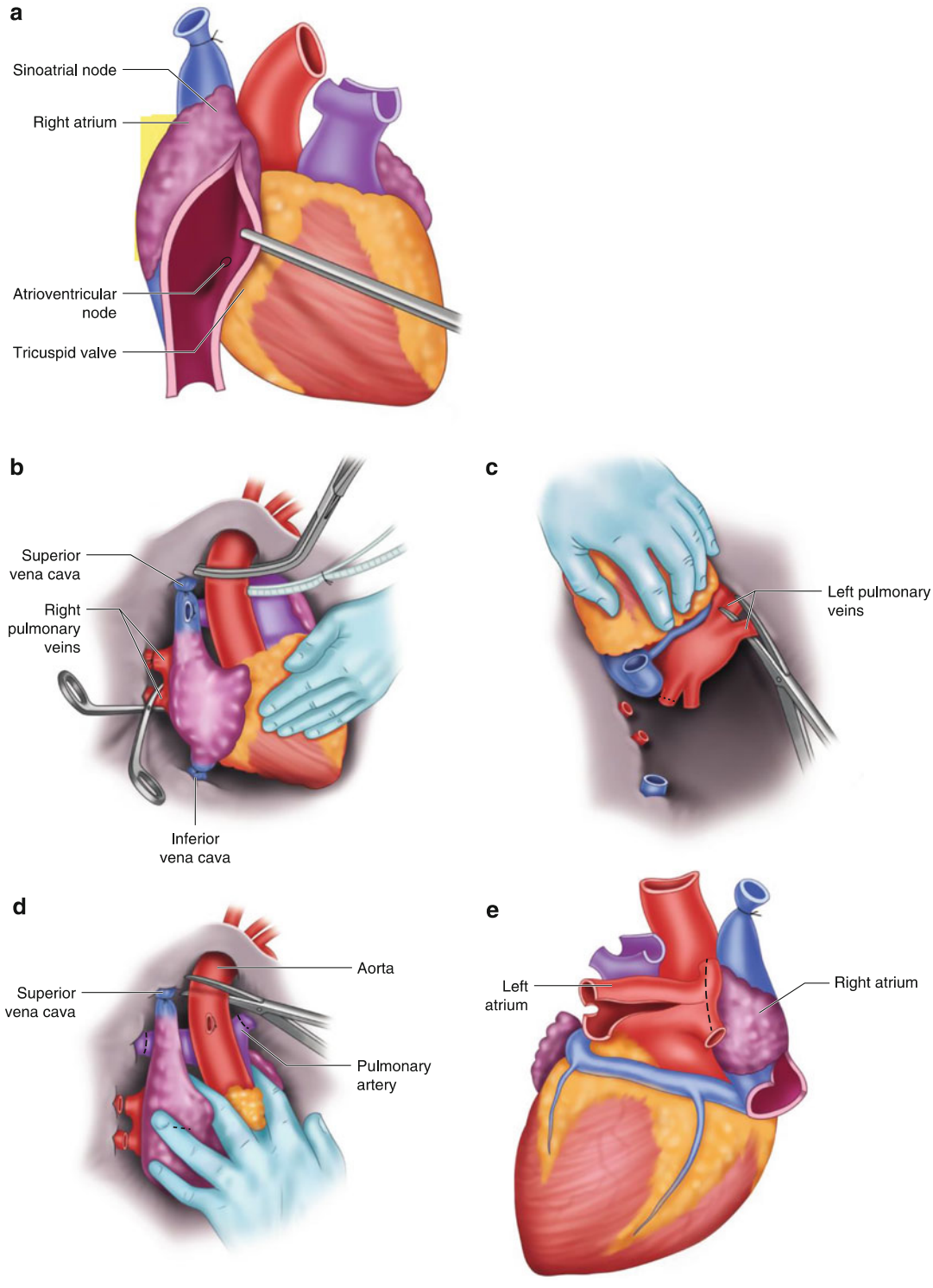

Fig. 1 (continued)

successfully perform the bicaval technique in dogs in 1959. They established an 8-anastomosis model, including individually connecting each of the pulmonary veins (Webb et al. 1959). Little over 3 decades later, a 6-anastomosis model was developed, which reduced the pulmonary vein connection to a left and a right pulmonary vein major orifice. The recipient's residual tissue is prepared with a left and right pulmonary vein cuff, which was anastomosed to the 2 orifices (Yacoub and Banner 1989; Dreyfus et al. 1991). In 1990s, this was first described and implemented. By the 2005, the bicaval surgical method was performed more than the biatrial strategy. However, in a large series examining the UNOS database, the results showed no difference in survival between the standard biatrial and the bicaval techniques (Weiss et al. 2008). With the bicaval strategy, the normal atrial morphology is retained which has the theoretical advantages of preserved atrioventricular valve competence, atrial contractility, and sinus node function. From a technical perspective, although there is an extra anastomosis to be performed, the bicaval technique is a simple and efficient surgical method without resulting in increased ischemic time. When compared to the biatrial technique, several studies have shown many advantages of the bicaval technique. These include lower right atrial pressures, lower incidence of tricuspid valve incompetence, and reduction in atrial arrhythmias as well as improvements in hemodynamics, cardiac chamber dimensions, cardiac output, right ventricular function, and exercise capacity. Today, the bicaval technique (5-anastomosis model) is the most common method in orthotopic heart transplantation and is associated with better hemodynamic outcomes than the standard biatrial method (Milano et al. 2000). This method has gained worldwide acceptance as the procedure of choice for OHT.

Organ Procurement

Upon arriving at the donor center, all reports are reviewed. These include donor/recipient blood group and compatibility, brain death notes, and reports of cardiac catheterization (if performed), echocardiograms, chest x-rays, and electrocardiograms. The images of the echocardiograms, chest x-rays, and cardiac catheterization should also be reviewed if available. Several communities will consent to organ donation with the exception of the heart. Hence, consent should also be reviewed with particular attention to cardiac donation. Finally, donor hemodynamics and inotropes/vasopressor requirements are also reviewed. If there are any concerns, a Swan-Ganz catheter and/or a transesophageal echocardiogram (TEE) should be performed. Any unanticipated cardiac abnormalities are discussed immediately with the recipient implant team.

In an effort to standardize thoracic organ procurement and preservation, Pasque describes an efficient and uncomplicated method (Pasque 2010). A standard midline incision is performed. This is usually connected to the abdominal incision if abdominal solid organs are also being procured. Bone wax is used and the chest is spread with a sternal retractor. The pleura are usually opened bilaterally if the lungs are also being procured. If only the heart is being procured from the thoracic cavity, then the right pleura should only be opened for access to the right pulmonary veins. A standard pericardial well is then made. Three pericardial sutures (large silk sutures) are placed on each side and snapped to a Kelly clamp. This

Fig. 1 Steps of isolated heart procurement. (**a**) In the atrial anastomosis technique, an incision is performed from the orifice of the IVC towards the right atrial appendage, avoiding the sinus node. (**b**) Cardioplegia has already been applied, the heart is arrested, and an aortic crossclamp has been applied. The SVC (superior vena cava) and IVC (inferior vena cava) are transected. (**c**) The heart is retracted towards the head to complete the transection of the PVs (pulmonary veins) at the pericardial edge. (**d**) With gentle retraction of the heart caudally, the pulmonary arteries are divided at the pericardial reflection and the aorta is transected (if possible after the left common carotid artery). (**e**) After the PVs are divided, an atrial cuff is formed with a left atrial incision in preparation for anastomosis during implantation (Blitz 2017)

will make it easier to gain access to the pleural spaces later in the procedure. At this stage, the heart and great vessels are inspected for any congenital, traumatic, or unanticipated abnormalities. The heart is examined for any palpable thrills and ventricular dysfunction. It is important to manually palpate the coronary arteries to assess for plaque or calcification. At this juncture, the expected crossclamp time should be ascertained and relayed back to the implantation team. Very minimal dissection is now performed so as not to cause much hemodynamic embarrassment until the patient is almost ready for crossclamp. The SVC is encircled at its origin from the innominate vein and the pericardial reflection is dissected off the origin of the arch vessels. The AP window is developed enough for a cross clamp to be placed. Once the patient is fully heparinized (30,000 units of heparin), an antegrade cardioplegia cannula is inserted in the mid ascending aorta and held in place with a Rommel tourniquet using a 5–0 polypropylene suture. The IVC is then encircled for ease of division at a later time so as not to injure the right inferior pulmonary vein. Waterson's groove can now be developed if the lungs are also to be procured. It is important to ensure that all organ procurement teams are ready prior to cross clamping. At that time, the SVC is ligated (after any upper body central venous lines are removed). A generous cut is made on the tip of the left atrial appendage to vent the left side of the heart. The incision needs to be big enough so as not to be obstructed by topical slush, but should not encroach upon the circumflex coronary artery. If the lungs are not being procured, the left atria can be vented by making a large cut on the pleural side of the right or left pulmonary veins. Finally the IVC is partially divided at a position suitable to both the liver and cardiac teams. These maneuvers will ensure optimization of left ventricular decompression and avoid distention upon crossclamping of the aorta. Once the aorta is crossclamped, the cardiac preservation fluid is infused at approximately 80 mmHg. At least 1 L of cold crystalloid cardioplegia solution is infused. There should be persistent aortic distension with rapid cessation of the cardiac activity without any ventricular distention. Topical cooling can now be used in the form of ice slush. If the heart feels full or hard, it is imperative to quickly assess the cause. The cross clamp may need to be removed and gentle pressure applied to empty the left ventricle prior to replacing the cross clamp. If the problem persists, it may result in a non-functioning or damaged graft. This is likely the most important element in the heart procurement process. Also, the cardioplegia should continue to be given until all the pulmoplegia is completed so as to avoid inadvertent pulmoplegia entering the coronary arteries. Next, the IVC and SVC are transected (Fig. 1b). The azygous vein is transected freeing the entire SVC. The azygous vein can be used as a guide to prevent twisting of the eventual SVC anastomosis. If the lungs are not being procured, then the pulmonary veins and arteries can be divided at the pericardial reflection (Fig. 1c). Otherwise, the atrial incision is started at Waterson's groove. Further extension of the left atrial incision is carried out towards the IVC and then parallel to the AV groove towards the left atrial appendage to the left. The right pulmonary veins can now be visualized and the left atrial incision is carried up the right keeping at least a 1 cm cuff for subsequent cardiac implantation. The rest of the atrial incision is completed from inside the left atrium, after the aorta and main pulmonary artery are divided. The left atrial appendage should be kept with the donor heart as a landmark for subsequent left atrial anastomosis. The innominate and left common carotid arteries are divided. If possible, the aortic arch is transected just beyond the left common carotid artery avoiding any injury to the pulmonary artery at the ligamentum arteriosum. However, division of the aorta before the aortic arch is adequate (Fig. 1d, e). The main pulmonary artery is transected at the level of the pulmoplegia cannulation site (distal main PA). This is only required if the lungs are also being procured. Otherwise, the pulmonary arteries would already have been divided at the level of the pericardium.

The heart is removed from the field and inspected for any previous undetected abnormalities or surgical damage. The atrial septum is inspected for a patent foramen ovale, and, if

present, will be closed by the donor surgeon or the implant surgeon. The aortic, mitral and tricuspid valves are inspected for thickening or adherent masses. The donor heart is now submerged in a plastic bag containing cold preservation solution without ice. This bag is sealed and placed within another bag containing cold fluid with ice. This second bag is sealed and now placed in a sterile plastic transportation canister, which is tagged with the donor's UNOS number and blood type and finally placed in an ice-filled cooler for transportation.

Donor Organ Preservation

It is imperative to maximally preserve the structure and function of the donor heart during transport. According to the International Society of Heart and Lung Transplant (ISHLT) registry, the 30-day mortality after heart transplantation is 8%. The leading cause of death 30 days after heart transplantation is primary graft failure (PGF). The 2 main risk factors for PGF are donor age and the length of ischemic time of the donor heart (Stehlik et al. 2012). Ischemic time for the donor heart starts with aortic cross clamp in the donor and ends with the removal of the aortic cross clamp in the recipient. A 3-h ischemic time is currently an acceptable time frame for graft preservation (Russo et al. 2007). The ISHLT registry has shown that the presence of PGF leads to a subsequent increase in 1-year and 5-year mortality rates; these increase once ischemic time surpasses 3 h. In the United States, the median ischemic graft time is 197 min (Fischer and Glas 2013). The length of the ischemic time is influenced by several factors, including experience of the procurement team, distance between the donor and recipient hospital, and experience of the receiving heart transplant team.

The Organ Care System (TransMedics, Andover, Massachusetts) is one strategy used to reduce the ischemic time. Organ Care System (OCS) is a transportable commercial system that allows a living organ transplant to be preserved during transport in a portable warm blood perfusion system. The Organ Care System consists of a miniature pulsatile pump with an inline heater and oxygenator. A solution that contains crystalloid combined with oxygenated warm donor blood allows the donor heart to beat ex vivo in a warm functioning state (Yeter et al. 2011; Ghodsizad et al. 2012). This is the first commercial device to transport donor hearts in a normothermic perfused state. The current OCS perfusion module maintains the heart in a state that was previously assessed within the donor and allows transportation to be feasible in a controlled state. During transport, the hearts are continuously assessed with aortic pressures, coronary blood flow, and metabolic profiles measurements. Two trials, 1 in Europe and 1 in the United States, evaluated the OCS in heart transplantation. The US-based Proceed II trial studied the safety and efficacy of OCS to the standard of care of cold storage and transport of the donor heart. In the Proceed II trial, the 30-day patient and graft survival were increased in the OCS arm versus the cold storage arm (Messer et al. 2015). Animal data has also shown normothermic blood perfusion to be superior to cold storage in preserving donor hearts in dogs (Rapse et al. 2010). For over four decades, cold storage has been the norm for donor preservation because of its simple and inexpensive technique. However, normothermic donor heart perfusion has expanded the number of potential donors and may improve 30-day outcomes after heart transplantation. OCS has the potential to retrieve donors from far geographic regions and extend beyond boundaries otherwise not possible. A donor heart can successfully be transplanted from far regions because OCS has the ability to maintain organ perfusion and minimize ischemic time. Also, OCS avoids high-speed journeys to the recipient hospital because there is no urgency related to ischemic time. OCS also offers flexibility to the receiving transplant team as it gives them time to assess the quality of the donor heart and to carefully prepare the recipient for the implant; this is particularly helpful with redo sternotomy cases especially those with LVADs in place. While OCS provides safety advantages and improved mortality outcomes due to reduced ischemic times, OCS also has the potential to capitalize on marginal hearts. Marginal hearts are those

hearts that are less desirable; these hearts may come from donors that are older, have some left ventricular hypertrophy or a lower ejection fraction. Using the standard cold preservation technique, marginal hearts would traditionally not be utilized for heart transplantation because they would have poor function and associated worse outcomes (Kilic et al. 2014). Normothermic donor heart perfusion with OCS offers many clinical advantages and opportunities given the current research.

Most transplant centers still prefer hypothermic storage with a single flush of a cardioplegic or preservative solution. There are many crystalloid solutions with a wide range of different compositions. Solutions are classified as intracellular or extracellular depending on the potassium and sodium concentrations (Conte and Baumgartner 2000). Intracellular solutions are characterized by high concentrations of potassium and low concentrations of sodium in order to reduce hypothermia-induced cellular edema. Examples of this composition include University of Wisconsin, Euro-Collins, intracellular Stanford solutions, and Bretschneider (Europe). University of Wisconsin is one of the most common solutions being used. Extracellular solutions are composed of low to moderate potassium and high sodium concentrations to avoid cellular damage. Examples include Hopkins, Celsior, Krebs, and St. Thomas Hospital solutions. Many studies have compared the different type of intracellular and extracellular cardioplegic solutions with variable results (Wildhirt et al. 2000; Garlicki 2003). There is no ideal solution despite on-going debates as to which is the best preservative solution.

In clinical trials, comparable levels of myocardial protection from ischemic injury were provided by these various crystalloid preservation solutions. There has been a focus on optimizing the composition of existing heart preservation solutions and creating new solutions. Anti-ischemic agents have been added to standard heart preservation solutions (Minasian et al. 2015). For example, glyceryl trinitrate, erythropoietin, and zoniporide have been added as single or combined supplements to Celsior solution, which activate the intracellular kinases and mediate ischemic pre-conditioning and post-conditioning (Iyer et al. 2014). The concept of cardio-protection by ischemic conditioning has been extensively demonstrated where recurrent episodes of short ischemic preconditioning protect the heart from a subsequent long period of ischemic insult (Murry et al. 1986). Additional advancements in the standard solutions include increasing the buffer capacity and adding colloid parts to the solutions. A balanced acid-base solution is crucial to maintain glycolytic ATP production during ongoing ischemia. Another important aspect is increasing colloids, such as high molecular weight dextran, gelatine, and hydroxyethyl starch (HES) to prevent intracellular edema and protect endothelial function (Zausig et al. 2013). Animal models have shown promise, but studies need to be investigated into plasma-based heart preservation solutions in marginal hearts (Jacob et al. 2009). Several new heart preservation solutions have been developed in animal models, including Somah, CRMB, Krebs-Henseleit buffer-based (KHB), and Custodiol-N. These new solutions have shown to be more effective than standard solutions. However, numerous pre-clinical studies need to be performed before being tested in clinical trials.

Other strategies of donor heart preservation include sub-zero temperature and oxygen persufflation. Prior reports have described decreased myocardial oxygen consumption during cold storage of the donor heart at +4 °C, but attempts are being made to achieve sub-zero temperatures at −3.0 °C. In order to prevent irreversible cell damage due to sub-zero temperatures, the donor hearts are submersed in anti-freeze proteins, which have cryoprotective properties. Kato et al. have shown submerging rat hearts in UW preservation solutions at sub-zero temperatures resulted in improved post-ischemic LV function, increased ATP levels, and decreased tissue edema (Kato et al. 2012). Oxygen persufflation, or perfusion of the coronary vascular bed with humidified gaseous oxygen, is another experimental technique dating back to the early 1960s (Suszynski et al. 2013). Oxygen persufflation was designed to reduce myocardial hypoxia during cold storage. This strategy makes myocardial perfusion possible to the heart even during reduced cold-induced

metabolic states. Animal models have shown antegrade persufflation resulted in better functional recovery of the LV function after orthotopic heart transplantation than the conventional cold storage method (Kuhn-Regnier et al. 2000). Thus, these 2 experimental strategies may be interesting options for donor heart preservation, and will need further clinical investigation.

At the center of donor heart preservation is minimizing graft dysfunction caused by ischemic-reperfusion injury, which occurs during the ex vivo transport to the receiving hospital. Currently, the universal method of transport involves cold storage in a crystalloid preservation solution. Although improvements have been made to the current strategy, ischemic injury continues to occur in a certain proportion of cardiac grafts due to increased transport times and poor preservation techniques. The growing shortage of donor hearts, the existence of "marginal donors," and the concern for graft dysfunction has stimulated the creation of new techniques of heart preservation, which have shown some initial promise.

Conclusion

Orthotopic heart transplantation is a definitive treatment for advanced heart failure patients. The field of heart transplantation has evolved immensely, especially with newer surgical strategies. With the advent of the bicaval technique, post-operative complication rates have diminished in comparison to the biatrial technique. Once a donor heart has been identified, the organ procurement team has to be precise and timely during the organ retrieval process. Even before the surgeon makes the first incision, the team must critically review the donor's clinical status and confirm that the organ is suitable for the recipient. It is only then the surgeon proceeds forward with the donor operation. It is understood there are variations in the proposed surgical procedure that was reviewed. Equally important, the team must maximally preserve the structure and function of the donor heart during transport. Currently, the universal method of transport involves cold storage in a crystalloid preservation solution. Alternative preservation examples include the Organ Care System, a portable warm blood perfusion system, and sub-zero temperature solutions with anti-freeze proteins. Many other preservation strategies are being tested in clinical trials. The organ procurement cascade ends when the donor heart has been successfully implanted into the recipient. The clinical outcomes of heart transplant recipients are dependent on the swift and precise actions of the donor procurement and recipient teams.

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Ex Vivo Perfusion

11

Jason W. Smith and Amy Fiedler

Contents

Abstract

Constant increases in the number of patients being listed for transplant and decreasing numbers of high-quality standard heart donors have placed a strain on heart transplant programs

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around the world. Efforts to increase the number of available donors with increased organ sharing and donor recruitment and use of extended criteria donors have had only modest effect at supplying needed organs. Because of these challenges, there has been a revival in interest in machine perfusion strategies to increase the use of marginal organs and improve the quality of organs when logistics demand long-distance organ procurement and to therapeutically intervene to improve organ quality. From early conceptual beginnings to the future potential of the therapy, this manuscript covers the evolution of ex vivo machine perfusion for support of heart transplantation.

Keywords

Ex vivo heart perfusion · Machine perfusion · Normothermic machine perfusion · Normothermic regional perfusion (NRP) · Expanded criteria donor · Donation after cardiac death (DCD) · Organ preservation · Organ care system (OCS)

Introduction

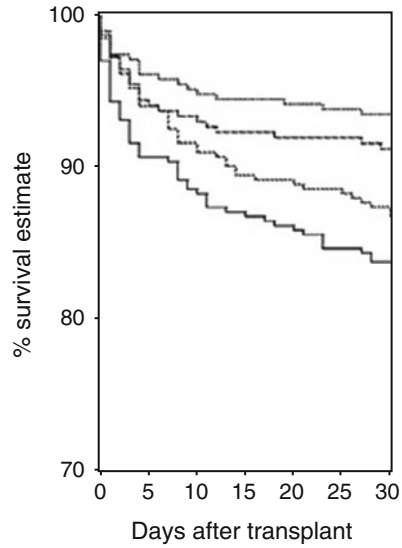
The most recent area of advancement in heart transplantation is machine perfusion for support of the heart after the donation process and before transplantation for the purpose of preservation or assessment. Machine perfusion addresses two major barriers that remain in heart transplantation today: the limitation of cold ischemic time and the inability to assess the organ outside of the donor milieu.

Why Is Machine Perfusion Needed in Heart Transplant?

Cold static storage with cardioplegic arrest remains the gold standard as it has been for almost 50 years. A machine perfusion strategy in heart transplantation addresses the tight time limits imposed by cold ischemic preservation strategies. This time begins with the application of the aortic cross-clamp in the donor and ends with removal of the cross-clamp from the recipient aorta, initiating reperfusion. Logistical issues such as donor organ packaging, transportation by ground and/or air, and back-table preparation may significantly impact the cold ischemic time. Traditionally, 4 h of cold ischemic time is the safe limit for routine transplantation (Minasian et al. 2015; Jacobs et al. 2010) (Fig. 1). In recent years, the literature has suggested that with careful donor selection, cold ischemic times of up to 6 h and sometimes beyond can be accomplished with good long-term results. Much beyond this mark, however, is generally seen as a barrier to safe heart transplantation (Gaffey et al. 2017). With additional donor factors including advanced age, left ventricular hypertrophy, or significant size mismatch, an increase in cold ischemic time becomes a more significant barrier and shortens the cold time allowable for safe transplantation (Reich et al. 2018). This can therefore significantly limit the distance that can be travelled for donor organs forcing tight regionalization in heart transplant that is at odds with the current allocation system. In 2018 the United Network for Organ Sharing (UNOS) changed the system of heart allocation to increase sharing across broader swaths of the country based increasingly on recipient need rather than co-localization with the donor (Stevenson et al. 2016).

Machine perfusion allows this time barrier to be broken, greatly extending the amount of time that the donor heart can be out of the body or "between cross-clamps." By minimizing cold ischemic time, machine perfusion expands the geographical range of transplant centers in excess of 2,000 miles. This expanded geographic reach permits a greater degree of organ sharing between population centers, assuring that those with the greatest need, from acute decompensated failure or the most highly sensitized recipients, have access to the most appropriate donor hearts (Schroder et al. 2019). This greater flexibility related to time and distance has the potential to realign the intentions of the new 2018 allocation system changes with the realities of transplant logistics.

An additional potential benefit of machine perfusion's expanding geographic reach is to consider introducing human leukocyte antigen (HLA)



IT (mins)	Number at risk at day 0	% survival estimate	95% CI
<155	305	93	90 – 96
155-189	284	91	87 – 94
190-229	332	87	83 – 90
≥230	332	84	79 – 87

Fig. 1 Thirty-day patient survival by total ischemia time ($P = 0.0005$, log-rank test). (Reproduced from The Importance of Cold and Warm Ischemia for Survival After Heart Transplantation. Transplantation 86(4):542–547, August 27th, 2008)

matching in heart transplantation as a component of organ allocation similar to what is done in abdominal solid organ transplantation. This strategy may reduce the incidence of rejection, reduce the degree of immunosuppression required for heart transplantation, and improve long-term outcomes (Jarcho et al. 1994).

Finally, active warm perfusion of organs promises the opportunity to intervene in organ function or antigen presentation by introducing somatic gene therapies into the donor heart directly, outside of the donor or recipient circulation avoiding both ethical and clinical risks (Bishawi et al. 2019).

Machine perfusion allows the continuous assessment of the donor organ outside of the donor and prior to implantation into the recipient while minimizing cold ischemic time. The ability to assess the physiologic capabilities of the donor organ function outside of the donor and prior to implantation in the recipient, especially in a donor who meets what is currently defined as expanded donor criteria, is of great significance. The use of machine perfusion has already been shown to be at least as safe and effective in preserving organs as cold static storage in routine heart transplantation (Ardehali et al. 2015). The next step in utilizing this technology was applying it to the expanded criteria donor who has an expected cold ischemic time greater than 4 h, is of at an age >55 years, has left ventricular hypertrophy greater than 1.2 cm, has suffered a cardiac arrest, or has documented coronary artery disease, among other factors (Schroder et al. 2019). In the current medico-legal environment of programmatic scrutiny with respect to transplant outcomes, programs feel an external pressure to avoid risks and protect outcomes (Khush et al. 2015). The use of marginal or "expanded criteria donor" organs, even in the very ill recipient, is limited primarily to transplant programs with high enough surgical volume to absorb significant mortality or organ failure risks (Grimm et al. 2015). Machine perfusion allows the transplant team to assess a high-risk organ which may have been discarded due to currently accepted criteria for donor metrics. If the organ performs well, it may be incorporated into the routine volume of transplant centers, therefore increasing the donor pool and expanding access to heart transplantation. Finally, active warm perfusion of organs promises the opportunity to intervene in organ function or antigen presentation by introducing somatic gene therapies into the donor heart directly, outside of

the donor or recipient circulation avoiding both ethical and clinical risks (Bishawi et al. 2019).

Machine perfusion provides the potential opportunity for the cardiac transplant team to utilize hearts from donors declared dead by cardiac criteria (DCD), a donor population that are not currently used in the United States for heart transplantation. Historically, the first heart transplants were performed using DCD donors that were located in neighboring operating rooms to the recipient. This minimized the time that the donor organ was out of the body, and the period of warm ischemia was short. The introduction of brain death (DBD) and its acceptance as a legal form of death declaration ushered in a change in strategy in organ transplantation, specifically for the heart transplant community, to rely entirely on DBD donors. Brain dead donors have the obvious advantage in cardiac transplantation of avoiding the obligate ischemic insult of cardiac death and the uncontrolled period of warm ischemia to which the heart is exceptionally vulnerable (Beecher 1968). The lack of predictability coupled with the inability to assess a DCD heart after arrest creates a high-risk donor situation when compared to the use of brain dead donors by which objective criteria can be measured and quantified and in which there is no period of uncontrolled warm ischemia. Machine perfusion reanimates the heart and allows the procurement team to assess the functional and metabolic performance of the organ prior to making a commitment to transplant the organ. In doing so, the transplant team has the ability to assess if the DCD organ will be suitable for transplantation. If the organ meets objective criteria for suitability for transplant during the perfusion period, this strategy provides an opening to significantly expand the donor pool (Dhital et al. 2017).

Machine perfusion truly expands the reach and the capabilities of cardiac transplantation by greatly expanding the amount of time that the heart can be outside of the body, as well as providing objective measures of organ performance. These abilities provide the opportunity for the cardiac transplant community to greatly expand the geographic reach of cardiac transplantation and refine matching criteria for better long-term outcomes, expand the donor pool with the potential of utilizing DCD hearts, and add to the objective assessment and possible transplantation of what may be perceived as a marginal organ prior to ex vivo perfusion. These opportunities are the primary reasons that the goal of creating a usable machine perfusion platform for transplantation has persisted through the decades. The fact that it has finally come to clinical practice is exciting and portends a new frontier in thoracic organ transplantation.

The History of Machine Perfusion

Le Gallois

For almost as long as people have dreamed of replacing diseased and damaged organs in the human body, they have imagined the support of these organs in an extracorporeal environment. In the late eighteenth century, renowned scientist Julian Jean-Cesar Le Gallois observed in his monumental work, "Experiments on the Principle of Life," that any organ in the body could be preserved indefinitely if a source of arterial blood could be provided to the organ for its nourishment (Fye 1995b) (Fig. 2). He made these observations by performing vivisection experiments on decapitated rabbits and demonstrating that organs could be kept alive in an otherwise dead animal with attention to preserving some source of perfusion (Legallois 1812). Additionally, Le Gallois made significant contributions to our understanding of the relationship between the central nervous system and the control of the heartbeat, initially contradicting and ultimately expanding on the work of Albrecht van Haller on the origins of automaticity in the heart (Fye 1987, 1995a).

Langendorff

The most familiar expression of ex vivo perfusion, or in vitro perfusion, of cardiac tissue was developed by Oskar Langendorff at the University of Rostock for studying the physiology of the beating heart. In his model, the heart is suspended

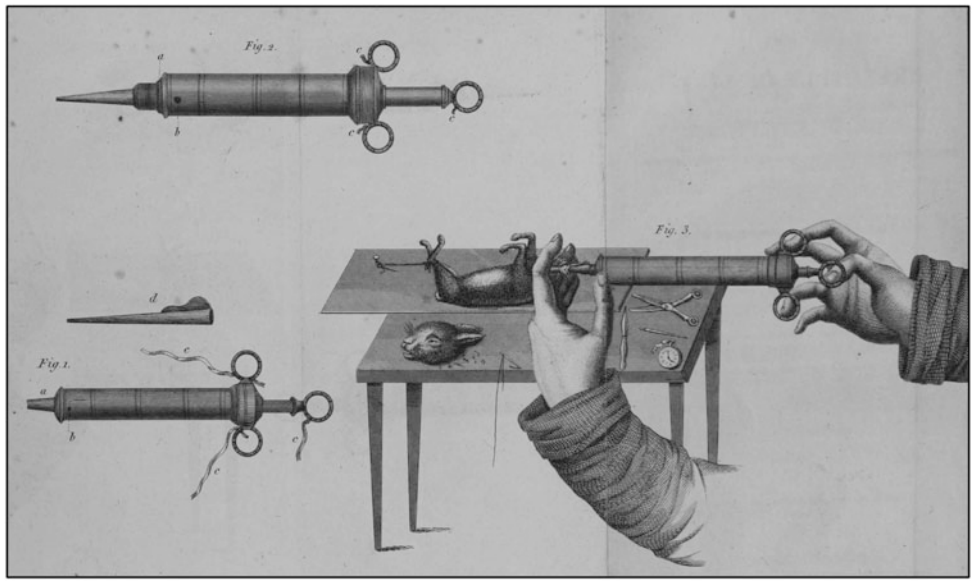


Fig. 2 Image from the inside cover of "*Experiments on the Principle of Life*" by Julien Jean Cesar Le Gallois showing the concept of maintaining perfusion to support organ function after a mortal injury (1812)

from the aorta and perfused in a retrograde fashion with a physiologic electrolyte solution (Bell et al. 2011) (Fig. 3). Langendorff leveraged his device to greatly expand our understanding of cardiac physiology and pharmacology. It is also his method of retrograde heart perfusion that has been the basis for retrograde perfusion of the heart in cardiopulmonary bypass, allowing the field of cardiac surgery to develop (Taegtmeyer 1995).

Carrel

At the dawn of the twentieth century, Alexis Carrel, the great pioneer in vascular surgery, in collaboration with the American aviator, explorer, and inventor Charles Lindbergh, developed an extracorporeal organ support device called the "Glass Heart" which was pictured on the cover of *Time* magazine in 1931 (Carrel 1931) (Fig. 4). The device provided a sterile mechanism to continuously pump and oxygenate blood to an isolated organ creating the ability for the organs to function for hours to days while perfused, providing proof of concept to what Le Gallois had proposed a century before (Legallois 1812). This work, in combination with efforts in the development of vascular anastomosis in collaboration with Mathieu Jaboulay, became the basis for the Nobel Prize which was awarded to Carrel in 1912 (Dente and Feliciano 2005). These tremendous achievements in the medical field provided practical and fundamental advances that were necessary for the later development of many exciting fields of medicine and surgery including solid organ transplant. Sadly, these significant contributions were overshadowed by profound racism and dark interest in eugenics that Carrel spent years propagating and writing about. His writings were used by members of the Nazi party in Germany in the 1930s as the basis for extermination programs. At the Nuremberg Doctors Trial in 1946, Dr. Karl Brandt, the head of a program for killing of the mentally handicapped, quoted Carrel's "Man, the Unknown" as justification for these terrible practices (Carrel 1935; Reggiani 2007).

Barnard

As the excitement surrounding the first human to human heart transplant exploded on the medical scene, the work on machine perfusion took a back

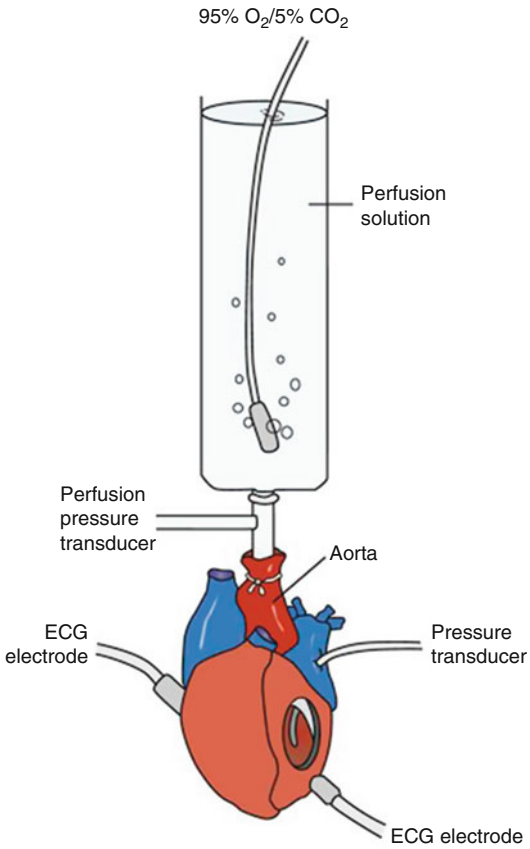


Fig. 3 The Langendorff heart preparation for retrograde perfusion of the heart. In the Langendorff prep, the heart is kept beating and different interventions can be directly measured in the isolated heart to elucidate normal physiology and response to different stimuli. This was the conceptual basis for cardiopulmonary bypass. (From Hearse and Sutherland 2000)

seat to important clinical questions about how to diagnose, monitor, and treat organ rejection while providing effective and safe immunosuppression (Lower et al. 1968; DiBardino 1999). These questions were answered, to some degree, by the granting of FDA approval for the use of cyclosporin A in clinical heart transplantation in 1983. Following the introduction of cyclosporin, transplant volume increased rapidly and then plateaued, reviving an interest in machine perfusion (DiBardino 1999; Colvin et al. 2019; Linden 2009). In 1984, Christiaan Barnard, who performed that first heart transplant in December of 1967, published on the experience at Groote Schuur Hospital in Cape Town, South Africa, transplanting four patients with hearts preserved with machine perfusion and transported from varying distances (Wicomb et al. 1982, 1984). This was the first clinical experience of hearts supported by machine perfusion, extending the time that the organ was outside the body, followed by successful transplant (Fig. 5). Barnard's machine was based on a cold perfusion model and did not keep the heart warm and beating, but was proof of concept with some remarkable results; one heart was preserved for over 16 h prior to transplant.

With the early success of machine perfusion, it may be difficult to understand why this technique failed to capture wide acceptance or become the clinical standard of care. An examination of the initial technique may lead to some answers. The apparatus that Barnard used in his efforts was quite substantial, requiring a large amount of equipment and personnel to perform a heart recovery and manage the organ during transport. In addition to the logistics of equipment and the cost of additional personnel, the introduction of machine perfusion brings with it a number of variables that are prone to failure. For instance, equipment failure could result in poor preservation or organ loss, and human error related to judgments about organ perfusion parameters and organ preservation may occur, complicating the process (Collins et al. 2008). These variables are all notably absent with cold static preservation, as it does not rely on anything other than a sterile container, ice, and a reliable mode of transportation back to the recipient hospital.

Early on, the simplicity of cold storage won out over the complexity of machine perfusion, especially in an era when there were many ideal donors available and few people undergoing heart transplantation. As the years went on, the number of recipients began to exceed the number of donor organs available. Due to the scarcity of the donor heart as a resource for transplantation, questions related to the allocation of donor organs began to center on time on the waiting list and waiting list deaths as compared to the

Fig. 4 The Glass Heart in the National Museum of American History. This is the device Carrel and Lindbergh used to maintain whole organs for days at a time to study function in isolated culture. (Reproduced from the NMAH website https://americanhistory.si.edu/collections/search/object/nmah_688713)

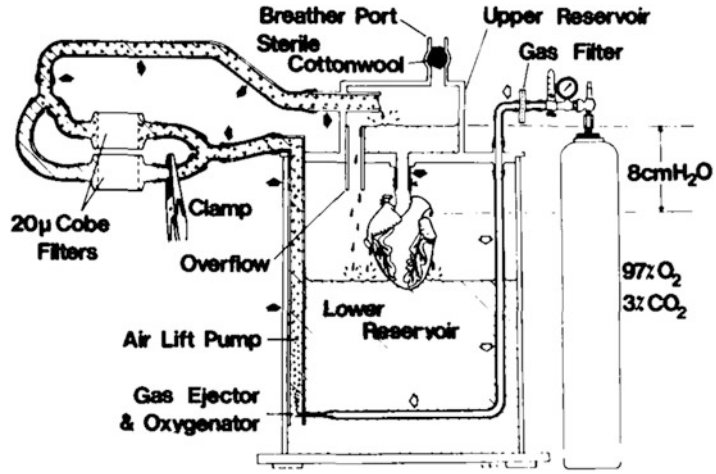


Fig. 5 Hypothermic machine perfusion device used by Christiaan Barnard to transport and preserve four hearts for transplant in 1984. (Reproduced from Wicomb et al. 1984)

recipient's severity of heart failure. Waiting list times and outcomes quickly became a measurable metric and variable when assessing transplant programs and quality. As a result, interest was renewed in the use of donors from longer distances, donors with more marginal performance characteristics, and hearts from DCD donors in order to minimize wait list times. With this reinvigorated interest in expanded criteria donors came a renewed effort to create a manageable machine perfusion platform.

Animal Experimentation

Hypothermic Machine Perfusion

As early as 1968, Proctor and Parker demonstrated that isolated hearts could be preserved for up to 72 h with hypothermic perfusion in a canine model. They reanimated the hearts in a heterotopic fashion where they were perfused but not loaded with the systemic cardiac output (Proctor and Parker 1968). The same group extended this

time to 96 h at 4 °C and were able to demonstrate normal sinus rhythm in the reanimated hearts after 10–20 min of reperfusion, again in an unloaded heterotopic model (Proctor 1972). In 1982, the group in Cape Town performed experiments on portable hypothermic machine perfusion of swine hearts for preservation of up to 24 h after which they were reanimated and then tested for functional capacity on a loaded Langendorff preparation (Wicomb et al. 1981, 1982). These experiments formed the basis for their human transplant series reported 2 years later. In 1986, the same researchers performed orthotopic heart transplants on baboons with baboon donor hearts that had been preserved with hypothermic perfusion for 48 h with a mean survival after transplant of 20 days (Wicomb et al. 1986). At the University of Texas, San Antonio, in the mid-1990s, hearts were perfused with oxygenated University of Wisconsin solution at 4 °C and compared to cold stored hearts at 12 h in a canine transplant model. The machine-perfused hearts recovered function comparable with controls that were directly transplanted, while cold storage hearts performed poorly (Calhoon et al. 1996). Using the same machine perfusion system, porcine hearts were preserved for 4 h in oxygenated Celsior solution and compared with cold storage. They demonstrated that both the perfused hearts and the cold storage hearts recovered function on an unloaded Langendorff preparation; the perfused hearts had preserved cellular structure and less endothelial dysfunction than cold stored hearts but did show increased edema formation (Michel et al. 2014). The device used in these studies became the Paragonix SherpaPerfusion™ transport system (Paragonix Technologies Inc., Braintree, MA). This device is not currently approved in the USA; however, they received European Conformity (CE) approval in February of 2018. In 2016, Steen and colleagues performed orthotopic heart transplants in swine after 24 h of hypothermic intermittent perfusion. The hyperoncotic cardioplegic solution was administered for 15 min out of every hour for 24 h, and then the organs were transplanted. All of the subjects survived 24 h after transplant (Steen et al. 2016). Additional animal studies continue to show that recovery of function, measured by widely varying methods, is possible after very long periods of hypothermic perfusion with multiple perfusate solutions from standard cardioplegic preparations to polyethylene glycol hemoglobin solutions (Jones et al. 2003).

In a canine model, Choong et al., in Melbourne, Australia, showed near-normal cardiac output, power, left ventricular dP/dt max, and lactate metabolism on reperfusion in a working Langendorff preparation after cold low-flow perfusion with an oxygenated crystalloid solution supplemented with oncotic elements and a vasodilator (Choong et al. 2016). This gravity-fed, hypothermic mode of preservation was chosen for the simplicity of the perfusion apparatus and its potential use in clinical practice. They also showed that low-flow hypothermic perfusion with supplemented St. Thomas' solution, which is a high potassium-, magnesium-, and procaine-based cardioplegia, could preserve hearts for up to 20 h in a small animal mode. These hearts demonstrated good recovery of function on a Langendorff working preparation (Ou et al. 2014).

These animal studies demonstrate proof of concept for the hypothermic perfusion approach, and some of the results reported above are quite remarkable in terms of the amount of time that organs were preserved and demonstrated at least some measure of recovery; however, the lack of functional assessment capability prior to committing the recipient to transplant is a major barrier for this approach in clinical transplantation. This is especially true for the applications of machine perfusion that are most in need which is the preservation of extended criteria donors and DCD donors.

Normothermic Machine Perfusion

In 1998 Hassanein et al. reported on their work with a portable warm perfusion device for heart preservation. In a swine model, they showed that 12 h of warm machine perfusion with a blood-based perfusate was superior to cold static storage for preservation of hearts and were able to demonstrate their method for functional assessment of the hearts on their system. This entailed

loading of the left ventricle to allow for LV ejection through the aortic valve. The machine-perfused hearts outperformed cold stored hearts on measures of LV developed pressure and had less myocardial edema, less tissue acidosis, and better endothelial vasomotor function (Hassanein et al. 1998). White et al. studied the effect of different perfusate compositions on the performance of normothermic machine perfusion. They looked at red blood cell concentrate, whole blood, an acellular hemoglobin-based fluid, and the same acellular hemoglobin mixed with plasma. They normalized the hemoglobin concentration in each group to 40 g/L and perfused swine hearts for 6 h. They found that whole blood-based solutions provided the best preservation and prevention of myocardial injury on histological examination and troponin-I measurement (White et al. 2015).

In a practical turn, a group from Fuwai Hospital in China developed a normothermic perfusion system from commercially available products dubbing it the "Heartbeat" system. These components included an ECMO circuit, centrifugal pump console, hard shell blood reservoir, roller pump, and hemofiltration set. They perfused hearts with a blood-based oncotic solution for an 8-h period where coronary flow and gas flow were adjusted to maintain normal blood gases. They found the Heartbeat system preserved organs better than cold static storage over the study period (Li et al. 2017).

Normothermic machine perfusion was shown to be a clinically viable pathway to organ preservation through the painstaking animal studies above and numerous parallel investigations. The opportunity to assess organ function during the perfusion period was especially appealing and was likely the rationale for adopting this approach for clinical evaluation in the human trials that followed.

Clinical Trials

PROTECT I was the first-in-man trial of the Organ Care System (OCS™) for the heart. It was conducted at four centers in Europe as a single-arm, nonrandomized safety study with a primary endpoint of 7-day survival. Twenty-five hearts were instrumented and 20 were transplanted, 3 did not pass the assessment, and 2 were found to not have met the inclusion criteria. All 20 patients met the primary endpoint, as well as the secondary endpoints of 30-day patient and graft survival. Based on this safety assessment, CE approval was obtained for the OCS™ heart in 2006. PROTECT II was launched as a post-approval registry but lapsed as commercial use in Europe increased (Messer et al. 2015).

PROCEED I was the US clinical safety trial in which 11 of 13 patients survived to the 30-day endpoint, and based on this and the PROTECT I data, the pivotal PROCEED II trial was performed as a multicenter, randomized, non-inferiority trial in 10 US centers (Ardehali et al. 2015). The primary endpoint was 30-day patient and graft survival, and the secondary endpoints were cardiac-related severe adverse events, severe rejection, and median ICU length of stay. Donor hearts had to be accepted for transplant prior to randomization and acceptable for both OCS™ machine perfusion and standard cold storage. This trial excluded high-risk recipients as well as expanded criteria donors, focusing on standard donor hearts. The 30-day patient and graft survival rates were 94% in the OCS™ group and 97% in the standard cold storage group ($p = 0.45$) demonstrating non-inferiority of the machine perfusion system.

EXPAND Heart was the natural progression of the technology to include expanded criteria donors at 10 centers in the USA. The criteria used to define expanded criteria donors were ischemic time greater than 4 h, or ischemic time greater than 2 h plus at least one additional risk factor such as greater than 20 min of cardiac downtime, ejection fraction (EF) of 40–50%, left ventricular hypertrophy (LVH) greater than 12 mm but no more than 16 mm, donors over 45 years of age, and donors with nonspecific coronary artery disease. In this donor population, the utilization rate was 81%; 30-day and 6-month survival were 94.7% and 88%, respectively. The average time on perfusion was 4.64 h and the severe primary graft dysfunction (PGD) rate was 10.7%. The EXPAND trial is currently under a continuing access protocol, while the FDA

reviews the results for commercial approval (Schroder et al. 2019). Based on the experience in the EXPAND trial, and the experience in Australia and the UK, a US DCD trial is being developed for the OCS™.

The NIHP Trial is a single-center trial of non-ischemic hypothermic perfusion versus standard cold storage being performed at Lund University in Sweden. The trial uses a portable cardiopulmonary bypass circuit, an automated pressure and flow regulator, and a submersion bath where the heart is bathed in a sanguineous oxygenated cardioplegic solution at 8 °C. The initial safety cohort of six patients have been transplanted and initial results are pending follow-up. The safety cohort will be followed by a larger 34-patient pivotal trial (Nilsson et al. 2019).

These trials have set the stage for a dissemination of this technology on a much broader scale. Machine perfusion will continue to evolve in the coming years as the devices become commercially available to clinicians and researchers around the world.

Single-Center Experience

Follow-up of the clinical trial patients and studies of commercial patients in Europe and around the world have added to the collective knowledge about machine perfusion and have demonstrated its value in organ preservation. Cedars-Sinai published their 2-year follow-up on patients that were enrolled in the PROCEED II trial to assess the longer-term outcomes of machine perfusion and found no difference at 24 months in patient survival or in heart-related adverse outcomes (Chan et al. 2017). Koerner et al. reported on a cohort of 29 OCS™ and 130 contemporary cold storage cases demonstrating no statistical differences but a trend toward improved survival, less primary graft dysfunction, less renal failure, and fewer episodes of severe acute rejection in the OCS™ supported patients (Koerner et al. 2014). Garcia-Saez and colleagues at Harefield Hospital in London report on their post-approval use of the OCS™ in cases where there was an extremely unfavorable donor or recipient profile (Garcia Saez et al. 2014). They describe 30 cases where donors were identified with severe LVH, prolonged expected ischemic time, low-ejection fraction, or coronary artery disease, with a utilization rate of 87% for this adverse cohort and a 92% survival with an average of 250 days of follow-up.

As the technology moves out of the realm of clinical research and into the hands of practitioners, the true test of the platforms lies just ahead as physicians push the limits of organ preservation to salvage additional hearts for patients with end-stage heart disease.

Current Technology

The current revival of interest in machine perfusion of the donor heart for preservation and assessment has revolved primarily around two strategies. The first being warm, normothermic perfusion with a beating heart. The second is cold perfusion and a static heart. There are advantages and disadvantages to each method and different models for each approach. A basic description for each is presented and then followed by details about published platforms and clinically available products.

The basic concept of normothermic machine perfusion is very similar to cardiopulmonary bypass. The heart is supported with a blood-based solution that is pumped through a heater and oxygenator and then to the heart. It can be set up as an unloaded heart where flow is into the aorta and through the coronary arteries similar to CPB, or it can be set up to flow to the pulmonary veins and allow the heart to eject in a "loaded" model of perfusion. The advantage of normothermic perfusion is the ability to make assessments about the mechanical and metabolic function of the heart during the perfusion period. There is also a theoretical benefit of reducing the formation of edema through the constant contraction of the heart which keeps lymph flowing through the myocardium.

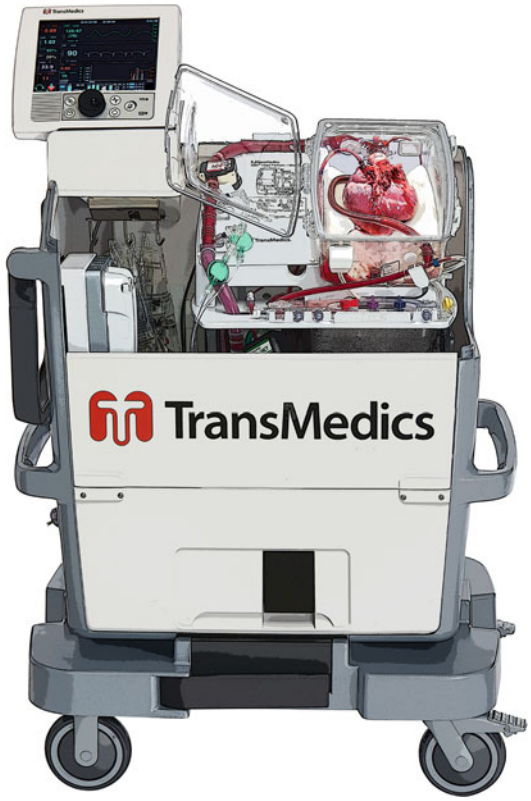


Fig. 6 Image of the Organ Care System for the heart by Transmedics, Inc., Andover, MA, USA

Organ Care System

Currently, the only commercially available machine perfusion device in the USA for cardiac support is the Organ Care System by TransMedics, Inc. (Andover, MA) (Fig. 6). This device consists of a pulsatile pump with a heater and oxygen-gas mixture, IV pumps, flow probes, and control panel. There is a disposable insert that contains the heart chamber, blood tubing, oxygenator, blood reservoir, and access ports (Fig. 7). The disposable unit is connected to the pump base, the oxygen mix is connected, and the flow probes are attached. The pump is then primed with a proprietary solution that contains mannitol, electrolytes, and a phosphate buffer. Other additives that supplement the priming solution include albumin, dextrose, amino acids, steroids, antibiotics, and other additives. IV solutions of adenosine and epinephrine are attached to the circuit. During the procurement process, 1200–1500 cc of heparinized whole blood is retrieved from the donor just prior to cross-clamp or preservative flush. The collected whole blood is then added to the priming solution in the blood reservoir of the system, and circulation of the blood through the system is initiated to begin the de-airing process while the donor heart is procured. After the heart is removed from the donor, it is prepared on the back table by placing the aortic connector in the ascending aorta and securing it with a tie band, securing the pulmonary artery cannula in the main PA with a purse-string suture, and closing the SVC. The heart is then placed in the heart organ chamber on the top of the OCS™ insert. The aorta is connected to the arterial limb of the circuit and de-aired. This connection initiates flow into the coronary arteries and is the beginning of the perfusion period. The heart is kept empty by manually compressing the LV until the heart begins to beat regularly or the pacing leads capture. Then the PA cannula is attached, the IVC is closed, and an LV vent is inserted through the open LA. This completes the circuit and the heart chamber can be closed for transport. Initial lactate levels are assessed, and pump flows and aortic pressures are adjusted to maintain adequate coronary blood flow and an optimal lactate profile. Coronary blood flow and lactate are measured at regular intervals throughout the perfusion period and adjustments are made in the pump flow or adenosine infusion to maintain adequate perfusion pressure. Once the organ is in the recipient OR and the recipient operation has progressed to the point of graft implantation, the OCS™ machine is connected to a standard heater/cooler and the temperature of the blood is gradually reduced to 14–16 °C. Once the target temperature is achieved, or if the heart distends with fibrillation, the aortic line is clamped, cardioplegia is administered into the aortic root, and the heart is removed from the circuit. It is then decannulated, and standard back-table preparation of the heart is undertaken to prepare for implantation.

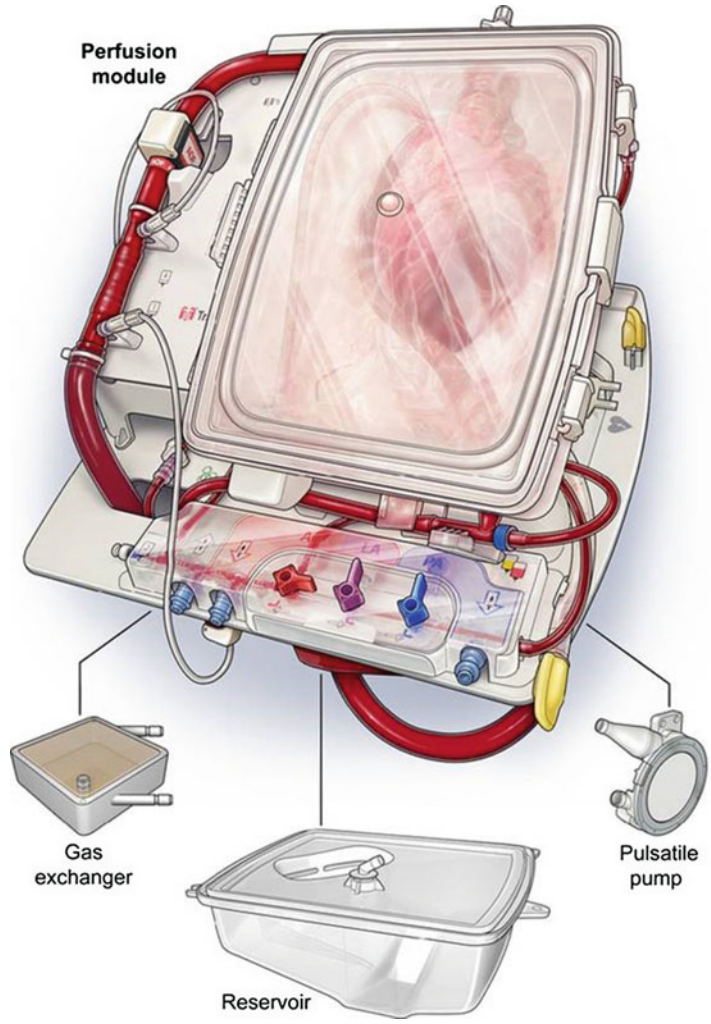


Fig. 7 Schematic breakout of the components of the OCS cartridge. Transmedics Inc. Andover. MA

Due to the numerous steps involved in the setup, cannulation, initiation, and maintenance of perfusion on the OCS™, there are many opportunities where failure can be introduced when compared to a cold static model. Care must be taken to ensure that each step is carried out correctly and that the physiology is understood to avoid human error. Several conceptual points can help improve outcomes, such as avoiding myocardial edema formation and rapidly establishing effective perfusion. The longer a heart remains perfused on the system in an unloaded state, the greater the amount of edema that collects in the interstitial tissue of the heart. This negatively impacts function and, if sufficiently impaired, will occasionally require 12–24 h of temporary mechanical support, such as extracorporeal membrane oxygenator (ECMO) support or a temporary left or right ventricular support device (LVAD or RVAD). Edema formation will resolve with time once the heart is ejecting and loaded in the recipient, and typically temporary support can be weaned fairly quickly. Specific maneuvers have been identified to reduce edema on machine perfusion which include keeping pump flow as low as possible for adequate coronary perfusion, placing the pump in synchronized pumping mode, adjusting the oncotic pressure of the perfusate, maintaining a stable lactate profile, and limiting the perfusion time to around 5 h. Beyond 5 h, the heart will still be perfused and

protected; however, edema begins to more significantly affect early graft function, and this may increase the likelihood of requiring temporary mechanical support posttransplantation (Kaliyev et al. 2019; Collins et al. 2008). This effect has been seen in large animal studies demonstrating myocardial functional decline after long periods of machine perfusion (Hatami et al. 2019). The other key element in the management of an OCS™ heart is that rapidly establishing sufficient perfusion after connecting the aortic cannula to heart is critical. This allows rapid control of the lactate levels, and the ability to wean flows down to minimal levels. When too much time is taken in the early phases of reperfusion, achieving a lactate profile that is favorable may take several hours and require high pump flows and high levels of adenosine administration, leading to unnecessary edema accumulation. Early pacing of the heart also helps accelerate the ability to complete the pulmonary artery connection and close the right side of the heart, allowing measurement of coronary flow.

An early version of the OCS™ device incorporated a working mode setting into the warm machine perfusion platform which allowed functional assessment of the organ during transportation and observation. The ability to ascertain a functional assessment of the heart was seen by some as essential to establish confidence in the donor heart prior to transplantation. Early experience in large animal studies and in clinical use in Europe showed that metabolic parameters, namely, the lactate, and a favorable coronary flow and aortic pressure profile were important factors in predicting good performance of hearts after transplant. The elimination of the working mode in the OCS™ platform was based on this experience and the additional complexity involved in the preparation and management of a heart in working mode.

Normothermic Regional Perfusion

The other clinically available approach to organ recovery with machine perfusion is normothermic regional perfusion (NRP). This entails using cardiopulmonary bypass to provide oxygenated blood to organs isolated from the cerebral circulation for support after cardiac determination of death. This approach has been used in the recovery of both abdominal organs and thoracic organs and typically entails the use of either a full cardiopulmonary bypass circuit (CPB) or simply an ECMO circuit, for blood oxygenation and pumping. For isolated abdominal organ procurement, the donor usually has an arterial cannula placed into the common femoral artery for pumping fresh oxygenated blood into the donor and a venous cannula placed into the common femoral vein for drainage of blood to the pump. A clamp is placed on the aorta at the diaphragm to prevent the flow of blood to the cerebral circulation, and the organs are resuscitated in situ. In the case of thoracic organ retrieval, the chest is opened and the arterial cannula is placed in the arch of the aorta and the venous cannula is placed in the right atrium. The innominate and carotid arteries are then clamped directly prior to starting the pump flow to both the thoracic and abdominal organs and the heart is reanimated in situ. After sufficient time has been given for the heart to recover from the ischemic insult of uncontrolled cardiac arrest, generally around 45 min, the ECMO or CPB is weaned off, and the isolated donor organs are supported entirely on the intrinsic cardiac function and ventilated lungs. This allows for detailed assessment of the heart and lungs including transesophageal echocardiography, placement of a pulmonary artery catheter for hemodynamic assessment, and measurement of cardiac output and blood gases. Once the assessment is complete, the remainder of the organ retrieval can proceed in a routine fashion as it would for a DBD donor.

The NRP approach to DCD heart retrieval is considerably less expensive than ex vivo heart perfusion if the heart is preserved after assessment and recovery in a cold static state for a short period of time. Most recently, this has been demonstrated on two patients in Liege, Belgium, where they obtained good results after NRP assessment and cold storage of the donor organs for transport to the recipient operating room. They were able to demonstrate excellent hemodynamics in the

donor after 30 min of perfusion and weaning of support. The recipients also had excellent hemodynamics in the early postoperative period, and the authors cite the ability to make a functional assessment and the reduced cost of procurement as the primary indications for the NRP approach (Tchana-Sato et al. 2019). If the recovery occurs at an institution that performs cardiac surgery or has access to ECMO support, then the logistics of organ retrieval are much simpler and less costly. Because management of hemodynamics on CPB and cardiac assessment post-CPB are much more familiar to surgeons and anesthesiologists, the learning curve for NRP is much less cumbersome, and practitioners can introduce the technology in a much more straightforward fashion. Lastly, the equipment for NRP are common and already in use at all heart transplant centers, and so no additional capital investment is necessary to engage in this strategy of organ recovery.

Ethical concerns regarding the reestablishment of cardiac function in a donor who has been declared dead have been raised surrounding the use of NRP in cardiac procurement. This seems ironic since the determination of death by cardiac cessation of function was initially felt to be the more ethically acceptable approach to cardiac transplant and the introduction of brain death criteria was ethically more challenged. With renewed interest in cardiac transplant using DCD donors, new ethical concerns have arisen. These have been particularly apparent with regard to NRP due to the reestablishment of circulation in the donor body. Although the cerebral circulation is isolated prior to reanimation, concerns remain about the possibility of consciousness in the donor. These concerns have been overcome in England where NRP for cardiac recovery has been accepted. Ongoing discussions in a multidisciplinary forum will be needed to allay fears and address concerns to make this feasible in the USA.

Future Applications

The most proximate application of machine perfusion technology is to expand the time that a heart can be out of the body to improve the utilization of organs. Machine perfusion has been shown to be as safe as cold static storage for clinical transplantation. Justification for the cost of technology will be found in bringing new hearts into the donor pool for transplantation. Standard donor hearts go unused fairly frequently from simple problems like no good blood type and antibody match within a reasonable distance, or from no recipient to match the size of the donor, or from a remote donor hospital with limited capability for organ assessment, or from donor family limitations that create unsurmountable logistic problems for remote transplant centers. All of these problems can be addressed by the technology as it exists today and with the donor system as it is set up today. The current technology available for the machine perfusion of donor hearts can safely preserve the organs for longer periods of time to allow for greater distances to be travelled to match unused hearts with potential recipients. Pending FDA approval for commercial use in the USA should greatly expand the application of this technology to improve donor utilization.

Expanded Criteria Donors

Another major area of interest is in using the technology to access more expanded criteria organs for transplantation. It has already been noted that the major limitation to cold static heart preservation is that the safe ischemic time is greatly reduced with increasing donor age and increasing left ventricular hypertrophy. Increased ischemic time may also be a factor in significantly undersized hearts, hearts with coronary artery disease, diabetes, significant downtime, or organs with marginal function. Machine perfusion may be a means of safely utilizing these extended criteria donors, and the results of the EXPAND heart trial are awaiting publication as of this writing, which should answer this question.

Donation After Cardiac Determination of Death

Probably the most exciting prospect for this technology, lying palpably on the horizon, is the use

of machine perfusion in the resuscitation and assessment of donation after cardiac death (DCD) donors. According to the United Network for Organ Sharing website, there were over 2100 DCD donors in the USA in 2018, and the numbers continue to increase with an expectation for close to 2500 DCD donors in 2019. Even conservative estimates are that 12–20% of DCD donors could be cardiac donors, and the real number could be as high as 35% (Osaki et al. 2014). This would lead to an increase in cardiac donors in the USA of between 375 and 875, which would correspond to a 12–25% increase in heart transplantation per year. That means nearly 500 additional lives could be saved with the adoption of a tool that has been in development for over 300 years. Before the term DCD was coined to differentiate it from the newer method of declaring a potential donor dead by brain death criteria and proceeding to the operating room with a beating heart and controlled arrest in the OR, all of the first heart transplants were donor with donors declared by cardiac death criteria and direct procurement and transplant. Outcomes in this era of heart transplantation were abysmal and part of the reason that brain death was readily adopted as the primary method of donor procurement. The use of DCD donors in heart transplant was unheard of after that time, until 2008 when Campbell et al., at the University of Colorado, reported on three DCD heart transplants done in neonates by direct procurement and with good results (Boucek et al. 2008). Unfortunately, there were questions about the extremely short standoff period provided for determination of death by cardiac criteria, and criticism may have led to the cessation of the practice. Again, the field was quiet, until three DCD heart transplants in adults were reported by Dhital et al., in Sydney, Australia (Dhital et al. 2015). The donor preservation was done using machine perfusion for resuscitation and assessment of the organ on the OCS platform. Outcomes were excellent and the practice continued. DCD heart transplants were then reported from two centers in England, Papworth and Harefield, also with good initial results (Messer et al. 2017). The most recent reports from these centers show 2-year survival surpassing standard criteria brain dead donor transplants (Messer et al. 2019). This raises the question of whether there may be additional benefits to DCD donors beyond just the expansion of the donor numbers.

HLA Matching in Heart Transplant

The use of machine perfusion to extend the organ out of body time may offer opportunities to improve our method of donor-recipient matching. In abdominal solid organ transplant, donors and recipients are matched not only by ABO blood typing but also by a set of proteins expressed on cell surfaces called human leukocyte antigens (HLA), encoded by a set of highly polymorphic genes that regulate the immune system. Matching these HLA antigens as closely as possible in addition to the ABO typing gives the best outcomes after abdominal solid organ transplant, and additional structure in the allocation of abdominal organs takes these HLA matches into account to allow for the best long-term outcomes in addition to the clinical need of the recipient (Jarcho et al. 1994). The complications of heart transplant are often related to the prolonged use of immunosuppressive agents which expose recipients to increased risks of infection, cancer, and kidney failure. Improving the HLA matching of donors and recipients in heart transplantation would result in the need for less intensive immunosuppression and opens the door to longer survival and fewer complications after heart transplant. Several studies have demonstrated that when even one or two of these HLA antigens are matched, the survival is increased and episodes of rejection are reduced (Kaczmarek et al. 2006). Throughout the history of heart transplant, the need to rapidly move the organ from the donor to the recipient to avoid a prolonged cold ischemic time has limited the ability to incorporate HLA matching into the heart transplant allocation schema.

Ex Vivo Therapeutics

Therapeutic interventions on machine perfusion of donor hearts are certainly one of the ultimate goals of this strategy of preservation. The presence of perfusion opens the door to being able

to deliver therapeutic agents broadly to an organ and reach the cellular level which is not reliably possible with static preservation. Strategies that target altering the milieu of the donor organ might include attempts to remove donor cytokines from the perfusate and improve heart function during the perfusion period. Other approaches could aim to permanently alter the donor graft perhaps by altering HLA gene expression. Studies have shown that it is possible to use machine perfusion to deliver much higher quantities of viral vector to a much more specific target in the ex vivo-supported heart (Bishawi et al. 2019). Alternatively, introduction of antiapoptotic signals may help reduce ischemia reperfusion injuries during graft implantation. The potential is truly enormous.

Conclusions

We have not achieved the perfect solution to organ preservation. The advantage of cold static preservation is the simplicity, low cost, and minimal opportunity for system failure or human error. Hypothermic machine perfusion has been shown in animal models to promise a very long preservation period and the potential for intervention on the organ. The warm machine perfusion models offer an intermediate period of preservation and opportunity for therapeutic intervention and have a more physiologic window into organ function for heart assessment. The winning technology will find a way to meld the advantages of several of these approaches, perhaps cold static transportation with prolonged hypothermic perfusion followed by a short period of normothermic assessment prior to implantation. It is very likely that FDA approval of machine perfusion in organ preservation is imminent and that this technology will have an impact on the practice of heart transplantation in the next 5–10 years. Having a thorough understanding of the possibilities and limits of the technology will be critically important to practitioners of heart transplant. The expansion of organ preservation to include machine heart perfusion will likely create a much larger role for organ selection, management, and preservation in the larger field of transplantation with increasing need for specialized knowledge.

Cross-References

- ▶ Current Listing System
- ▶ Donation After Circulatory Death Donor Use
- ▶ Donor Operation and Organ Preservation
- ▶ Extracorporeal Membrane Oxygenation
- ▶ History of Heart Transplant
- ▶ Recent Changes and Future Challenges in the Heart Allocation System

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Part VI

Transplant Operation

Surgical Complications

12

Ezequiel J. Molina and Danjing Zhao

Contents

Abstract

Surgical complications following heart transplantation include a wide variety of clinical scenarios that can occur intraoperatively, early after surgery or even years following transplantation. An increasing number of patients are at risk of surgical injuries and bleeding complications as more patients are currently being bridged to transplantation with durable mechanical support devices and therefore have a history of prior sternotomies and are anticoagulated. CT imaging of the

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chest, optimal anticoagulation reversal, careful operative planning, and meticulous surgical technique are very important tools to prevent catastrophic complications or life-threatening bleeding. Primary and secondary graft dysfunction is common after heart transplantation and one of the most important causes of death within the first year. Although the initial therapeutic strategies include inotropes, vasopressors, and pulmonary vasodilators, many patients require temporary mechanical support to rest the heart and allow graft recovery. Other less common acute and chronic complications are also discussed in this chapter including aortic complications, heart oversizing, wound infections, pericardial effusions, constrictive pericarditis, and tricuspid regurgitation.

Keywords
Heart transplantation · Surgical complications · Redo sternotomy · Reentry injury · Primary graft dysfunction · Perioperative bleeding · Wound infections · Pericardial effusion · Constrictive pericarditis · Tricuspid regurgitation

Introduction

Heart transplantation represents the gold standard therapy for advanced heart failure. However the availability of suitable donors is limited, and unfortunately only a minority of patients eligible for heart transplantation will benefit from this procedure. Prevention and management of complications are of paramount importance to maximize outcomes. Surgical complications during or early after the procedure contribute to a significant proportion of early deaths. Some of them represent classic surgical complications such as surgical injuries, bleeding, and wound infections. Other complications are specifically related to the transplanted organ such as heart oversizing and valvular problems. Primary graft dysfunction represents one of the most feared complications and accounts for a significant proportion of early deaths after transplantation. Although graft dysfunction is not strictly a surgical complication, it will be discussed in this section as it usually manifests intraoperatively, and it is often treated with temporary mechanical support devices.

Since the first heart transplant performed by Christiaan Barnard in South Africa in 1967, the baseline characteristics of heart transplant recipients have changed dramatically. The relatively stable low number of donor hearts available worldwide and the high patient mortality on the heart transplant waiting list have resulted in the increasing use of durable mechanical circulatory support as a bridge to transplantation. Currently a significant proportion of heart transplant recipients have a history of previous cardiac surgical procedures, and at least half of them are being supported by some form of mechanical circulatory support at the time of transplantation (Lund et al. 2017). Furthermore, many patients have a history of more than one sternotomy, and most of them are receiving some form of anticoagulation therapy. As a result, the overall duration, complexity, and logistics of heart transplant surgical procedures have significantly increased which may be associated with a higher incidence of surgical complications.

As a reoperative sternotomy is necessary in more than 50% of current heart transplant recipients, careful preoperative evaluation and operative planning are of paramount importance to avoid catastrophic reentry injuries. Also, patients undergoing heart transplantation who are anticoagulated and require a redo sternotomy present a higher risk of significant perioperative bleeding due to more complex, time-consuming operations and coagulopathy.

Graft dysfunction is the most common early complication of heart transplantation and is associated with significant morbidity and mortality (Kobashigawa et al. 2014). Although milder forms of graft dysfunction frequently respond to pharmacologic management, the early institution of temporary mechanical circulatory support is often required. However, the use of this supportive technology prolongs operative times, increases the management complexity of these patients, and also is associated with a specific set of complications.

Tricuspid regurgitation is the most common valvular problem following heart transplantation and is associated with worse long-term outcomes (Wong et al. 2008). Although most patients respond to medical therapy, selected patients require valve repair or replacement to prevent symptomatic right ventricular failure and decreased long-term survival.

Less common but not less important surgical complications of heart transplantation such as aortic complications, heart oversizing, wound healing problems, pericardial effusions, and constrictive pericarditis will also be discussed in this chapter.

Reentry Injury

Although the risk of reentry injury during a redo sternotomy in general cardiac surgery is low, this complication can occasionally be catastrophic. Furthermore, patients with reentry injuries during redo sternotomy have increased morbidity and mortality secondary to bleeding, prolonged cardiopulmonary pump time, and increased blood product transfusion requirements (Imran Hamid et al. 2015). In heart transplant recipients, this complication can be particularly deleterious to the allograft, as increased bleeding and transfusion requirement are associated with RV failure, graft dysfunction, and potentially increased incidence of rejection (Kedziora et al. 2016).

Due to the shortage of donor hearts, an increasing number of patients are being bridged to heart transplantation with the use of durable mechanical circulatory support devices. Therefore the proportion of transplant recipients with a history of previous sternotomy continues to increase (Lund et al. 2017). Currently more than 50% of overall heart transplant recipients have a history of prior cardiac surgery. The use of different commercial biomaterials to reconstruct the anterior pericardium during previous cardiac procedures such as durable ventricular assist device insertion can ameliorate the development of adhesions between mediastinal structures and the posterior table of the sternum and minimize the risk. However reentry injuries can still occur during a redo sternotomy in these patients.

Preoperative planning is the best strategy to prevent this potentially catastrophic complication. Many centers have successfully adopted reoperative sternotomy protocols that include a preoperative 256-slice computed tomography (CT) scan of the chest to investigate the presence of potentially dangerous sternal adhesions (LaPar et al. 2013). Furthermore, careful evaluation of chest CT imaging has become standard of care at many transplant programs, as this imaging study has been incorporated to the heart transplant workup in patients with a history of previous heart surgery. Reoperative CTs are invaluable to safely plan reentry to the chest in patients with a history of multiple sternotomies, patent coronary grafts, patients with a history of high-dose radiation to the mediastinum, or a combination of these. Occasionally reoperative CT scan imaging can identify patients that may present excessively high-risk features for a redo sternotomy (i.e., aortic adhesions to the midline of the sternum) and therefore may be considered ineligible for heart transplantation. In these challenging patients, the final decision regarding patient eligibility for heart transplantation often relies on the surgical judgment of experienced transplant surgeons after carefully evaluating reoperative CT imaging and assessing the risk of potential catastrophic complications of a redo sternotomy.

High-risk features for reentry injury include adhesions between posterior table of the sternum and important mediastinal structures including the innominate vein, ascending aorta, pulmonary artery, right atrium, previous patent coronary grafts, free wall of the right ventricle, left ventricular assist device outflow graft, etc. A safe logistic approach prior to redo sternotomy in these patients includes either percutaneous or open wire cannulation of the femoral vessels under transesophageal echocardiography or fluoroscopic guidance in preparation for potential emergent groin cannulation if an injury occurs. In patients with extremely high-risk features on preoperative chest CT imaging, establishing cardiopulmonary bypass via femoral or axillary arterial

and femoral venous cannulation prior to redo sternotomy can represent the safest strategy.

If an injury unfortunately occurs, immediate institution of cardiopulmonary bypass may become the only viable strategy to maintain hemodynamic stability. In extreme cases deep hypothermic circulatory arrest may be necessary to control bleeding and repair the injury. As the entire mediastinal dissection is performed on a heparinized patient on cardiopulmonary bypass in these challenging cases, intraoperative and postoperative bleeding can become a significant problem. Experienced surgical teams can still achieve good outcomes in these circumstances by following meticulous surgical technique, minimizing cardiopulmonary bypass times, and appropriately correcting coagulopathy with the use of blood products. Avoiding right ventricular dilatation from excessive perioperative blood product administration is of paramount importance to prevent right ventricular dysfunction.

Primary Graft Dysfunction

Although graft dysfunction is very common after heart transplantation and is associated with significant morbidity and mortality, most major cardiac transplant centers have historically used different definitions and parameters of cardiac dysfunction. Single center studies have reported an incidence between 2.3% and 28.2% (Russo et al. 2010; D'Alessandro et al. 2010; Segovia et al. 2011). The consensus conference on primary graft dysfunction after cardiac transplantation took place during the 33rd Annual International Society of Heart and Lung Transplant meeting in 2013. Several specialists of 45 international transplant programs sought to unify diagnostic criteria and therapeutic strategies (Kobashigawa et al. 2014).

Graft dysfunction is associated with significantly increased 30-day and 1-year mortality. It remains the main cause of early death accounting for nearly 40% of the deaths in the first 30 days after the procedure and 18% at 1 year (Lund et al. 2017). Graft dysfunction is classified as primary and secondary graft dysfunction. Primary graft dysfunction must be diagnosed within 24 h of completion of surgery and very frequently starts in the operating room. Primary graft dysfunction is not associated with a discernible cause. Risk factors for the development of primary graft dysfunction include donor, recipient, and surgical procedural risk factors. The most consistently identified donor risk factors for primary graft dysfunction include donor age (Russo et al. 2010), cardiac dysfunction on echocardiography, female donor to male recipient (Hong et al. 2011), and cause of brain death (Iyer et al. 2011). Important recipient risk factors are age (Segovia et al. 2011), high pulmonary vascular resistance, and more severe pretransplant condition, including bridging to transplant with inotropes, mechanical circulatory support, and/or mechanical ventilation (Russo et al. 2010; Hong et al. 2011; Young et al. 2001). Significant procedural factors include ischemic time longer than 4 h (Russo et al. 2010; Marasco et al. 2012), suboptimal logistics of graft procurement, and donor-to-recipient weight mismatch.

Some of the associations between primary graft dysfunction and the risk factors previously mentioned are poorly understood. For example, our understanding of the increased risk of primary graft dysfunction in patients bridged with mechanical support devices remains obscure. Longer cardiopulmonary bypass times and tissue trauma during complex reoperations may lead to a greater inflammatory response in these patients. Also, increased graft ischemia due to longer explant times of the native heart may be implicated in graft dysfunction in some cases. The transition from continuous flow physiology to pulsatile physiology after transplantation may also play a role. More recently the preoperative use of amiodarone in patients awaiting heart transplantation has gained attention as some studies have shown a potential relationship (Wright et al. 2017). However this topic remains controversial. The development of more effective donor heart preservation strategies is an area of active research and may lead to procedures that reduce the incidence of primary graft dysfunction in the future. There is also evidence that additional blood cardioplegia administration may protect donor hearts (Wagner et al. 2013). Although the

etiology of primary graft dysfunction remains unknown in many cases, a recent validation study has suggested that the allocation of risky donors to risky recipients amplifies the risk of primary graft dysfunction (Sabatino et al. 2017).

Primary graft dysfunction is further classified as primary graft dysfunction – left ventricle (includes left and biventricular dysfunction) – and primary graft failure, right ventricle (includes right ventricular dysfunction alone). As shown in Table 1, primary graft failure – left ventricle – has been graded as mild, moderate, and severe based on hemodynamic variables, echocardiographic parameters, level of inotropic support, and the need for mechanical circulatory support (Kobashigawa et al. 2014).

Primary graft dysfunction is initially treated with low-dose inotropes and pulmonary vasodilators such as nitric oxide or inhaled epoprostenol. Allowing additional reperfusion time on cardiopulmonary bypass maybe helpful in some cases, but the negative consequences of a prolonged cardiopulmonary bypass time need to be considered. When climbing doses of inotropes are not sufficient to support the newly transplanted heart, the use of temporary mechanical circulatory support becomes necessary. Furthermore, the early institution of mechanical circulatory support may minimize the deleterious consequences of a very prolonged cardiopulmonary bypass time and the secondary negative effects of high-dose vasoactive drugs on end-organ function such as kidneys and liver. Although intra-aortic balloon pumps have been routinely used as first-line short-term devices, more robust forms of support are currently preferred such as extracorporeal membrane oxygenation (ECMO) or temporary ventricular assist devices. Venoarterial ECMO has become a preferred strategy to support patients with primary graft dysfunction over left, right, or biventricular assist devices at many transplant centers (Kobashigawa et al. 2014). ECMO provides biventricular support in addition to pulmonary support in patients with severe pulmonary edema and hypoxemia. Although additional studies are needed, the success rate of venoarterial ECMO to treat primary graft dysfunction approaches 50% (D'Alessandro et al. 2010). Central venoarterial

Table 1 Definition of severity scale for primary graft dysfunction (PGD) (from Kobashigawa J et al.)

PGD-left ventricle (PGD-LV)	Mild PGD-LV: one of the following criteria must be met	LVEF r 40% by echocardiography, or hemodynamics with RAP 4 15 mm Hg, PCWP 4 20 mm Hg, CI o 2.0 L/min/m^2 (lasting more than 1 h) requiring low-dose inotropes
	Moderate PGD-LV: Must meet one criterion from I and another criterion from II	I. One criteria from the following: Left ventricular ejection fraction r 40%, or hemodynamic compromise with RAP 4 15 mm Hg, PCWP 4 20 mm Hg, CI o 2.0 L/min/m^2, hypotension with MAP o 70 mm Hg (lasting more than 1 h) II. One criteria from the following: i. High-dose inotropes – Inotrope score 4 10[a] ii. Newly placed IABP (regardless of inotropes)
	Severe PGD-LV	Dependence on left or biventricular mechanical support including ECMO, LVAD, BiVAD, or percutaneous LVAD. Excludes requirement for IABP
PGD-right ventricle (PGD-RV)	Diagnosis requires either both i and ii or iii alone	i. Hemodynamics with RAP 4 15 mm Hg, PCWP o 15 mm Hg, CI o 2.0 L/min/m^2 ii. TPG o15 mm Hg and/or pulmonary artery systolic pressure o 50 mm Hg, or iii. Need for RVAD

BiVAD, biventricular assist device; CI, cardiac index; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; LVAD, left ventricular assist device; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RVAD, right ventricular assist device; TPG, transpulmonary pressure gradient

[a]Inotrope score 1/4 dopamine (%1) þ dobutamine (%1) þ amrinone (%1) þ milrinone (%15) þ epinephrine (%100) þ norepinephrine (%100)67 with each drug dosed in μg/kg/min

ECMO is established cannulating the aorta and the right atrium, with cannulae exiting the mediastinum through the upper abdominal wall to allow for chest closure. Peripheral venoarterial ECMO requires femoral arterial and venous cannulation and also allows for chest closure. A separate catheter should be used for distal limb perfusion in most patients to prevent limb ischemia. The main advantage of peripheral cannulation is the ability to eventually explant ECMO without reopening the chest. The main disadvantage is related to the increased risk of vascular injury and limb ischemia. As venoarterial ECMO does not directly unload the left ventricle, from a physiologic standpoint, it may not represent the best strategy for LV recovery particularly in patients with severe LV dysfunction. The concomitant afterload increment that occurs following initiation of ECMO support in cardiogenic shock patients shifts the left ventricular pressure-volume loops to the right (Fig. 1). This leads to increased left ventricular wall stress and may impact the chances of left ventricular recovery. Patients with profound left ventricular dysfunction and minimal or no ejection represent a particularly challenging problem as they are also at risk of thrombus formation secondary to blood stasis in the left-sided chambers. The addition of a left ventricular unloading device may be necessary in these patients to prevent thrombosis of the left-sided chambers and maximize the chances of recovery. The least invasive strategy to accomplish this goal is the insertion of a percutaneous left ventricular assist device while on ECMO. Conversion to surgical temporary left ventricular or biventricular support devices is an alternative option but is associated with more surgical trauma and potentially higher bleeding risk. Less invasive left ventricular assist devices placed percutaneously or via axillary arterial cannulation represent alternative options. Left ventricular assist devices directly unload the left ventricle and shift the pressure-volume loops to the left, decreasing wall stress and maximizing the chances of recovery. Further studies are needed to define the optimal device that provides to the best chances of recovery with minimal adverse events. Retransplantation may be an option for selected patients with severe early primary graft dysfunction not responsive to the previously described therapeutic strategies.

Secondary Graft Dysfunction

Secondary graft dysfunction has a discernible cause such as hyperacute rejection, pulmonary hypertension, or known surgical complications such as uncontrolled bleeding requiring massive blood transfusions that overdistends a vulnerable right ventricle (Kobashigawa et al. 2014). Additional etiologies of secondary graft dysfunction

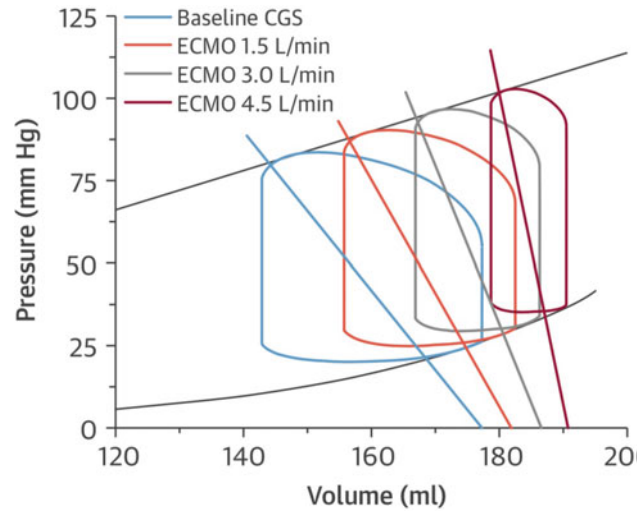

Fig. 1 Pressure-volume loops for ECMO in patients with cardiogenic shock. (Burkhoff et al. 2015)

include unrecognized coronary artery disease, anastomosis narrowing or kinking, etc.

The diagnosis of isolated right ventricular dysfunction secondary to pulmonary hypertension is supported by a postoperative pulmonary gradient ≥15 mm Hg associated with a low cardiac output (Sabatino et al. 2017). A well-demonstrated preoperative recipient risk parameter that increases the occurrence of right ventricular dysfunction is a pulmonary vascular resistance of more than 4 Woods units. Patients with elevated pulmonary vascular resistance are not eligible for heart transplantation. Preoperative identification of pulmonary hypertension is key to prevent this serious complication. Left ventricular assist devices and inotropes are used to reduce pulmonary vascular resistance and allow transplantation. In borderline cases, evaluation of responsiveness of the pulmonary vasculature to pulmonary vasodilators and optimization of heart failure treatment with inotropes and systemic vasodilators are mandatory. The recent trend toward a decrease incidence of secondary graft dysfunction may be related to improved patient selection and improved pretransplant pulmonary hypertension management (Sabatino et al. 2017).

Low cardiac output in the presence of elevated central venous pressure is the hemodynamic manifestation of right ventricular failure. Poor contractility and right ventricular dilatation can be easily observed in the operative field during surgery or assessed intraoperatively with the use of transesophageal echocardiography. Transthoracic or transesophageal echocardiography is essential to asses right ventricular function postoperatively. In cases of isolated right ventricular dysfunction, the left ventricle is underfilled and usually contracts vigorously in response to the inotropes used to treat right ventricular failure. Severe tricuspid regurgitation secondary to dilatation of the tricuspid valve annulus is often also seen on transesophageal echocardiography.

When severe right ventricular failure occurs intraoperatively, the surgeon must rule out mechanical problems at the level of the pulmonary artery anastomosis (kinking, anastomotic stenosis, etc.). Therapeutic strategies to treat right ventricular failure include preload optimization (CVP <15 mm Hg), improved contractility with the use of increasing doses of inotropes, afterload reduction with the use of pulmonary vasodilators, and chronotropic optimization (pharmacologic with β agonists or pacing). Because the right ventricle is very sensitive to systemic hypotension, it is critical to maintain an adequate systemic arterial blood pressure to ensure adequate ventricular perfusion. As the vasoconstrictors used to increase arterial blood pressure may also increase pulmonary vascular resistance, achieving a proper balance between pulmonary and systemic vascular resistances can be difficult. Adequate oxygenation and ventilation must also be assured to avoid the pulmonary vasoconstricting effects of hypoxia and hypercarbia. If these therapeutic maneuvers fail, the use of temporary mechanical circulatory support may be necessary including isolated right ventricular assist devices or venoarterial extracorporeal membrane oxygenation. The use of a newly approved percutaneous temporary right heart pump system may represent the least invasive strategy to support a failing right ventricle.

Hyperacute rejection is mediated by preformed recipient antibodies against donor graft causing widespread hemorrhage and thrombosis within the allograft (Kaczorowski et al. 2013). Because of comprehensive preoperative screening, hyperacute rejection is fortunately a rare complication. Besides graft failure, gross signs of rejection include dusky discoloration, edema, and petechiae (Kaczorowski et al. 2013; Kennel et al. 2012). Diagnosis should be confirmed with intraoperative endomyocardial biopsy (Costanzo et al. 2010). Treatment should be initiated as soon as diagnosis is made. Treatment options include high-dose corticosteroid, plasmapheresis, IVIG, immunosuppressive therapy, inotropes, and vasopressors (Costanzo et al. 2010). Ventricular assist devices and venoarterial ECMO can help provide support during immunotherapy (Kaczorowski et al. 2013). Urgent re-retransplantation may be needed but is associated with high mortality (Costanzo et al. 2010).

Right ventricular dysfunction associated with perioperative bleeding and massive transfusion of blood products is also treated with optimization of

preload, inotropic support, and pulmonary vasodilators. However, rapid control of surgical bleeding and/or correction of coagulopathy is of paramount importance to prevent further right ventricular dilatation, tricuspid regurgitation, worsening dysfunction, and elevated central venous pressure. Once bleeding is controlled, aggressive diuresis, ultrafiltration, or even dialysis may be necessary in some patients to normalize right ventricular preload and relieve venous hypertension that can lead to worsening renal and liver function.

Perioperative Bleeding

In addition to primary graft failure, perioperative bleeding is one of the most common complications after heart transplantation (Kim et al. 2013). Not surprisingly, postoperative bleeding after cardiac surgery is associated with increased morbidity and mortality (Kedziora et al. 2016). As the number of heart transplant patients with a history of previous cardiac surgery is increasing (Lund et al. 2017), the number of reoperative sternotomies associated with this procedure is growing. Furthermore, as many patients are bridged to transplant with a durable left ventricular assist device requiring anticoagulation, the incidence of perioperative coagulopathy is higher. Minimally invasive LVAD insertion techniques, which may result in lower perioperative bleeding at the time of transplantation, have not been widely adopted but hold promise.

Although there are no universal recommendations to guide the reversal of a prolonged INR before redo sternotomy, most centers follow institutional guidelines to achieve this goal. The administration of fresh frozen plasma (FFP) has been historically the only strategy to reverse warfarin in LVAD patients. However, this may be problematic in heart transplantation as it can lead to volume overload when the administration of several units of FFP is necessary. The use of concentrated coagulation factors, such as prothrombin complex concentrate (PCC), has recently become commercially available and is gaining popularity. Low-volume concentrated factors along with vitamin K are very effective and rapidly reverse the effects of warfarin with low side effects (Fig. 2).

Perioperative bleeding represents a significant problem in heart transplantation as it may contribute to exacerbation of primary graft failure and increase rejection rates (Kedziora et al. 2016; Jahangirifard et al. 2017). Postoperative bleeding can be surgical or secondary to coagulopathy. In a study including over 1,400 patients undergoing on-pump cardiac surgery, Kristensen et al. found that 7% of patients underwent at least one reoperation within 24 h due to excessive bleeding. Approximately 56%

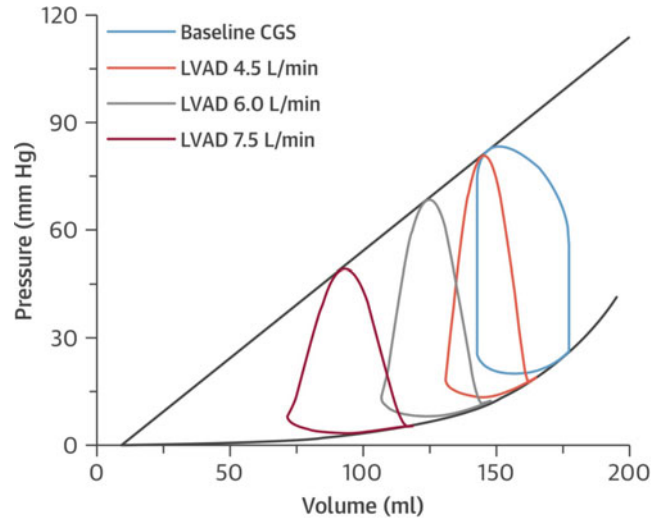

Fig. 2 Pressure-volume loops for LVAD in patients in cardiogenic shock. (Burkhoff et al. 2015)

of those patients had surgical bleeding that required clips or sutures, and 42% had coagulopathic bleeding or diffused oozing. Prolonged cardiopulmonary bypass times can induce coagulopathy by causing decrease in coagulation factors and platelets and activate fibrinolysis (Jahangirifard et al. 2017). Furthermore, intraoperative heparin use, hypothermia, and inflammatory cascade all contribute to abnormal hemostasis (Jahangirifard et al. 2017).

Some of the risk factors contributing to postoperative bleeding after general cardiac surgery include older recipient age, low body mass index, prolonged on-pump times, low ejection fraction, procedures other than CABG, elevated preoperative creatinine, and high EuroSCORE (Kristensen et al. 2012). The first postoperative hemoglobin after heart transplant can be predictive of excessive blood loss as a low level has been shown to correlate with higher chest tube output, need for re-exploration, and higher transfusions rates (Kedziora et al. 2016).

To prevent postoperative bleeding in heart transplant recipients, the International Society for Heart and Lung Transplantation (Costanzo et al. 2010) recommends that active clotting time be checked at multiple points during surgery to monitor level of heparin activity. Thromboelastography may be used during or after transplant to monitor hemostasis. FFP, platelets, and fibrinogen should be transfused based on measured levels. Recombinant factor VIIa may also be used in cases of intractable or excessive bleeding. Tranexamic acid and epsilon-aminocaproic acid can be used before cardiopulmonary bypass to reduce risk of bleeding in selected patients. Intraoperative use of fibrinogen after termination of bypass pump and heparin reversal may help reduce postoperative bleeding but may enhance postoperative acute kidney injury (Jahangirifard et al. 2017). Few studies have investigated postoperative bleeding in heart transplant recipients. Therefore, most recommendations are extrapolated from general cardiac surgery literature (Costanzo et al. 2010). Further studies are needed to improve prevention and management of postoperative bleeding after heart transplantation. Meticulous surgical technique, short cardiopulmonary bypass times, and properly correction of medical coagulopathy play a major role.

In patients that demonstrate excessive bleeding following surgery which cannot be obviously explain by medical coagulopathy, early return to the operating for an exploration is mandatory to minimize the amount of bleeding and prevent development of right ventricular failure secondary to massive administration of blood products. Patients bridged with extracorporeal membrane oxygenation may be more susceptible of bleeding and require especial attention. Also, patients who require temporary mechanical support for the treatment of primary graft dysfunction are at increased risk of postoperative bleeding. Mediastinal exploration for bleeding should be undertaken persistent high chest tube output (400 mL/hr. for 1 h, $>$ 300 mL/hr. for 3 h, and 200 mL/hr. for 4 h), any circulatory instability associated with bleeding, or radiographic or echocardiographic evidence of retained thrombus (Costanzo et al. 2010).

Tricuspid Regurgitation

Tricuspid valve regurgitation (TVR) is the most common valvular complication following orthotopic heart transplantation and affects up to 84% of the patients (Wong et al. 2008). The use of bicaval implantation technique and the construction of tension free anastomosis are important to reduce the risk of TVR in the cardiac allograft (Davies et al. 2010; Aziz et al. 1999). While concomitant tricuspid annuloplasty during heart transplantation has been proposed to decrease the incidence of TVR (Jeevanandam et al. 2006), this adjunct procedure is not currently widely accepted by the transplant community. Most patients with tricuspid valve regurgitation develop only mild to moderate regurgitation. In severe forms, however, tricuspid regurgitation can lead to right-sided failure symptoms including lower extremity edema, hepatorenal dysfunction, ascites, and dyspnea. The decision to surgically correct TVR can be very difficult, as

certain clinical scenarios have high risk of failure. Functional etiologies of tricuspid regurgitation associated with high pulmonary vascular resistance must be carefully evaluated. As it typically occurs with the native heart, anatomic etiologies have the greatest chances of success compared to functional etiologies. While repair techniques have been successfully described, there is an emerging body of evidence to support replacement as the more durable option (Raghavan et al. 2006). As mechanical valves are impractical in the heart transplant patient, biologic valves are preferred as they allow continued access to the right ventricle for biopsies. Furthermore, durability is acceptable in the low pressure system of the right-sided heart chambers.

Aortic Complications

Aortic complications can occur in 1–2% of patients receiving heart transplantation (Vigano et al.). The incidences may be higher in patients with aortic risk factors such as Marfan syndrome (Audenaert et al. 2015). Acute aortic ruptures can occur early after transplantation due to weakness of aortic tissue, technical errors, or severe hypertension (Vigano et al. 1999). The difference in compliance between donor and recipient aortic tissue may create excess tension on the suture line and subsequent predisposition to rupture or dissection. A double layer of non-absorbable suture technique is advocated by many surgeons. Atherosclerosis and hypertension are also additional risk factors. Preoperative CT of the chest and intraoperative epiaortic ultrasound can facilitate evaluation of aortic atherosclerosis and calcifications that can predispose to aortic complications. Additionally, mediastinitis and infection can lead to the development of mycotic pseudoaneurysm at the aortic anastomosis. In such cases, antibiotics and early surgical intervention are key to successful treatment. Both Dacron and homograft have been successfully used for aortic replacement and reconstruction in these challenging cases (Patane et al. 2009).

Heart Oversizing

Proper donor-to-recipient organ size matching represents a critical aspect of heart transplantation. It has been suggested that heart undersizing is associated with worse outcomes in nonobese recipients (Bergenfeldt et al. 2017). Although heart oversizing has not been associated with worse outcomes, extreme cases of oversizing can lead to the inability to properly close the sternum. Female recipients who receive male hearts and recipients with non-dilated hearts are at particular risk. Forcing sternal closure in these cases can have deleterious hemodynamic consequences secondary to right ventricular compression and dysfunction. However, leaving the chest open for a prolonged period of time hoping for a successful delayed sternal closure can increase the risk of mediastinal infections. Early consultation with plastic surgery is recommended in these difficult cases. The plastic surgeon armamentarium includes a variety of surgical options including pectoralis, omental, rectus abdominis, latissimus dorsi, as well as skin and subcutaneous flap closures. A sternectomy may be necessary in some of these cases. It is very important to avoid this problem by selecting an appropriate size heart following the recommended guidelines (Costanzo et al. 2010).

Wound Complications

Surgical wound infections (SWI) are an important source of morbidity and mortality after heart transplantation. These complications can often lead to life-threatening events such as sternal dehiscence and mycotic aneurysm formation of the aorta. The incidence of SWI after heart transplant has been reported in 8–15% of patients and is higher than after other types of cardiac surgery procedures (Zuckermann et al. 2011). Data on risk factors for SWI are limited and controversial due to small study sizes. However, some potential risk factors identified include age, body mass index, diabetes mellitus, immunosuppressive regimens (i.e., sirolimus vs. mycophenolate mofetil), prolonged cardiopulmonary bypass time,

reoperation, and pretransplant use of ventricular assist devices (Zuckermann et al. 2011). The most commonly isolated organisms are Gram-positive organisms, such as methicillin-resistant *Staphylococcus aureus*. Infections that demonstrated mixed organisms can also occur. In rare instances infection with Gram-negative organisms (i.e., *E. coli*, *Acinetobacter*) and fungal organisms (i.e., *Aspergillus*) has been reported as well (George et al. 2006).

The diagnosis of surgical wound infections after heart transplant requires high clinical suspicion. The typical signs of infection such as fever and leukocytosis may be absent due to immunosuppression. In two retrospective review studies (Senechal et al. 2004; Filsoufi et al. 2007), fever and leukocytosis were present in only 30 and 40% of patients with deep sternal wound infections and mediastinitis. Sternal pain out of proportion was the most common presentation (Senechal et al. 2004). Local signs of wound infection such as purulent drainage or erythema were present in only 33 to 40% of cases. Most patients present with more than one clinical signs. Computed tomography of the chest demonstrating mediastinal air or fluid collection can be supportive of this diagnosis.

Successful treatment of sternal wound infections requires early and aggressive surgical management in addition to antimicrobials. Several surgical management options have been described to successfully treat mediastinitis following heart transplantation. These include early debridement with substernal irrigation and primary closure (Abid et al. 2003), sternal debridement and closed-chest drainage (Senechal et al. 2004), as well as open debridement with vacuum-assisted drainage (Filsoufi et al. 2007). Muscle or omental flaps may also be used to help close dead space after debridement (Carrier et al. 2001).

Pericardial Effusion

Pericardial effusions not secondary to bleeding are commonly observed after heart transplantation, occurring in 20–36% of patients receiving heart transplant (Quin et al. 2002; Urbanowicz et al. 2015). There is no clear etiologic explanation for its occurrence. One proposed theory is that pericardial effusions represent an immune-related process. Several studies have suggested that pericardial effusions are associated with higher incidence of acute rejection episodes with more severe histologic grading (Ciliberto et al. 1995). A positive recipient-donor weight mismatch and absence of previous cardiac surgery have also been observed to contribute to development of large pericardial effusions (Hauptman et al. 1994). This is thought to be due to relatively well-preserved pericardium and large recipient-donor weight mismatch providing favorable anatomy for exudation of fluid into the pericardial space (Hauptman et al. 1994). Other risk factors identified include prolonged donor ischemia time (Al-Dadah et al. 2007), intraoperative aminocaproic acid use (Quin et al. 2002), postoperative immunosuppression with mTORi (Bouzas-Mosquera et al. 2008), and worse preoperative clinical condition (Urbanowicz et al. 2015). Rare cases of pericardial effusion due to lymph leak (chylopericardium) have also been reported (Wierzbicki et al. 2016).

While the clinical course is generally benign, significant large pericardial effusions causing cardiac tamponade can occur. Therefore, close early postoperative monitoring is recommended. Transthoracic echocardiography is generally the modality of choice (Costanzo et al. 2010). Most effusions will resolve within 3 months and are not associated with adverse clinical outcomes (Al-Dadah et al. 2007). Therefore, pericardial effusions not causing hemodynamic instability do not require intervention unless an infectious etiology is suspected (Costanzo et al. 2010). Patients with echocardiographic evidence of tamponade or hemodynamic instability can be successfully treated with percutaneous or surgical drainage (Costanzo et al. 2010). Those with recurrent symptomatic effusion or failing pericardiocentesis may be treated with subxiphoid pericardial window or pericardiectomy (Hauptman et al. 1994). A pericardial soft drain can help reduce pericardial effusions, but the duration of drainage should be balanced against the potential risks for wound infection and length of hospital stay (Kim et al. 2016).

Constrictive Pericarditis

Although constrictive pericarditis is usually considered a particularly rare complication following heart transplantation, some series report a higher incidence than constrictive pericarditis following general heart surgery (Carrier et al. 1994). Among the risk factors associated with this increased incidence, we can list recurrent pericardial effusions from traumatic right ventricular biopsies, mediastinal infections, and increased inflammation after multiple sternotomies. Recurrent episodes of rejection have also been linked to an increased risk of constrictive pericarditis. Constrictive pericarditis is characterized physiologically by impaired ventricular diastolic filling due to a fixed pericardial volume resulting in the classic dip-and-plateau pattern observed on intracardiac pressure tracings (Kumar et al. 2008). Elevation of central venous pressures and Kussmaul sign is frequently seen on physical examination. Clinically patients demonstrate symptoms of right-sided heart failure, including peripheral edema and liver and bowel congestion, leading to ascites and early satiety. Pleural effusions can present later during progression of the disease. The definitive treatment of chronic pericardial constriction is surgical pericardiectomy. This is a significant surgical procedure associated with considerable morbidity and a mortality greater than 6% (Bertog et al. 2004). Because of the high operative risk, most patients undergo multiple diagnostic procedures to ensure a correct diagnosis.

Conclusions

With the introduction of durable mechanical circulatory support, the landscape of the heart transplant recipient population has changed significantly since the early heart transplants were performed 50 years ago. As the use of circulatory support devices as a bridge to transplantation continues to grow, an increasing number of patients are brought to the operating room with a history of multiple cardiac surgical procedures. Furthermore, most of these patients are anticoagulated with warfarin. The rapidly evolving characteristics of this patient population result in longer and more complex surgical procedures, higher risk of reentry injuries, longer cardiopulmonary bypass times, greater probability of coagulopathy and bleeding, higher incidence of primary graft failure, increased exposure to wound healing problems, pericardial effusions, etc. The skills and experience of the surgical team is key to prevent and treat these surgical complications that can be associated with high morbidity and mortality in this complex patient population.

Despite the increasing technical and management challenges posed by this unique patient population during surgery, outcomes after heart transplantation have continued to improve over the last two decades thanks to improved early survival. This is likely secondary to improved recognition and management of primary graft dysfunction in the operating room and early ICU course (Kobashigawa et al. 2014). The diagnosis of primary graft dysfunction was historically associated with very poor prognosis before temporary mechanical support was adopted as a lifesaving strategy. Recent studies have found that more than 50% of primary graft failure patients supported with extracorporeal membrane oxygenation or ventricular assist devices demonstrate recovery. Current and future percutaneous or minimally invasive ventricular assist devices may improve chances of graft recovery with less adverse events. The expertise and clinical judgment of the transplant team play a significant role in the successful management of surgical complications following heart transplantation.

Cross-References

- ▶ Cardiac Allograft Rejection
- ▶ Donor Operation and Organ Preservation
- ▶ Matching Donor to Recipient

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Part VII

Postoperative Care

Intensive Care Unit and Stepdown Management

13

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Contents

Abstract

Heart transplant is the definitive treatment for patients with end-stage heart failure. Patients who undergo a transplant have the same physiologic burden as typical cardiac procedures with the added strain of organ transplant and immunosuppression. In this chapter, current principles in the postoperative management of the heart transplant patient are discussed. This includes a systematic review of surgical issues presenting in the immediate postoperative

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period and the physiological perturbations unique to the transplant patient. Standard of care in hemodynamic monitoring and mechanical ventilatory support methods are discussed with a focus on the postoperative transplant patient. Management of hemodynamic instability and common arrhythmias occurring in the perioperative period will be discussed with a review of pharmacological and mechanical approaches used in the management of these problems. Finally, nutritional guidelines pertaining to postcardiotomy patients with specific recommendations related to the transplant patient are reviewed.

Keywords

Heart transplant · Cardiac surgery · Cardiac critical care · Heart failure · Intensive care

Introduction

Heart transplantation remains the gold standard for treatment of end-stage heart failure. Short- and long-term outcomes are excellent compared to conventional medical and surgical therapy for heart failure. Potential recipients of a heart transplant undergo extensive eligibility screening prior to listing (see ▶ Chaps. 3, "Contraindications to Heart Transplantation," and ▶ 9, "Matching Donor to Recipient"). Patients with significant noncardiac comorbidities (e.g., cancer, CVA, poor pulmonary function) may not be eligible for listing. Many patients who undergo heart transplantation have had at least one prior cardiac surgery such as coronary artery bypass grafting, valve replacement/repair, or left ventricular assist device (LVAD) implantation. Nonetheless most patients who undergo heart transplantation have had end-stage heart failure for an extended period of time, many of which have experienced the long-term sequala of heart failure including volume overload, decreased exercise capacity, poor nutrition, and some measure of end organ dysfunction. These preoperative patient characteristics, in addition to the heart transplant surgery and the immunosuppression required to mitigate allograft rejection, make heart transplant a unique and challenging area of clinical care. Details of heart transplant surgery are discussed further (see ▶ Chap. 12, "Surgical Complications").

Heart transplant postoperative care requires a highly coordinated multidisciplinary team involving the work of the cardiac surgeon, cardiologist, and critical care team. The immediate postoperative care of a heart transplant patient is not dissimilar to other postcardiotomy patients in terms of attention to hemodynamic and metabolic optimization; however, for posttransplant patients, donor characteristics and immunosuppression therapies must also be taken in to account. Heart transplant recipients are more susceptible to infection in the setting of immunosuppression. In this regard, three key factors to successfully manage postoperative heart transplant patients include: (1) optimized cardiopulmonary support, (2) limited warm ischemic time, and (3) directed immunosuppression. High-quality supportive care in the ICU is a pivotal factor impacting 30-day and long-term survival, reducing perioperative complications, and mitigating length of hospital stay, and overall cost (Costanzo et al. 2010; Kouchoukos and Blackstone 2013; Kobashigawa et al. 2014; Liao and Shumway 2014; Shemin and Deng 2018; Yazdchi and Rawn 2018). Management of immunosuppression and allograft surveillance is discussed separately (see ▶ Chaps. 16, "Cardiac Allograft Rejection," ▶ 19, "Monitoring for Rejection," ▶ 14, "Induction and Maintenance Agents," and ▶ 17, "Chronic Immunosuppression Medications").

Handoff and Communication

The importance of care team communication cannot be overstated. Having a well-defined system of communication between the surgical, anesthesia, and critical care teams is vital for optimal patient outcome. Care of the post-heart transplant patient include: (1) **Review of the patient's history.** A thorough review of the patient's medical history should include a review of prior surgeries, discussion of comorbidities (e.g., diabetes, renal insufficiency), as well as a review of pertinent preoperative medications. Given that most heart

transplant operations occur within hours of notification of the recipient, medications such as ACE inhibitors/ARBs or other extended release medications may still be in the patient's system. Many patients are on oral warfarin therapy, and although they may receive partial reversal (e.g., fresh frozen plasma, FFP), the extended half-life of warfarin may result in rebound anticoagulation shortly after surgery. (2) **Surgical details.** The surgical sign-out should include the pertinent details of the surgery. This includes any findings or complications that may affect postoperative care. Additionally, sites of drain placement, access to the pleural spaces, and location and function of temporary pacer wires should be elucidated for the ICU team. (3) **Anesthesia management.** Anesthesia sign-out should review airway and respiratory management, anesthesia administration, hemodynamic support, medication administration, and fluid/blood product management. Discussion of the airway and intubation process should occur to ensure optimal airway access in the event that reintubation is required postop. (4) **Medications administered including immunosuppression medications**. It is imperative that the ICU team understands the immunosuppression strategy for heart transplant patients, including timing of medications, whether induction agents were used, and when to start oral immunosuppressive medications. (5) **Review of allograft function**. The donor heart and recipient will have separate medical histories; therefore, any pertinent history of the donor heart (e.g., cocaine use, cardiac catheterization findings) should be communicated to the ICU team. Discussion of the postbypass transesophageal echocardiogram including review of biventricular function, valve function, vessel patency, as well as a review of hemodynamic support medications, heart rhythm, and filling pressures are invaluable data for postoperative patient management. (6) **Initial management strategies**. A clear discussion of postoperative management strategies between the surgical and ICU teams should occur in order to synchronize the care plan. This should include a discussion of all major organ systems (neurological, respiratory, cardiac, GI, renal, endocrine, and hematology).

Cardiopulmonary Physiology in the Transplanted Patient

A keen understanding of the physiology of the transplanted heart is required to understand the tenets of postoperative care. The donor heart is denervated as the cardiac nerve plexus is cut during procurement. This results in a lack of autonomic innervation that results in a higher intrinsic heart rate, reduced rate variability, altered diastolic function, abnormal baroreflexes, depletion of cardiac norepinephrine (NE), higher sensitivity to circulating endogenous catecholamines, diminished inotropic reserve, abnormal chronotropic response to stress, and somewhat reduced exercise capacity. Although the postsynaptic adrenergic receptor density seems to be normal, there is a change in distribution from beta1 to beta2 receptors (Liao and Shumway 2014; Shemin and Deng 2018).

The resting heart rate of the transplanted allograft typically ranges from 90 to 110. However, the transplanted heart may initially be bradycardic in the days following transplantation secondary to atrial node ischemic injury (Liao and Shumway 2014; Shemin and Deng 2018). The sinus rate increases steadily over the first 1–2 weeks posttransplant without respiratory variation and normal responses to changes in position. Intrinsic functions such as electrical automaticity and conduction as well as the Frank-Starling mechanisms are intact (Liao and Shumway 2014; Shemin and Deng 2018). Nevertheless, the response mechanism to increase cardiac output in the immediate postoperative care is primarily catecholamine-dependent and results in increased chronotropy. Although the transplanted heart often demonstrates diastolic dysfunction with a restrictive filling pattern (stunned heart) due to the reperfusion injury and myocardial edema that occurs within the first 24 h, higher filling pressures can augment cardiac output.

Recipient pulmonary vascular resistance (PVR) can be abnormally increased due to changes at the capillary level secondary to chronic left heart failure. This pulmonary hypertension (PH) and high PVR (ref) may not initially be responsive to medical and pharmacologic therapy

(i.e., fixed PH) although there is evidence that these pulmonary changes are reversible after heart transplant or LVAD (Liao and Shumway 2014; Yazdchi and Rawn 2018). Although accepted donor hearts typically have normal right ventricular function, this is in the setting of a normal or near normal PVR state of the donor. Donor hearts are typically not conditioned for an elevated PVR environment that may be present in the recipient, and thus the donor right ventricle may have reduced function posttransplant.

In many cases, the recipient's systemic arterial circulation adapted to chronic systemic hypotension (heart failure) with long-standing peripheral vasoconstriction/elevated systemic vascular resistance (SVR). Donor hearts are typically transplanted from an environment of near normal or low SVR and must therefore contend with the elevated SVR state. Once transplanted, fixed stroke volume of the allograft in the high systemic vascular resistance circuit often leads to a rapid arterial blood pressure increase and increased cardiac output as the recipient SVR decreases. This may occur shortly after transplant or may take several days (Kouchoukos and Blackstone 2013; Liao and Shumway 2014; Shemin and Deng 2018).

Monitoring

According to *The International Society of Heart and Lung Transplantation* (ISHLT), perioperative monitoring of heart transplant recipients should measure continuous rhythm, invasive arterial pressure, central venous pressure (CVP), left atrial pressure, and pulmonary artery wedge pressure (PAWP). Similarly, the patient should have continuous arterial oxygen saturation and urine output assessment. The following monitoring devices should be considered to aid in the initial management of cardiac transplant patients managed in an ICU.

- Arterial line
- Central venous catheter
- Pulmonary artery catheter (Swan–Ganz catheter)
- Continuous electrocardiogram
- Oxygen saturation monitor
- Bladder catheter

Although some hospitals do not use the Swan-Ganz Catheter routinely, it is recommended for high-risk patients for the diagnosis and treatment of pulmonary hypertension and for the identification and differentiation of right and left ventricular dysfunction. Further, it enables the monitoring of several hemodynamically significant parameters such as the cardiac output (CO), cardiac index (CI), peripheral vascular resistance, pulmonary vascular resistance (PVR), PCWP, and the mixed-venous oxygen saturation (SvO2) which can provide objective metrics for goal-directed clinical management.

Ventilation Management

Nearly all post-heart transplant surgery patients arrive in the ICU intubated and sedated with full mechanical ventilatory support. Immediately upon ICU arrival, an arterial blood gas (ABG) is drawn and the ventilator parameters are adjusted to correct hypoxemia, acidosis, and hypercarbia. Ventilator settings should aim to minimize barotrauma and transition to a spontaneous ventilatory mode in a timely manner. The transplanted heart must adapt to a new environment related to recipient lung function and elevated PVR, so that any maneuvers that increase PVR must be avoided. Likewise, care must be taken to limit high inspiratory pressure to avoid hemodynamic compromise from impaired venous return. The use of vasodilators including nitroglycerin, milrinone, sodium nitroprusside, and nicardipine can increase shunt fraction (by inhibiting hypoxic pulmonary vasoconstriction in poorly ventilated regions of the lung) which may cause significant hypoxia. Increasing PEEP to improve alveolar recruitment is frequently beneficial. Early extubation is encouraged to reduce sedation requirements, improve hemodynamics, and reduce infection risk from ventilator-associated pneumonia. Once hemodynamic stability is achieved and acceptable oxygenation and ventilation are achieved, mechanical ventilation support should be weaned (Yazdchi and Rawn 2018).

Table 1 Inotropes and vasoactive medications

Medication	Dosage, recommendation, and hemodynamic profile
Isoproterenol	1–10 mcg/min IV; consider for ventricular dysfunction Chronotropic effect ++++; inotropic effect ++++; arrhythmia risk ++++; peripheral vasodilation +++; no vasoconstriction effect
Dobutamine	1–10 mcg/kg/min IV; consider for ventricular dysfunction Inotropic effect +++; peripheral vasodilation ++; chronotropic effect +; arrhythmia risk +; no vasoconstriction effect
Dopamine	1–10 mcg/kg/min IV; consider for ventricular dysfunction Inotropic effect +++; vasoconstriction effect ++; no chronotropic effect; no arrhythmia risk; no peripheral vasodilation
Milrinone	0.375–0.75 mcg/kg/min IV; consider for ventricular dysfunction Inotropic effect +++; chronotropic effect++; arrhythmia risk ++; peripheral vasodilation ++
Epinephrine	0.01–0.1 mcg/kg/min IV; consider for low output or hypotension Cardiac contractility ++++; vasoconstriction effect +++; chronotropic effect++; arrhythmia risk ++; peripheral vasodilation +
Norepinephrine	0.01–0.1 mcg/kg/min IV; consider for low mean arterial pressure Vasoconstriction effect ++++; inotropic effect+++; chronotropic effect+; arrhythmia risk +; no peripheral vasodilation
Phenylephrine	0.01–0.1 mcg/kg/min IV; consider for low mean arterial pressure Vasoconstriction effect ++++; no inotropic effect; no chronotropic effect; no arrhythmia risk; no peripheral vasodilation
Vasopressin	0.03–0.1 U/min IV; consider for refractory low mean arterial pressure Vasoconstriction effect ++++; no inotropic effect; no chronotropic effect; no arrhythmia risk; no peripheral vasodilation
Methylene Blue	0.5–2 mg/kg bolus during 20 min, then 0.25–2 mg/kg/h IV; consider for refractory low mean arterial pressure Vasoconstriction effect ++++; no inotropic effect; no chronotropic effect; no arrhythmia risk; no peripheral vasodilation

Adapted from Kirklin et al. (2002)

Vasoactive and Mechanical Support

Posttransplant early hemodynamic instability is common and can be a manifestation of bleeding, conduction abnormalities, ventricular dysfunction, cardiac vasoplegic syndrome, and acute allograft rejection, among others. The goals of hemodynamic support are to optimize preload, contractility, heart rate, and afterload of both the right and left ventricles (RV and LV) while at the same time ensuring adequate organ perfusion. Before the initiation of any vasoactive agent, the volume status must be assessed since large fluid shifts occur intraoperative due to bleeding, administration of fluids (blood and crystalloids), and ultrafiltration (UF) performed during cardiopulmonary bypass (CBP).

As mentioned before, the loss of baroreceptor regulation and dependence of the transplanted heart on catecholamines underlies the need for immediate postoperative use of adrenergic agonists to maintain an adequate mean arterial pressure, chronotropy, and inotropy. Table 1 outlines the dosages and recommendations of vasoactive agents. In addition to pharmacologic therapy, epicardial pacing, either atrial pacing, ventricular pacing, or atrial-ventricular pacing, can be utilized to optimize heart rate.

The ISHLT guidelines recommend (*level of evidence C*) the continuous infusion of inotropes during the first 3–5 postoperative days, and the regimen suggested is isoprotenerol and dopamine, dobutamine and dopamine, or milrinone (Costanzo et al. 2010), but this is largely center dependent. The lowest maintenance dose providing adequate hemodynamic support should be used and titrated according to the hemodynamic response. Vasodilatory shock may occur in the postcardiotomy period as a result of hypovolemia, ischemia/reperfusion injury, and postcardiopulmonary systemic inflammatory response syndrome. Infusions of vasopressors such as norepinephrine and phenylephrine should be titrated to maintain adequate mean arterial pressure (MAP). Agent selection should be based on the physiology. Patients exhibiting low cardiac output should receive agents

with inotropic properties while those with adequate output and decreased SVR should receive agents with more alpha1 and less beta2 agonism. Alternative agents for low SVR include vasopressin and NO scavenging agents such as methylene blue. Accordingly, ISHLT recommends an early low dose of vasopressin or methylene blue for refractory low MAP with a level of evidence B.

RV and LV dysfunction may occur in the early postoperative period and requires a progressive therapeutic approach ranging from medical management to mechanical support. In cases where the optimal medical management is not enough to maintain cardiopulmonary function, the use of intraaortic balloon counterpulsation (IABP) is often the first choice for mechanical circulatory support for ventricular dysfunction. The ISHLT guidelines suggest its use as early as possible if there is poor cardiac performance in the setting of high dose inotropic agents or worsening hemodynamic instability in the ICU upon optimal full medical management. This topic is discussed in subsequent chapters covering ventricular support.

Right Ventricular Failure

The ISHLT identifies right ventricular failure as one of the principal causes of early postoperative morbidity and mortality, 50% and 20%, respectively (Konstam et al. 2018). Several risk factors have been identified including inadequate preservation of the allograft, coronary malperfusion, inadequate myocardial protection on bypass, hypotension, reperfusion injury, mechanical obstruction at the level of pulmonary artery anastomosis, and donor-recipient size mismatch, among others. Nevertheless, pulmonary hypertension and increased PVR are independent risk factors to RV dysfunction development (Konstam et al. 2018). When a secondary cause is not identified, RV failure is considered primary graft dysfunction (PGD).

Specific to the RV is its ability to handle volume instead of pressure load. However, in patients with chronic left heart failure, increased pulmonary artery pressures leads to increased PVR which results in chronic remodeling of the RV to adapt to the increased afterload (ref). Increased pulmonary afterload on the donor heart is poorly tolerated, and RV performance depends on adequate perfusion pressure, coordinated contraction, ventricular interdependence, and physiologic afterload. Preoperative identification and evaluation of pulmonary hypertension and its responsiveness to vasodilators is fundamental in order to optimize immediate postoperative management of RV function. Risk factors for RV dysfunction are pulmonary vascular resistance of more than four wood units, systolic pressure in the pulmonary artery >60 mmHg or transpulmonary gradient (TPG) (difference between mean pulmonary arterial pressure and pulmonary capillary wedge pressure) >15 mmHg (Konstam et al. 2018), although some of these parameters may improve after ventricular assist device support.

Adequate RV support during the early postoperative period can minimize RV dysfunction. This is achieved by optimizing the preload, maintaining adequate perfusion pressure, increasing contractility, and reducing the right ventricular afterload. Strategies to achieve these goals include controlled volume therapy using diuretic agents to avoid pulmonary edema, selective ventilator management (target: PaO2: 100 mmHg, PCO2:30 mmHg, pH > 7.5, PEEP <6), and the administration of inotropic medications such as milrinone, dobutamine, or epinephrine. Agents which reduce PVR–including inhaled nitric oxide and intravenous or inhaled prostaglandin–can improve RV output, and are used in combination with inotropic agents (Konstam et al. 2018). If the combination of all therapeutic options fails to restore right ventricular function or if low cardiac output persists despite these interventions, an echocardiogram should be obtained to rule out cardiac tamponade and assess left and right ventricular function.

Primary Graft Dysfunction

The healthy donor heart has to tolerate a series of insults in order to adapt to the recipient's modified cardiovascular physiology. Primary graft dysfunction (PGD) is the principal early complication

Table 2 Diagnostic criteria and classification for primary graft dysfunction

International Society for Heart and Lung Transplantation Diagnostic Criteria and Classification for Primary Graft Dysfunction	
PGD-LV	
Mild PGD-LV; one of the following criteria must be met	LVEF < 40% by echocardiography or hemodynamics with RAP >15 mm Hg, PCWP > 20 mm Hg, CI < 2.0 L/min/m^2 (lasting > 1 h) requiring low-dose inotropes
Moderate PGD-LV; must meet one criterion from I and another criterion from II	I. LVEF < 40% by echocardiography or hemodynamics with RAP >15 mm Hg, PCWP > 20 mm Hg, CI < 2.0 L/min/m^2 (lasting > 1 h) requiring low-dose inotropes
	II. High-dose inotropes – inotrope score > 10 (inotrope score = dopamine (×1) + dobutamine (×1) + amrinone (×1) + milrinone (×15) + epinephrine (×100) + norepinephrine (×100) drug dosed in μg/kg/min) or newly placed IABP (regardless of inotropes)
Severe PGD-LV	Dependence on left or biventricular mechanical support including ECMO, LVAD, BiVAD, or percutaneous LVAD. Excludes requirement for IABP
PGD-RV	
Diagnosis requires either both I and II or III alone	I. Hemodynamics with RAP > 15 mm Hg, PCWP < 15 mm Hg, CI < 2.0 L/min/m^2
	II. TPG <15 mm Hg and/or pulmonary artery systolic pressure <50 mm Hg
	III. Need for RVAD

Adapted from Kobashigawa et al. (2014)
BiVAD biventricular assist device, *CI* cardiac index, *ECMO* extracorporeal membrane oxygenation, *IABP* intra-aortic balloon pump, *LVAD* left ventricular assist device, *PCWP* pulmonary capillary wedge pressure, *RAP* right atrial pressure, *RVAD* right ventricular assist device, *TPG* transpulmonary pressure gradient

during the first month posttransplant. In the 2015 heart transplant registry report, PGD represented 1,155 (3.6%) deaths and 44 (0.1%) of retransplants (Kobashigawa et al. 2014). In 2017, the ISHLT PGD consensus criteria was validated (Table 2), establishing its definition as any echocardiographic and/or hemodynamic evidenced dysfunction occurring within the first 24 h after surgery and after secondary graft dysfunction had been ruled out (Kobashigawa et al. 2014). Secondary graft dysfunction is due to hyperacute rejection, unresponsive pulmonary hypertension, or technical surgical complications.

PGD is a syndrome manifested as hypotension, low cardiac output in the presence of adequate or high filling pressures as a consequence of either single or biventricular dysfunction. Classification is determined by the level of inotropic or mechanical support required in the patient. It is believed to be the result of multiple donor, procedural and recipient factors. These include age, myocardial dysfunction on echocardiogram, ischemic times, previous inotropic support, diabetes/obesity, donor recipient size mismatching, among others (Kobashigawa et al. 2014). The RADIAL score was developed to identify the patients at risk, which has shown to predict mortality after transplantation (Costanzo et al. 2010). This scoring system takes into account the right atrial pressure, donor age > 30 year, diabetes, inotropic support, recipient age > 60 year, and ischemia time > 240 min. Surprisingly ischemic time < 1 h has also been related to the development of PGD (Segovia et al. 2011).

Arrhythmias

The majority of transplanted hearts recover sinus rhythm. However, after heart transplantation, early and late conduction abnormalities may occur, and it has been reported that between 10% and 20% will require permanent pacemaker (Kouchoukos and Blackstone 2013). Post-transplant arrhythmias can be the result of preservation or reperfusion injury, surgical injury,

implant technique, or early signs of allograft rejection (Costanzo et al. 2010; Yazdchi and Rawn 2018). Nevertheless, adequate chronotropic stimulation is mandatory to achieve sufficient cardiac output since the Frank-Starling mechanism may be limited secondary to reperfusion injury. External pacing via temporary epicardial pacemaker leads placed intraoperatively and pharmacological chronotropic support are the two important strategies to maintain adequate heart rate.

Early sinus node dysfunction is reported to occur in 15–50% of heart transplanted patients, requiring only temporary pacing during the first day posttransplantation. Up to 75% of these patients will regain independence before discharge from the hospital (1–3). The ISHLT suggests the pharmacological management or temporary pacing to at least 90 bpm (Costanzo et al. 2010). Isoprotenerol or theophiline are the principal pharmacologic agents to increase chronotropy in posttransplant bradycardia as a bridge to sinus node function.

Atrial fibrillation is the most common *early* arrhythmia after heart transplantation, with an incidence of 0.3% and 24%. Atrial flutter is more common late after heart transplant, with an incidence between 2.8% and 30%. If pharmacological therapy of the atrial fibrillation is indicated, amiodarone and digoxin are considered first-line therapies. If medical treatment does not lead to conversion, biphasic electrocardioversion should be carried out expeditiously.

Nutrition

Heart transplant is the definitive treatment for patients with end-stage heart failure. It is a major surgery with a long and arduous recovery. Patients who undergo a transplant have the same physiologic burden as typical cardiac procedures with the added strain of organ transplant and immunosuppressive medications. By going on cardiopulmonary bypass (CBP), the exposure to the oxygenator and artificial surfaces elicit a systemic inflammatory response (Kim et al. 2016). Additionally, potentiation of myocardial ischemia due to going on pump or with lack of cardioprotective measures can cause the release of pro-inflammatory cytokines (Dreymueller et al. 2016; Stoppe et al. 2016, 2017). These effects are often deleterious to the patient, are affected by the patient's nutritional status, and require aggressive therapy to achieve long-term success.

Nutrition in this population is critical for both short- and long-term recovery. Significant postoperative depletion of nutrients occurs which can hinder energy metabolism and wound healing (Sanchez et al. 2011). Malnutrition in this patient population is an established risk factor following cardiac surgery (Engelman et al. 1999). The study by Engelman et al. showed that a body mass index (BMI) less than 20 and an albumin level < 2.5 g/dl were independently associated with increased mortality. Despite this, underfeeding remains an issue in the cardiac surgery population (Drover et al. 2010; Rahman et al. 2016). It is no surprise then that this population is the most associated with iatrogenic malnutrition. Rahman et al. showed that patients only received around 50% of their required nutrition (Rahman et al. 2016). Additionally, well-nourished cardiac patients prior to surgery have been shown to have better outcomes (Sanchez et al. 2011, Chermesh et al. 2014). That is why it is recommended that preoperative nutritional therapy is started between 2 and 7 days prior to surgery in patients who are at risk for malnourishment (Jakob and Stanga 2010). However, due to the typical undernourishment of these patients, it is important to avoid refeeding syndrome (Ljungqvist and Soreide 2003). It then makes sense to look to nutritional scoring and risk stratification metrics to identify patients who need and would most benefit from nutritional intervention.

To date, there is no validated presurgical risk stratification system that can detect patients early enough to allow for nutritional intervention (Stoppe et al. 2017). Current systems are used to identify patients that are already in the malnourished state, not those who are close and will be pushed into that category following a cardiac procedure and would thus benefit from proactive nutritional supplementation. The three main nutritional assessment tools are the Mini Nutritional

Assessment (MNA), the Malnutrition Universal Screen Tool (MUST), and the Short Malnutrition Screen Questionnaire (SNAQ)(20)]. Lomivorotov et al. showed that the MUST and MNA are comparable in predicting postoperative complications in cardiac surgery (Lomivorotov et al. 2013). This lends favor with the MUST metric due to its ease of use and adoption in the patient's surgical evaluation. In the postoperative setting, the Nutrition Risk in the Critically ill (NUTRIC) score has shown some promise. Although not verified in the cardiac surgery population and only in prospective trials, this score has been shown to be able to determine patients that will benefit from nutritional intervention (Heyland et al. 2013; Heyland et al. 2015). More nutritional data needs to be collected to develop metrics able to determine malnourished or near malnourished patients who would benefit from nutritional intervention at an early enough time that such intervention would be feasible.

While nutrition is important for general healing and recovery, there can be an additional benefit by counteracting the inflammatory response generated by cardiopulmonary bypass. However, the data is largely split on this topic. Theoretically, administration of pharmaconutrients that effect the inflammatory response and oxidative stress (Vitamins A and E, omega 3 fatty acids, etc.) would be beneficial in the postoperative course. Yet, large-scale clinical trials have not shown much benefit (National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome Clinical Trials Network et al. 2012; Heyland et al. 2013). Leong et al., however, demonstrated in 117 patient sample undergoing a CABG and/or valve surgery that perioperative administration of antioxidants such as coenzyme Q10, omega 3 fatty acids, and others resulted in improved antioxidant levels and reduced myocardial damage (Leong et al. 2010). Along similar lines, Berger et al., in a randomized controlled trial, demonstrated that three perioperative fish oil infusions decreased an IL-6 increase following the surgery (Berger et al. 2013). There are ongoing large-scale studies investigating the use of key pharmaconutrients in the surgical setting to attenuate the inflammatory response. It is only a matter of time before validated therapies enter into the perioperative workflow to improve the outcomes for patients.

Stepdown Management

Once the posttransplant patient has stabilized and no longer requires the acuity of the ICU, patients are transferred to the cardiothoracic stepdown unit. During this recovery period, patients are followed by the multidisciplinary heart transplant team for care and preparation for discharge. At this point, the patients no longer require ventilatory support and can meet oxygen requirements with a nasal cannula delivering less than 6 L/min. Catecholamines have been weaned off although select patients may still require milrinone or dopamine which can be managed in the stepdown unit. After moving to the stepdown unit, patients undergo ongoing testing and medication adjustment, especially with their immunosuppression medications and will undergo their first endomyocardial heart biopsy to evaluate any evidence of rejection.

Patients at this stage are ambulatory and will initiate exercise regimens under the guidance of the physical and occupational therapists. The therapists will evaluate each patient's physiologic status and develop and implement a strength and exercise recovery plan. Along these lines, nutrition is critical in functional recovery, and nutritional status is monitored closely by the nutritionist and speech therapist. A diet plan fit to an energy intake >25 kcal/kg/ideal bodyweight/day and aligned to the American Heart Association step one diet guidelines with an emphasis on daily activity was shown to be beneficial in decreasing and controlling bodyweight and metabolic parameters such as cholesterol and triglycerides(1988; Guida et al. 2009). Compliance to this diet is beneficial in patient populations within their first year after transplant and after their first year. Additionally, patients had an additional 10% decrease in cholesterol levels with this dietary intervention. A complete evaluation of a patient's nutritional status, pre- and postoperatively, is necessary to

provide optimal care of patients. A heart transplant is a lifelong operation, and the nutritional consideration for the patients should not end at their immediate postoperative course but extend to their everyday life.

Conclusion

Successful cardiac transplantation requires a multidisciplinary approach to orchestrate the evidence-based practice guidelines for the management of this complex postoperative patient population. Improvements in postoperative care of the heart transplant recipient have undoubtedly contributed to the increased survival seen over the past two decades as compared to 1980s and 1990s. This is made evident as the gains in survival have been largely limited to the first 6–12 months posttransplantation. Advances in immunosuppression and the prevention and treatment of opportunistic infections in the immediate postop period have also contributed significantly. Currently, the median survival after heart transplantation is 11 years, and 1-year survival approaches 85% in the current era. The highest mortality occurs in the first 6 months after transplantation and thereafter is reduced to a mortality rate of 3–4% per year, thus reflecting the importance of optimized early management in the ICU and stepdown unit. Despite these advances, further research is needed to identify the best ways to predict, prevent, and treat primary graft dysfunction, right ventricular failure, and cellular and antibody-mediated rejection and other associated postop complications limiting survival in the transplanted patient.

Cross-References

- ▶ Cardiac Allograft Rejection
- ▶ Chronic Immunosuppression Medications
- ▶ Contraindications to Heart Transplantation
- ▶ Induction and Maintenance Agents
- ▶ Matching Donor to Recipient
- ▶ Monitoring for Rejection
- ▶ Surgical Complications

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Part VIII

Transplant Immunology

Induction and Maintenance Agents

14

Adam Cochrane

Contents

Abstract

Immunosuppression has increased the success of human heart transplant. There are specific patient groups that benefit from the use of induction therapy though the use of induction therapy has not shown universal benefit for all patients. Currently heart transplant centers employ dual or triple immunosuppression regimens with a calcineurin inhibitor as the base of the regimen and consideration given to antiproliferative agents or PSI/mTOR as the additional agent, with or without corticosteroids. The tolerability of agents can limit their use despite the therapeutic benefit, in addition to immunosuppression, toward renal sparing effects, viral sparing effects, or vasculopathy benefits. The choice of agents make individualization of immunosuppression possible based on a specific patient's needs.

Keywords

Maintenance immunosuppression · Heart transplant induction · PSI/mTOR antiviral properties · PSI/mTOR CAV · C2 monitoring · Calcineurin inhibitors · Antiproliferative agents

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Introduction

The first heart transplant in 1967 had very limited immunosuppression choices, and with no prior experience in human heart transplantation, the use of available immunosuppressants was part of the experiment of human heart transplant. 6-Mercaptopurine and steroids were the extent of immunosuppressive medications, with presumed rejection treated with increased doses of steroids.

Finally, more than 15 years after the first heart transplant was performed, another immunosuppressant choice, cyclosporine, was available. Before the introduction of cyclosporine, 1-year survival for heart transplant was less than 60%, where Table 1 shows the 1-year survival before

Table 1 Kaplan-Meier 1-year patient survival rates for transplants performed between 1980 and 2015

Era of cyclosporine	Year of transplant	Number of transplants	Survival rate	95% confidence interval
Pre-cyclosporine	1980	97	43.85	[33.81,53.88]
	1981	106	58.50	[48.57,68.42]
	1982	167	62.78	[55.12,70.44]
Cyclosporine approved	1983	293	65.84	[60.17,71.51]
	1984	584	68.83	[64.92,72.74]
	1985	1,202	73.90	[71.34,76.47]
	1986	2,232	76.16	[74.34,77.99]
	1987	2,816	76.54	[74.93,78.14]
	1988	3,303	77.61	[76.16,79.06]
	1989	3,608	76.94	[75.54,78.34]
	1990	4,276	78.75	[77.50,80.01]
	1991	4,565	78.63	[77.41,79.85]
	1992	4,540	79.29	[78.09,80.49]
	1993	4,713	79.49	[78.31,80.67]
	1994	4,476	79.57	[78.36,80.77]
	1995	4,462	80.02	[78.83,81.22]
	1996	4,373	80.95	[79.76,82.14]
	1997	4,534	81.49	[80.33,82.65]
	1998	4,505	82.14	[80.99,83.29]
	1999	4,232	81.29	[80.08,82.50]
	2000	4,130	83.17	[81.99,84.34]
	2001	4,060	82.67	[81.48,83.86]
	2002	4,156	84.54	[83.41,85.67]
	2003	4,076	84.86	[83.73,85.99]
	2004	4,067	83.52	[82.35,84.69]
	2005	4,216	82.77	[81.60,83.94]
	2006	4,323	83.67	[82.54,84.81]
	2007	4,312	83.97	[82.84,85.10]
	2008	4,358	83.87	[82.74,85.00]
	2009	4,404	84.65	[83.55,85.74]
	2010	4,437	85.70	[84.64,86.77]
	2011	4,550	85.83	[84.79,86.88]
	2012	4,526	85.16	[84.09,86.23]
	2013	4,768	86.60	[85.60,87.60]
	2014	4,918	85.74	[84.73,86.75]
	2015	4,809	87.07	[86.06,88.08]
	Overall	121,697		

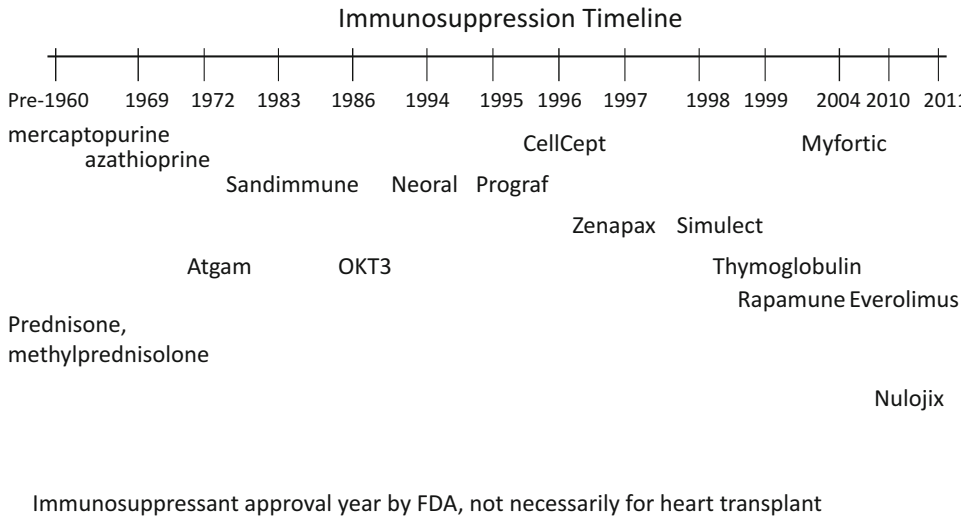

Fig. 1 Immunosuppression timeline

and after approval of cyclosporine; and within 2 years after the approval of cyclosporine, the 1-year survival had increased to over 70%. Figure 1 shows the approval date of additional immunosuppression choices. With additional agents introduced and added, years of experience with available agents survival rates increased to over 80%.

Immunosuppression is used in three ways – induction, maintenance, and rejection. There is not a uniform approach with different induction and maintenance protocols utilized at different transplant centers. The use of induction therapy has varied with the changing availability of agents over time. In order to avoid rejection, maintenance immunosuppression has to be taken by patients life long after heart transplantation. These two uses of immunosuppression will be discussed in this chapter, while the treatment of rejection will be discussed elsewhere.

Induction

Most heart transplant centers utilize some sort of augmented increased immunosuppression at the time of transplant – either steroids alone or antibody products. These are generally used for a short period of time and limited to the time surrounding the transplant surgery. Maintenance immunosuppression may be started at the time of transplant, but induction therapy allows adequate immunosuppression, while maintenance immunosuppression gets to therapeutic levels, or it can also allow a delay of some parts of maintenance immunosuppression. While some transplant centers implement a universal induction protocol, others selectively utilize induction based on certain clinical considerations, e.g., high immunological risk and renal dysfunction.

Induction therapy choices have been limited due to market availability. There were two IL-2 receptor antagonists available historically; however daclizumab was removed from the market leaving basiliximab as the only IL-2 antagonist available. Basiliximab has been compared to no induction, and compared to antithymocyte globulin, rabbit (rATG) with the primary outcome studied being biopsy-proven acute rejection (BPAR). The confounding issues with these studies are that the grade of BPAR varied among different studies (i.e., any BPAR, grade $\geq$ 1B, or grade 3 or 4) and the time of follow-up differs from months to up to a year posttransplant. A multicenter study examining 56 patients undergoing heart transplant who were randomized to the use of basiliximab versus

matched placebo with the same schedule of administration on postoperative days 0 and 4 and initiation of maintenance immunosuppression matched between study arms showed that there was a non-statistical difference in time to grade 3A or greater rejection between the groups (Mehra et al. 2005). A different study which examined basiliximab versus no induction showed that there was a numerical difference but not a statistical difference in rejection rates between basiliximab induction and immediate cyclosporine initiation (Rosenberg et al. 2005). The results of these studies did not demonstrate any statistical difference in BPAR between patients treated with basiliximab and those who were randomized to no basiliximab. Despite the lack of differences in these studies, there remain a large number of patients who receive basiliximab induction at heart transplant centers worldwide.

Antithymocyte globulin products have been used in transplant since nearly the beginning of transplant; however it has been more recently that these products are standardized and available commercially. The initial availability of these products was from universities that were making a horse-derived ATG product for their own use and occasionally making it available to other centers as part of a clinical trial. There are one rabbit-derived ATG (rATG) product licensed in the USA and an additional rATG product available in Europe. Although rATG is not approved for induction therapy in the USA, it has gained favorability as an induction agent. There have been a few studies that examined the use of rATG versus basiliximab for induction. In an examination of non-inferiority of rATG to basiliximab, a group in Canada looked at 35 patients and found that the 2 agents were not equivalent but that grade 3A or 4 rejection was seen less often in the rATG group compared to basiliximab induction (Carrier et al. 2007). A retrospective evaluation for safety and efficacy of 48 patients who had received either rATG or basiliximab as part of their standard induction at the time of heart transplant showed that there were more infections in the group that received rATG; however, the average biopsy score, equating to less severe rejection, was lower at all time points over the first year in the rATG group. Further, there were more episodes of grade 3A or higher rejection in the first 6 months in the basiliximab versus rATG groups (Flaman et al. 2006). There have been safety concerns with the more widespread use of rATG as an induction agent, and it has been shown to have more fever, leukopenia, and thrombocytopenia, which are known and transient side effects when it is used for rejection or induction, but there was no increase in the rate of serum sickness, rash, or anaphylaxis between rATG and basiliximab (Mattei et al. 2007). The concern for posttransplant lymphoproliferative disease (PTLD) has been associated with monoclonal antibodies from the start of their use in transplant. With the current induction regimens (basiliximab, a monoclonal antibody, and rATG, a polyclonal antibody) with lower cumulative doses of rATG used and the near standard use of antiviral prophylaxis after transplant, there is a less than 1% per year incidence of PTLD that has been seen with rATG use as induction (Hertig and Zuckermann 2015; Marks et al. 2011).

Heart transplant centers that do not use induction therapy as a standard practice frequently employ it for specific patient populations. Induction therapy has been employed in patients who are at risk for renal dysfunction and for those patients who are at an increased risk for rejection.

Induction therapy has been employed to delay the initiation of calcineurin inhibitors and avoid further renal insult in patients with renal dysfunction pre-transplant or at potential risk of renal dysfunction during the perioperative and postoperative periods. Basiliximab has been compared to rATG (Delgado et al. 2005) with a delayed initiation of calcineurin inhibitors of 3–7 days. Renal function improved after transplant in both groups with no differences in renal function at 1 week, 1 month, or 6 months post-heart transplant; however there were fewer episodes of rejection seen in the rATG group, compared to basiliximab, over the first 6 months. In a population who developed renal dysfunction after heart transplant, Cantarovich et al. (2004) treated these patients with rATG after heart transplantation and delayed the start of cyclosporine until there was an

improvement in renal function. Antithymocyte globulin was administered every 2–5 days with dose frequency determined by keeping the lymphocyte count below 200/mm^3 with cyclosporine introduced when the creatinine fell below 150 μM, which was around posttransplant day 12 in the renal dysfunction group versus day 2 in the nonrenal dysfunction group. Patient survival was similar through 1 year, ejection fraction was not different between groups, and there was no difference in rejection rates over the first year after transplant in those patients who had delayed initiation of cyclosporine.

Patients who are identified to be an increased risk of rejection have been treated with induction therapy in an effort to decrease the rate of hyperacute rejection and early acute rejection. Antibody sensitization is a growing and continued problem in heart transplantation with an increasing number of patients presenting for transplant with a ventricular assist device which has been associated with the formation and persistence of antibody formation which can lead to antibody-mediated rejection (AMR) after heart transplantation. For patients who are at a higher risk for AMR (patients with circulating anti-HLA antibodies, multiparous women, patients who have received blood transfusions, or patients who are supported pre-transplant with a left ventricular assist device) or who have undergone a strategy to decrease the antibody load (see other chapters), rATG has been recommended as induction therapy (Kobashigawa et al. 2009; Aliabadi et al. 2013).

Alemtuzumab, a monoclonal antibody against CD-52, is currently available through a company supported distribution program to transplant programs with established induction protocols in place. There has been limited data regarding the use of alemtuzumab as induction in heart transplant patients. Data shows that compared to a no-induction group, alemtuzumab allowed lower levels of maintenance immunosuppression and less significant rejection over the first year (Teuteberg et al. 2009). However there have been no additional studies analyzing the use of alemtuzumab as an induction therapy, and with limited availability, it is not a recommended agent to be used as such.

Around half of patients undergoing heart transplantation currently receive induction therapy; however the current literature does not indicate a definitive benefit nor a detriment to using induction therapy in an entire population. There does appear to be a clear benefit of induction therapy in specific populations undergoing heart transplantation and should be used in these patients and further studied in other patient populations.

Maintenance

Maintenance immunosuppression choices were limited in the first years of heart transplantation; programs were dependent on the use of steroids and azathioprine. However as the choices expanded, survival improved; the introduction of cyclosporine in 1983 changed the success trajectory of heart transplant (Table 1). Maintenance regimens generally consist of a combination of a calcineurin inhibitor, an antiproliferative agent, and a steroid. Contemporary heart transplant has variations on this regimen where a proliferation signal inhibitor could be substituted for one of the above agents, steroids are not a part of many long-term maintenance regimens, and there are centers that use monotherapy early after transplant.

Calcineurin Inhibitors

Calcineurin inhibitors (CNI) were added to the heart transplant armamentarium in the early 1980s. Cyclosporine was the first medicine advance in heart transplantation used as an investigational agent at a couple of centers as early as 1981 and became commercially available in 1983.

The CNIs inhibit T-lymphocyte activation by inhibiting the transcription of IL-2 and other cytokines. The available CNIs have different binding proteins, as well as different pharmacokinetic and pharmacodynamics, and different side effect profiles.

The initial use of cyclosporine was promising but limited by renal dysfunction. Despite the renal dysfunction, cyclosporine was incorporated

into heart transplant protocols, over the up to that time standard of care. Conventional maintenance immunosuppression before the early 1980s consisted of azathioprine and prednisone. Early experience revealed that cyclosporine was effective, when compared to azathioprine/prednisone standard treatment, in preventing rejection, masking rejection (thereby making endomyocardial biopsy more telling of rejection episodes), and improving 1-year survival. With additional experience, after approval of cyclosporine, it was found that lower doses of prednisone could be used and lymphomas could be avoided with lower amounts of induction therapy and lower target levels of cyclosporine. Although cyclosporine (Sandimmune®) was first on the market, the majority of patients on a cyclosporine product now are on cyclosporine microemulsion (Neoral®) which increased absorption and decreased intrapatient trough level measures.

The CNIs are dosed based on blood levels. While tacrolimus trough level monitoring correlates will with AUC, cyclosporine has more intrapatient pharmacokinetic differences, and it has been found that 2-h blood concentration level monitoring (C2 monitoring) is a better indicator cyclosporine AUC than trough level monitoring. Initial C2 levels in the first 3 to 6 months after transplant should be 1000 ng/mL, and after 6 months, the C2 level can be decreased to 200–400 ng/mL (Cantarovich et al. 1998; Levy et al. 2002).

One analysis showed that in patients far out from transplant, there was no overt benefit of changing from trough level (C_0) to C2 monitoring; neither rejection rates, blood pressure, or kidney function improved, but patients were able to take less cyclosporine after conversion to C2 monitoring (Hermann et al. 2011). C2 monitoring has shown to be related to lower rejection rates early after heart transplantation when the level exceeds the goal C2 level even if the C0 level is below goal. Severe rejection has shown to occur more often under C0 monitoring versus C2 monitoring. In the same study, kidney function was better in the C2 group versus the C0 group (Barnard et al. 2006). A narrow window of time to draw the C2 level makes this method a bit burdensome though it is likely a better method for monitoring cyclosporine.

Tacrolimus was introduced in the late 1990s and compared to cyclosporine in the initial trials. Despite the clear superiority of tacrolimus in kidney and liver transplant patients, there was initially no rejection or survival benefit of tacrolimus over cyclosporine. Two early studies examining tacrolimus in heart transplantation compared to cyclosporine (in combination with azathioprine and prednisone) showed comparable rejection rates and similar outcomes with regard to severity of rejection (Grimm et al. 2006; Taylor et al. 1999). One analysis showed a significant difference in rejection rates, favoring tacrolimus, when the biopsy samples were centrally graded versus local grading (Grimm et al. 2006). One of these studies also showed similar number of episodes of recurrent rejection, number of treated rejections, or number of patients dropping out of study due to intolerance of study drug (Taylor et al. 1999).

Tacrolimus-treated patients did have significantly lower blood pressures and less often required antihypertensive medications at all study time points up to the end of the 1-year study period than cyclosporine-treated patients. New-onset hypertension was seen more often in cyclosporine-treated patients. Cholesterol levels were significantly higher in cyclosporine-treated patients at all time points during the studies. New-onset diabetes after transplantation (NODAT) was seen at similar rates in cyclosporine-treated patients and tacrolimus-treated patients in one study, while the other study showed higher rates of NODAT in tacrolimus-treated patients (Grimm et al. 2006; Taylor et al. 1999). With wider use of tacrolimus after its introduction when comparing it to the microemulsion formulation of cyclosporine, numerous studies have shown less rejection episodes, longer survival, less recurrent rejection, and less severe rejections with tacrolimus while still noting that NODAT has a higher incidence with tacrolimus than cyclosporine microemulsion-treated patients.

Steroids have long been a part of every aspect of heart transplantation. As more maintenance immunosuppression came to market and was

shown to be better at preventing rejection, when considering the cosmetic and metabolic effects of steroids, there was a desire to consider steroid minimization or steroid withdrawal maintenance immunosuppression protocols. Under cyclosporine-based regimens, steroid avoidance was attempted in numerous studies that showed comparable survival and similar rejection rates. With the introduction of tacrolimus as a replacement for cyclosporine in immunosuppression regimens, the general practice, now, is steroid avoidance/withdrawal when one of the dual immunosuppression agents is tacrolimus. There are two different steroid weaning strategies with both early and late steroid weaning showing advantages and disadvantages depending on the patient population and concurrent immunosuppression, so recommending a strategy based on the benefits of an early versus late strategy, or vice versa, is not possible. In one analysis of patients who had steroid withdrawal attempted 6 months after transplant, 92% of patients were successfully weaned off steroids. Those patients that were weaned off steroids had a higher 5-year survival and a high freedom from nonfatal major adverse cardiac events (Kittleson et al. 2013). Patients who should not be considered for automatic steroid withdrawal are patients that have a history of rejection (either ACR or AMR), the presence of donor-specific antibody, drug levels suggestive of nonadherence, re-transplant, or a heart transplant that was due to sarcoid or giant cell myocarditis.

But even dual immunosuppression has been too much for some centers. In the TICTAC study, patients were randomized to monotherapy tacrolimus versus dual therapy tacrolimus/mycophenolate after a short course of prednisone. The rejection scores at 6 and 12 months were not different between the two groups showing that monotherapy did not predispose to worse outcomes or more rejection. In fact, there was no rejection after 210 days after transplant. There were two episodes of antibody-mediated rejection that occurred in the first 3 months after transplant (Baran et al. 2011). There are not many centers that adopted tacrolimus monotherapy as a result of this study, but the immunosuppression properties of tacrolimus made this study possible to succeed.

Currently calcineurin inhibitors, more specifically tacrolimus, are still the most common agents used for immunosuppression after heart transplant. As the majority of programs employ dual or triple immunosuppression, the agent in addition to calcineurin inhibitor is less standardized.

Antiproliferative Agents

The first heart transplants had a simple immunosuppression approach; due to lack of other immunosuppressants, 6-mercaptopurine, which was indicted for leukemia, was utilized as it was another year before azathioprine was approved by the FDA. Azathioprine, which is a derivative of 6-mercaptopurine, can be incorporated into replicating DNA and block purine synthesis in the de novo pathway.

However, even with years of experience with azathioprine, the acceptance of a new drug was quickly widespread. Mycophenolate mofetil was approved in 1996, in combination with cyclosporine and steroids. Mycophenolate mofetil is a prodrug of mycophenolic acid (MPA) which is an inhibitor of inosine monophosphate dehydrogenase which is the rate-limiting enzyme for de novo purine synthesis affecting lymphocytes. Patients taking mycophenolate have shown lower lymphocytes circulating than patients taking azathioprine.

The adverse effects of azathioprine, e.g., skin cancer and hepatotoxicity, made acceptance of an agent without these effects relatively easy. Mycophenolate was found, in early studies, to have gastrointestinal effects and bone marrow issues, but these could be treated with dose decreases. The initial mycophenolate study in heart transplant, in combination with cyclosporine, showed a reduction in the incidence of acute rejection (at 6 months) and a decrease in mortality at 12 months in mycophenolate- compared to azathioprine-treated patients (Kobashigawa et al. 1998). Mycophenolate 3 g daily was superior to azathioprine with regard to number of patients

treated for rejection, less severe rejection, less rejection with hemodynamic compromise, and less death. The dosing of mycophenolate is somewhat varied across programs. Though mycophenolate was approved at 3 g daily in heart transplant, it was approved at 2 g daily in kidney transplant because the pivotal trial in kidney transplant showed no difference in rejection rates between doses, but 2 g daily was better tolerated than 3 g daily (Sollinger 1995). That comparison has not been done in heart transplantation. When looking at pharmacokinetic studies of mycophenolate in combination with cyclosporine or tacrolimus, they show higher MPA exposure in tacrolimus-treated patients at a constant mycophenolate dose. Lower doses of mycophenolate mofetil are required to achieve a similar MPA concentration when used in combination with tacrolimus versus cyclosporine (van Gelder et al. 2001). Cyclosporine inhibits enterohepatic recirculation of MPA glucuronide and therefor causes a lower MPA area under the curve then tacrolimus-co-treated patients or any patient on mycophenolate not in combination with cyclosporine. Trough level monitoring of mycophenolate does not correlate well with the area under the curve measurements, and if therapeutic drug monitoring is going to be employed for mycophenolate, it should be AUC measurements instead of trough level monitoring (Jeong and Kaplan 2007). Since full 12-h AUC measurements are not possible on a routine basis, a mini-AUC measurement over 4 h has been used (Van Gelder et al. 2006). Despite the literature on AUC measurements of mycophenolate, there has not been literature to show that universal implementation of mycophenolate AUC monitoring has had a benefit on heart transplant recipients.

Mycophenolate mofetil was quickly accepted in heart transplantation in place of azathioprine. Its initial use as a renal sparing agent or cardiac allograft vasculopathy (Kaczmarek et al. 2006) treatment has mostly been supplanted by proliferation signal inhibitors, but it is still an important part of triple or dual immunosuppression agents, especially early posttransplant.

Proliferation Signal Inhibitors/mTOR

Triple immunosuppression, or dual immunosuppression with prednisone removed, has proven to be effective for decreasing the incidence of cellular rejection after heart transplantation. There has been a desire for an agent that could afford longer survival and have decreased toxicities and to address adverse effects of other maintenance immunosuppressants. In 1999 sirolimus was approved by the FDA for prevention of rejection in kidney transplantation.

The two currently available PSI/mTOR, sirolimus and everolimus, block mammalian target of rapamycin which inhibits T-cell proliferation. These agents can also inhibit B-cell differentiation and proliferation. Both agents are only approved for kidney transplantation in the USA, though everolimus is approved for use in heart transplantation in most of the European Union.

When sirolimus was approved, there was a noted lack of nephrotoxicity in the labelling and in clinical trials in kidney transplant which made it an attractive agent for patients with calcineurin inhibitor-associated nephrotoxicity. However, it was found that sirolimus was not effective at reversing existing nephrotoxicity. The place of sirolimus in maintenance therapy was not immediately clear with some centers using it in place of calcineurin inhibitors, while others used PSI/mTOR inhibitors in conjunction with calcineurin inhibitors, in place of the antiproliferative agent. Despite the desire for an agent to use in nephrotoxicity, it was found that sirolimus caused proteinuria and delayed renal recovery in acute kidney injury.

The PSI/mTOR inhibitors cause a delay in wound healing so they have not been used immediately after transplant. Another effect of PSI/mTOR that limits the tolerability is the development of interstitial pneumonitis. This has been seen when patients are treated with either sirolimus or everolimus, it is usually reversible when the agent is removed and does not always reappear in changing to the alternate PSI/mTOR (Bouvier et al. 2009; Molas-Ferrer et al. 2013).

Sirolimus and, more recently, everolimus have been found to be advantageous in preventing/treating cardiac allograft vasculopathy (CAV), to have benefit in certain cancers, and to have an association with lower incidence of CMV when compared to other immunosuppression regimens.

The PSI/mTOR inhibitors have shown to be effective at decreasing CMV after heart transplantation. Viral entry into macrophages does not involve mTORC1, so there is no beneficial effect of PST/mTOR in early CMV. Late CMV replication is dependent on mTORC1 for production of pp65 and UL-44, which are late-phase proteins (Brennan et al. 2013), so PSI/mTOR inhibitors can prevent CMV replication and be beneficial in difficult-to-treat CMV infections or equates to lower rates of CMV infections in patients that are started early on PSI/mTOR inhibitors.

PSI/mTOR inhibitors have been found to be advantageous in slowing the progression of CAV. The antiproliferative effects of PSI/mTOR inhibitors may play a part in the slowing progression or preventing CAV through preventing neointimal thickening. PSI/mTOR inhibitors have also shown to decrease homocysteine levels thus reducing the possibility of hyperhomocysteine driving CAV development. Studies examining mycophenolate versus everolimus showed that there was a higher incidence of early CAV at 1 year in patients treated with mycophenolate, with a significant difference in the mean intimal thickening in the CAV patients. There was no difference in CAV progression between mycophenolate and everolimus patients when everolimus was added late after heart transplantation (Masetti et al. 2013). A smaller increase in mean intimal thickening or plaque volume was found in patient on PSI/mTOR versus calcineurin inhibitor; this finding appears limited to early inclusion (whether de novo or conversion) of PSI/mTOR agent in maintenance immunosuppression regimen (Masetti et al. 2013).

PSI/mTOR were initially investigated as anticancer drugs before being approved for prophylaxis of organ rejection. The PSI/mTOR inhibitors have anticancer effects with effects on the PI3/Akt pathway that subsequently decreases tumor cell proliferation while also blocking angiogenesis due to inhibition of VEGF production (Guba et al. 2004). The most robust data with PSI/mTOR inhibitors after transplant is in kidney transplant patients with skin cancer, with everolimus having been approved for cancer indications under a separate brand name and with different dosing, demonstrating there are clearly anticancer properties of everolimus.

In two studies that consisted of kidney transplant patients with no previous skin cancer and randomized to sirolimus or continuation of prior immunosuppression, there were a statistically lower rate of non-melanoma skin cancer (NMSC) in sirolimus groups versus continued immunosuppression and a statistically significant decrease in melanoma in the sirolimus group. However, one-quarter to one-third of sirolimus-treated patients needed to discontinue sirolimus during the study period (Salgo et al. 2010; Alberu et al. 2011). In two studies that looked at kidney transplant patients with prior NMSC, there was significant decrease in new NMSC in patients converted to sirolimus, with a statistically longer time to development of new NMSC in the sirolimus patients; however one-quarter of patients could not tolerate sirolimus (Campbell et al. 2012; Euvrard et al. 2012).

More relevant, there is one analysis of heart transplant patients. That study consisted of patients who had previous NMSC and were converted from azathioprine to everolimus. At a little over 2 years, the mean number of NMSC was significantly lower compared with a similar timer period before conversion, with some patients not developing any new squamous cell carcinomas; however half of the patients had to discontinue everolimus (Euvrard et al. 2010).

The literature is convincing that PSI/mTOR inhibitors have an effect on reducing malignancies and finding the best time to introduce and best dose to treat cancers is research that needs to come.

Conclusion

The introduction of new immunosuppression agents were the key to allowing heart transplantation to succeed. There is still not uniform agreement about the optimal immunosuppression protocol, but perhaps the options allow for individualized immunosuppression, whether it includes a PSI/mTOR for its antiviral properties in a patient who has had recurrent CMV infections or a history of skin cancers. The need for a better immunosuppression regimen is there when looking at 1-year and 5-year survival rates; is there a regimen that will get more people to 5 years after heart transplantation? There are additional agents being investigated (see separate chapter) that will fit into contemporary heart transplantation immunosuppression protocols, but where and replacing what are to be determined.

Cross-References

- ▶ Advances in Immunosuppression
- ▶ Chronic Immunosuppression Medications
- ▶ Complications of Immunosuppression

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Complications of Immunosuppression 15

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Contents

Abstract

Immunosuppression management after heart transplantation continues to evolve, with an increasing number of immunosuppressant agents available for use in various combinations allowing for more choice and individualization of immunosuppressive therapy. Therapeutic developments have led to improved outcomes including lower acute rejection rates and improved survival. However, drug-related toxicities including nephrotoxicity, neurotoxicity, hyperglycemia, hyperlipidemia, weight gain, edema,

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and myelosuppression are frequently encountered leading to the need for dose adjustment or alternate therapy. Malignancy continues to be a frequent complication of immunosuppression and is a leading cause of death after heart transplantation. Skin cancer is the most commonly encountered type of malignancy; thus routine preventative strategies and screening are warranted. Infectious complications, including donor-derived, recipient-derived, nosocomial, and community-acquired exposures, are frequently encountered after heart transplantation and continue to contribute to post-transplant mortality. Antimicrobial preventative strategies including vaccinations, surgical prophylaxis, and opportunistic infection prophylaxis have greatly decreased post-transplant infection morbidity and mortality over time. Herein, complications of immunosuppression and considerations for management will be reviewed.

Keywords

Heart transplant · Immunosuppression · Complications · Drug-related toxicity · Myelosuppression · Nephrotoxicity · Neurotoxicity · Infection · Malignancy · Skin cancer · Post-transplant lymphoproliferative disorder

Introduction

Over the past 50 years, since the first heart transplant in 1967, heart transplantation and associated management have greatly evolved. Both advances in immunosuppressive therapy and infection prophylaxis and treatment have led to improved survival. An increasing number of induction and maintenance immunosuppressive agents have become available over time for use in various combinations allowing for more choice and personalization of immunosuppressive therapy based on individual tolerability (Table 1). Despite several advancements, there are pros and cons to each immunosuppressive agent, and a regimen that leads to prolonged survival and yet is void of associated morbidity including drug-related toxicities, infection, and malignancy has not been identified.

T-cell-depleting agents including anti-thymocyte globulin and alemtuzumab are sometimes utilized after heart transplantation either for induction immunosuppression or treatment of rejection but can be associated with myelosuppression, infusion-related reactions, and increased risk of infection and malignancy. Corticosteroids, calcineurin inhibitors (CNI), cell cycle inhibitors, and mammalian target of rapamycin (mTOR) inhibitors also known as proliferation signal inhibitors (PSI) are all associated with multiple and varying adverse effects that can impact long-term tolerability and complicate post-transplant management. Nephrotoxicity and resulting renal dysfunction, neurotoxicity, new-onset diabetes after transplant or worsening blood glucose control in patients with diabetes mellitus, hypertension, hyperlipidemia, weight gain, edema, and myelosuppression are frequently encountered complications of immunosuppressive therapy leading to the need for dose adjustment or alternate therapy.

Infectious complications and malignancy after heart transplantation continue to be common complications of immunosuppression and contribute to both morbidity and mortality. According to ISHLT registry data, both infection and malignancy are among the leading causes of death post-transplant. Herein, this chapter will review complications of immunosuppression including specific drug-related toxicities, diabetes mellitus, hypertension, hyperlipidemia, infection, and malignancy.

Drug-Related Toxicities

Specialized Induction Agents

Induction immunosuppression is intense prophylactic therapy including a potent targeted agent utilized at the time of the transplant to prevent early acute rejection. Three specialized induction agents are currently utilized in heart transplantation: a non-lymphocyte-depleting agent, basiliximab (Simulect®), and

Table 1 Immunosuppressive agents: adverse effects and monitoring parameters

Immunosuppressive agent	Class/Mechanism	Uses in heart transplantation	Adverse effects	Monitoring parameters	Additional considerations
Basiliximab (Simulect®)	Anti-CD25 monoclonal antibody; binds to the α subunit of the IL-2 receptor present only on activated and non-resting T cells	Induction	Rare; possible hypersensitivity reaction	None	
Anti-thymocyte globulin, rabbit (Thymoglobulin®)	Polyclonal antibody; polyclonal IgG against human T lymphocytes derived from rabbits; reduces the number of circulating T lymphocytes, which alters T-cell activation, homing, and cytotoxic function	Induction, treatment of rejection	Leukopenia, thrombocytopenia, fever, chills, dyspnea, pulmonary edema, tachycardia, hypotension, phlebitis, pruritus, erythema, rash, serum sickness, infection	Vital signs, CBC, absolute lymphocyte count, CD3 count	Premedication recommended with diphenhydramine and acetaminophen
Alemtuzumab (Campath®)	Anti-CD52 monoclonal antibody; binds CD52 antigen on T and B cells, on NK cells, and less densely on monocytes and macrophages causing cell lysis through antibody-dependent cellular cytotoxicity resulting in profound depletion of T cells and to a lesser degree B cells and monocytes	Induction, treatment of rejection	Leukopenia, thrombocytopenia, headache, fever, chills, dyspnea, tachycardia, hypotension, phlebitis, pruritis, erythema, rash, infection	Vital signs, CBC, absolute lymphocyte count	Premedication recommended with diphenhydramine and acetaminophen
Corticosteroids: prednisone, prednisolone, methylprednisolone, dexamethasone	Inhibit NF-AT, thereby blocking transcription of cytokine genes (interleukins 1, 2, 3, 5, TNF-alpha, and interferon gamma) and inhibiting cytokine production by T cells and macrophages	Induction, treatment of rejection, maintenance	Hyperglycemia, hypertension, hyperlipidemia, psychosis, mood swings, insomnia, photosensitivity, acne, osteoporosis, bone fractures, avascular necrosis, weight gain, fluid retention, increased appetite, hirsutism, Cushing's syndrome, menstrual irregularities, growth retardation, GI disturbance, cataracts,	Glucose, blood pressure, fasting lipid panel, weight, DEXA scan, eye exams	

(*continued*)

Table 1 (continued)

Immunosuppressive agent	Class/Mechanism	Uses in heart transplantation	Adverse effects	Monitoring parameters	Additional considerations
			impaired wound healing, infection		
Tacrolimus (Prograf®, Envarsus XR®, Astagraf®)	Calcineurin inhibitor; results in blockade of signal transduction by NF-AT, thereby preventing gene transcription for formation of lymphokines and ultimately inhibiting T-cell activation	Maintenance	Nephrotoxicity, neurotoxicity (Tac > CsA), hyperglycemia (Tac > CsA), hypertension (CsA > Tac) hyperlipidemia (CsA > Tac), hyperkalemia, hypomagnesemia hyperuricemia, HUS/TMA, infection, gingival hyperplasia (CsA only), hirsutism (CsA only), alopecia (Tac only)	12-h trough levels (Prograf®) or 24-h trough levels (Envarsus XR®, Astagraf®), serum creatinine, potassium, magnesium, uric acid	
Cyclosporine (Neoral®, Gengraf®, Sandimmune®)	Calcineurin inhibitor; results in blockade of signal transduction by NF-AT, thereby preventing gene transcription for formation of lymphokines and ultimately inhibiting T-cell activation	Maintenance		12-h trough levels or 2-h post-dose levels, serum creatinine, potassium, magnesium, uric acid	Modified formulations (Neoral®, Gengraf®) are not bioequivalent to non-modified formulations (Sandimmune®)
Mycophenolate mofetil (CellCept®): prodrug of mycophenolic acid Mycophenolate sodium (Myfortic®): delayed-release, enteric-coated tablet of mycophenolic acid	Antimetabolite/cell cycle inhibitor; inhibits lymphocyte purine synthesis by reversibly and noncompetitively inhibiting IMPDH	Maintenance	Nausea, vomiting, diarrhea, abdominal pain, leukopenia, thrombocytopenia, anemia, infection, cytomegalovirus infection	CBC, pregnancy test in women of childbearing potential (REMS)	REMS requirements to communicate increased risks of pregnancy loss and congenital malformations associated with mycophenolate exposure during pregnancy Females of reproductive potential must be counseled on pregnancy prevention and planning and need to report pregnancies to the Mycophenolate Pregnancy Registry
Azathioprine (Imuran®)	Antimetabolite/cell cycle inhibitor; metabolized to 6-mercaptopurine which is incorporated into nucleic acids (substitutes for the	Maintenance	Leukopenia, thrombocytopenia, macrocytic anemia, nausea, vomiting, abdominal pain,	CBC, LFT, amylase, lipase, TPMT enzyme level	Low or absent TPMT activity is associated with increased azathioprine-associated myelosuppression

	purine base guanine) ultimately inhibiting DNA and RNA synthesis		alopecia, pancreatitis, hepatotoxicity, infection		
Sirolimus (Rapamune®)	mTOR inhibitor/proliferation signal inhibitor; blocks signal transduction pathways ultimately inhibiting IL-2 and other cytokine-induced activation and proliferation of T and B cells	Maintenance	Thrombocytopenia, leukopenia, anemia, hyperlipidemia, impaired wound healing, wound-related reactions, peripheral edema, mouth ulcers, bone pain, diarrhea, proteinuria, pneumonitis, pneumonia, venous thromboembolism, HUS/TMA, infection	24-h trough levels (C0), fasting lipid panel, CBC, LFT	Frequent dosage adjustments based on nonsteady-state sirolimus concentrations can lead to overdosing or underdosing due to the long elimination half-life of sirolimus
Everolimus (Zortress®)	mTOR inhibitor/proliferation signal inhibitor; blocks signal transduction pathways ultimately inhibiting IL-2 and other cytokine-induced activation and proliferation of T and B cells	Maintenance	Thrombocytopenia, leukopenia, anemia, hyperlipidemia, impaired wound healing, wound-related reactions, peripheral edema, mouth ulcers, bone pain, diarrhea, proteinuria, pneumonitis, pneumonia, venous thromboembolism, HUS/TMA, infection	12-h trough levels (C0), fasting lipid panel, CBC, LFT	
Belatacept (Nulojix®)	Costimulation blocker; blocks the CD28-mediated costimulation of T lymphocytes by binding to CD80 and CD86 on antigen-presenting cells	Maintenance (off-label)	Fever, hypertension, headache, cough, anemia, leukopenia, nausea, vomiting, diarrhea, constipation, peripheral edema, PTLD, PML, infection	EBV serostatus (prior to treatment)	Contraindicated in transplant recipients who are EBV seronegative or with unknown EBV serostatus

Abbreviations: *CBC* complete blood count, *CsA* cyclosporine, *DEXA* dual-energy X-ray absorptiometry, *EBV* Epstein-Barr virus, *HUS/TMA* hemolytic uremic syndrome/thrombotic microangiopathy, *IMPDH* inosine monophosphate dehydrogenase, *LFT* liver function tests, *mTOR* mammalian target of rapamycin, *NF-AT* nuclear factor of activated T cells, *PML* progressive multifocal leukoencephalopathy, *PTLD* post-transplant lymphoproliferative disorder, *REMS* risk evaluation and mitigation strategy, *Tac* tacrolimus, *TPMT* thiopurine methyltransferase

two T-cell-depleting agents, rabbit anti-thymocyte globulin (rATG, Thymoglobulin®) and alemtuzumab (Campath®) (Table 1). According to ISHLT registry data for heart transplants from January 2009 through June 2016, 52.6% received a specialized induction agent. Basiliximab is a monoclonal antibody directed against CD25, the interleukin-2 receptor alpha chain of activated T cells, and is well tolerated with minimal adverse effects (Berard et al. 1999). rATG is prepared by immunizing rabbits with human thymocytes with resulting rabbit immune globulins against human T cells. rATG reduces the number of circulating T lymphocytes, which alters T-cell activation, homing, and cytotoxic function and ultimately affects cell-mediated and humoral immunity (Thymoglobulin® [package insert] 2017; Bonnefoy-Berard and Revillard 1996; Preville et al. 2001). Alemtuzumab is a humanized monoclonal antibody targeting CD52 which is located on T and B cells, NK cells, and to a lesser degree monocytes and macrophages (Calne et al. 1998; Kirk et al. 2003). The resultant antibody-dependent cellular cytotoxicity results in profound depletion of T cells and to a lesser degree B cells and monocytes. Adverse effects of both rATG and alemtuzumab include myelosuppression (leukopenia and thrombocytopenia) as well as infusion-related reactions due to cytokine release (Table 1). Survival was not significantly different in heart transplants between January 2004 and June 2015 that received no induction, IL-2 receptor antagonist or polyclonal anti-thymocyte globulin (International Society for Heart and Lung Transplantation Registry Slides: Adult heart transplantation statistics 2017). There are no randomized controlled trials in heart transplantation comparing all three induction agents. However, in the INTAC trial conducted in kidney transplant recipients, the rate of all infectious adverse events was higher with rATG than with alemtuzumab (81% vs. 60%; $p = 0.009$), and the rate of serious infectious adverse events was higher with alemtuzumab than with basiliximab (35% vs. 22%; $p = 0.02$) (Hanaway et al. 2011).

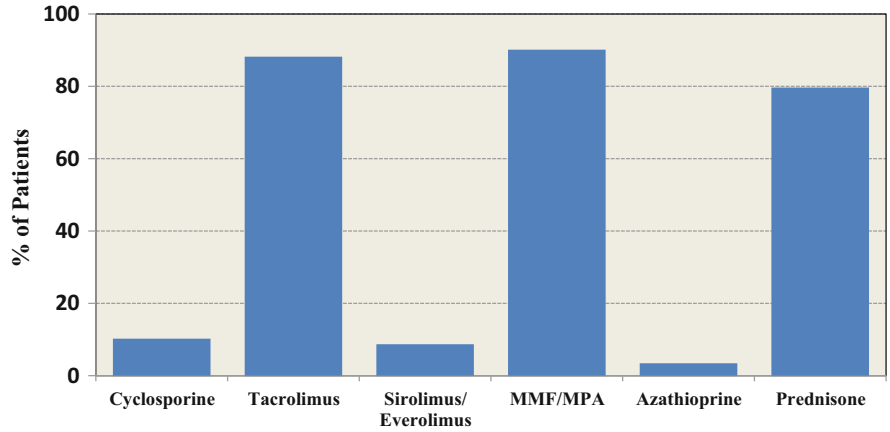
There are both potential concern and conflicting data regarding malignancy risk with use of T-cell-depleting induction agents. In kidney transplant recipients, while rATG was associated with significantly increased post-transplant lymphoproliferative disorder (PTLD) risk ($p = 0.0025$), alemtuzumab and basiliximab were not (Kirk et al. 2007). In an additional study including a total of 111,857 kidney recipients, linked transplantation and cancer registry data was examined. Alemtuzumab was associated with increased risk of non-Hodgkin's lymphoma, colorectal cancer, and thyroid cancer. Polyclonal induction was associated with increased risk of melanoma (Hall et al. 2015). Since malignancy is a frequently encountered complication after heart transplant, this is an important consideration.

Corticosteroids

Corticosteroids continue to be a cornerstone of immunosuppressive therapy and are utilized for induction and maintenance immunosuppression as well as treatment of rejection. They are utilized as part of the maintenance immunosuppressive regimen in approximately 80% of heart transplant recipients at 1 year post-transplant (Fig. 1). However, as they also have multiple side effects including hypertension, hyperglycemia, hyperlipidemia, weight gain, and osteoporosis, strategies have been employed to withdraw or minimize dosing over time (International Society for Heart and Lung Transplantation Registry Slides: Adult heart transplantation statistics 2017; Opelz et al. 2005; Lake et al. 1993; Miller et al. 1992; O'Connell et al. 1990; Pirsch et al. 2015).

Corticosteroid withdrawal strategies have been associated with reducing adverse effect-related complications. According to ISHLT consensus guidelines, corticosteroid withdrawal can be successfully achieved 3–6 months post-transplant in low-risk heart transplant patients including those without a history of rejection or circulating anti-HLA antibodies (Costanzo et al. 2010).

In a large multicenter prospective study including 420 heart transplant recipients retrospectively matched to controls maintained on corticosteroids, corticosteroid withdrawal over at least 6 months post-transplant was associated



Data source: International Society for Heart and Lung Transplantation Registry Slides: Adult heart transplantation statistics. 2017 JHLT 2017 Oct; 36(10): 1037-1079

Fig. 1 Adult heart transplants maintenance immunosuppression at time of 1-year follow-up (follow-ups: January 2009–June 2016). (Data source: International Society for Heart and Lung Transplantation Registry Slides: Adult heart transplantation statistics 2017 JHLT 36 (10):1037–1079)

with significantly improved graft survival, similar acute rejection rates, decreased frequency of new patients who experienced SBP >150 mmHg, decreased frequency of patients developing cholesterol >300 mg/dL, as well as significantly lower rates of new osteoporosis and cataracts when steroids were withdrawn during the first post-transplant year (Opelz et al. 2005). In addition, in a prospective, randomized, double-blind, placebo-controlled trial of early corticosteroid withdrawal versus long-term low-dose corticosteroid maintenance, corticosteroid withdrawal was associated with improvements in cardiovascular risk factors including triglycerides, new-onset diabetes after transplant requiring insulin, and weight gain (Woodle et al. 2008).

Calcineurin Inhibitors: Cyclosporine and Tacrolimus

CNIs, first cyclosporine and later tacrolimus, are standard of care for immunosuppression after heart transplantation as they have reduced rejection rates and improved overall graft survival. Cyclosporine binds to cyclophilin, whereas tacrolimus binds to FKBP-12. Both inhibit the phosphatase activity of calcineurin, which regulates nuclear translocation and subsequent activation of nuclear factor of activated T-cell (NF-AT) transcription factors ultimately inhibiting T-cell activation. Tacrolimus is utilized more commonly after heart transplant (Fig. 1; 88% at 1-year follow-up) due to decreased acute rejection as compared to cyclosporine and 24% versus 37%, $p < 0.0001$, in patients receiving concomitant mycophenolate through 1 year post-transplant (International Society for Heart and Lung Transplantation Registry Slides: Adult heart transplantation statistics 2017; Ye et al. 2009). Although calcineurin inhibitors (CNI) have reduced rejection rates and improved overall survival, they are associated with significant adverse effects including nephrotoxicity, neurotoxicity, hypertension, glucose intolerance, and hyperlipidemia.

CNI-Associated Nephrotoxicity

CNI-associated nephrotoxicity, which is caused by vasoconstriction of afferent and efferent glomerular arterioles, can be both acute and chronic and is one of the main contributing factors of renal dysfunction after heart transplantation (Naesens et al. 2009; Baran et al. 2004; Sikma et al. 2015).

Therapeutic drug monitoring of trough blood concentrations is routinely utilized and important to ensure efficacy and minimize adverse effects including nephrotoxicity. Target trough levels are higher early post-transplant and generally decrease over time but can be increased in the setting of rejection or reduced in the setting of infection, adverse effects, malignancy, and renal dysfunction to minimize nephrotoxicity. Trough blood levels should be monitored at least one to three times weekly in the immediate post-transplant period with more frequent monitoring warranted in the setting of hepatic dysfunction, shock, gastrointestinal dysfunction (malabsorption, diarrhea, etc.), change in formulation or route (including change from brand to generic, from generic to brand, or from one generic to another), and drug-drug interactions (Sikma et al. 2015). Both hepatic dysfunction and diarrhea can result in increased tacrolimus blood levels and resulting toxicity including acute nephrotoxicity (Lemahieu et al. 2005; Sikma et al. 2015).

Chronic kidney disease remains a common complication in heart transplant patients. According to ISHLT registry data, within 5 and 10 years post-transplant, 51.1% and 68.4% have renal dysfunction, 13.8% and 18.7% have creatinine >2.5 mg/dL, 3.2% and 6.7% are on chronic dialysis, and 1.4% and 3.8% require renal transplant. Severe renal dysfunction, defined as creatinine >2.5 mg/dL, dialysis, or renal transplant, within the first year after heart transplant, is also associated with decreased survival (International Society for Heart and Lung Transplantation Registry Slides: Adult heart transplantation statistics 2017). In addition to long-term utilization of CNIs, other identified risk factors for chronic kidney disease following heart transplantation include advanced age, female gender, pretransplant renal dysfunction, early post-transplant renal dysfunction, diabetes, and hypertension (Lachance et al. 2015; Sikma et al. 2015). While the majority of heart transplant recipients continue to be maintained on a CNI, studies have been conducted aiming to minimize these agents in an attempt to reduce associated nephrotoxicity and preserve or improve renal function (Gullestad et al. 2010, 2016; Andreassen et al. 2014; Zuckermann et al. 2012; Kaczmarek et al. 2013). CNI minimization or withdrawal studies have utilized mTOR inhibitors, either everolimus or sirolimus, to either decrease the CNI dosing and target trough level or to withdraw the CNI. Despite being associated with more improvement in renal function, CNI withdrawal is less frequently conducted as compared to CNI minimization after heart transplantation due to increased incidence of acute rejection (Kaczmarek et al. 2013; Andreassen et al. 2014; Zuckermann et al. 2012). CNI minimization has been associated with improved renal function, although the absolute increase in GFR is modest. The multicenter NOCTET trial included 282 heart or lung transplant patients with renal dysfunction greater than 1 year post-transplant randomized to continue CNI-based immunosuppression or start everolimus with reduced CNI. In all patients, mean change in measured glomerular filtration rate (GFR) from baseline to month 12 was 4.6 mL/min with everolimus and −0.5 mL/min in controls ($p < 0.0001$) (Gullestad et al. 2010).

CNI-Associated Neurotoxicity

Neurotoxic adverse effects of CNI can be observed although tend to be more common with tacrolimus. Mild effects are common and can include tremor, peripheral neuropathy, and headache. In a randomized multicenter trial, tremor was the most frequent neurotoxic adverse effect occurring in 15% and 6% of heart transplant recipients maintained on tacrolimus and cyclosporine, respectively (Prograf [package insert] 2015). Severe effects can include seizures, confusion, altered level of consciousness, hallucinations, visual disturbances, cortical blindness, cerebellar ataxia, motoric weakness, and leukoencephalopathy (Bechstein 2000). Severe neurotoxicity has been associated with high levels of CNIs; management includes dose reduction or withdrawal of the offending immunosuppressant agent depending on severity, correcting electrolyte abnormalities including hypomagnesemia, and controlling blood pressure (Bechstein 2000). Cyclosporine, as an alternate therapy, may offer

benefit in patients that experience neurologic adverse effects from tacrolimus (Abouljoud et al. 2002).

Cell Cycle Inhibitors: Mycophenolate and Azathioprine

Mycophenolate is a potent, selective, reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH) and inhibits the de novo pathway of guanosine nucleotide synthesis without incorporation into DNA. Mycophenolate has cytostatic effects on T and B lymphocytes since they are critically dependent on de novo synthesis of purines for their proliferation. In addition, mycophenolate has also been shown to suppress antibody formation by B lymphocytes. Azathioprine is a prodrug of 6-mercaptopurine and incorporates into nucleic acids (substitutes for the purine base guanine) ultimately inhibiting DNA and RNA synthesis. Mycophenolate is more frequently utilized; 90% of heart transplant patients were maintained on mycophenolate at 1-year follow-up according to ISHLT registry data (Fig. 1) (International Society for Heart and Lung Transplantation Registry Slides: Adult heart transplantation statistics 2017). In a randomized, double-blind, controlled trial, mycophenolate mofetil has been associated with decreased mortality and graft loss as compared to azathioprine after heart transplantation (Eisen et al. 2005).

Mycophenolate is available in two formulations: MMF and an enteric-coated, delayed-release product mycophenolate sodium. The enteric coating on mycophenolate sodium allows for mycophenolic acid to be released directly into the small intestine for absorption rather than in the stomach. Routine therapeutic drug monitoring with mycophenolate trough levels is not recommended as there is a poor correlation with drug exposure as measured by the area under the curve (Monchaud and Marquet 2009; Pou et al. 2001). Mycophenolate is frequently associated with both hematologic (leukopenia, neutropenia) and gastrointestinal (diarrhea, nausea, abdominal pain) adverse effects which may warrant dose adjustment or alternative therapy. In patients maintained on MMF with gastrointestinal adverse effects, switching to mycophenolate sodium may offer benefit (Ortega et al. 2011). Also, diarrhea may occur less frequently with azathioprine as compared to MMF (Eisen et al. 2005). Mycophenolate exposure during pregnancy is associated with an increased risk of first trimester pregnancy loss and congenital malformations. Because of this, the Food and Drug Administration (FDA) requires a Risk Evaluation and Mitigation Strategy (REMS) for mycophenolate. Prior to initiation, the prescriber should educate females of reproductive potential on risks, pregnancy prevention including contraception, planning, and need to report pregnancies to the Mycophenolate Pregnancy Registry. Pregnancy tests should be checked in women of childbearing potential prior to initiation, 8–10 days after initiation, and periodically while on therapy at routine follow-up visits thereafter (Kim et al. 2013).

Azathioprine can also result in leukopenia/neutropenia. Of note, patients with absent or low thiopurine methyltransferase (TPMT) activity are at increased risk of azathioprine-associated myelosuppression (Relling et al. 2013). TPMT genotyping or phenotyping may assist in identifying patients at risk for developing toxicity and should be considered prior to azathioprine initiation or in patients maintained on azathioprine with abnormally low white blood cell count or platelets unresponsive to dose reduction. Consensus guidelines recommend considering an alternative agent or dose reduction of azathioprine for patients with low or deficient TPMT activity and to start at 30–70% of the target dose for patients with intermediate enzyme activity (Relling et al. 2013). Of note, Liang et al. found more acute rejection in heart transplant patients with TPMT genetic variant alleles and concluded such patients should be monitored carefully given this (Liang et al. 2013). Thrombocytopenia, hepatotoxicity, and pancreatitis are also possible adverse effects. Patients on concomitant therapy with medications that inhibit TPMT (i.e., 5-aminosalicylic acid derivatives and furosemide) or xanthine oxidase inhibitors (i.e., allopurinol) are more susceptible to myelosuppression

necessitating azathioprine dose adjustment (Gao et al. 2012; Xin et al. 2005).

Mammalian Target of Rapamycin (mTOR) Inhibitors (Proliferation Signal Inhibitors (PSI)): Everolimus and Sirolimus

Mammalian target of rapamycin (mTOR) inhibitors also known as proliferation signal inhibitors (PSI) including everolimus and sirolimus have been utilized for various reasons after heart transplantation including as a cell cycle inhibitor alternative in the setting of adverse effects or cytomegalovirus infection, to minimize or withdraw CNI in order to preserve or improve renal function, and in patients that develop cardiac allograft vasculopathy (CAV) or malignancy, but high rates of adverse events have limited their widespread use (Gullestad et al. 2010, 2016; Karia et al. 2016; Andreassen et al. 2014; Arora et al. 2015; Vigano et al. 2007; Gonzalez-Vilchez et al. 2012). Potential adverse effects of mTOR inhibitors include hyperlipidemia, edema, impaired wound healing, proteinuria, pneumonitis, mouth ulcers, myelosuppression including anemia and leukopenia, and increased risk of venous thromboembolism (Fine and Kushwaha 2016; Rothenburger et al. 2007). Despite their potential uses and benefits, according to ISHLT registry data, only 8.7% of transplant recipients are maintained on everolimus or sirolimus at 1 year post-transplant (Fig. 1) (International Society for Heart and Lung Transplantation Registry Slides: Adult heart transplantation statistics 2017). Low usage is likely related to high rates of discontinuation due to tolerability issues as in clinical studies; premature discontinuation due to adverse effects was as high as 55% (Eisen et al. 2013; Kaczmarek et al. 2013). Adverse effects more common with everolimus or sirolimus in clinical studies include edema, hyperlipidemia, diarrhea, pericardial effusion, pneumonia, anemia, thromboembolic events, and impaired wound healing, whereas cytomegalovirus infections occurred less frequently (Gullestad et al. 2010; Eisen et al. 2013; Kaczmarek et al. 2013; Kobashigawa et al. 2006; Andreassen et al. 2014).

Diabetes Mellitus

Both corticosteroids and calcineurin inhibitors are associated with glucose intolerance contributing to increased incidence of diabetes mellitus after transplant. The rate of new-onset diabetes mellitus after transplant (NODAT) requiring insulin treatment was higher with tacrolimus as compared with cyclosporine in a meta-analysis including 885 heart transplant patients (Ye et al. 2009). According to ISHLT registry data for adult heart transplants between January 1994 and June 2015, 22.2% of patients have diabetes within 1 year, and 35.5% of patients have diabetes within 5 years post-transplant. In addition, diabetes has been associated with a significant decrease in survival after heart transplantation (International Society for Heart and Lung Transplantation Registry Slides: Adult heart transplantation statistics 2017). Additional risk factors for NODAT include pretransplant glucose intolerance, immediate post-transplant hyperglycemia, a family history of diabetes, African American or Hispanic ethnicity, increased age, increased body weight, and hepatitis C (Wallia et al. 2016). Management includes tight glycemic control during the inpatient stay after transplant; typically with insulin therapy while in the hospital. When transitioning to the outpatient setting, other agents including oral medications can be utilized depending on blood glucose control as well as renal function. For patients with preexisting diabetes mellitus, it is not uncommon for therapy to require intensification due to increased blood glucose levels in the setting of higher corticosteroids in the early post-transplant period (Wallia et al. 2016). As the corticosteroid dose tapers, careful follow-up is warranted regarding blood glucose levels and to determine if adjustments to the diabetes therapeutic regimen are needed.

Hypertension

The development of hypertension is common after heart transplantation and is related to multiple factors. It is a common adverse effect of both CNI and corticosteroids. Although common

with both CNIs, it is more frequently encountered with cyclosporine as compared to tacrolimus (Penninga et al. 2010; Ye et al. 2009). After heart transplantation, there is a loss of nocturnal decline in blood pressure; therefore, optimal blood pressure control may be better by giving larger antihypertensive doses at night (Bennett and Ventura 2017). Calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARB) are first-line options for treatment of hypertension after heart transplantation (Bennett and Ventura 2017). Calcium channel blockers have been studied to evaluate their vasodilatory properties in counteracting CNI vasoconstriction and associated nephrotoxicity with favorable outcomes on both decreasing blood pressure and preservation of renal function (Leenen et al. 2007; Naesens et al. 2009). In addition, since diltiazem inhibits the metabolism of immunosuppressant agents that are substrates of CYP 3A4 including cyclosporine, tacrolimus, sirolimus, and everolimus, it can be utilized to both lower blood pressure and lower the immunosuppressant dose requirement (Bourge et al. 1991). ACE inhibitors and ARBs have an overlapping adverse effect of hyperkalemia with some of the transplant-related medications including CNIs and sulfamethoxazole/trimethoprim. Because of this, potassium levels should be monitored routinely, especially when initiating therapy and with dose titration. Renal function can also worsen, and/or transient increases in serum creatinine can occur during ACE inhibitor, or ARB therapy, especially in patients with low renal blood flow, therefore, should also be monitored closely.

Hyperlipidemia

Hyperlipidemia including both hypercholesterolemia and hypertriglyceridemia is frequently encountered post-transplant occurring in over 50% of heart transplant recipients and an adverse effect of corticosteroids, CNI (cyclosporine > tacrolimus), and mTOR inhibitors (Becker et al. 1987; Agarwal and Prasad 2016; Taylor et al. 1999; Eisen et al. 2013). Consequences of dyslipidemia post-transplant can include acceleration of atherosclerosis and development of post-transplant cardiovascular disease (Agarwal and Prasad 2016). Suggested laboratory monitoring after transplant includes checking a fasting lipid panel 3 months post-transplant and at least annually thereafter (Costanzo et al. 2010; Agarwal and Prasad 2016). Management includes both lifestyle modifications and pharmacologic treatments, with HMG-CoA reductase inhibitors (i.e., statins) as the cornerstone for therapy. Strict control of cardiovascular risk factors including hyperlipidemia is important for primary prevention of cardiac allograft vasculopathy (CAV) (Costanzo et al. 2010). Importantly, in adult heart transplant recipients, the use of statins beginning 1–2 weeks post-heart transplant is recommended regardless of cholesterol levels as they have been associated with reduced accelerated graft atherosclerosis and mortality (Bilchick et al. 2004; Costanzo et al. 2010; Vallakati et al. 2016). In addition, statins are recommended for pediatric heart transplant recipients with evidence of hyperlipidemia, CAV, or after re-transplantation. Due to drug-drug interactions with CNI (cyclosporine > tacrolimus) and associated risk of toxicity (myopathy/rhabdomyolysis, hepatotoxicity), initial lower statin doses are recommended per ISHLT consensus guidelines, although high-intensity statin therapy appears safe if needed for treatment of refractory hyperlipidemia in patients maintained on tacrolimus (Costanzo et al. 2010; Heeney et al. 2019). Per package labeling, due to substantial increases in the statin AUC partly due to CYP 3A4 inhibition and associated increased risk of myopathy/rhabdomyolysis, simvastatin, lovastatin, and atorvastatin are not recommended to be utilized in patients maintained on cyclosporine (Mevacor® [package insert] 2012; Zocor® [package insert] 2019; Lipitor® [package insert] 2019). Other LDL-lowering drugs include ezetimibe, bile acid sequestrants, and PCSK9 inhibitors. Ezetimibe has a significant drug-drug interaction with cyclosporine resulting in increased exposure of both medications that warrants close monitoring, and the extent of increased ezetimibe exposure may be greater in patients with severe renal insufficiency (Zetia®

[package insert] 2013). Bile acid sequestrants are not preferential in transplant recipients due to gastrointestinal side effects as well as potential interference with immunosuppressive medication absorption (Agarwal and Prasad 2016). PCSK9 inhibitors, including alirocumab and evolocumab, are the newest class of medications to treat hyperlipidemia that may have a role for patients with residual hyperlipidemia despite maximum tolerated statin doses or those intolerant to statin therapy, although current published efficacy and safety data in heart transplant patients is limited to small case series and reports (Di Nora et al. 2019; Moayedi et al. 2019; Kuhl et al. 2019). For patients intolerant to statins, niacin could be considered as an option to reduce LDL cholesterol and triglyceride levels although adverse effects including flushing, hepatotoxicity, and glucose intolerance may limit use (Bilchick et al. 2004; Agarwal and Prasad 2016). For hypertriglyceridemia despite LDL-lowering therapy, the addition of omega-3 fatty acids can be considered and has shown benefit in heart transplant recipients maintained on mTOR inhibitors (Celik et al. 2008). Use of fibrates in heart transplant recipients for further lowering triglyceride levels is not routinely recommended (Bilchick et al. 2004).

Infection

Infectious complications are frequently encountered after heart transplantation although risk of infection for the recipient post-transplant is based on both epidemiologic exposure and the patient's net state of immunosuppression. Epidemiologic exposure categories include donor-derived, recipient-derived, nosocomial, and community-acquired. Net state of immunosuppression includes all factors that contribute to the risk of infection including immunosuppressive therapy, prior therapies such as chemotherapy or antimicrobials, mucocutaneous barrier integrity, neutropenia, lymphopenia, hypogammaglobulinemia, technical complications such as wounds or fluid collections, underlying immune defects, metabolic conditions including diabetes and advanced age, and infection with immunomodulating viruses (Fishman 2007, 2017; Green 2013). Early infections, occurring up to 30 days post-transplant, can result from surgical complications, donor-derived infections, preexisting recipient infections, or nosocomial infections including *Clostridium difficile* colitis or aspiration. Most infections are caused by bacteria or yeast during this time period (Green 2013; Fishman 2017). From 1 to 6 through 12 months post-transplant, opportunistic infections including cytomegalovirus are often present, especially in the absence or recent cessation of prophylaxis (Green 2013; Fishman 2017). After 6–12 months post-transplant, infection type and etiology are variable and also depend on various factors including net state of immunosuppression and antimicrobial prophylaxis. Types of infection can include community-acquired infection as well as later presentation of opportunistic infections in patients maintained on longer prophylactic courses (Green 2013). Infections that occur after the usual period or that are unusually severe could be related to excessive immunosuppression. In addition, intensification of immunosuppression (e.g., due to treatment of acute rejection episodes) resets this timeline and associated infection risk (Fishman 2007). According to ISHLT registry data, infection is a leading cause of mortality during the first year post-transplant accounting for 31.6% of deaths (International Society for Heart and Lung Transplantation Registry Slides: Adult heart transplantation statistics 2017). However, antimicrobial preventative strategies including vaccinations, surgical prophylaxis, and opportunistic infection prophylaxis have greatly decreased post-transplant infection morbidity and mortality over time. Opportunistic infection prophylaxis for cytomegalovirus, pneumocystis jiroveci pneumonia, toxoplasmosis, and fungal infections is recommended and routinely employed after heart transplantation (Fishman 2007; Razonable and Humar 2013; Martin and Fishman 2013; Derouin and Pelloux 2008). Routine assessment of vaccination status and updates including annual influenza vaccination is an important component of post-transplant care (Danziger-Isakov and Kumar 2013).

Malignancy

De novo post-transplant malignancy is a devastating and frequent complication associated with immunosuppression after heart transplant occurring in 15.9% of 5-year survivors and 27.7% of 10-year survivors per ISHLT registry data. Skin cancer is the most common encountered type of malignancy after heart transplantation occurring in 9.5% of 5-year survivors and 18.4% of 10-year survivors (International Society for Heart and Lung Transplantation Registry Slides: Adult heart transplantation statistics 2017). In a registry analysis of the US Organ Procurement Transplant Network/United Network for Organ Sharing database, the incidence of post-transplant malignancy excluding skin cancer after primary heart transplantation was 14.3 per 1000 person-years with lung and bronchial cancer (3.24%), prostate cancer (3.07%), and PTLD (2.24%) being the most common types of cancer observed (Sampaio et al. 2012). Malignancy (including lymphoma) was the most common cause of death for patients greater than 5 years post-transplant accounting for 24.9%, 23.9%, and 21.3% at >5–10 years, >10–15 years, and > 15 years, respectively (International Society for Heart and Lung Transplantation Registry Slides: Adult heart transplantation statistics 2017). Survival after heart transplant is significantly decreased ($P < 0.0001$) in patients that develop malignancy within 3 years of transplant compared with those without malignancy (International Society for Heart and Lung Transplantation Registry Slides: Adult heart transplantation statistics 2017).

Skin Cancer

Skin cancer is frequently encountered with incidence increasing over time after transplant, ultimately affecting over 50% of white transplant recipients (Euvrard et al. 2003). The majority of skin cancers after transplant are either squamous cell or basal cell carcinoma (Euvrard et al. 2003). Risk factors include ultraviolet radiation exposure, increasing age, fair skin, duration and intensity of immunosuppression, prior skin cancer, human papillomavirus (HPV) infection, and smoking (Euvrard et al. 2003; Ulrich et al. 2008). Preventative measures are key and include patient education regarding sun avoidance, sun screen SPF 30 or higher, protective clothing, and skin self-examination monthly. In addition, dermatologist skin surveillance should occur at least annually but more frequent if pretransplant history of skin cancer and/or diagnosis of post-transplant skin cancer (Acuna et al. 2017; Ulrich et al. 2008). Immunosuppression modification or reduction may be warranted, especially if multiple or aggressive skin cancer lesions (Tessari and Girolomoni 2012; Ulrich et al. 2008). Replacing a cell cycle inhibitor with an mTOR inhibitor may offer benefit in decreasing the incidence of skin cancers (Salgo et al. 2010; Campbell et al. 2012; Euvrard et al. 2010).

Post-transplant Lymphoproliferative Disorder (PTLD)

PTLD includes a spectrum of lymphoproliferative conditions ranging from infectious mononucleosis to malignancy. Epstein-Barr virus (EBV) is known to be involved in the pathogenesis of more than 50% of PTLD cases (Allen and Preiksaitis 2013; San-Juan et al. 2014; Kinch et al. 2014). The incidence of PTLD post-transplant ranges from 1% to 16% and varies depending on the type of organ transplant and associated risk factors (San-Juan et al. 2014). In one of the largest single-center analyses of PTLD in heart and lung transplant recipients, PTLD occurred in 7.59% of heart-lung and 5.37% of heart transplant recipients (Kumarasinghe et al. 2015). Risk factors for PTLD include EBV mismatch, EBV seronegativity, young and older (> 60 years) recipient age, and anti-thymocyte globulin and OKT3 use (Dharnidharka et al. 2012; Allen and Preiksaitis 2013; San-Juan et al. 2014). In addition, belatacept, a selective T-cell costimulation blocker, has been associated with a ninefold higher rate of PTLD in EBV seronegative patients or with unknown serostatus and, due to this, is contraindicated for use in such patients (Nulojix

[package insert] 2014). EBV serostatus should be checked on all donors and transplant recipients to better characterize PTLD risk (Allen and Preiksaitis 2013; San-Juan et al. 2014). Weekly to biweekly serial EBV quantitative DNA monitoring should be considered in high-risk patients for the first year after transplant (Allen and Preiksaitis 2013). Serial viral load monitoring to detect primary infection or reactivation with subsequent reduction in immunosuppression with or without rituximab has been associated with reducing PTLD incidence in heart transplant recipients (Choquet et al. 2014). Histopathology remains the gold standard for PTLD diagnosis (Allen and Preiksaitis 2013). Extranodal disease with diffuse large B-cell lymphoma was reported as the most common presentation in heart and lung transplant recipients (Kumarasinghe et al. 2015). Treatment of PTLD includes reduction of immunosuppression (usually by 25–50% of baseline) plus rituximab, chemotherapy, surgical resection, and/or local radiotherapy depending on histopathology, location, and extent of disease (Allen and Preiksaitis 2013; San-Juan et al. 2014; Parker et al. 2010). A complete response within 3 months of treatment has been associated with improved survival although overall survival at 5 years is poor at 29% (Kumarasinghe et al. 2015).

Conclusion

Immunosuppression management after heart transplantation continues to evolve, with an increasing number of immunosuppressant agents available. Therapeutic developments have led to improved outcomes including lower acute rejection rates and improved survival. However there are several complications associated with immunosuppression including drug-related toxicities, infectious complications, and malignancy. While maximizing efficacy and minimizing toxicity of immunosuppressive therapy continues to be a delicate balancing act, maintenance immunosuppression minimization strategies and targeted immune therapy continue to advance the transplant immunosuppression field. Infectious complications, including donor-derived, recipient-derived, nosocomial, and community-acquired exposures, are frequently encountered after heart transplantation and continue to contribute to post-transplant mortality. However, antimicrobial preventative strategies including vaccinations, surgical prophylaxis, and opportunistic infection prophylaxis have greatly decreased post-transplant infection morbidity and mortality over time. Malignancy continues to be a frequent complication of immunosuppression, thus ensuring preventative strategies including routine screening is an important component of post-transplant care. Ultimately, a one size fits all approach for any immunosuppressive strategy and monitoring plan may not be best suited to the individual patient, and patient-specific factors must be considered when designing and adjusting the immunosuppressive regimen.

Cross-References

- ▶ Cardiac Allograft Rejection
- ▶ Chronic Immunosuppression Medications
- ▶ Induction and Maintenance Agents
- ▶ Infection Prophylaxis
- ▶ Monitoring for Rejection

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Cardiac Allograft Rejection

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Abstract

Cardiac transplantation has been largely successful due to current effective immunosuppressive regimens; however, despite improvements in immunosuppression and overall longevity of the cardiac allograft, acute rejection still poses a risk for poor outcomes. Newer agents hold promise in reducing further acute and chronic rejection episodes including cardiac allograft vasculopathy. Endomyocardial biopsy remains the gold standard to diagnose acute rejection, but its invasive nature and repetitive use during posttransplant surveillance pose risk for complications. Noninvasive diagnostic studies of acute rejection are feasible with newer imaging modalities holding promise in early detection of rejection. Gene expression analysis, donor cell DNA, and cardiac MRI can be strong auxiliary methods to determine risk for rejection. Contemporary treatment of acute rejection episodes has improved due to our understanding of the immunological pathways involved in cellular- and antibody-mediated rejection. Chronic rejection however remains a challenge to treat due to interplay of complex immune mechanisms. This chapter will review the immunology of rejection, the diagnosis of cardiac allograft rejection determined by endomyocardial biopsy, and other novel noninvasive modalities and the treatment of rejection.

Keywords

Cardiac transplant · Cellular rejection · Antibody-mediated rejection · Noninvasive

Introduction

Heart transplantation (HT) is the definitive treatment for selected end-stage heart failure patients. Maintaining allograft function through immunosuppression and rejection surveillance is a cornerstone of post-HT management. Cardiac allograft rejection (CAR) including acute cellular rejection (ACR), acute antibody-mediated rejection (AMR), and chronic allograft rejection is a complex process involving both T- and B-cell pathways of the immune system that result in graft dysfunction and poor survival (Mills et al. 1997). Acute rejection is always a concern after heart transplantation, despite declines in its incidence in the 1-year period post-HT. Recent international registry data shows that across different eras of immunosuppression, the incidence of any rejection between discharge post-HT and 1-year follow-up has declined to 17% (30% in 2004–2006 to 25% in 2010–2012). The incidence of any treated rejection has decreased by 43% (23% in 2004–2006 to 13% in 2010–2012), due to an improved grading system where milder forms of rejection do not always warrant treatment lowering the number of rejection-related hospitalizations. Despite improvements in immunosuppression and surveillance protocols, survival declines in those experiencing an episode of rejection compared to those who do not have a rejection (87% vs. 93% at 3 years, 80% vs. 87% at 5 years, respectively). To date however, there is no suitable single diagnostic method beyond endomyocardial biopsy to detect early rejection before clinical signs ensue. This is important, as

early recognition of cardiac allograft rejection can halt the progression to graft dysfunction and sustain the longevity of the graft. Evermore, there are multiple factors associated with increased risk of rejection (pre-sensitization, timing of transplantation, the immunosuppressive regimen, HLA mismatch, age, gender, and ethnicity) that need to be considered pre- and posttransplantation. Acute rejection is more commonly seen early after heart transplantation, while late rejection can occur years after transplant predominantly associated with cardiac allograft vasculopathy and donor-specific antibody formation, especially in those with multiple rejections in the first year of transplant and cytomegalovirus infection (Kubo et al. 1995; Loupy et al. 2011). This chapter will review the mechanisms of CAR, current diagnostic methods, and overview of treatment strategies.

Immunology of Cardiac Transplantation

The major histocompatibility complex (MHC) antigens of the graft cells are mainly responsible for the immunologic cascade generated after transplant. Natural killer cells, T cells, and B cells recognize the plethora of antigens and mediate the compatibility between the donor and recipient. There are two MHC classes, I and II, expressed in the endothelium and parenchyma of the graft with immense variations in the expression of both MHC classes making it impossible to find a perfect match in transplant. Rejection begins when the donor MHC antigens are recognized as different from self, a term called allorecognition. These antigens are either directly presented to recipient T cells by allogenic antigen-presenting cells (APCs), dendritic cells, macrophages, B cells, and endothelial cells from the donor graft, or indirectly by antigens shed from the donor graft which in turn are presented by recipient APCs to recipient T cells. The allorecognition complex between MHC class II molecules present in APCs and T-cell receptors (TCR-CD3 complex) is the key component of the immune activation. In response to this allorecognition, activated T helper cells (CD4+) proliferate and produce cytokines that stimulate cytotoxic (CD8+) T cells, B cells, and macrophages. The outcome of the immune activation will lead to destruction of targeted graft cells, antibody production, and delayed hypersensitivity reactions. The TCR-CD3 complex results in calcineurin activation in the cytoplasm of T helper cells (ThC) which then activate nuclear factors of activated T cells (NFAT). This latter factor enters the nucleus and promotes IL2 production. When IL2 is secreted in the cytoplasm of T cells, it stimulates surface IL2 receptors (IL2R) allowing clonal expansion of ThC, cytotoxic T cells, B cells, and natural killer cells. Activation of the IL2R then triggers the enzyme target of rapamycin (TOR) which regulates the T-cell cycle.

Once rejection occurs, it can present in two ways: (1) Acute rejection – antigen-activated ThC infiltrate the donor graft causing endothelial inflammation and myocyte damage mainly a cell-mediated immune response with some contribution from antibodies. If graft structure and function are partially preserved, immunological adaptation occurs and can be stabilized by immunosuppressive drugs. (2) Chronic rejection – involves cell, antibody, and non-immunologic mechanisms that replace normal parenchyma of epithelium, arteries, and capillaries with fibrous tissue. This indolent process leads to neointimal hyperplasia, matrix deposition, and lumen narrowing within the donor graft known as cardiac allograft vasculopathy (CAV).

Acute Cellular Rejection

Epidemiology: Acute cellular rejection (ACR) is most frequently seen in the first 3 to 6 months after HT, with its incidence rapidly decreasing after 1 year of HT (Lund et al. 2016). ACR, however, can occur at any time after HT when there is a cessation or lapse in immunosuppressive therapy. Approximately 40% of adult HT patients will have $\geq$1 acute rejection episodes within 1 month post-HT, 60% will have an episode of rejection (ISHLT grade $\geq$ 1R) within 6 months, and 30% of patients will have rejection that requires adjustment in their immunosuppressive therapy within

the first year (Kirklin et al. 1992). ACR is one of the leading causes of morbidity during the initial 6 months post-HT with repetitive ACR episodes having a cumulative effect risk on CAV development (Raichlin et al. 2009). Moreover, HT recipients who are treated for severe ACR in the first year after HT have worse long-term survival compared to those without rejection (Soderlund et al. 2014). Between 1 and 3 years after HT, ACR is responsible for 8% of deaths. However, beyond 3 years after HT, rejection-related death is rare (Lund et al. 2015). Advances in postoperative management, graft function surveillance, and immunosuppression regimens have reduced rejection rates significantly and improved survival rates after HT (John et al. 2001).

Risk Factors. Factors such as donor-to-recipient HLA mismatching, younger recipient, female recipients, female donors, African American recipient, donor-to-recipient gender mismatching, CMV infection, intensity of maintenance immunosuppression, and long ischemic time have been associated with a high risk for ACR (Kirklin et al. 1992; Kobashigawa et al. 1993; Aziz et al. 1998; Kilic et al. 2012).

Pathology. ACR is defined histologically by a predominantly lymphocytic inflammatory infiltrate that is associated with myocyte injury. The hallmark features of ACR include a T-cell-mediated response and myocardial cellular infiltration of macrophages which may result in myocardial necrosis in severe cases (Fig. 1). The T-cell infiltrates are composed mostly of CD4 + and CD8+ T cells targeting graft antigens and are accompanied by a variable number of macrophages and dendritic cells with a good correlation between mean number of CD8+ cells and rejection severity (Tan et al. 2007). Presence of B cells and NK cells can also be seen in moderate rejection, which has been associated with a high risk for ACR recurrence (Sorrentino et al. 2006). Histologically, the first change noted is a perivascular infiltrate of mononuclear cells, which spread away to the interstitial tissue. In severe ACR, the myocyte injury takes the form of "coagulation necrosis" with significant infiltrate of neutrophils, eosinophils, and vasculitis. In addition, NK cells can be seen in severe cases causing myocyte injury and microvessel disruption. The affected myocyte loses their structure with a loss of the sarcoplasmic organelles and occasionally prominent nucleoli.

Diagnosis. Definite diagnosis of ACR is made by histological and immunohistochemical evidence of inflammatory infiltrates on endomyocardial biopsy (EMB). The inflammatory infiltrate present is defined by distinct patterns based on extent and severity of rejection of the cardiac allograft. Billingham and colleagues at Stanford devised the first grading system in 1990 to describe the different levels of inflammatory responses to the transplanted heart. The old "1990" ISHLT grading system was divided into focal and diffuse infiltrates and with and without myocyte injury. The pattern of inflammatory infiltration was categorized into subdivisions A and B in grades 1 and 3. However, subsequent small studies found the application of the system by pathologists from different centers to be variable and inconsistent (Stewart et al. 2005). Due to lack of consensus, a new grading system was proposed by ISHLT in 2005 which utilizes a suffix "R" to indicate the new revised system: (1) No rejection is reported when there is absence of inflammation. (2) Mild rejection consists of a perivascular or interstitial infiltrate of mononuclear cells without myocyte structure alteration or a focus of inflammation with myocyte damage. (3) Moderate rejection consists of two or more foci of mononuclear cell infiltrates associated with myocyte damage. (4) Severe rejection consists of diffuse myocyte damage with profound inflammatory infiltrates of mononuclear cells that may be accompanied by edema and hemorrhage (Table 1).

Differential Diagnosis. Several conditions may mimic ACR and need to be distinguished. The differential diagnoses include Quilty effect, ischemic injury, infection, and recurrent disease in patients transplanted for inflammatory processes such as sarcoidosis.

Quilty lesion is an organized endocardial cellular infiltrate which is predominantly B cells and to a lesser degree T cells and macrophages which can be mistaken for grade 2 ACR (Marboe et al. 2005). It can include a rich supply of small capillary blood vessels (Forbes et al. 1990). Despite previous studies suggesting otherwise, a Quilty lesion is not associated with adverse outcomes. With

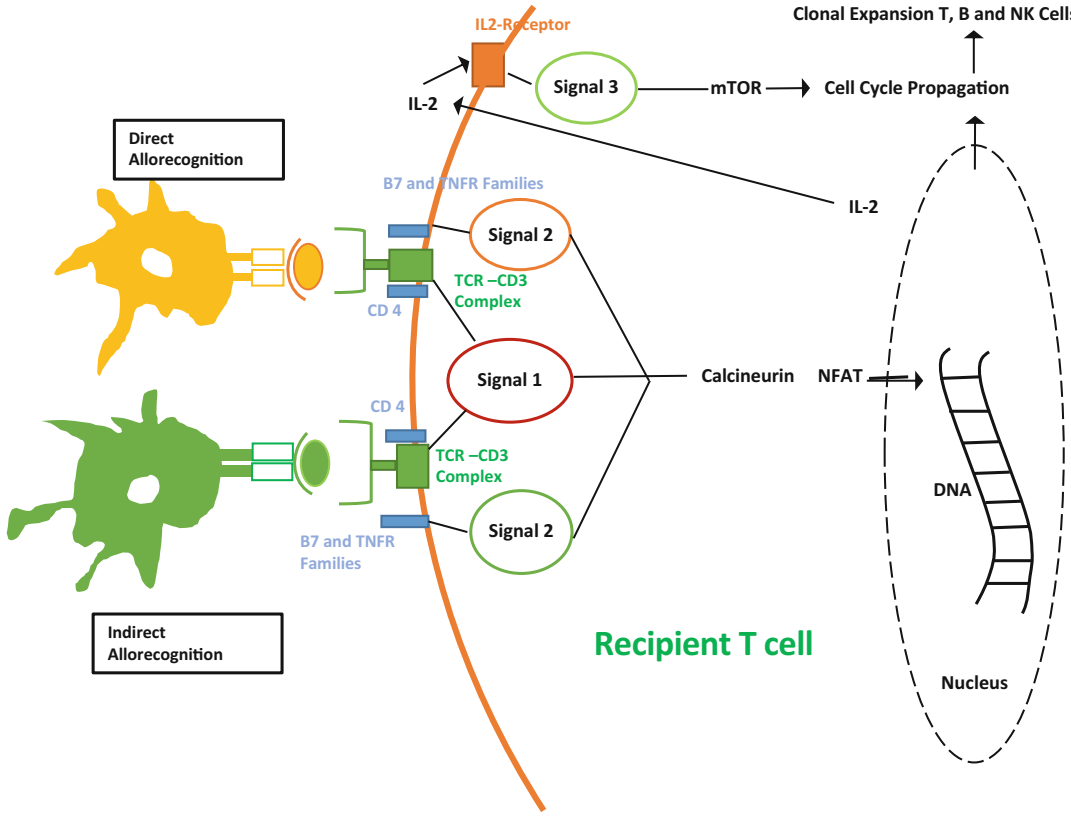


Fig. 1 Immunological interactions leading to rejection. Allorecognition is the first step of the acute cellular and antibody-mediated rejection cascades. Direct and indirect allorecognitions are two mechanisms whereby donor antigens are presented to recipient T helper (CD4) cells. The interaction between the major histocompatibility complex (MHC) class II antigens of the graft cells and T-cell receptors (TCR-CD3 complex) signals downstream events which produce cytokines that proliferate CD8 + T cells, B cells, and macrophages. After antigen recognition on the TCR-CD3 complex, costimulatory molecules (B7 and tumor necrosis factor (TNF) families) fully activate the recipient T cells and allow translocation of nuclear factor of activated T cells (NFAT) into the nucleus. The IL-2 cytokine promotes cell cycle propagation and clonal expansion of activated T, B, and NK cells. The activated immune system destroys targeted graft cells through acute cellular and/or acute antibody-mediated rejection mechanisms

immunohistochemistry stains, a Quilty lesion can be confirmed and distinguished from ACR. Additional serial sections can help differentiate a Quilty lesion from true rejection (Hiemann et al. 2008).

Ischemic injury results from hypoxic injury and irreversible coagulation necrosis at the time of donor heart harvesting and can be mistaken for ACR. It has been associated with prolonged ischemic times. Typically, in ischemic injury the extent of myocardial necrosis is out of proportion to the inflammatory infiltrate with a predominant neutrophil and macrophage conglomerate. Reports have suggested that ischemic injury has been associated with future episodes of acute rejection, allograft vasculopathy, and early graft failure (Fyfe et al. 1996; Yamani et al. 2002).

Infections can be a contributor for cardiac rejection with the histological pattern similar to a viral myocarditis (Schowengerdt et al. 1997). Several viruses have been implicit in the presence of an ACR with the viral genome present in the myocardium of those with concomitant rejection. A study of 40 pediatric patients undergoing surveillance EMB found that 62% had a positive viral genome tested by polymerase chain reaction assay with biopsy results consistent with multifocal

Table 1 ISHLT biopsy grading scale for ACR

ISHLT 1990		ISHLT 2005	
Grade 0	No inflammation	Grade 0R	No inflammation
Grade 1A, mild focal	Focal infiltrate	Grade 1R, mild	Infiltrate + ≤ 1 focus of muscle damage
Grade 1B, mild diffuse	Diffuse infiltrate		
Grade 2, moderate focal	Single focal infiltrate + muscle damage		
Grade 3a, moderate multifocal	Multifocal infiltrate + muscle damage	Grade 2R, moderate	Multifocal infiltrate + muscle damage
Grade 3b, moderate diffuse	Diffuse infiltrate + muscle damage	Grade 3R, severe	Diffuse infiltrate + muscle damage +/− edema, hemorrhage
Grade 4, severe	Diffuse infiltrate + muscle damage, edema, hemorrhage		

ACR acute cellular rejection, *ISHLT* International Society for Heart and Lung Transplantation, "*R*" revised

moderate to severe rejection. Cytomegalovirus was predominantly seen among all the assay samples obtained followed by adenovirus, enterovirus, and parvovirus (Schowengerdt et al. 1996). Even more, cytomegalovirus infection has been frequently associated with loss of graft function, increase rates of graft rejection, and presence of inclusion bodies in tissue (Grattan et al. 1989).

Treatment. Current options for ACR treatment are dictated by clinical symptoms, degree of graft function, and hemodynamic presentation at the time of diagnosis. Generally, grade 1 does not typically require any change in the treatment regimen as many episodes can occur in asymptomatic patients and is found on routine surveillance EMB. For those presenting with grades 2 or greater, the overall goal consists of optimizing immunosuppression by raising therapeutic levels or addition of other drugs that will enhance immunosuppression by modifying different signaling pathways of T- or B-cell function. These include changing from cyclosporine to tacrolimus and azathioprine to mycophenolate mofetil or the addition of rapamycin, cyclophosphamide, or methotrexate (Onsager et al. 1999; Yamani et al. 2000). A more detailed description on treatment for ACR will be covered in other chapters of this book (Table 2). If there is evidence of hemodynamic instability or cardiogenic shock, in addition to augmented immunosuppression doses, supportive therapy with inotropes, intra-aortic balloon pump (IABP), or extracorporeal membrane oxygenation (ECMO) is mandated to stabilize and support the patient. When ACR is diagnosed, EMB should be performed 1–2 weeks after to evaluate for resolution of ACR changes (Mills et al. 1997) (Fig. 2).

Antibody-Mediated Rejection

Epidemiology. Advances in immunosuppression have resulted in a reduced incidence of ACR with antibody-mediated rejection (AMR) now recognized as an increasing cause of rejection. AMR has been associated with worse survival and predisposes patients to develop CAV (Reed et al. 2006). First described in 1987 as an arteriolar vasculitis associated with graft failure and poor survival in HT recipients, studies have found that 19% of HT recipients develop vascular findings of endothelial edema and immunoglobulin deposition as soon as weeks post-HT indicating an early presence of antibodies. Others have found that by 100 days post-HT, 85% of recipients had their first AMR (Hammond et al. 1989; Kfoury et al. 2007). Due to these findings and the poor outcomes related to AMR, it is recommend to routinely screen EMB samples with immunohistochemistry in the early post-HT period starting at 2 weeks and repeat at 1, 3, 6, and 12 months after transplant and/or when AMR is clinically suspected (Kobashigawa et al. 2011a; Colvin, Cook et al. 2015).

Table 2 Treatment options for ACR and AMR

Clinical severity	ACR	AMR
Asymptomatic	Increase CNI dose Oral steroid bolus OR IV pulse steroids[a,b]	Uncertain therapy
Reduced EF	Oral steroid OR IV pulse steroids[b]	Oral steroid OR IV pulse steroids[b] +/− IVIG
Heart failure/shock	IV pulse steroids[b] Cytolytic therapy Plasmapheresis IVIG PSI Inotrope(s) IABP or ECMO	
Adjunctive	Cyclophosphamide or methotrexate	
Prevention		Rituximab Bortezomib *Eculizumab*[c]

AMR antibody-mediated rejection, *ACR* acute cellular rejection, *CNI* calcineurin inhibitor, *IVIG* intravenous immunoglobulin, *PSI* proliferation signal inhibitors, *IABP* intra-aortic balloon pump, *ECMO* extracorporeal membrane oxygenation

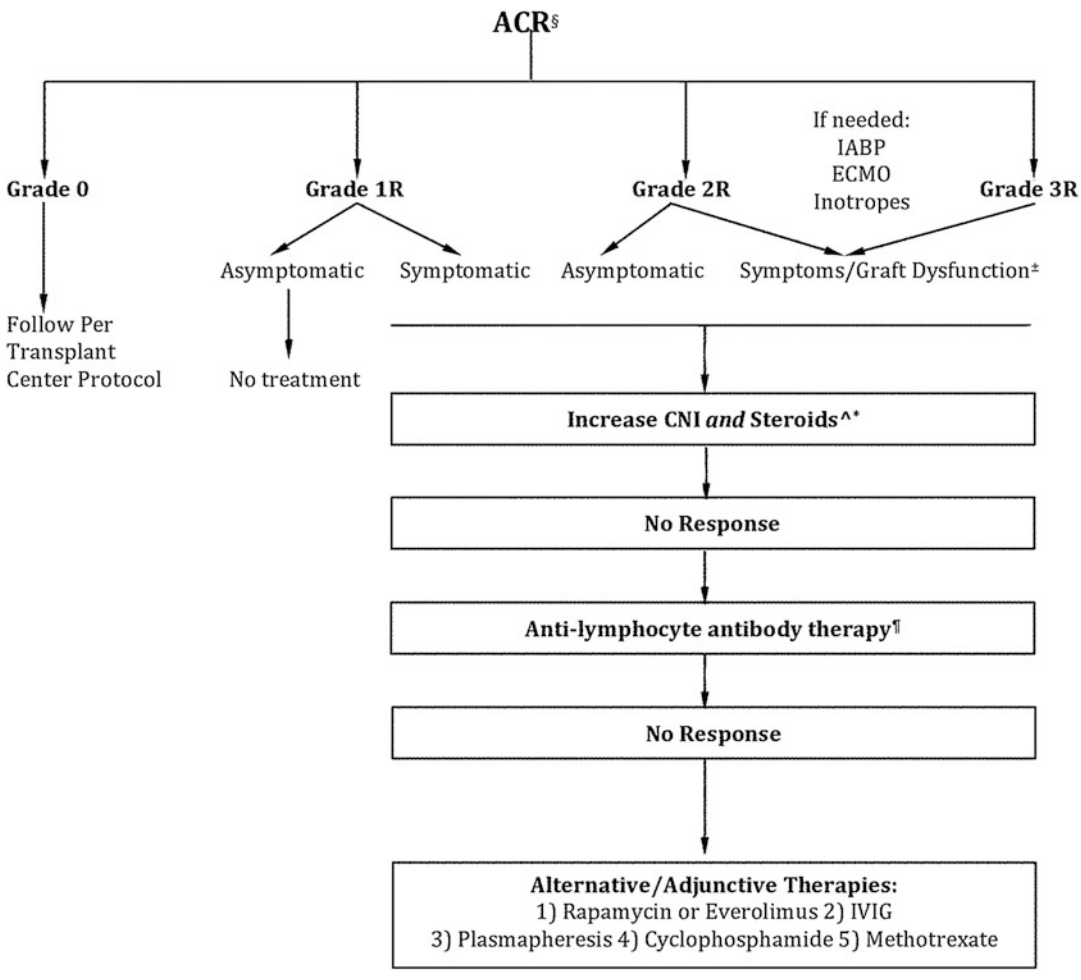
[a]In severe ACR cases, such as ISHLT grade 3R

[b]Usual administration is prednisone 1–3 mg/kg/day for 3–7 days or methylprednisolone 3–10 mg/kg/day for 3–7 days

[c]*Currently being investigated*

Risk Factors. Observational studies have shown that risk factors associated with AMR include female recipients, multiparity, prior blood exposure, elevated pretransplant panel reactive antibodies (PRA), prior blood transfusions, prior VAD (ventricular assist device) implant, prior OKT3 induction therapy, CMV seropositive, and re-transplantation (Hammond et al. 1990; Reed et al. 2006; Almuti et al. 2007).

Pathology. AMR occurs when recipient antibodies develop against donor graft HLA endothelial antigens. These antibodies may result in direct injury to capillary endothelium or indirect injury via complement activation. Upregulation of cytokines, presence of macrophages, increased vascular permeability, and microvascular thrombosis occurs. Histopathological findings show evidence of endothelial injury by cytoplasm swelling, nuclear enlargement, and accumulation of intravascular mononuclear cells and macrophages. In severe AMR, neutrophils around and in capillaries, interstitial hemorrhage, necrosis, and vascular thrombosis may exist (Berry et al. 2013). Classic immunopathologic features of AMR include antibodies against C4d and CD68 shown by immunohistochemistry (IH), while C4d and C3d and HLA-DR staining are shown by immunofluorescence (IF) techniques. The current guidelines propose a grading scale based on the intensity and distribution of these antibodies. C4d and C3d staining are visualized in the interstitial capillaries of intact myocardium. CD68 staining is evaluated only in macrophages within microvessels as interstitial macrophages may be due to infections and/or ischemia. In evaluating EMB, more than 50% of the sample should show C4d staining to be considered strong evidence of AMR, while 10%–50% staining of the sample should be correlated to DSA status. CD68 staining $\geq$10% of the sample in a beading and clustering pattern will also be strong marker of AMR (Fig. 3) (Kobashigawa et al. 2011a). C3d is used as a secondary or complementary diagnostic tool in AMR with similar criteria as used for C4d staining. HLA-DR is an important marker to assess the integrity and structure of the capillaries. It aids diagnosis in cases where there is severe damage to the capillaries which can diminish available endothelium for C4d and C3d staining. HLA-DR is considered strongly positive when $\geq$10% sample shows staining and is considered anytime when quality of C4d and C3d staining is



ACR = Acute cellular rejection; EMB = Endomyocardial biopsy; CNI = Calcineurin inhibitor; "R" = Revised; IABP = Intra-aortic balloon pump; ECMO = Extracorporeal membrane oxygenation; IVIG = Intravenous immunoglobulin

§Biopsy is obtained 1 week after rejection diagnosed and 1 week after therapy completed
^Increase tacrolimus dose to achieve higher tacrolimus blood levels
*Prednisone 1-3 mg/kg/day for 3-7 days or Methylprednisolone 3-10 mg/kg/day for 3-7 days
±Systolic or diastolic dysfunction and/or elevated intra-cardiac filling pressures
¶Polyclonal anti-thymyocyte antibodies or OKT3 for 3-10 days; Anti-thymocyte globulin for 3-10 days; or Basiliximab for 4 day

Fig. 2 General management for ACR

poor (Berry et al. 2013). Once a sample is positive for C4d, it is recommended to repeat IF/IH until clearance is demonstrated.

Diagnosis. AMR is clinically diagnosed when heart failure symptoms and evidence for left ventricular dysfunction are present along with proven AMR histological findings (Table 3). The degree of graft dysfunction can vary across all patients, and hemodynamic measurements may be needed to truly assess severity of dysfunction. Prior studies have suggested a $\geq$ 30% decrease in cardiac index to indicate graft dysfunction (Michaels et al.

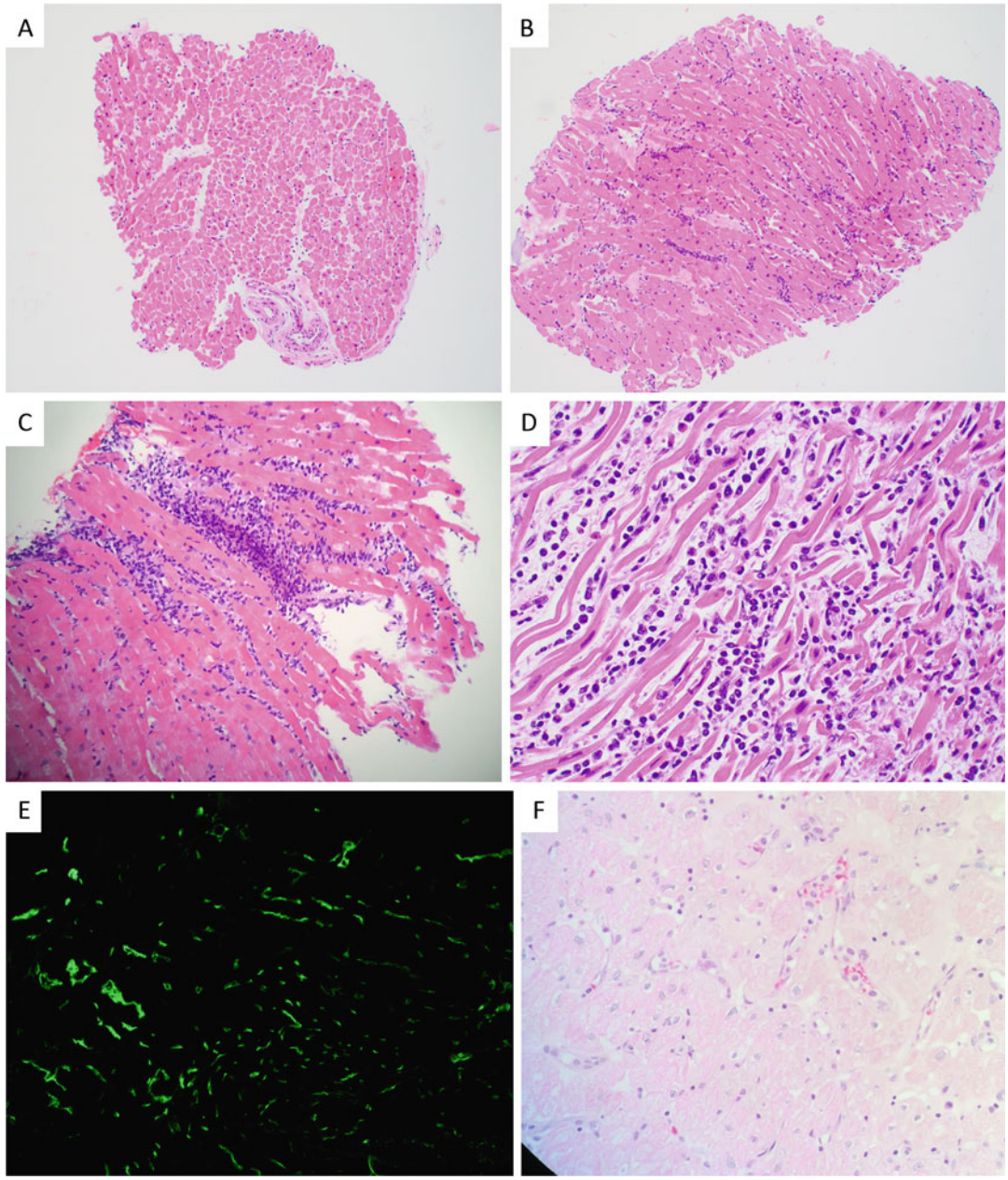


Fig. 3 (**A**) No evidence of acute cellular rejection (ISHLT 2005 grade 0R, 1995 grade 0), 100x. (**B**) Mild acute cellular rejection (2005 grade 1R, 1995 grade 1A), 100x. (**C**) Moderate acute cellular rejection (2005 grade 2R, 1995 3A), 100x. (**D**) Severe acute cellular rejection (2005 grade 3R, 1995 grade 4), 200x. (**E**) Positive C4d immunofluorescence (200x). (**F**) Antibody mediated rejection (ISHLT 2013 pAMR2, 200x)

2003). AMR can present early post-HT (within 1 month) due to pre-existing donor-specific antibodies (DSA) or de novo DSA and is associated with hemodynamic compromise and graft dysfunction requiring inotropic and mechanical circulatory support (Michaels et al. 2003; Reed et al. 2006). Rarely, "hyperacute rejection" can occur due to ABO incompatibility or with

Table 3 The 2013 ISHLT working formulation for AMR diagnosis

Grade	Definition	Description
pAMR 0	Negative for AMR	Negative for H+ AND I+
pAMR 1 (H+)	Histopathologic[a] AMR alone	Positive for H+ ONLY
pAMR 1 (I+)	Immunopathologic[b] AMR alone	Positive for I+ ONLY
pAMR 2	Pathologic AMR	Positive for H+ AND I+
pAMR 3	Severe pathologic AMR	Interstitial hemorrhage/edema, capillary destruction, mixed inflammatory cells, endothelial cell apoptosis AND positive for I+

AMR antibody-mediated rejection, *pAMR* pathologic antibody-mediated rejection, *ISHLT* International Society for Heart and Lung Transplantation, "*H+*" histopathologic, "*I+*" immunopathologic

[a]1. Intravascular macrophage collection 2. Endothelial cells with large nuclei and cytoplasmic projections that narrow/occlude the vascular lumen

[b]1. C4d + and CD68+ by immunohistochemistry 2. C4d+, C3d+, and anti-HLA-DR by immunofluorescence

pre-existing circulating anti-HLA antibodies, resulting in immediate and irreversible rejection (Kobashigawa et al. 2011b). In recent years an interest in noninvasive methods has risen to predict development of AMR with current diagnostic tools. Development of DSA has been associated with graft dysfunction and mortality and may aid in noninvasively diagnosing AMR. Although presence of DSA prior to transplant is rare with reports showing a 6–9% incidence, post-HT recipients can develop de novo DSA at long-term follow-up (Smith et al. 2011). In a study of 221 patients, 38 had pathologic AMR with 31% of them having DSA (24% of those were de novo). Presence of DSA increases the odds of graft dysfunction by fivefold, and those with de novo DSA to HLA class II were three times more likely to have a future AMR and a 151% risk for graft loss (Clerkin et al. 2016a). In some instances AMR can present without serum evidence of DSA suggesting other mechanisms involved in antibody formation and graft dysfunction. Recent studies have investigated the role of non-HLA antibodies specifically anti-angiotensin type 1 receptor antibodies (AT1R) in AMR. AT1R have been associated with vascular remodeling, hypertension, and graft failure in renal allografts. In HT recipients with AT1R, studies have shown decreased graft survival and early vasculopathy regardless of the presence or absence of DSA. The combination of de novo DSA and ATR1 has also been associated with poor outcomes (Reinsmoen et al. 2010, 2014).

Late AMR. With current donor-recipient matching systems and immunosuppressive regimens, early AMR risk has decreased. Nonetheless detection of late AMR has increased likely due to improved recognition with more sensitive diagnostic tests. The definition of late AMR is however unclear as the timeline for occurrence varies across studies with prevalence reported between 3 and 85% (Crespo-Leiro et al. 2005; Kfoury et al. 2007). Recent data on late AMR (defined as $\geq$1 year after HT) have reported a prevalence of 35% (Clerkin et al. 2016b). Occurrence of late AMR is associated with presence of symptoms, a fourfold increase risk for mortality in those with development of accelerated CAV with 50% of patients having de novo CAV within 1 year after late AMR diagnosis (Clerkin et al. 2016b). Moreover, there is a 40–50% mortality risk at 1 year after late AMR diagnosis with among those who survive showing persistence or recurrence of AMR, left ventricular dysfunction, and advanced CAV (Coutance et al. 2015). Additionally a significant number of transplant recipients presenting with late AMR can present with hemodynamic dysfunction characterized by hypotension, decrease cardiac output/index, and rise in the pulmonary capillary wedge pressure (Michaels et al. 2003). Others have found late AMR to be associated with presence of malignancy and recent infection (Almuti et al. 2007). Current management of late AMR is similar to early AMR, but prospective studies are needed to identify targeted therapies.

Asymptomatic AMR. Although earlier studies suggest that asymptomatic AMR patients with normal graft function have similar 5-year post-HT survival rates compared to patients without AMR, recent studies have shown that asymptomatic

AMR confers a high risk for cardiovascular mortality (21% AMR vs. 13% ACR over a period of 91 months) (Kfoury et al. 2009a). This is likely due to increased risk of CAV and impairment of long-term graft function regardless of AMR type (Kfoury et al. 2009b; Wu et al. 2009).

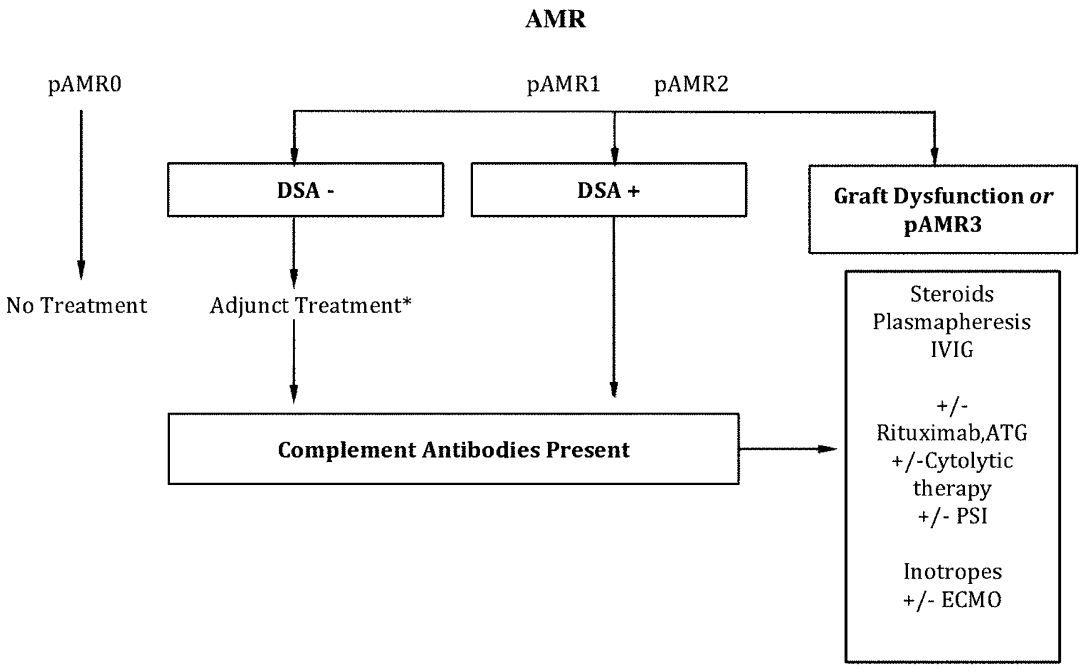
Differential Diagnosis. There are several conditions that can mimic AMR. Acute myocardial ischemia can simulate AMR due to endothelial swelling, interstitial macrophages, and interstitial edema seen on histological review. However, acute myocardial ischemia is a focal process with myocyte damage and edema to a certain area rather than a diffuse process as in AMR. During the healing process, acute myocardial ischemia has evidence of granulation tissue and/or hemosiderin-laden macrophages, while AMR does not. Intramyocardial foci of adipose tissue like AMR can sometimes play a role in the development of inflammation by producing inflammatory cytokines, such as IL-6 and TNF-α. These cytokines will recruit inflammatory cells, such as macrophages and other mononuclear cells which are also involved in the development of AMR. However, adipose tissue can be distinguished from myocytes due to the absence of striations (Talman et al. 2014). Artifactual disruption of myocytes due to technical processing generally presents as cardiac myocytes with "shrunken appearance" or "pink-staining amorphous material" that is easily distinguished from normal or pathological tissue components.

Treatment. The management strategies for AMR can vary depending on the histological and clinical presentation. In cases of acute AMR with allograft dysfunction and hemodynamic compromise, aggressive hemodynamic support is required leading to resolution of the initial event in greater than 90% of cases (Michaels et al. 2003; Crespo-Leiro et al. 2005). The overall treatment goal is to remove circulating antibodies, reduce production of antibodies, and suppress T- and B-cell activity. Plasmapheresis is the cornerstone of AMR therapy as it mechanically removes circulating alloantibodies by extracorporeal membrane filtration of the recipient plasma from blood components and reconstituting the recipient blood with albumin or fresh frozen plasma (Grauhan et al. 2001; Wang et al. 2006). However, adjunct treatments are needed to suppress the continuing production of the antibodies including high-dose methylprednisolone, cytolytic therapy, and intravenous immunoglobulin. Similar to ACR, pulse-dose steroid therapy with or without a prednisone taper is commonly utilized and has been shown to be effective in restoring left ventricular systolic function (Olsen et al. 1993). Anti-thymocyte globulin suppresses B-lymphocyte function by preventing proliferation and differentiation of B cells, and prospective trials have shown to reduce the occurrence of AMR after HT (Zand 2006). However limited data exists, and only few case reports have demonstrated efficacy (Malafa et al. 1992; Grauhan et al. 2001). IVIG also augments immunosuppression and modulation in patients treated for AMR by blockage of Fc receptors, complement inhibition, and downregulation of B-lymphocyte receptors (Montgomery et al. 2000). Its application in acute AMR has shown efficacy of improvement in graft function (Rodriguez et al. 2005). Despite aggressive treatment, however, AMR can reoccur, and alternative therapies are needed. Rituximab, bortezomib, eculizumab, total lymphoid irradiation (TLI), and photopheresis have been reported to be used in recurrent or refractory AMR (Table 2) (Colvin et al. 2015). A more detailed review on AMR management will be covered in another chapter of this book (Fig. 4).

Biopsy Negative Rejection

There are some HT patients who experience left ventricular systolic dysfunction-associated heart failure symptoms, who do not have signs of ACR or AMR on endomyocardial biopsy. This entity has been recognized as biopsy-negative rejection (BNR) which is typically associated with graft dysfunction (Berry et al. 2013).

In a case series of 11 patients, all presented with an LVEF $\leq$35%, and 33% presented with heart failure symptoms. Most cases occurred during the first year of transplant with a mean time to occurrence of 7.8 $\pm$ 7.5 months. Only 25% developed de novo DSA, and 58% of all cases recovered their graft function (Tang et al. 2013). The authors noted that although BNR is a rare



AMR = Antibody Mediated Rejection; pAMR = pathological Antibody Mediated Rejection; ATG = thymoglobulin; IVIG = Intravenous immunoglobulin; PSI = Proliferation Signal inhibitors (eg. Sirolimus/Everolimus); DSA = Donor-specific antibodies; ECMO = Extracorporeal membrane oxygenation

***Adjunct to AMR Treatment**:
Increase surveillance
Optimization of immunosuppression
Consider CAV
Check Complement binding antibodies

Fig. 4 General management for AMR

phenomenon with 11 cases occurring in 10 years, it can still present clinically as a severe form of rejection. The treatment approach entails standard antirejection therapy with the majority requiring either oral or IV steroids and selected cases requiring anti-thymocyte globulin and IV immunoglobulin. The limitation of EMB from potential sampling error or nonuniformity of the histopathological changes can also lead to misdiagnose negative rejection. In the 2010 AMR consensus document, 10–20% of cardiac allograft recipients were diagnosed with BNR when in reality the majority experience AMR. In cases where the clinical presentation does not correlate with the EMB results, the utility of noninvasive diagnostic testing can increase diagnostic accuracy. With cardiac magnetic resonance (CMR), it is possible to increase the sensitivity and negative predictive value for rejection compared to EMB the diagnose BNR (Butler et al. 2015).

Mixed Cellular and Humoral Rejection

Mixed rejection is defined as the presence of ACR with characteristic cellular infiltrates associated with complement and immunoglobulin deposition in capillaries and interstitial tissue as seen with AMR. Previous reports show a prevalence of 18–25% of cases (Kfoury et al. 2009a), while more current data show a prevalence of 7.8% occurring predominantly in the first year

post-HT. Most AMRs can be easily distinguished in cases of mild ACR, but in severe rejection episodes, ACR can frequently overlap with AMR due to interstitial lymphocytes and macrophages infiltrates making it difficult to distinguish the mechanism of rejection. However, intravascular macrophages are characteristic of AMR and not typically seen with ACR. IH and IF are important in refining the diagnosis in cases where recurrent ACR occurs or if mixed ACR and AMR coexist (Stewart et al. 2005). Mixed rejections occur usually in the early post-transplantation course and are associated with allograft dysfunction. The coincidence of the two forms of rejection may be associated with more frequent grade 3 rejection episodes during follow-up and is associated with a significant risk of mortality including cardiovascular death (Kfoury et al. 2016).

Chronic Allograft Rejection

Chronic allograft rejection in the cardiac allograft manifests as vasculopathy, distinct from atherosclerosis in native hearts. Cardiac allograft vasculopathy (CAV) is also known as graft coronary artery disease, transplant coronary artery disease, or chronic rejection. Data from the 2013 ISHLT registry shows that CAV affects 8% of patients at 1 year, 30% at 5 years, and 50% at 10 years post-HT (Lund et al. 2013).

Risk factors vary depending on the timing of occurrence for CAV. For early CAV (< 3 years post-HT), factors include donor hypertension, infection within 2 weeks post-HT, and rejection during the first year. For late CAV (occurring within 7 years of heart transplant), factors include donor history of diabetes, donor intracranial hemorrhage, and donor cause of death. Risk factors shared between the development of early and late CAV are older donor age, younger recipient age, and recipient pretransplant BMI, while female gender is associated with lower risk of CAV development (Braga et al. 2012).

Cytomegalovirus infection has been shown to be strongly associated with CAV (Delgado et al. 2015). Potential mechanisms that may explain this association are cross-reactivity of viral antigens with vascular wall peptides increasing expression of pro-inflammatory cytokines or direct viral infection of blood vessels leading to smooth muscle proliferation (Epstein et al. 2009).

CAV is characterized by concentric, diffuse thickening and progressive occlusion of arteries and veins of the transplanted heart. It can affect one or more vascular layers of the epicardial vessels and their branches. Histologic sections of explanted hearts show three key features: (1) chronic infiltration of lymphocytes and macrophages which line up beneath the vascular endothelium, (2) large amounts of collagen and extracellular matrix proteins, and (3) variable amounts of vascular smooth muscle cells. The combination of these changes causes significant chronic inflammation and fibromuscular hyperplasia (Lu et al. 2011).

The pathophysiology of CAV involves an immune response by the recipient causing persistent inflammation with subsequent endothelial dysfunction (Tanaka et al. 2005). Non-HLA antibodies, repeated rejection episodes, CMV infection, and HLA mismatch have been shown to play a role toward CAV development (Seki and Fishbein 2014). As allograft endothelial cells are exposed to recipient T cells, there is secretion of pro-inflammatory cytokines resulting in endothelial adhesion molecule activation and recruitment of inflammatory cells. Some studies have shown that recipient smooth muscle cells (SMC) differentiated from endothelial progenitor cell and donor SMC bound to vessel wall causing expansion of the neointima resulting in narrowing of the coronary artery (van den Hoogen et al. 2015). There are other non-immunological factors related to atherosclerosis risk that have been associated with CAV; however major morphological differences exist as outlined in Table 4.

In the early post-HT period, the clinical signs of CAV often develop insidiously without any symptoms due to lack of innervation of transplanted heart. Angina can occur after years of transplant and is atypical in nature. However once CAV develops with or without symptoms, the outcomes are poor due to graft failure leading to congestive heart failure, myocardial infarction,

Table 4 Differences between CAD and CAV

Pathological and clinical features	CAD	CAV
Vessel distribution	Epicardial vessels; intra-myocardial vessels not involved	All vessel types, especially intra-myocardial vessels and veins
Plaque distribution	Focal stenosis, sometimes eccentric	Diffuse, concentric stenosis
Calcification	Usually seen	Usually not seen
Inflammation	Usually seen in intima	Usually seen in intima, media, adventitia layers
Internal elastic lamina	Usually disrupted	Intact
Risk factors	Age, gender, race, FH, and common comorbidities[a]	Immunological and non-immunological factors[b]
Diagnosis Treatment	Angiography +/− IVUS Antiplatelet, statins	IVUS Statins

CAD coronary artery disease, *CAV* cardiac allograft vasculopathy, *FH* family history, *IVUS* intravascular ultrasound
[a]Hypertension, hyperlipidemia, diabetes mellitus, smoking, obesity
[b]Non-immunological: hypertension, hyperlipidemia, diabetes mellitus, smoking, CMV infection, HSV infection, *C. pneumoniae*, hyperhomocysteinemia

arrhythmias, or sudden cardiac death (Chantranuwat et al. 2004). Coronary angiography and intravascular ultrasound (IVUS) are tools utilized to detect presence of CAV. Angiography is the clinical standard for CAV detection and can serve to risk stratify patients as the presence of severe disease can predict the likelihood of death or re-transplantation (Costanzo et al. 1998). Angiography only measures intraluminal epicardial vessel anatomy. IVUS instead provides information about intimal thickness, intimal area, and vessel area. It can determine accelerated forms of CAV by assessing the rate of maximal intimal thickening per year before angiographic findings appear (Kobashigawa et al. 2005). Furthermore, IVUS can aid the angiogram when luminal findings are inconclusive by excluding significant disease (Tsutsui et al. 2001). The current ISHLT working formulation for CAV recommends coronary angiography coupled with allograft functional assessment in CAV surveillance. IVUS may be helpful, but more evidence needs to exist to allow this experimental tool to be used for CAV surveillance and CAV-guided treatment (Mehra et al. 2010).

CAV is an important factor to the long-term survival of the cardiac allograft. As CAV can develop during the first year post-HT, those with early CAV (< 1 to 2 years post-HT) portends a grim prognosis compared to a slow course >2 years with risk of re-transplantation, death, or graft failure occurring sooner compared to late CAV (Mehra 2006). Thus emphasis now exists on early detection to delay the progression of the disease. Three main strategies exist for CAV prevention: (1) inhibition of growth factors and cytokines, (2) cell therapy, and (3) tolerance induction. Calcium channel blockers and angiotensin-converting enzyme inhibitors have been shown to slow CAV progression by IVUS (Erinc et al. 2005). Pravastatin has been shown to lower the incidence of CAV and improve survival (Kobashigawa et al. 1995). Immunosuppression with mycophenolate mofetil, rapamycin, and everolimus has all demonstrated to reduce intimal thickening and smooth muscle cell proliferation on consecutive IVUS studies (Eisen et al. 2003, 2005; Kobashigawa et al. 2013; Matsuo et al. 2013).

Once CAV is established, coronary artery stenting and coronary artery bypass grafting are palliative treatment options when focal disease is present. However, no survival benefit has been demonstrated in those with intervention vs. medical therapy, while bypass grafting has been associated with increased periprocedural mortality (Agarwal et al. 2014; Dasari et al. 2015). Re-transplantation is the last option for

this cohort of patients, but annual rates of re-transplantation are low 2–4% limiting availability of organs only to those with advanced CAV. Re-transplantation however remains associated with low survival (70% at 1 year and 38% at 10 years) with the leading cause of death due to graft failure (Lund et al. 2014).

Diagnosis of Cardiac Allograft Rejection

Routine monitoring of cardiac allograft function is recommended to detect rejection opportune and treat with aggressive immunosuppression. Endomyocardial biopsy (EMB) is currently the gold standard to diagnose cardiac allograft rejection. It can characterize the type of rejection and severity and dictate the appropriate therapy. However, newer biomarkers and noninvasive modalities are being investigated that can circumvent the risk of repetitive biopsies and potentially identify early signs of rejection in the HT recipient.

Endomyocardial biopsy. The strongest indication to use endomyocardial biopsy is for cardiac allograft rejection monitoring and diagnosis of undifferentiated ventricular dysfunction. The endomyocardial biopsy (EMB) technique, developed in Japan in 1962, is performed under local anesthesia by gaining vascular access through the right internal jugular vein or femoral vein with samples taken from the right ventricular septum. The current form of the flexible bioptome was developed in 1972 by Stanford Caves-Schulz allowing prompt tissue removal. Newer disposable devices exist that are safer and associated with a low complication rate.

Under single-plane fluoroscopy guidance, the bioptome is position anteriorly followed by careful torsion to be situated in the septum. Position should be confirmed at the 30° of left anterior oblique view. Echocardiography has been used to guide the position of the bioptome in the ventricular septum, but it can miss the tip of the bioptome due to rarefaction of sound from the metallic tip. When both fluoroscopy and echocardiography are used simultaneously, it can reduce sampling error by obtaining tissue from different areas of the septum.

Despite some of the visual limitations, the risk of overall procedural complications is 1% (Holzmann et al. 2008; Yilmaz et al. 2010). EMB major complications include hemopericardium, tamponade, and third-degree AV block requiring pacemaker in 0.12–1%, and minor complications include transient chest pain, non-sustained ventricular tachycardia, transient hypotension, and small pericardial effusion present in 0.2–2%. The tricuspid regurgitation is a long-term complication of EMB that occurs in up to 23% of patients which may require tricuspid valve repair or replacement (Wong et al. 2008).

The standard care for the use of EMB in adult HT is to detect CAR before presence of clinical signs or symptoms occurs. As rates of CAR during the first year on surveillance EMB range from 0.3% to 14% (Kuhn et al. 2003), the need for repetitive EMB is highest during the first 3–6 months post-HT but decreases close to the 1-year mark. The ISHLT guidelines give a class IIa (level of evidence C) recommendation for the use of EMB in rejection surveillance during the first year and even after the first year for an extended period in those at high risk for late acute rejection. The frequency of routine EMB in patients 1 year after HT has not been well established (Costanzo et al. 2010). However, if the patient presents with a clinical picture concerning of allograft rejection, an EMB is indicated as the results will dictate the type of therapy required.

Noninvasive Diagnosis

Although EMB remains to date the gold standard to detect rejection, its high cost, complications, and sampling error with false-negative rates reported in 20% of cases limit its use beyond the first year after HT. There are current noninvasive tools that can readily identify those patients at risk with accuracy, high sensitivity, and specificity before symptoms develop. Serum biomarkers and advanced imaging techniques have been studied and postulated as an alternative to the standard

approach of allograft surveillance. Some of the current technologies utilized to achieve this goal will be discussed below.

Biomarkers

Troponin. Cardiac troponins (TnT and TnI) have been extensively studied for assessment of CAR. Initial studies done with the use of these markers to detect rejection were compared to EMB for CAR detection; however in the first 3 months after transplantation, their values can be elevated due to perioperative ischemia and injury. However, in patients more than 3 months after HT, troponin T concentrations increased in those with severe allograft rejection compared to controls (ISHLT grade 1, 27.8 ± 1.8 ng/L; grade 2, 33.2 ± 2.7 ng/L; grade 3A, 54.6 ± 6.5 ng/L; grade 3B and 4, 105.4 ± 53.7 ng/L; $p < 0.001$ for grades 3 and 4 vs. grades 0 and 1). The sensitivity and specificity for severe graft rejection (grade ≥ 3) were 80.4% and 61.8%, respectively, with a NPPV of 96.2%. The findings of this study identified troponin T as an ancillary diagnostic parameter in excluding severe rejection (Dengler et al. 1998).

Larger studies have shown a lower sensitivity due to conflicting results in HT recipients with renal dysfunction as well as changes with age, LV mass, BMI, and history of heart failure post-HT (Mullen et al. 2002). Obtaining serial troponins and comparing them to a mean value may circumvent this issue. In a study of 47 HT recipients, high-sensitivity cardiac troponin-I (hs-cTnI) and conventional cTnI were used for prediction of CAR. An index ratio was calculated for each patient based on observed to expected mean hs-cTnI values to detect CAR at 60 days HT. hs-cTnI median index ratio was significantly related to rejection compared to those without (1.37 vs. 0.9). After ROC analysis, an hs-cTnI index of ≥1.17 could predict CAR with an 82.4% sensitivity and 77.1% specificity (Ahn et al. 2015). Troponin elevations have been demonstrated to predict cardiac events at long-term follow-up >7 years after transplantation especially in those with presence of coronary vasculopathy (Kirchhoff et al. 2004; Ambrosi et al. 2015).

Brain Natriuretic Peptide. Studies have shown that after cardiac transplant, serum BNP levels are elevated but decrease gradually although not to normal levels even at 1-year follow-up (Talha et al. 2008). This persistent elevation may be due to an active immune system, cardiac structural remodeling, vascular injury, and inflammation. In a study of 28 HT recipients where BNP correlated to 54 genes that examined different domains of the immune activity (human leukocyte antigen, mast cell, and B-cell lineage), collagen degradation, and platelet function, authors found that BNP may serve as a marker for adaptation of the cardiac allograft to the recipient (Mehra et al. 2006). Moreover, BNP has been shown to correlate with allograft ejection fraction, hemodynamics (pulmonary capillary wedge pressure and right atrial pressure), and serum creatinine 6 months after HT, suggesting that BNP may aid in monitoring graft function (Bader et al. 2009). Similar to troponin level, serial measurements of BNP evaluated as percent of change over time can predict rejection (Garrido et al. 2009). It is possible that numerous factors contribute to the persistent elevated BNP levels after transplant; whether related to extent of RV and LV dysfunction or immunological pathways involved in cardiac repair is still to be investigated in prospective studies.

Gene Profile Markers. Circulating ribonucleic acid has been useful to provide insights into the genes involved in allograft immunology. Initial single-center studies utilizing RNA from peripheral blood mononuclear cells (PBMCs) identified 40 genetic markers associated with rejection (Horwitz et al. 2004). These findings were validated in the CARGO (Cardiac Allograft Rejection Gene Expression Observational) study where gene expression profile (GEP) of PBMCs was used to discriminate grade 0 rejection from moderate-severe rejection. A set of 11 genes were correlated with rejection and converted into a score of values from 0 to 40. Patients with ≥1 year post-HT with a score < 30 were unlikely to have moderate-severe rejection (negative predictive value 99.6%) (Deng et al. 2006).

The results of CARGO were confirmed in the landmark IMAGE (Invasive Monitoring Attenuation through Gene Expression) trial where 602 patients with previous HT (6 months to 5 years) prior to enrollment were monitored for rejection with either GEP or routine EMB in addition to clinical and echocardiographic assessment of graft function. The study aim was non-inferiority of GEP vs. EMB for the primary endpoint of rejection with hemodynamic compromise, graft dysfunction due to other causes, death, or re-transplantation. After a 19-month follow-up, GEP-monitored patients had a similar 2-year outcomes to EMB (14.5% vs. 15.3%, $p = 0.86$). Both groups showed similar rates of death (6.3% and 5.5%; $p = 0.82$). Fewer biopsies and less treated episodes of rejection occurred in the GEP cohort (34 vs. 47) (Pham et al. 2010). One limitation of this study was that only patients with 6 months post-HT were enrolled more, while risk of rejection occurred in the early post-HT period (< 6 months).

The E-IMAGE (Early IMAGE) followed the same study design and primary endpoints as IMAGE although it recruited patients 55 days post-HT. If a GEP score $\geq$ 30 at 2 months or $\geq$ 34 at 6 months occurred, a biopsy was performed. The composite endpoint was found to be similar in both groups (10% vs. 17%, $p = 0.44$) (Kobashigawa et al. 2015). As the risk for rejection is higher during the first year after transplant, repeated EMB are required during that period to detect signs of rejection. Similar to this approach, GEP can be repeated early on to identify variability in the individual scores and possibly predict future risk of allograft dysfunction or death. A sub-study from the IMAGE trial analyzed variability of the GEP score to predict allograft dysfunction or death. Variability was defined as the standard deviation of an individual's cumulative test scores with the threshold score $\geq$ 34. The variability score ranged from 0.5 to 2, and those with a value of 1.6 (SD $\pm$ 1.4) were associated with IMAGE primary outcome, while those with a value of 1 (SD $\pm$ 0.7) were not. After multivariate analysis, the GEP variability score was independently associated with the primary outcome. The hazard ratio for 1 unit increase was 1.76 (95% CI 1.4–2.3) (Deng et al. 2014).

To expand on the prior findings of E-IMAGE, a sub-study from the CARGO II (Cardiac Allograft Rejection Gene Expression Observational) European dataset was analyzed. The authors found that those with variability score < 0.6 had a NPV of 97% while those with a score 1.5 had a PPV 35.4% (Crespo-Leiro et al. 2015). The limitations to variability score are that all studies were case-control and retrospective and the score requires statistical computation and has not been validated in other centers beyond the clinical trial populations.

Donor-Derived Cell-Free DNA. This novel marker is an attractive alternative to current diagnostic methods of rejection as it may prove to be proportional to the degree of cardiac injury and repair that occurs during a rejection episode. Vlaminck et al. studied in a cohort of 65 patients the use of donor-derived cell-free DNA (cfdDNA) to detect AR after transplantation. In the study the authors count the number of donor and recipient cfdDNA after SNP genotyping of donor and recipient. Rejection episodes were compared to EMB, and cfdDNA had an AUC of 0.83 (sensitivity = 0.58 and specificity = 0.93). The levels of cfdDNA fell by 1 week after transplant (De Vlaminck et al. 2014). This marker however is not able to distinguish between ACR and AMR, and no clear cutoff value exists. More studies are needed to predict the variability of this test in long-term follow-up and detection of rejection.

MicroRNA (miRNA). Small noncoding RNA called microRNA (miRNA) have been associated with posttranscriptional gene expression regulation. miRNA have tissue-specific expression patterns which make them attractive biomarkers. They have been involved in distinct biological processes including immunomodulation of T and B cells and MHC class I rejection (Shan et al. 2011; Wei et al. 2012). A pilot study of ten patients with proven rejection found seven miRNAs elevated during rejection that decreased after treatment (Sukma Dewi et al. 2013). A larger study of 113 patients with 60 patients as test cohort and 53 as validation cohort determined miRNA expression in heart tissue and

concomitant serum. There were seven miRNAs differentially expressed in normal and rejection allografts with strong correlation between tissues and serum values. Four of the seven miRNA identified in serum discriminated patients with rejection and characterized the type of rejection (T cell mediated or antibody mediated) (Duong Van Huyen et al. 2014). However due to variation in the miRNAs associated with rejection, it has limited its applicability to identify specific markers related to rejection. Larger studies are needed to identify which miRNAs are associated with type and severity of rejection.

Imaging Studies

Echocardiography. Standard 2D echocardiography is the first-line imaging modality routinely used as part of surveillance protocols. It provides value into allograft anatomy and function but limited by poor sensitivity and specificity. It can serve in conjunction with EMB when there is clinical suspicion of rejection despite a negative EMB. In the immediate postoperative period, echocardiographic studies show impairment of diastolic indices, increase in LV wall thickness or echogenicity of myocardial tissue possibly caused by inflammatory cell infiltration, and graft edema that can occur as early as 7 days post-HT and normalize by 3 months (Ciliberto et al. 1994; Goland et al. 2011). Other findings include RV size and geometry alterations, tricuspid regurgitation, and pericardial effusions.

Ejection fraction has been utilized to determine graft stability after HT, but EF reduction associated with rejection is usually a late finding (Streeter et al. 2005). Its low sensitivity and poor correlation with rejection grades may limit its use as a stand-alone parameter to determine rejection. Diastolic function changes can be more sensitive to detect CAR than reductions in EF with evidence suggesting that impairment in diastolic indices during CAR can improve after treatment (Sun et al. 2005). Unfortunately, diastolic function can be affected by pre-load conditions, atrial dynamics, LV compliance, LV contractility, heart rate, and end-systolic volume leading to inconsistency in the diastolic indices utilized to predict CAR (Mena et al. 2006).

Myocardial velocity analysis using tissue Doppler imaging (TDI) parameters can improve accuracy to determine diastolic function and can detect ventricular dysfunction earlier than standard echocardiography (Badano et al. 2015). In normal HT recipients, LV peak early diastolic velocity (E') is low in early post-HT period but improves over time. E' has been shown to correlate with rejection severity in patients with CAR. In a study of 363 HT recipients, a $>$ 10% reduction in the E' was associated with CAR with a PPV 92% and NPV 96%. In this study serial pulse wave-TDI (PW-TDI) measurements could predict CAR and need for EMB (Dandel et al. 2001). Others have determined that a reduction below the cutoff value of 0.16 m/s can predict moderate allograft rejection with a NPV of 92% (Puleo et al. 1998). PW-TDI has optimal temporal resolution and is easier to perform than other echocardiographic indices, but it is limited by angle dependency, data capture from one region at a time in the myocardium, and variability in the reported sensitivity and specificity values (69–92% and 59–92%, respectively. Moreover, LV diastolic velocities tend to reduce 1 year post-HT due to fibrosis and restrictive physiology (Badano et al. 2015).

Perhaps a global TDI of diastolic function can detect more accurately rejection as it encompasses TDI E' velocities from all regions of the LV including lateral, septal, and posterior walls. A recent study of 33 patients showed a 100% sensitivity and 90.9% specificity with normalization of all velocities after treatment for CAR (Hernandez et al. 2015). However, more studies are needed to confirm the accuracy of this parameter.

Myocardial deformation analysis using speckle tracking echocardiography (STE) imaging enables a comprehensive assessment of global myocardial contractile function independent of loading conditions, angle dependency, and better spatial resolution. Most studies have shown significant reduction in LV global longitudinal strain (GLS) with others reporting improvement in GLS

after treatment (Sera et al. 2014; Clemmensen et al. 2015). A retrospective study of 59 asymptomatic HT recipients evaluated 160 EMB and echocardiograms with only 42% showing evidence of CAR grade $\geq$ 1B when an absolute value of $< -14.8\%$ was detected (sensitivity 64%, specificity 63%, PPV 24%, and NPV 90%). Others have used a cutoff value of $< -15.5\%$ to detect $\geq$2R with NPV 98.8% (Mingo-Santos et al. 2015).

Although GLS values are able to exclude AR, the variability in cutoffs and low prevalence of CAR from published data have limited its diagnostic capacity. GLS changes over time can independently predict 1-year mortality of HT recipients, but causes of death in allograft recipients can be multifactorial, and no association can be explained between GLS and AR with mortality (Sarvari et al. 2012). GLS can be used as a parameter to diagnose subclinical graft dysfunction independent of the etiology. To date, there is no single echocardiographic parameter that can identify CAR as many indices utilized are sensitive to load changes, differences in CAR severity definition at study entry, and diverse patient population. It is recommended to obtain serial echocardiographic studies in the immediate postoperative period to establish a baseline allograft function and detect early rejection.

Cardiac Magnetic Resonance (CMR). CMR is a newer imaging modality that detects edema and injury due to myocardial inflammation as demonstrated in cases of myocarditis and HT. The advantage of CMR over other imaging modalities is accurate measurement of volumes, morphology, mass calculation, and systolic and diastolic function. It is easily reproducible with less inter-observer and intra-observer variability. Recent studies have shown CMR has the advantage of being an excellent screening tool for CAR due to full assessment of the entire myocardium for inflammation and correlation with systolic and diastolic functional indices. In a study of 60 HT recipients who underwent CMR within 24 hrs of EMB for the diagnosis of rejection, myocardial edema found by T2 relaxation time and right ventricle end diastolic volume index were significant predictors of rejection by EMB (specifically those with grade $>$ 2R) with a high sensitivity and high negative predictive value (Butler et al. 2015). Other studies have confirmed prolonged T2 relaxation times to be associated with severe ISHLT grade 2–3R and can predict future rejection episodes in those with absent rejection on EMB compared to those with normal relaxation times and normal EMB samples (Marie et al. 2001). In the previous studies, most patients presented with cellular rejection, while only a small number of humoral rejection cases were studied. One of the limitations to CMR is that T2 times are not predictive in the early posttransplant period likely due to the immediate postoperative changes seen after HT including myocardial edema. Additionally, repeated testing may be limited due to costs and risk of using gadolinium contrast in HT patients with renal impairment.

Conclusion

Effective immunosuppressive therapies have allowed for cardiac transplantation to improve survival and outcomes. Although rejection rates have decline over time, they remain elevated and are associated with poor outcomes. The early period after heart transplantation is critical for surveillance and diagnosis of rejection. Endomyocardial biopsy is the gold standard for CAR diagnosis, but newer noninvasive modalities hold promise in early detection of rejection before symptoms occur. Gene expression profile and donor-derived cell-free DNA of heart transplantation can be of advantage in detecting ACR and reducing the number of EMB. Treatment strategies for CAR involve enhancing immunosuppression, while more severe episodes require cytolytic, plasmapheresis, and hemodynamic support. The early diagnosis of AMR and early detection and management of CAV may allow to reduce rejection and graft failure episodes while extending the longevity of the cardiac allograft.

Cross-References

- Advances in Immunosuppression
- Chronic Immunosuppression Medications
- Chronic Rejection
- Induction and Maintenance Agents
- Matching Donor to Recipient
- Monitoring for Rejection

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Part IX

Long-Term Outpatient Management of the Heart Transplant Patient

Chronic Immunosuppression Medications

17

Christopher M. Bianco and Monique R. Robinson

Contents

Abstract

Improved outcomes in cardiac transplant outcomes can be largely attributed to advances in immunosuppressive strategies. When formulating modern immunosuppressive regimens, one must recognize the changing landscape of outcomes including decreased mortality risk related to rejection and increased risk related to infection, malignancy, renal insufficiency, cardiac allograft vasculopathy, and metabolic disease. These conditions are impacted significantly by specific agents,

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and a patient-tailored, dynamic immunosuppressive strategy may prove advantageous.

Keywords

Tacrolimus · Cyclosporine · Sirolimus · Everolimus · Mycophenolate mofetil (MMF) · Azathioprine · Corticosteroids · Cardiac allograft vasculopathy (CAV) · Calcineurin inhibitor (CNI) nephrotoxicity · Malignancy · Pregnancy · Elderly · Immunosuppression

Introduction

The landscape of cardiac transplantation has changed immensely since the first transplant in 1967. Improved mortality and morbidity can be largely attributed to advances in immunosuppressive strategies, as well as improved donor selection criteria and comorbid disease management. Historically, survival following transplantation was primarily limited by acute rejection and infection (Rider et al. 1975). Therefore, a major focus of the early transplant effort was on reduction of acute, mortal rejection. Modern immunosuppressive regimens have achieved excellent efficacy in this regard. Although the incidence of histologic rejection remains approximately 25% during the first postoperative year, only about half of these rejections require treatment, and less than 15% of deaths occurring during the first year following transplant are attributable to acute rejection. After 3 years, fewer than 10% of deaths are attributable to rejection. In contrast, infection remains a leading cause of death in contemporary transplant medicine. Between 1 month and 1 year, infection is the number one cause of death, and it remains a leading cause of death throughout the recipients' lifetime. Malignancy has emerged as the primary long-term cause of death following cardiac transplant (see Fig. 1). Immunosuppressant agents likely contribute to posttransplant morbidity including chronic kidney disease, diabetes, hypertension, and hyperlipidemia (see Table 1) (Lund et al. 2016). Furthermore, cardiac allograft vasculopathy (CAV) is a leading cause of long-term death and is impacted by metabolic, non-immunologic factors, as well as immunologic factors, which can be modified with current immunosuppressive agents. When formulating modern immunosuppressive regimens, one

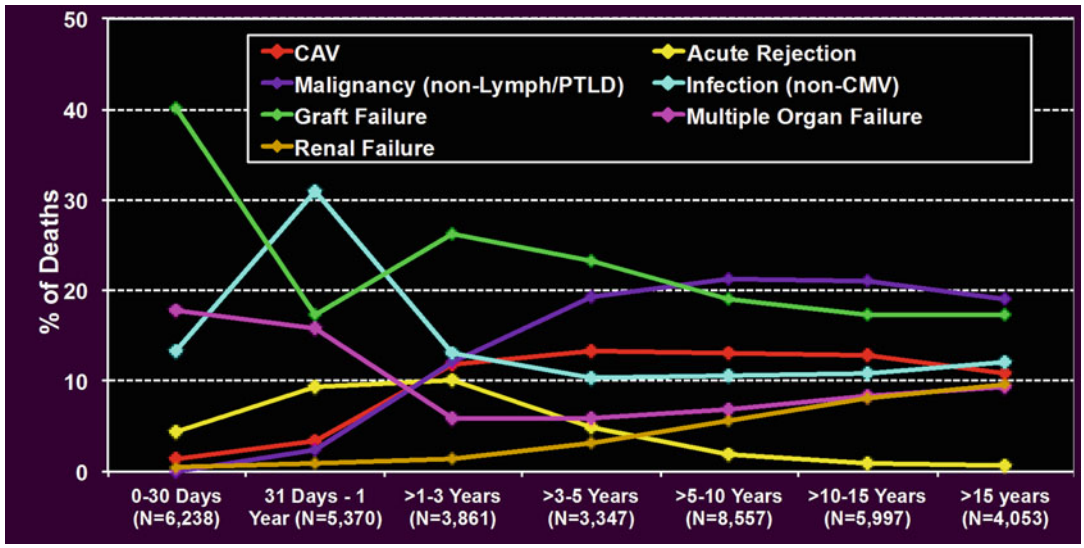

Fig. 1 Adult heart transplants: relative incidence of leading cause of death (January 1994–June 2015). *CAV* Cardiac Allograft Vasculopathy. (Source: Lund et al. 2016)

Table 1 Cumulative morbidity rates in survivors at 1, 5, and 10 years following cardiac transplant

Outcome	Within 1 year %	Within 5 years %	Within 10 years %
Hypertension	41	91	n/a
Renal dysfunction	25	51	68
SCr <2.5[a]	17	33	40
SCr >2.5	6.1	14	19
Chronic dialysis	1.7	3	6.2
Renal transplant	0.3	1.3	3.7
Hyperlipidemia	60	88	n/a
Diabetes	23	37	n/a
CAV	7.8	29	48

Source: Modified from Lund et al. 2016
SCr serum creatinine in mg/dL, *CAV* cardiac allograft vasculopathy, *n/a* not available
[a]Abnormal

must take into account this changing landscape of decreased mortality risk related to rejection and increased risk related to infection, malignancy, renal insufficiency, CAV, and metabolic disease.

Maintenance Immunosuppressant Drugs

The major classes of maintenance immunosuppressant drugs and examples of commonly used agents in those classes include:

1. Calcineurin inhibitors (tacrolimus and cyclosporine)
2. Antiproliferative agents (mycophenolate and azathioprine)
3. Proliferation signal inhibitors (everolimus and sirolimus)
4. Corticosteroids (prednisone and prednisolone)

Each drug class has a specific mechanism of action, pharmacodynamics, and side effect profile that are briefly summarized in Tables 2 and 3 and explored in depth below.

Calcineurin Inhibitors

Calcineurin inhibitor (CNI)-based therapy remains the foundation of immunosuppressive protocols utilized after heart transplantation. The currently available CNIs include cyclosporine and tacrolimus.

CNI: Mechanism of Action

CNIs inhibit calcium-activated calcineurin, which ultimately prevents transcription of interleukin-2 (IL-2) (Clipstone and Crabtree 1992; Kahan 1989). Both CNIs enter the cell via diffusion and bind to specific immunophilins; cyclosporine binds to cyclophilin, while tacrolimus binds to FK-binding protein-12 (FKBP-12). The immunophilin-drug complex binds to calcineurin, which inhibits dephopsphorylation of nuclear factor of activated T cells (NFAT), a molecule that when dephoshorylated translocates to the cell nucleus activating several cytokine genes including IL-2, as well as other costimulatory molecules necessary for full T-cell activation.

CNI: Pharmacodynamics

Cyclosporine is a cyclic endecapeptide, while tacrolimus is a macrolide antibiotic. Both CNIs are metabolized by the cytochrome (CYP) P-450 isoenzymes CYP3A4 and CYP3A5 in the gut lumen and liver, although liver metabolism and biliary excretion are the major elimination pathways (Schiff et al. 2007). P-glycoprotein partially counteracts drug absorption by promoting efflux into the lumen of the intestine, as well as the bile. After the CNI is absorbed in the gut, they are subject to first pass metabolism and systemic metabolism by CYP3A4 and CYP3A5 in the liver (Utecht et al. 2006). Genetic heterogeneity in expression of P-glycoprotein (encoded by the ABCB1 gene) and CYP3A impacts bioavailability via enterocyte secretion and intestinal absorption, while variability in organic anion transporting polypeptide-C (encoded by the SLCO1B1 gene) impacts biliary excretion. Variable expression and function of CYP3A4 and CYP3A5 may impact metabolism significantly. Polymorphisms associated with CYP3A5∗1 or CYP3A5∗3 have a profound impact on tacrolimus

Table 2 Maintenance immunosuppressant drugs

Class	Mechanism of action	Metabolism and elimination	Major drug-drug interactions[b]	Major adverse effects[c]
Calcineurin inhibitors Tacrolimus (Prograf®) Cyclosporine Microemulsion (Gengraf® or Neoral®)[a] Oil-based (Sandimmune®)	Inhibit calcium-activated calcineurin, which ultimately prevents transcription of IL-2 and other costimulatory molecules	Hepatic metabolism CYP 450: CYP3A4, CYP3A5 isoenzymes P-glycoprotein substrate Polymorphisms 3A5∗1 or 3A5∗3 impact tacrolimus dose requirements Hepatic elimination via biliary excretion	Ca^+ channel blockers Azole antifungals Antimicrobials Statins Anti-epileptics Anti-retrovirals Antidepressants Nutraceuticals St. John's wort Basiliximab	Nephrotoxicity Hyperglycemia Hypertension Hyperlipidemia Neurotoxicity Hyperuricemia Hypomagnesemia Hyperkalemia Hirsutism (CYC) Gingival hyperplasia (CYC) Alopecia (TAC) QT prolongation
Antimetabolites Mycophenolate MMF (Cellcept®) Mycophenolate sodium (Myfortic®) Azathioprine (Imuran®)	Interfere with the synthesis of nucleic acids, leading to ineffective synthesis and proliferation of lymphocytes	Hepatic metabolism Enterohepatic circulation MYC active form: MPA AZA active form: 6-MP Renal elimination	MYC: Oral iron Antacids Cholestyramine AZA: Allopurinol Warfarin	Bone marrow suppression/ leukopenia GI disturbances (MYC) Teratogen (MYC) Pancreatitis (AZA)
Proliferation signal inhibitors Everolimus (Zortress®) Sirolimus (Rapamune®)	Inhibits mTOR, results in the blockage of cell cycle progression at the juncture of the G1 and S phase	Hepatic metabolism CYP 450: CYP 3A4 P-glycoprotein substrate GI elimination via biliary excretion and gut lumen efflux	Ca^+ channel blockers Azole antifungals Cyclosporine Antimicrobials Statins Anti-epileptics Anti-retrovirals Antidepressants Nutraceuticals St. John's wort	Oral ulcers Hyperglycemia Hyperlipidemia Bone marrow suppression Edema Poor wound healing Pulmonary toxicity Infertility QT prolongation Proteinuria
Corticosteroids Prednisone Prednisolone (Deltasone®)	Alter gene transcription and physiochemical interactions with cytosolic or membrane-bound proteins. Net result in decreased IL-1, IL-2, IL-6, TNF-α, INF-γ	Hepatic metabolism Prednisone (prodrug) prednisolone (active form) Renal elimination	Calcineurin inhibitors Proliferation signal inhibitors	Hypertension Hyperlipidemia Hyperglycemia Poor wound healing Weight gain Acne Cataracts Peptic ulcer disease Osteopenia

TAC tacrolimus, *CYC* cyclosporine, *IL-2* interleukin-2, *CYP* cytochrome, *MYC* mycophenolate, *MMF* mycophenolate mofetil, *MPA* mycophenolic acid, *AZA* azathioprine, *IMPDH* inosine monophosphate dehydrogenase, *mTOR* mammalian target of rapamycin

[a]Recommended formulation

[b]See Table 5 for details

[c]See Table 4 for details

Table 3 Maintenance immunosuppressant drugs pharmacology

Agent	Time to peak concentration	Half-life elimination	ISHLT recommended trough	Mode of elimination	Oral to intravenous conversion
Tacrolimus (Prograf®)	0.5–6 h	23–40 h	First 3 months: 10–5 ng/ml 3–6 months: 8–12 ng/ml 6 months on: 5–10 ng/ml	Hepatic elimination via biliary excretion	5:1
Cyclosporine Microemulsion (Gengraf® or Neoral®)[a]	~2 h	5–18 h	First 6 weeks: 275–375 ng/ml[b] 6–12 weeks: 200–350 ng/ml[b] 3–6 months: 150–300 ng/ml[b] 6 months on: 150–250 ng/ml[b]	Hepatic elimination via biliary excretion	3:1
Oil-based (Sandimmune®)	2–6 h	10–27 h			
Mycophenolate	1–2 h	~18 h	Monitoring not recommended; however an MPA level of <1.5 mg/L is considered subtherapeutic	Renal elimination	1:1 1000 mg MMF equivalent to 720 mg mycophenolate sodium
MMF (Cellcept®) Mycophenolate sodium (Myfortic®)	1.5–2.75 h	9–17 h			
Azathioprine (Imuran®)	1–2 h	~2 h	Monitoring not recommended	Renal elimination	1:1
Everolimus (Zortress®)	1–2 h	~30 h	When used with cyclosporine: 3–8 ng/ml	GI elimination via biliary excretion and gut lumen efflux	Oral only
Sirolimus (Rapamune®)	1–3 h	46–78 h	When used with cyclosporine: 4–12 ng/ml	GI elimination via biliary excretion and gut lumen efflux	Oral only

MMF mycophenolate mofetil, *MPA* mycophenolic acid
[a]Recommended formulation
[b]Abbot TDX® assay (or equivalent)

dose requirements (Nair et al. 2015; Sikma et al. 2015). Frequent allele polymorphisms may account for increased dose requirements observed in those of African descent (Oetting et al. 2016; Jacobson et al. 2011). At present, genotype-guided dosing has not been shown to improve clinical outcomes; however as the field matures, it may play a greater role in the future.

Cyclosporine

The use of a microemulsion formulation (Gengraf® or Neoral®) of cyclosporine is recommended over the oil-based compound (Sandimmune®) (Costanzo et al. 2010). The microemulsion formulation allows improved bioavailability and more predictable pharmacokinetics (Cooney et al. 1998), as well as improved tolerability (Shah et al. 1998). Lower rates of rejection requiring treatment have also been demonstrated utilizing the microemulsion formulation (Eisen et al. 2001). Terminal half-life elimination of the microemulsion formulation is between 5 and 18 h and may be prolonged in patients with hepatic impairment. Although oral absorption of the microemulsion is improved compared to the oil-based formulation, erratic and incomplete

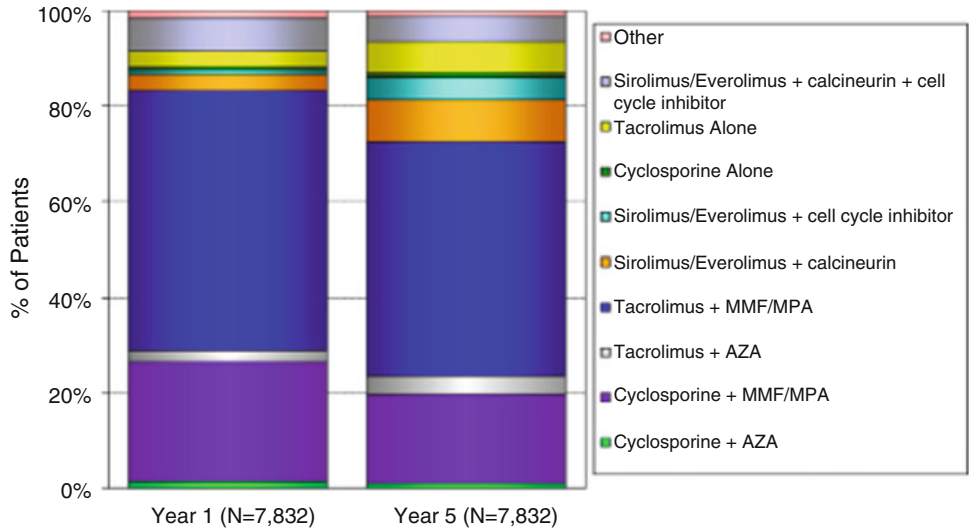

Fig. 2 Maintenance immunosuppression drug combinations at 1 year and at 5 years after adult heart transplant. *MMF* Mycophenolate Mofetil, *MPA* Mycophenolic Acid, *AZA* Azathioprine. (Source: Lund et al. 2016)

absorption related to food, bile acids, GI motility, and functional intestinal length continues to be problematic. Bioavailability of the oral solution is about one-third compared to parenteral administration (Lexicomp Online Cyclosporine 2016). If a transition of therapy from oral to intravenous is necessary, one-third of the oral daily dose either as a continuous infusion over 24 h or divided into two 6-h infusions can be administered.

Measurement of 12-h trough cyclosporine concentration is the recommended form of therapeutic drug monitoring for routine clinical use. The target levels are dependent on the method used for monitoring, concomitant immunosuppression, toxicity risks, and time duration following transplantation. Current guidelines reference average cyclosporine trough concentration target using the Abbot TDX assay (or equivalent) as 275–375 ng/ml for the first 6 weeks, 200–350 ng/ml for weeks 6–12, 150–300 ng/ml for months 3–6, and 150–250 ng/ml from month 6 onward. Two-hour post-dose cyclosporine (C2) levels reflecting peak level may be useful in selected patients in whom a better characterization of the pharmacokinetic profile is desired, as it may correlate well with the drugs pharmacokinetic area under the curve (Cantarovich et al. 2004). However, there is little prospective evidence to support the theoretical benefits of C2 monitoring in clinical practice (Knight and Morris 2007), and it should not replace 12-h trough levels for routine monitoring in most patients (Costanzo et al. 2010).

Tacrolimus

Tacrolimus is currently the most commonly used immunosuppressant following heart transplant (see Fig. 2) (Lund et al. 2016). Tacrolimus-based regimens may be associated with lower rejection rates, but not with superior survival after heart transplant, compared to cyclosporine based regimens (Grimm et al. 2006). An immediate release form dosed twice daily or an extended release daily form is available. Current ISHLT guidelines recommend the immediate release form (Costanzo et al. 2010). Oral absorption is variable (5–67%). Time to peak level is between 30 min and 6 h. High fat or high carbohydrate meals may substantially increase the time to maximal concentration and decrease the maximal concentration (Bekersky et al. 2001). Half-life elimination is variable and may be as long as 40 h, particularly in patients with severe hepatic impairment (Lexicomp Online Tacrolimus 2016). Generally, steady-state concentrations are expected 2–3 days after dose adjustment (Sikma

et al. 2015). If a transition of therapy from oral to intravenous is necessary, one-fifth of the oral daily dose may be delivered as a continuous infusion over 24 h. Alternatively, sublingual tacrolimus can be used. When converting from oral to sublingual tacrolimus capsules, 50% of the oral dose should be administered and serum drug levels monitored frequently until therapeutic steady-state trough levels are achieved (Pennington and Park 2015).

Measurement of 12-h trough concentration for immediate release tacrolimus or a 24-h trough concentration for once-daily tacrolimus is the recommended drug monitoring method for routine clinical use. The therapeutic range of tacrolimus levels varies depending on concomitant drugs, toxicity concerns, and time after heart transplant. Current ISHLT guidelines recommend trough concentration targets range between 10 and 15 ng/ml during the early postoperative period, between 8 and 12 ng/ml for the next 3–6 months, and between 5 and 10 ng/ml in stable patients 6 months after HT. In patients with a therapeutic 12-h trough concentration for twice-daily dosing, but evidence of potential drug-related toxicity or reduced efficacy, a 3-h post-dose level (C3) can be considered. C3 levels may aid in dose adjustment (Costanzo et al. 2010), as this corresponds to the time of maximal drug concentration and correlates well with the 12-h area under the curve in stable transplant patients.

CNI: Adverse Effects

Hypertension, hyperlipidemia, renal dysfunction, and diabetes (in descending order) are the most common comorbidities following heart transplantation (see Table 1) (Lund et al. 2016). Although posttransplant metabolic changes and contributions from other immunosuppressants impact the development of these comorbidities, CNIs are strongly associated with each of these conditions (see Table 4) (Lindenfeld et al. 2004). Both tacrolimus and cyclosporine are associated with aforementioned conditions; however, the whole tacrolimus seems to be better tolerated and associated with fewer side effects. Tacrolimus use is associated with less hypertension (CYA 71% vs. TAC 48%, $p = 0.05$) and hyperlipidemia (CYA 71% vs. TAC 41%, $p = 0.01$) requiring pharmacologic treatment (Taylor et al. 1999). In contrast, the incidence of diabetes may be increased with tacrolimus (up to 20%) compared to cyclosporine (approx. 10%) (Grimm et al. 2006). However, diabetes associated with tacrolimus may be less common with contemporary regimens utilizing MMF than azathioprine containing regimens. Certain ethnic groups including Koreans (Cho et al. 2003) and African-Americans (Neylan 1998) may also be at particularly higher risk for tacrolimus-induced diabetes. CNIs cause diabetes predominantly through an inhibitory effect on insulin secretion (Lane and Dagogo-Jack 2011). Although few clinical studies (Israni et al. 2016; Kobashigawa et al. 2006a) and mechanistic data (Klein et al. 2002; Jain et al. 2000) suggest that tacrolimus may be associated with less nephrotoxicity than cyclosporine, the totality of data to date in cardiac transplant suggest a similar incidence of nephrotoxicity between CNIs (Ojo et al. 2003; Penninga et al. 2010; Ye et al. 2009). Tubulointerstitial nephron changes frequently lead to hypomagnesaemia and hypophosphatemia occur via urinary wasting (Chang et al. 2007), hyperkalemia via reduced urinary potassium excretion, hypercalciuria, distal renal tubular acidosis (Lee and Kim 2007), and hyperuricemia (Lee and Kim 2007; Lin et al. 1989). Fludrocortisone (Dick et al. 2011) and thiazide diuretics have been used for CNI-associated hyperkalemia; the agent of choice is usually guided by desired impact on blood pressure (Hoorn et al. 2011).

Up to one-quarter of patients experience some form of neurological toxicity with CNI use, most commonly tremors (Bechstein 2000). Tacrolimus may be associated with a higher incidence of tremor, headaches, and sleep disorders compared to cyclosporine (Frank et al. 1993). Rare complications include visual hallucinations or cortical blindness. Contemporary literature suggests seizure disorder is relatively rare at <2% (Perez-Miralles et al. 2005). Management should include reduction of CNI doses and correction of hypomagnesemia if present or consideration of CNI withdrawal and substitution with a PSI. Posterior reversible encephalopathy

Table 4 Major adverse effects of maintenance immunosuppressive drugs

	TAC	CYA	MMF	AZA	SIR	EVR	Steroids
Potential for drug-drug interactions	4	4	1	1	4	4	1
Hypertension	3	4			2	2	2
Diabetes	2–3	1–2			2	2	3
Obesity							2
Hyperlipidemia	3	3			3	2	2
Renal insufficiency	3	3			1–2	1–2	
Osteoporosis	1–2	1–2					3
Avascular necrosis							1
Poor wound healing					2	2	2
Neurologic minor[a]	3	3					2
Neurologic major[b]	1	1					
Hirsutism		3					2
Alopecia	2			1			
Gingival hyperplasia		3					
Gastrointestinal[c]	3	2	3	2	3	3	
Hepatotoxicity	2	1		2	1	1	
Hypomagnesaemia	3	3					
Hyperkalemia	2	2			2	2	
Hyperuricemia	3	3			3	3	
Anemia			3	2	2	2	
Thrombocytopenia	3		2	1	2	2	
Leukopenia			3	3	2	2	
Cushingoid features							3

Source: Modified from Lindenfeld et al. 2004
1 = rare (<5%), 2 = common (5–15%), 3 = very common, 4 = most patients
TAC tacrolimus, *CYA* cyclosporine, *MMF* mycophenolate mofetil, *AZA* azathioprine, *SIR* sirolimus, *EVR* everolimus
[a]Tremors, paresthesias
[b]Seizures, cerebritis
[c]Diarrhea, nausea, vomiting

syndrome (PRES) is a rare neurologic complication, which manifests as headaches, altered mental status, seizures, and visual loss. PRES is managed with a reduction of CNI doses or substitution with an alternative CNI (Costanzo et al. 2010). Overall, ischemic stroke is the most common serious neurologic complication associated with cardiac transplantation (Perez-Miralles et al. 2005) and should be strongly considered in the initial workup of neurologic deficits. Rarely CNIs can result in thrombotic microangiopathy (Lin et al. 2003). Mild CNI-related thrombocytopenia is not uncommon; rarely tacrolimus has been associated with refractory immune-mediated thrombocytopenia (Woytowitz et al. 2013). Cyclosporine is more commonly associated with gastrointestinal side effects including cholestasis and cholelithiasis (Stone et al. 1987). Gingival hyperplasia or hypertrichosis occurs in approximately 50% of patients taking cyclosporine (Penninga et al. 2010). In contrast, tacrolimus use has been associated with alopecia (Tricot et al. 2005). Both CNIs may cause QTc prolongation; this is clinically relevant when combined with other QTc prolonging drugs. Limited evidence suggests greater QTc prolongations with cyclosporine than tacrolimus (Cosansu et al. 2011).

CNI: Drug-Drug Interactions

There are a number of important drug-drug interactions associated with CNIs (see Table 5). The majority of drug interactions for both antimicrobials and non-antimicrobials are mediated by CYP3A and P-glycoprotein

Table 5 Drugs that affect the levels of calcineurin inhibitors and proliferation signal inhibitors

Decrease immunosuppression levels	Increase immunosuppression levels
Anti-epileptics: Carbamazepine Phenytoin Fosphenytoin Phenobarbital	Cardiovascular: Amiodarone Verapamil Diltiazem
Antimicrobials: Nafcillin Rifampin Rifabutin Rifapentine	Antimicrobials: Clarithromycin Erythromycin Metronidazole Quinupristin/Dalfopristin Levofloxacin
Antifungals: Caspofungin	Antifungals: Clotrimazole Itraconazole Ketoconazole Fluconazole Posaconazole Voriconazole
Anti-retrovirals: Efavirenz Etravirine Nevirapine	Anti-retrovirals: Protease inhibitors (general) Amprenavir Atazanavir Darunavir Fosamprenavir Indinavir Nelfinavir Ritonavir Saquinavir Tipranavir
Herbals/nutraceuticals: St. John's wort	Herbals/nutraceuticals: Bitter orange Grapefruit juice
Others: Antacids Deferasirox Modafinil Thalidomide Troglitazone	Others: Rilonacept Theophylline Cimetidine Fluvoxamine Glipizide Glyburide Imatinib Nefazodone

Source: Costanzo et al. 2010

interactions. Azole antifungals increase CNI concentrations dramatically via CYP3A, as well as P-glycoprotein interactions. Ketoconazole and itraconazole are the most potent inhibitors of CNI metabolism (Back and Tjia 1991), and when initiating these agents, a CNI dose reduction up to 50% is recommended (Page et al. 2005). Echinocandins behave differently, e.g., caspofungin decreases tacrolimus concentrations. Concomitant use of cyclosporine may lead to toxic caspofungin levels and increased hepatotoxicity (Lexicomp Online Cyclosporine 2016). Micafungin inhibits cyclosporine metabolism leading to increased cyclosporine levels (Hebert et al. 2005). Concomitant use of amphotericin B and cyclosporine synergistically increases the risk of nephrotoxicity (Wingard et al. 1999). All macrolide antibiotics, with the exception of azithromycin, are moderate to strong inhibitors of CYP3A4, therefore decreasing the metabolism of both cyclosporine and tacrolimus (as well as the PSIs). The magnitude of this effect varies between the macrolides, with erythromycin and clarithromycin having the greatest impact (Trofe-Clark and Lemonovich 2013). Conversely, the rifamycins are strong inducers of CYP3A4; rifampin and rifabutin may cause dramatic increases in clearance and resultant decreases in plasma levels of the CNIs (as well as the PSIs).

Notable non-antimicrobial drug-drug interactions leading to increased CNI levels include calcium channel blockers (CCB), particularly non-dihydropyridines, which may increase CNI concentrations 1.5- to 6-fold (Page et al. 2005; Grino et al. 1986; Hebert and Lam 1999). The onset of CCB interaction may be delayed, and empiric decreases in CNI dose of 20–50% are recommended when initiating diltiazem or verapamil (Page et al. 2005). This CCB drug interaction has been used advantageously to boost CNI levels using minimal CNI doses. Several statins are CYP3A4 substrates, and CNI interactions lead to increased risk of statin-associated myopathy. The safest statins for use with CNIs appear to be pravastatin (non-CYP metabolism) (Kobashigawa 1995), fluvastatin, (Sadoni et al. 2007) and rosuvastatin (CYP2C9 metabolism) (Barge-Caballero et al. 2015). Fibrates may actually decrease CNI concentrations (Boissonnat et al. 1994); the combination of statin, fibrate, and CNI likely increases myotoxicity synergistically (Ballantyne et al. 2003). The interaction between CNIs and amiodarone is complex, but overall

increased levels of CNI can be expected with concomitant use (Chitwood et al. 1993). Several antidepressants are CYP3A4 inhibitors and can lead to increased CNI concentrations; citalopram has one of the lower risk drug-drug interactions in this class (Crone and Gabriel 2004). St. John's Wort increases P-glycoprotein expression and may lead to dramatic decreases in CNI levels precipitating rejection (Ruschitzka et al. 2000). If concomitant cyclosporine and sirolimus are employed, sirolimus should be administered at least 4 h after the cyclosporine dose; everolimus can be administered concomitantly (Lexicomp Online Cyclosporine 2016). Basiliximab, a chimeric monoclonal antibody commonly used in induction, may increase tacrolimus concentrations through unknown mechanisms (Sifontis et al. 2002). The elimination half-life of basiliximab is approximately 13 days; therefore tacrolimus levels may be impacted for several weeks after a single basiliximab dose (Onrust and Wiseman 1999). Corticosteroids are substrates of CYP3A4 and P-glycoprotein and thus may theoretically interact with CNI metabolism (Lam et al. 2008). Closer monitoring of CNI levels during steroid withdrawal is warranted given these interactions.

CNI: Transplant Outcomes

Several studies have compared cardiac transplant outcomes between tacrolimus and cyclosporine. Early, smaller trials comparing CNIs (in combination with azathioprine plus steroids and selective induction therapy) showed similar survival and rejection outcomes (Taylor et al. 1999; Reichart et al. 2001). However, a multicenter trial of over 300 patients undergoing polyclonal antibody induction and azathioprine plus steroids demonstrated similar survival but less frequent rejection at 6 months (both first biopsy-proven acute rejection (BPAR) of grade $\geq$1B and first BPAR of grade $\geq$3A) associated with tacrolimus use (Grimm et al. 2006). Another more contemporary trial utilizing combination therapy with mycophenolate mofetil (MMF) confirmed a lower incidence of rejection (defined as $\geq$3A rejection or rejection with hemodynamic compromise rejection requiring treatment) associated with tacrolimus more frequently than with cyclosporine (Kobashigawa et al. 2006a). A recent prospective, randomized study tested tacrolimus monotherapy versus combination therapy of tacrolimus plus MMF (the TICTAC trial). The study population consisted of 150 patients: 81% male, 19% African American, 27% with mechanical bridge to transplantation, and nearly 30% with panel reactive antibodies $\geq$10%. All patients received tacrolimus, MMF, and steroids for the initial 2 weeks following transplantation. After 2 weeks, patients were randomly assigned to continued combination therapy with MMF or tacrolimus monotherapy in which MMF was discontinued 14–28 days following transplant. The primary end point, a composite biopsy score at 6 months after transplant, was similar between groups, as was freedom from rejection grade 2R or greater at 6 and 12 months (Baran et al. 2007). Furthermore the addition of MMF to tacrolimus failed to provide an advantage over single-agent immunosuppression in terms of allograft vasculopathy or 3-year survival (Baran et al. 2011). One patient in the study received induction therapy, and all patients were weaned from corticosteroids within 8–9 weeks posttransplant. The event rates of the primary end point were unexpectedly low in either group, and these results have yet to be validated. Current ISHLT registry data shows that $<$5% and $<$10% of patients are maintained on tacrolimus monotherapy alone at 1 and 5 years, respectively (Lund et al. 2016). Current guidelines state that CNI monotherapy with early CS withdrawal may be considered in highly selected individuals (Costanzo et al. 2010).

Antiproliferative Agents

Combination therapies including antiproliferative agents form the backbone of contemporary triple drug maintenance therapy. Recent ISHLT registry data reports that approximately three-fourth of all cardiac transplant patients are maintained at 1 and 5 years on a combination of CNI plus mycophenolate mofetil (MMF). Fewer than 5% of current cardiac transplant recipients are treated with azathioprine (Lund et al. 2016).

MMF is the predominant antimetabolite used in contemporary regimens. A large, multicenter prospective study of 650 patients comparing MMF versus azathioprine (both in combination cyclosporine, steroids, and selective induction therapy) demonstrated a significant reduction in 1-year mortality (18 deaths [6.2%] vs. 33 deaths [11.4%]; $p = 0.031$). Furthermore, MMF was associated with a significant reduction in the requirement for rejection treatment. MMF therapy was also associated with increased opportunistic infections, predominantly herpes simplex viruses (Kobashigawa et al. 1998). A subsequent ISHLT registry analysis of over 5000 patients also demonstrated the survival advantage of MMF-containing regimens over azathioprine (Hosenpud and Bennett 2001). MMF also attenuates the progression of cardiac transplant vasculopathy (CAV) compared to azathioprine (Kobashigawa et al. 2006b). The use of MMF, instead of azathioprine, allows for reduced CNI requirements, which potentially causes fewer deleterious renal outcomes in those with CNI-related nephropathy (Aleksic et al. 2000). MMF is also better tolerated than azathioprine and is associated with less myelosuppression (Ensley et al. 1993).

Mycophenolate: Mechanism of Action

As a class, antiproliferative agents interfere with the synthesis of nucleic acids, leading to ineffective synthesis and proliferation of both T and B lymphocytes. MMF is a prodrug that is hydrolyzed in the liver to mycophenolic acid (MPA). MPA is an inhibitor of inosine monophosphate dehydrogenase (IMPDH), which is the rate-limiting enzyme in de novo synthesis of guanosine nucleotides. Both T and B lymphocytes are more dependent on this pathway than are other cell types. Furthermore, MPA is a particularly potent inhibitor of the type II isoform of IMPDH expressed in activated lymphocytes, rather than the type I isoform expressed in most cell types; thus it exerts relatively selective cytostatic effects on lymphocytes as opposed to other cell lines. Other minor immunosuppressant mechanisms include apoptosis of activated T lymphocytes, suppression of expression of adhesion molecules, thereby decreasing the recruitment of lymphocytes and monocytes into sites of graft rejection, as well as suppressing primary antibody responses (Allison and Eugui 2000).

Mycophenolate: Pharmacodynamics

MMF has high bioavailability (up to 94%); therefore if a transition from oral to intravenous therapy is necessary, the same dosage can be given over a 2-h intravenous infusion twice daily. The enteric coated, delayed release form, mycophenolate sodium (Myfortic^{R}), has a slightly lower bioavailability (72%); thus 1000 mg of MMF is thought to be equivalent to 720 mg of mycophenolate sodium. MMF is hydrolyzed by esterases in the liver to MPA and enterohepatic recirculation is common. Following MMF administration, maximum MPA concentration occurs in 1–2 h. Mycophenolate sodium exhibits a lag time in absorption of MPA of approximately 60 min. A secondary peak in the concentration of MPA, due to enterohepatic recirculation, often appears 6–12 h after dosing. MPA is eventually glucuronidated to its major metabolite MPA glucuronide (MPAG), which is eliminated predominantly (87%) via urination. The mean elimination half-life of MPA ranges from 9 to 17 h (Staatz and Tett 2007). Current guidelines do not recommend routine therapeutic drug monitoring of MPA levels to adjust MMF doses. In selected situations (rejection, infection, renal failure, malnutrition, and certain ethnic populations) where altered MMF exposure contributes to cardiac allograft dysfunction, measurement of trough MPA levels may be used to guide drug dosing (Costanzo et al. 2010). In such cases an MPA level of <1.5 mg/l is considered to be subtherapeutic.

Mycophenolate: Adverse Effects

MMF is well tolerated, but nausea, vomiting, and loose stool are the most common side effects. Typically these GI side effects are responsive to a decrease in dosage (Renlund et al. 1996) or transition to mycophenolate sodium (Gozdowska et al. 2011). Rarely, severe oral or gastrointestinal ulcerations require switching to azathioprine (Mahdavi and Hejri 2016; Tayyem et al. 2018). Leukopenia is another major side effect, but MMF cause less bone marrow suppression than

azathioprine (Ensley et al. 1993). MMF use has been associated with increased incidence of opportunistic infections, particularly herpes simplex (Kobashigawa et al. 1998). Increased incidence of cytomegalovirus (CMV) has been inconsistently associated with MMF use in renal transplant patients, and data on cardiac transplant patients are lacking (Song et al. 2006). MMF is teratogenic and associated with miscarriage (Moritz et al. 2017). Women of childbearing potential must have contraceptive counseling and use of acceptable birth control while taking MMF. Mycophenolate absorption may be impaired by oral iron or antacid co-administration via chelation. Administration of these drugs should be staggered by 2–4 h. Cholestyramine may inhibit enterohepatic recirculation, resulting in lower drug concentrations, and should be avoided (Page et al. 2005).

Azathioprine

Azathioprine use has declined in contemporary cardiac transplant. It is predominantly used in those transplanted with Chagas disease (de Andrade et al. 2011) and has been used for the pregnant transplant patient. Azathioprine is a prodrug that is hydrolyzed in the blood into 6-mercaptopurine (6-MP). 6-MP is further converted into the active metabolite thioinosine monophosphate, which is then converted into a purine analog 6-thioguanine and incorporated into DNA. Its incorporation inhibits further nucleotide synthesis, preventing mitosis and proliferation of lymphocytes. The drug is metabolized in the liver via glutathione S-transferase reduction back into 6-MP. 6-MP is then metabolized further via one of three pathways: thiopurine methyltransferase (TPMT), hypoxanthine-guanine phosphoribosyltransferase, or xanthine oxidase. The latter pathway is relevant with concomitant administration of the xanthine oxidase inhibitor allopurinol which may lead to accumulation of 6-MP, resulting in hematologic toxicity and GI symptoms (Venkat Raman et al. 1990). Variable expression of thiopurine methyltransferase (TPMT) may predispose those with nonfunctional TPMT mutant alleles to hematologic toxicity (TPMT 2009; Formea et al. 2004). Major side effects include dose-dependent myelosuppression (leukopenia, anemia, or thrombocytopenia) or gastrointestinal toxicity. Other less frequently encountered side effects include hepatitis, pancreatitis, and progressive multifocal leukoencephalopathy (Lexicomp Online Azathioprine 2016). MMF use in transplantation for Chagas disease is associated with increased rates of reactivation; therefore azathioprine remains the drug of choice in that situation (Bacal et al. 2005).

Proliferation Signal Inhibitors

Growing interest in the potential benefits of proliferation signal inhibitors (PSI) on cardiac allography vasculopathy (Topilsky et al. 2012) and transplant nephropathy (Kushwaha et al. 2005; Raichlin et al. 2007a) has led to increased use. Recent ISHLT registry data shows that proliferation signal inhibitors are utilized in nearly 20% of contemporary maintenance regimens at 5 years (Mehra et al. 2016). However, concerns over medication intolerance (Gonzalez-Vilchez et al. 2012) and perhaps increased rejection rates (Zuckermann et al. 2012; Andreassen et al. 2014) have curbed more extensive adoption of this maintenance strategy. The two available PSIs studied in cardiac transplant are sirolimus and everolimus.

PSI: Mechanism of Action

The mechanism of action involves binding to the mammalian target of rapamycin (mTOR); thus they are often referred to as mTOR inhibitors. Both agents are macrolide lactone antibiotics and have a chemical structure similar to tacrolimus. Like tacrolimus, PSIs first binds to the immunophilin cytosolic FK-binding protein-12 (FKBP-12). The drug-immunophilin complex then inhibits the serine-threonine kinase mTOR. Inactivation of mTOR results in the blockage of cell cycle progression at the juncture of the G1 and S phase. Both interleukin (IL)-2 receptor-dependent and CD28-dependent signaling

pathways are inhibited by these effects on mTOR. PSIs also inhibit vascular and smooth muscle proliferation via inhibition of key growth factors, including vascular endothelial growth factor (VEGF) (Ensor and Doligalski 2013), as well as indirectly blocking effector functions of CD4+ T-helper cells and CD8+ cytotoxic T cells, activation of monocytes, and proliferation and differentiation of B cells (Schmidbauer et al. 1994).

PSI: Pharmacodynamics

Both drugs have overall low bioavailability (14–30%). Everolimus has a significantly shorter half-life (30 h) compared to sirolimus (62 h) (Lexicomp Online Everolimus 2016; Lexicomp Online Sirolimus 2016). Sirolimus absorption may be increased with ingestion of a fatty meal (Zimmerman et al. 1999), while everolimus absorption is decreased (Kovarik et al. 2002). PSIs should be administered consistently in individual patients, either with or without meals to avoid fluctuations in bioavailability. Metabolism is mainly via hepatic CYP3A4 although intestinal wall P-glycoprotein also plays a role. Therefore, those with hepatic impairment may need dose adjustments. Genetic heterogeneity or co-administration of drugs that interfere with CYP3A4 enzyme activity may alter drug levels. PSIs are subject to many of the same interactions seen with CNIs, notably non-dihydropyridine CCBs and azole antifungals raise PSI drug levels. In the case of a combined regimen with microemulsion cyclosporin, the sirolimus should be administered at least 4 h after cyclosporine to avoid excessive sirolimus exposure. This may result from competition for the intestinal p-glycoprotein counter transporter between cyclosporin and sirolimus or by competitive suppression of CYP3A (Bai et al. 2004). This effect is not seen with co-administration of tacrolimus. Therapeutic drug monitoring for PSIs using trough concentration levels is recommended. Levels should be measured at least 5 days after adjustment of the dose, when a new steady state is achieved. ISHLT guidelines suggest that when used in combination with CYA, the optimal trough target level for everolimus is 3–8 ng/ml, and sirolimus is 4–12 ng/ml (Costanzo et al. 2010).

PSI: Adverse Effects

A high rate of adverse drug effects associated with PSIs has been described in the literature. In a Spanish registry of 548 cardiac transplant patients taking PSIs, 16% and 25% of patients, at 1 year and 4 years, respectively, discontinued use of PSI due to intolerable side effects (Gonzalez-Vilchez et al. 2012). Everolimus appeared to be better tolerated with a discontinuation rate approximately half that of sirolimus. The most frequent causes for PSI discontinuation were edema (4.7%), gastrointestinal toxicity (3.8%), pneumonitis (3.3%), and hematologic toxicity (2.0%). Stomatitis is common and may occur in up to 60% of patients (Mahe et al. 2005). Microcytic anemia with low iron levels is characteristic (Sofroniadou et al. 2010). Thrombocytopenia and neutropenia frequently occur simultaneously and usually resolve spontaneously (Hong and Kahan 2000). Menstrual cycle disturbances and ovarian cysts are common in females, with infertility in both sexes (Braun et al. 2012). PSIs may cause QTc prolongation, and this is relevant when combined with other QTc prolonging drugs (Cosansu et al. 2011).

Poor postoperative wound healing is well described in the pulmonary (King-Biggs et al. 2003) and renal (Ueno et al. 2016) transplant literature. PSI introduction earlier than 3 months after cardiac transplant is contraindicated due to the risk for delayed wound healing per current ISHLT guidelines (Costanzo et al. 2010); however several studies with reassuring findings have been published since these guidelines regarding early PSI use (Eisen et al. 2013; Zuckermann et al. 2011). Those bridged to transplant with durable mechanical circulatory support may be particularly vulnerable to postoperative wound complications (Filsoufi et al. 2007); however PSI impact on this cohort has not been well studied (Zuckermann et al. 2011). Given concerns over postoperative wound healing, PSI therapy is generally withdrawn in those listed for retransplantation.

PSI-associated pneumonitis has been infrequently described in solid organ transplant but is more common with oncologic use (up to 10% of patients) (Albiges et al. 2012). The mechanism of disease is poorly understood. Pneumonitis is generally considered reversible, and withdrawal of PSI is associated with improvements (Chhajed et al. 2006). Sirolimus may also be associated with an increased risk of venous thromboembolism in cardiac transplant recipients (Thibodeau et al. 2012). Increased rates of pleural and pericardial effusions have been reported (Eisen et al. 2013).

Metabolic side effects including hypertension, diabetes, hypertriglyceridemia, and elevated LDL cholesterol have all been described. Associated hyperlipidemia is at least partially dose-dependent (Kahan and Camardo 2001). Everolimus may be associated with less severe elevations of triglycerides and LDL compared to sirolimus (Tenderich et al. 2007). PSI-induced hyperlipidemia responds to statin therapy; however CYP3A4-related interactions may increase the risk for myopathy (Page et al. 2005). The incidence of PSI-induced diabetes is lower when used without concomitant CNI, but when used in combination with CNI, the risk increases from 11.0% to 38.1% (Peddi et al. 2013). Likewise, combination PSI and standard dose cyclosporine therapy may worsen renal function, due to drug-drug interactions leading to increased intracellular cyclosporine concentrations (Anglicheau et al. 2006). Proteinuria is a well-known PSI side effect. Transplant recipients with baseline proteinuria >0.15 g/24 h or diabetes mellitus with any degree of proteinuria are at higher risk for developing worsening proteinuria and decreasing GFR (Potena et al. 2012). Focal segmental glomerulosclerosis has also been reported in renal transplant patients with elevated sirolimus levels (Letavernier et al. 2007).

PSI: Transplant Outcomes

In current practice, PSI use is primarily restricted to maintenance therapy; however the majority of recent PSI trials have been published in de novo transplants. Regimens using lower dose everolimus (trough 3–8 ng/ml) or higher dose everolimus (trough 6–12 ng/ml) plus low dose cyclosporine and tapered steroids have been compared to standard dose cyclosporine with MMF and tapered steroids in a large, multicenter clinical trial of de novo cardiac transplant. Approximately two-thirds of the patients in this trial underwent induction therapy, with an even match between basiliximab and rabbit antithymocyte globulin (rATG). The high dose everolimus arm was stopped prematurely due to excessive early mortality. The low dose everolimus plus low dose cyclosporine arm was non-inferior to the MMF plus standard dose cyclosporine arm using a 12-month primary composite end point of biopsy-proven acute rejection, acute rejection associated with hemodynamic compromise, graft loss, retransplantation, or death. Early mortality (at 3 months) was increased in the low dose everolimus arm in those who underwent induction with rATG. Maximal intimal thickness by IVUS at 12 months was favorable in the everolimus arm; however serious adverse events were more frequent, and no clear renal advantage was demonstrated (Eisen et al. 2013). These results are consistent with those found in a smaller, earlier trial of de novo transplants who received a similar regimen, with no significant nephropathy advantage, but similar outcomes with regard to severe (grade 3R) rejection. Notably, less frequent cytomegalovirus infection was seen in the everolimus arm (Lehmkuhl et al. 2009).

Long-term data of de novo initiation of sirolimus (trough 6–8 ng/ml until month 6, thereafter 5–7 ng/ml) plus low dose tacrolimus (trough 6–8 ng/ml until 12 months, 5–7 ng/ml years 1–4, and 4–6 ng/ml beyond) and tapered steroids compared to standard dose tacrolimus plus MMF and tapered steroids showed similar outcomes with regard to mortality, rejection, presence and severity of CAV, and renal function. Early renal function benefits were observed in the sirolimus arm but did not persist past 5 years posttransplant. Adverse events requiring treatment switch was far more common in the sirolimus group (Guethoff et al. 2015).

A strategy of combination everolimus and CNI followed by early CNI withdrawal has been evaluated in the SCHEDULE trial. All 115

patients underwent induction with ATG and received concomitant maintenance MMF and tapered steroids. Posttransplant low dose everolimus (trough 3–6 mg/ml) plus low dose cyclosporine, followed by cyclosporine withdrawal between weeks 7 and 10 with increased intensity everolimus (trough 6–10 ng/ml) was compared to a standard dose cyclosporine regimen. At 1 and 3 years, everolimus use was associated with beneficial CAV and renal function effect. The incidence of acute rejection episodes requiring treatment was significantly higher in the early CNI withdrawal arm at 12 months (43 vs. 17, $p < 0.01$). Mortality and graft function were similar between groups (Andreassen et al. 2014, 2016). Similarly, a CNI-free regimen of sirolimus plus MMF in de novo management was associated with a trend toward lower rates of CAV and renal dysfunction, as well as a trend toward increased rates of rejections at 5 years compared to tacrolimus-based therapy (Kaczmarek et al. 2013).

PSI use in current clinical practice is largely restricted to maintenance therapy in patients with impaired renal function or CAV and often in substitution of a CNI. Other potential reasons for substitution include malignancy, CMV infection, or recurrent rejection. Several, smaller single-center studies have demonstrated beneficial effects of PSI substitution for CNI without compromising cardiac function or rejection (Kushwaha et al. 2005; Raichlin et al. 2007a; Groetzner et al. 2004). The largest, multicenter randomized trial examining sirolimus initiation and CNI withdrawal in patients with renal insufficiency greater than 1 year posttransplantation (mean 4.1 years posttransplant in sirolimus conversion group) was beneficial with regard to renal function but associated with a more late rejection requiring treatment (15 sirolimus group vs. 2 CNI group, p value not reported) (Zuckermann et al. 2012). Risk factors identified for rejection using this strategy included lower concomitant MMF dose and nonwhite race (Zuckermann et al. 2014). Therefore, CNI-free regimens should be used with caution. Per current ISHLT guidelines, a PSI may be substituted for CNIs at more than 6 months after HT to reduce CNI-related nephrotoxicity and CAV in low-risk recipients (Costanzo et al. 2010). Further discussion on the merits of PSI-based therapy with regard to CNI nephrotoxicity, malignancy, and CAV can be found later in this chapter.

Corticosteroids

Corticosteroids were among the first immunosuppressive agents used in transplantation. Successful corticosteroid minimization and withdrawal in cardiac transplantation were first reported in 1985 (Yacoub et al. 1985). Despite several side effects, largely related to dose and duration of therapy, these drugs continue to play a prominent role in contemporary maintenance regimens. ISHLT registry data from 2009 to 2010 demonstrated that 80% of patients remained on steroids at 1 year posttransplant, and by 5 years, only about half were weaned from prednisone (Stehlik et al. 2011). Despite the common misconception that maintenance steroid therapy is rare in the modern era, these statistics are essentially identical in the most recent ISHLT registry data published in 2016 (Lund et al. 2016). The most recent ISHLT guidelines recommend corticosteroid avoidance, early corticosteroid weaning, or very low dose maintenance corticosteroid therapy as acceptable therapeutic approaches.

Corticosteroids: Mechanism of Action

Broadly, glucocorticoids work through genomic mechanisms involving modification of gene transcription, as well as non-genomic mechanisms involving physiochemical interactions with cytosolic or membrane-bound proteins. The latter effects are independent of protein synthesis, which occur immediately within minutes to seconds, while the former are responsible for most durable immunomodulatory effects. The classic genomic mechanism involves glucocorticoid receptors in the cytoplasm that exist as an inactive complex involving heat shock proteins. Corticosteroids cross into the cytoplasm and bind to these receptor complexes. The binding of corticosteroid to the glucocorticoid receptors leads to

a conformational change and dissociation of the heat shock protein component. This allows the newly formed corticosteroid-glucocorticoid receptor complex to translocate to the cell nucleus and dimerizes on palindromic DNA sequences in many genes, leading to altered gene transcription (Ramamoorthy and Cidlowski 2016).

Corticosteroids affect the number, distribution, and function of all lines of leukocytes, as well as modifying endothelial cell function. In lymphocytes, inhibition of transcription factors, nuclear factor (NF) κ-B and activator protein-1, appear to alter transcription of several genes impacting cell function and proliferation. In nonlymphoid cells, steroids cause a decrease in chemokines and vasoactive factors, leading to impaired neutrophil adhesion to endothelial cells and the prevention of macrophage differentiation. Steroids also induce reduction in lipocortin, with subsequent decreased production of leukotrienes and prostaglandins. The net result is a decrease in interleukin (IL)-1, IL-2, IL-6, tumor necrosis factor-α, interferon-γ, chemokines, prostaglandins, major histocompatibility class II, and proteases (Lindenfeld et al. 2004; Ramamoorthy and Cidlowski 2016).

Corticosteroids: Pharmacodynamics

Maintenance therapy for solid organ transplant typically consists of prednisone or prednisolone. Both forms are rapidly absorbed following oral administration with peak plasma concentrations occurring within 1–3 h of dosing in most transplant recipients. Prednisone is a prodrug, while prednisolone is the active drug form. At a molecular level, only free prednisolone crosses the cell membrane to gain entry into the cytoplasm. Following absorption, prednisolone and prednisone undergo interconversion via a reversible metabolism and exist in both active and inactive forms. Both drugs are cleared primarily by hepatic metabolism, and half-life is typically 2–4 h in stable transplant recipients, plasma concentrations do not directly determine duration of response, and greater than threefold variability in dose-adjusted exposure to total prednisolone has been observed in transplant recipients (Bergmann et al. 2012). Increased drug concentrations have been observed with decreasing liver function, but no study to date has examined the impact of hepatic dysfunction on the pharmacokinetics of corticosteroids in solid organ transplant populations (Renner et al. 1986). Both drugs are substrates of CYP3A4 and P-glycoprotein and thus may theoretically interact with CNI or PSI metabolism (Lam et al. 2008). Closer monitoring of immunosuppressive agents during steroid withdrawal is warranted given these interactions.

Corticosteroids: Adverse Effects

Metabolic complications are common in transplant patients and are exacerbated by chronic glucocorticoid use, perhaps synergistically with other components of their immunosuppression regimens. Corticosteroids can independently cause hyperlipidemia, hyperglycemia, and hypertension (Wang 2005). These side effects are related to dose and duration of therapy. Steroid weaning and withdrawal are associated with improvements in several disease markers of these conditions; however long-term comorbid prevalence may persist despite withdrawal (Pascual et al. 2010). Furthermore, limited data suggest that prolonged steroid maintenance therapy may be associated with CAV, through nonimmune-mediated mechanisms such as hyperglycemia, hypertension, and hyperlipidemia (Caforio et al. 2004; Ratkovec et al. 1990). Complications such as cataracts and osteoporosis are important considerations in older recipients. The incidence of cataracts was found to be as high as 55% in renal transplant patients (Matsunami et al. 1994). Bone mineral density is inversely associated with cumulative steroid dose in solid organ transplant (Patel et al. 2001). Poor wound healing and skin fragility may be seen (Wang et al. 2013). Dyspepsia, gastritis, and peptic ulcer disease are associated with steroid use (Conn and Poynard 1984). Acne, easy bruising, and truncal obesity are all commonly encountered cosmetic side effects. The risk for infections, particularly pneumocystis jiroveci pneumonia (PJP), is elevated in solid organ transplant patients receiving maintenance steroids (Yale and Limper 1996). ISHLT guidelines recommend that corticosteroid weaning should be

attempted if significant side effects are encountered and there are no recent rejection episodes (Costanzo et al. 2010).

Steroid Minimization Strategies

Given the numerous steroid associated side effects and the realization that rejection is responsible for a minority of deaths, particularly at later intervals posttransplant, attempts at steroid minimization and weaning have been made. Steroid withdrawal protocols can be defined as early (within the first 6 months after transplant) or late (between 6 and 12 months).

Early Steroid Withdrawal

The available data concerning early corticosteroid withdrawal in cardiac patients are largely restricted to observational studies. The largest review to date demonstrated that 30% of patients were able to be successfully weaned from steroids within 2 months of transplantation. These patients had received induction therapy with murine anti-human mature T cells (OKT3) along with maintenance cyclosporine plus azathioprine. Mortality, both short term and long term, was lower in the early withdrawal group (1.7% per year vs. 4.7% per year, $p < 0.0001$). Failed early steroid withdrawal was identified as an independent predictor of mortality. Furthermore, there was less frequent acute allograft rejection at greater than 1 year after transplantation in patients successfully withdrawn from steroid therapy early (0.07 pt-yr vs. 0.15 pt-yr, $p = 0.002$). The authors concluded that successful early corticosteroid withdrawal identifies a subgroup of "immunologically privileged" patients with a low risk for long-term mortality or late rejection (Taylor et al. 1996). A retrospective single-center study compared an initial era in which early corticosteroid withdrawal was not attempted, to a later era in which a protocol of early steroid taper with discontinuation by 6 months was adopted. All patients were treated with cyclosporine and azathioprine; none underwent induction therapy. Successful steroid withdrawal was possible in 57% of patients at 6 months after transplantation. With early withdrawal there was a twofold increase in acute rejection without worse survival. In fact, there was a trend toward improved survival and decreased frequency of infection in the group weaned from steroids within 6 months (Rosenbaum et al. 2006).

A more recent prospective, randomized study examining tacrolimus monotherapy versus combination therapy with MMF documented successful corticosteroid weaning in all patients by 8–9 weeks. One patient in the study received induction therapy. The addition of MMF to tacrolimus failed to provide an advantage over single-agent immunosuppression in terms of rejection, allograft vasculopathy, or 3-year survival (Baran et al. 2011). This study was designed to evaluate monotherapy with tacrolimus versus combination therapy with MMF; the ability to wean steroids successfully at approximately 2 months posttransplant in all patients is intriguing and requires further study.

Late Steroid Withdrawal

The risk of acute rejection is greatest during the initial months following transplant (Graham et al. 1974; Kubo et al. 1995), and late withdrawal occurs after the highest risk period for rejection has passed. The largest experience of late steroid withdrawal was reported by the Collaborative Transplant Study investigators, representing 13 centers' experiences with a median follow-up of 6.3 years (Opelz et al. 2005). Patients with highly reactive (>80%) preformed lymphocytotoxic antibodies, rapid rejection, and previous severe rejection were excluded. Steroids were reduced slowly in a stepwise fashion, leading to steroid-free maintenance after 6 months. Information regarding induction therapy was not reported. Withdrawal was delayed in the case of graft deterioration or rejection. Prospective data on steroid withdrawal were available for 450 heart patients and compared to 420 matched control heart transplant patients. Steroid withdrawal was associated with a significant improvement in graft survival. Rates of acute rejection requiring treatment were similar between groups at 5 years follow-up. The development of osteoporosis and cataracts was

lower in patients taken off steroids during the first posttransplant year (Opelz et al. 2005). A retrospective single-center study of cardiac transplants taking place over a 7-year period compared outcomes of an initial era void of a corticosteroid withdrawal protocol to a later one utilizing a weaning protocol with the goal of steroid discontinuation by month 6–7. Patients in the later era were eligible for steroid taper if they were clinically stable and free of significant rejection. All patients were treated with combination CNI and antimetabolite therapy; none underwent induction therapy. Patients in the latter group with protocolized steroid weaning were more likely to be on a tacrolimus and MMF-based regimen. The mean duration of steroid use utilizing the weaning protocol was just over a year versus 2.8 years in the no weaning protocol group. The incidence of any ISHLT grade $\geq$3A rejection was similar between groups at both 1 and 2 years posttransplant. Furthermore, the overall survival was no different after the weaning protocol was introduced (Teuteberg et al. 2008).

Steroid-Free Regimens

Corticosteroid-free regimens utilizing cyclosporine plus azathioprine have resulted in excessive rates of rejection and need for maintenance corticosteroids. The largest, prospective steroid-free trial to date compared cyclosporine plus azathioprine with or without corticosteroids. All study patients underwent induction therapy with antithymocyte globulin (ATG) for the initial 7 postoperative days. Rejection in the first 3 months was significantly higher in the steroid-free group but did not differ beyond 3 months. Patients receiving the steroid-free regimen who required four treatments for rejection were converted to maintenance steroids, which occurred in approximately one-half of the cohort. Survival at 5 years was similar between the two groups in an as-treated analysis. Patients receiving steroid therapy had higher serum cholesterol level at 3 years and required more antihypertensive agents (Keogh et al. 1992). Livi et al. subsequently reported their observational experience of a steroid-free maintenance regimen following induction with OKT3 or ATG and maintenance cyclosporine plus azathioprine. Almost one-quarter of patients required the addition of oral prednisone to a maintenance regimen for persistent or repeated rejection. Among the 112 operative survivors, there were 5 early deaths in the first 3 postoperative months, 4 of which died of acute rejection refractory to intense immunosuppressive therapy. Actuarial survival was 95% and 94% at 12 and 48 months, respectively (Livi et al. 1993).

A small single-center, prospective, randomized trial was conducted utilizing a contemporary maintenance regimen including tacrolimus plus MMF. ATG induction without subsequent corticosteroids was compared to a regimen free of induction with subsequent corticosteroids. Pulse steroid therapy was used for the treatment of acute cellular rejection in either group. At 1 year there was no significant difference in the mean incidence of acute cellular rejection ($\geq$3A) episodes or mortality between groups. The steroid-free cohort had significant improvement in muscle strength and less bone loss and a trend toward improved glycemic control (Yamani et al. 2008). In totality, these data suggest that a corticosteroid-free strategy with "bailout" maintenance steroids is feasible and may not increase midterm mortality. However, acute rejection may occur more frequently. It is postulated that induction therapy with contemporary regimens including tacrolimus and MMF may attenuate early severe rejection and allow the use of corticosteroid-free regimens; however further study is needed.

The most recent ISHLT guidelines recommend corticosteroid avoidance, early corticosteroid weaning, or very low dose maintenance corticosteroid therapy as acceptable therapeutic approaches. Corticosteroid withdrawal can be successfully achieved 3–6 months after heart transplant in many low-risk patients (those with- out circulating anti-HLA antibodies, non-multiparous women, those without a history of rejection, and older recipients). Corticosteroid weaning should be attempted if there are significant steroid side effects and no recent rejection episodes (Costanzo et al. 2010).

Special Considerations

CNI Nephrotoxicity

Renal dysfunction following transplantation is highly prevalent, and recent ISHLT registry data report chronic kidney disease in over half of patients at 5 years and 68% at 10 years. Furthermore, advanced kidney disease associated with serum creatinine >2.5 mg/dL or the need for dialysis or renal transplant was present in nearly one-fifth of patients by posttransplant year 5 (see Table 1) (Lund et al. 2016). Although posttransplant renal disease may be of multifactorial origin, chronic CNI exposure can play a large contributory role (Flechner et al. 2008). Data examining cardiac transplant in the pre-cyclosporine era compared to the cyclosporine era demonstrates a marked reduction in GFR with cyclosporine use (Myers and Newton 1991). Although few clinical studies (Israni et al. 2016; Kobashigawa et al. 2006a) and mechanistic data (Klein et al. 2002; Jain et al. 2000) suggest that tacrolimus may be associated with less nephrotoxicity, the totality of data to date in cardiac transplant suggest a similar incidence of nephrotoxicity between CNIs (Ojo et al. 2003; Penninga et al. 2010; Ye et al. 2009).

CNI nephrotoxicity can be divided in acute injury and chronic disease. Acute injury may be reversible and is mediated by vasoconstriction of the afferent and efferent renal arterioles, resulting in a decrease in renal blood flow and GFR (Barros et al. 1987; Laskow et al. 1990). Renal blood flow and GFR acutely fall 2–4 h post cyclosporine dose, correlating with maximal blood drug levels, and return to baseline as the cyclosporine concentration approaches its trough level (Ruggenenti et al. 1993). Acute arteriolopathy results from an increase in vasoconstricting factors including endothelin (Nakahama 1990) and activation of the renin-angiotensin-aldosterone system (RAAS) (Kurtz et al. 1988), as well as a reduction of vasodilator factors such as prostacyclin, prostaglandin E2, and nitric oxide (NO) (Hortelano et al. 2000; Olyaei et al. 2001). CNI-induced adrenergic stimulation can also cause increased renal vascular resistance and secondary decreases in GFR (Zhang and Victor 2000). Rarely, thrombotic microangiopathy has been described with both cyclosporine (Roberts et al. 1998) and tacrolimus (Trimarchi et al. 1999), as well as the PSIs (Barone et al. 2003).

Chronic nephrotoxicity is one of the major limiting factors of long-term CNI-based therapy. Histologic evidence of nephrotoxicity can be found in the large vasculature (arteriolar hyalinosis), tubulo-interstitium (tubular atrophy and striped interstitial fibrosis), and at the glomerular level (thickening/fibrosis of Bowman's capsule and focal segmental or globular glomerular sclerosis). Chronic vascular change characterized by replacement of media smooth muscle cells with nodular hyaline deposits in the afferent arteriole (arteriolar hyalinosis) is considered one of the hallmarks of CNI nephrotoxicity.

Recommendations for management of CNI nephrotoxicity are difficult as available literature is scant and conflicting. Although local drug exposure may impact the occurrence of renal dysfunction (Podder et al. 2001), several studies in cardiac transplant patients have failed to demonstrate a dose-dependent or serum drug level-dependent relationship between cyclosporine and nephrotoxicity (Zietse et al. 1994; Lindelow et al. 2000). Extended-release formulations of tacrolimus allow a reduced Cmax peak and have been associated with favorable dose-related renal blood flow compared to immediate release formulations (Zaltzman et al. 2014); however long-term clinical implications of this strategy in heart transplant recipients is unknown. The combination of ketoconazole and CNI has been utilized to allow for a relatively low CNI dose and to reduce the generation of nephrotoxic metabolites. In renal transplant patients, this strategy was found to be beneficial when systemic levels of CNI were maintained at similar levels between study groups (El-Dahshan et al. 2006; el-Agroudy et al. 2004), but no renal benefits were demonstrated in heart transplant patients (Keogh et al. 1995). Dihydropyridine calcium channel blockade mitigates acute drops in renal blood flow and GFR (Ruggenenti et al. 1993) and preserves renal function during

long-term cyclosporine use (Leenen et al. 2007). Verapamil has also been shown to have favorable effects on renal function and additionally allows for a relatively lower CNI dose (Chan et al. 1997). However, at least one contemporary study failed to demonstrate a protective effect of CCB in prevention of CNI nephrotoxicity (Lindelow et al. 2000). RAAS inhibition has been shown to reduce cyclosporine-induced interstitial fibrosis in animal models and reduce expression of TGF-β (Shihab et al. 1997). Although ACE inhibition has been proven safe and effective as antihypertensive agents in heart transplant recipients, little clinical literature exists supporting concomitant improvements in CNI nephropathy (Brozena et al. 1996).

A strategy of CNI minimization may prove beneficial in avoiding nephropathy. Utilization of MMF instead of azathioprine in contemporary regimens allows for safe reductions in CNI exposure, which have translated into improved renal outcomes in several series (Angermann et al. 2004; Baryalei et al. 2003; Tedoriya et al. 2002). The safety and efficacy of further minimization of CNI exposure in contemporary MMF-based regimens are less well studied.

The introduction of everolimus with concomitant CNI dose reduction was evaluated in heart and lung transplant patients >1 year posttransplant with a GFR between 20 and 90 ml/min/1.73 m^2. CNI dose reduction (trough level 50 ± 20% lower than previous target; cyclosporine trough <75 ng/ml or tacrolimus trough <4 ng/ml) plus everolimus (trough 3–6 ng/ml) was compared to a standard dose CNI regimen. The everolimus plus-reduced dose CNI group was associated with modest but statistically significant improvements in GFR (mean improvements of 5–7 ml/min/1.73 m^2 vs. reductions in mean GFR of approximately 1 ml/min/1.73 m^2). These benefits were mainly driven by patients with moderate to severe renal dysfunction (with baseline GFR <60 ml/min/1.73 m^2) and were limited to patients undergoing conversion less than 5 years after transplant, indicating a limited window of opportunity (Arora et al. 2012). Biopsy-proven acute rejection requiring treatment was no different between groups (Gullestad et al. 2010). A substitution strategy of complete CNI withdrawal and introduction of PSI has been studied. CNI withdrawal following introduction with sirolimus (trough 10–14 mg/ml if first year post-OHT and 8–12 ng/ml if 2nd year post-OHT) combined with MMF in patients with severe, progressive renal failure (defined as serum creatinine >1.9 mg/dl for >3 months and a creatinine increase over 3 months of >30%) was associated with a significant improvement of renal function, compared to a historical control CNI-based cohort who continued to have renal function deterioration. Mean timing of conversion was 3.9 years posttransplant. Rejection and survival outcomes were unchanged between groups (Groetzner et al. 2004). Similarly, Kushwaha et al. demonstrated significant improvements of renal function without compromising cardiac function or rejection in patients converted from CNI-based regimens to sirolimus at least 1 year posttransplant (Kushwaha et al. 2005; Raichlin et al. 2007a). PSI substitution of the CNI may have the greatest potential to augment renal function within the first year posttransplant (Gude et al. 2010). However, this period is also known to be the highest risk period for significant rejection (Kubo et al. 1995). A large, multicenter randomized trial of sirolimus initiation and CNI withdrawal in patients with renal insufficiency with a mean of 4.1 years posttransplantation was associated with a numerically, strikingly higher rate (sevenfold) of late rejection requiring treatment (Zuckermann et al. 2012). Per current ISHLT guidelines, a PSI may be substituted for a CNI later than 6 months after transplant to reduce nephrotoxicity; however CNI-free regimens should be used with caution in recipients with persistent renal insufficiency despite CNI reduction due to the potential for precipitating rejection. Induction therapy with polyclonal antibody preparations may be beneficial in patients at high risk of renal dysfunction when used with the intent to delay or avoid the use of a CNI (Costanzo et al. 2010).

Cardiac Allograft Vasculopathy

Cardiac allograft vasculopathy (CAV) is a major limitation to long-term graft function and accounts for up to one in eight deaths beyond 1 year posttransplant (Lund et al. 2015). The prevalence of CAV is 7.8% at 1 year, almost a third (29%) at 5 years, and almost half (48%) of recipients at 10 years posttransplant (Lund et al. 2016). Accelerated CAV in the first year following transplantation is a marker of particularly poor outcomes (Kobashigawa et al. 2005).

CAV is characterized by an accelerated fibroproliferative process primarily affecting the allograft vascular intima. Histopathologic changes include smooth muscle proliferation, accumulation of inflammatory cells, and lipid deposition leading to circumferential intimal thickening. Early intima proliferative thickening is accommodated by expansion of the external elastic membrane, allowing for relative preservation of luminal area, followed by a constrictive remodeling phase, leading to luminal narrowing (Tsutsui et al. 2001). Conceptually, the ability of successful therapeutic intervention on clinical outcomes may depend upon when in this biphasic process the plaque lies at time of drug initiation (Topilsky et al. 2012; Masetti et al. 2013).

Pathogenesis and progression are impacted by both immunologic and non-immunologic factors. Non-immunologic risk factors include typical atherosclerotic metabolic risk factors (older age, male sex, obesity, diabetes, hyperlipidemia) (Escobar et al. 1994; Costanzo et al. 1998), ischemia-reperfusion injury, organ preservation, and brain death (Johnson 1992). Immune-mediated mechanisms include T lymphocyte activation and proliferation leading to upregulation of endothelial adhesion molecules and recruitment of inflammatory cells causing smooth muscle cell migration to the intima, proliferation, and extracellular matrix deposition. Humoral immunity is at least partially implicated in pathogenesis as the presence of HLA-directed antibodies after heart transplantation are associated with CAV development (Tambur et al. 2005). Cytomegalovirus (CMV) infection is associated with the development of CAV, perhaps through both nonimmune-mediated vascular inflammation and immune-mediated endothelial injury (Lunardi et al. 2005).

Regimens utilizing MMF and PSIs have demonstrated benefits for CAV reduction. MMF and mTOR inhibitors inhibit B-cell proliferation and immunoglobulin production and induce B-cell apoptosis (Heidt et al. 2008), properties that ultimately influence CAV pathogenesis. In addition to immunomodulatory effects, PSIs are also associated with attenuation of vascular smooth muscle proliferation and neointimal proliferation (Marx et al. 1995; Aono et al. 2016) Furthermore PSIs are associated with less incidence of CMV (Lehmkuhl et al. 2009), which may play a role in CAV development.

Current guidelines recommend that contemporary immunosuppressive regimens include MMF, everolimus, or sirolimus as tolerated, because therapies including these drugs have been shown to reduce onset and progression of CAV as assessed by intravascular ultrasound IVUS (Costanzo et al. 2010). Antimetabolite therapy with MMF, compared to azathioprine, has been shown to result in an increased mean luminal area on IVUS from baseline to 12 months after transplant and fewer patients with intimal thickening greater than or equal to 0.3 mm at 1 year (Kobashigawa et al. 1998, b). MMF has also demonstrated long-term advantages over azathioprine for the development of angiographically apparent CAV at 5 years (Kaczmarek et al. 2006). Sirolimus is superior to azathioprine for reduction of a number of CAV IVUS parameters including intima-plus-media thickness and area, as well as plaque burden and volume (Keogh et al. 2004). Everolimus has demonstrated incremental benefits over MMF with regard to maximal intimal thickness at 1 year posttransplant and halved incident development of IVUS detected CAV (Kobashigawa et al. 2013). Substitution of CNI with sirolimus may attenuate long-term CAV progression and improve survival owing to favorable coronary remodeling. However, these data also demonstrate increased rejection associated with sirolimus use within 2 years of transplant

(Topilsky et al. 2012). Also at least one major trial of recipients with renal insufficiency has shown increased rates of late rejection, in patients converted from a CNI to everolimus-based regimen (Zuckermann et al. 2012). Further, PSI-associated CAV benefits may be greater in those who undergo early PSI introduction prior to development of significant CAV and less beneficial for late introduction or in the treatment of established CAV (Topilsky et al. 2012; Masetti et al. 2013; Raichlin et al. 2007b; Arora et al. 2011; Matsuo et al. 2013); risk of acute rejection is greatest early after transplant (Graham et al. 1974; Kubo et al. 1995). Thus, an individualized patient approach balancing risk of CAV, CKD, and rejection should be taken into account when utilizing PSI therapy under these circumstances.

Malignancy

Malignancy is the second leading cause of death in cardiac transplant patients after the first postoperative year and the number one cause of death by 5 years (Lund et al. 2016). Approximately one-third of patients will develop some form of malignancy by 10 years following cardiac transplantation (Doesch et al. 2010). Furthermore, cancer death rates in solid organ transplant recipients are increased compared with that expected in the general population (Acuna et al. 2016).

Among heart transplant recipients, the incidence and specific malignancy type may vary depending on the studied geographic location and length of follow-up. Consistently, skin cancers are by far the most common posttransplant malignancies. Lung cancer is the next most common malignancy (Yoosabai et al. 2015; Yagdi et al. 2009) found in over 3% of heart transplant recipients. Other solid organ cancers including colorectal and prostate are also prevalent, and both may be detected with routine screening. Hematologic malignancies may represent up to one-quarter of post heart transplant malignancies (Yagdi et al. 2009), affecting approximately 2% of heart transplant recipients (Sampaio et al. 2012). The incidence of posttransplant lymphoproliferative disease (PTLD) is particularly high during the first year post-transplant (Opelz and Henderson 1993), likely due to heavy immunosuppression during this period.

Risk factors associated with malignancy after cardiac transplant include older age at transplant, male gender, white race, ischemic cardiomyopathy, and therapy with azathioprine or a CNI for more than 1 year (Doesch et al. 2010; Yoosabai et al. 2015). The risk of PTLD is higher in EBV negative recipients, and the highest risk exists when an EBV negative patient receives an EBV positive donor organ (McDonald et al. 2008). Registry data suggests that statin use is associated with improved cancer-free and overall survival after cardiac transplantation (Fröhlich et al. 2012).

Immunosuppression is implicated in oncogenesis, both through impaired immunosurveillance and direct oncogenic activity. CNIs may promote tumorigenesis and tumor growth through a number of potential mechanisms including inhibition of DNA repair mechanisms (Herman et al. 2001), increased expression of TGF-β1 (Maluccio et al. 2003), and promotion of tumor angiogenesis (Guba et al. 2002). Conversely, PSIs may inhibit tumor genesis via inhibition of metastatic tumor growth and angiogenesis (Guba et al. 2002). Furthermore, several tumor genesis pathways are mTOR dependent; thus blockade with a PSI would seem advantageous (de Fijter 2017).

Both cyclosporine and tacrolimus are associated with increased risk of malignancy (Doesch et al. 2010); no clear advantage between agents regarding cancer risk has been appreciated in the cardiac transplant literature (Penninga et al. 2010; Ye et al. 2009). Antimetabolite therapy with MMF, compared to azathioprine, is associated with a significantly lower risk of developing malignancy (O'Neill et al. 2006). Several retrospective series have demonstrated a lower risk for malignancy associated with PSI-based cardiac transplant regimens (Doesch et al. 2010; Wang et al. 2016). Also data exists to support a lower incidence of posttransplantation malignancy associated with everolimus use instead of MMF in triple drug combination maintenance regimens otherwise including a CNI and tapered dose

steroids following induction therapy. Median survival in that series was approximately 2 years following malignancy diagnosis and did not differ between everolimus and MMF (Wang et al. 2016). Conversion to a PSI-based, CNI-free regimen has been associated with lower malignancy rates in renal transplant (Campistol et al. 2006; Schena et al. 2009). Renal transplant data also suggests a reduction in cutaneous squamous cell carcinoma with preferential PSIs use for secondary prevention of recurrent skin cancers (Dantal et al. 2018).

The mainstay of immunosuppression-related cancer therapy has been reduction in immunosuppression, as safely possible, combined with surgical resection and cancer-specific radiotherapy and chemotherapy. However, little evidence supports a reduction in immunosuppression in patients with solid tumors unrelated to the lymphoid system. Retrospective data showed a trend toward improved survival in cardiac transplant patients switched to a CNI-free protocol after diagnosis with solid organ malignancy (Doesch et al. 2010). Treatment of PTLD includes reduction in immunosuppression, as well as rituximab, given combined or in sequence with combination chemotherapy (Choquet et al. 2006; Evens et al. 2010). Surgery or radiation may be considered in select cases. Factors shown to predict poor outcomes in PTLD include age >55 years, serum creatinine level >133 μmol/L, elevated LDH, disseminated lymphoma, brain localization, invasion of serous membranes, monomorphic PTLD, and T-cell PTLD (Dierickx et al. 2013).

Special Populations

Pregnancy

Successful pregnancy, without excess congenital defects, and a low incidence of graft loss are possible in transplant recipients. Data from the National Transplantation Pregnancy Registry (NTPR) shows that approximately two-thirds of pregnancies in cardiac transplant recipients resulted in live birth. Of live births, birth defects were present in 7.5% of newborns. The majority of pregnant heart recipients experienced hypertension, and 22% experienced preeclampsia. Rejection during pregnancy is not uncommon at 10%. Postpartum rejection occurred in 7.5%, but graft loss within 2 years of delivery was only 2.2% (National Transplantation n.d.).

Recipients should be encouraged to seek counseling regarding pregnancy risks before attempting to become pregnant. Current ISHLT guidelines recommend an individualized management plan, formulated by a multidisciplinary team involving experienced specialists that takes into account status of the mother and her transplanted heart, including the risk of acute rejection and infection. Typically, it is not recommended that pregnancy occurs sooner than 1 year after transplant and avoidance of pregnancy is recommended for patients with CAV (Costanzo et al. 2010).

CNIs and corticosteroids may be continued in a pregnant HT recipient, but MMF should be discontinued (Costanzo et al. 2010). Blood levels of CNI should be monitored closely during pregnancy to minimize large fluctuations in levels due to changes in plasma and interstitial volume and hepatic and renal blood flow. The incidence of malformations in offspring exposed to CNI is approximately 4–5% (Kainz et al. 2000; Bar Oz et al. 2001). There has not been a specific pattern or increase in the incidence of malformations in recipient offspring in CNIs as a whole or between tacrolimus and cyclosporine. Neonatal hyperkalemia and renal impairment have been reported with tacrolimus use (Kainz et al. 2000). MMF exposure any time in the first trimester is associated with significantly higher risks of miscarriage and phenotypic birth defects (Moritz et al. 2017). In 2007, the FDA pregnancy category for MMF was changed from category C to D. Product labeling recommends that MMF be discontinued at least 6 weeks prior to conception. PSI exposure during pregnancy does not appear to be associated with an increased risk or a pattern of birth defects, although the available data is restricted to case reports (Veroux et al. 2011; Framarino dei Malatesta et al. 2011; Chu et al. 2008).

Breastfeeding for transplant recipient mothers remains an area of uncertainty. The NTPR

has received data from numerous transplant recipients who breastfed while taking immunosuppression and have documented reassuring findings. In 2014, the NTPR published a review of breastfeeding after transplantation and concluded that it appears to be safe to breastfeed while taking normal maintenance doses of prednisone, azathioprine, cyclosporine, and tacrolimus. Due to a lack of data, breastfeeding should continue to be avoided while taking MMF or PSIs (Constantinescu et al. 2014). In 2015 approximately two-thirds of childbearing transplant recipients breastfed.

Elderly

For many years, advanced age was considered an absolute contraindication to cardiac transplantation; however given an aging population and improved survival, age cutoffs have been relaxed in recent years. Current listing criteria recommend that adults 70 and under should be considered for heart transplant and that carefully selected recipients >70 years of age may be feasible (Mehra et al. 2016; Daneshvar et al. 2011). Approximately one-third of North American cardiac transplants from 2006 to 2012 were in recipients 60 years old or greater, and 2% were in patients 70 years old or greater (Lund et al. 2013).

The overall incidence of rejection is progressively less common with increasing age (Lund et al. 2013). Also the relative antirejection benefit associated with tacrolimus over cyclosporine appears somewhat attenuated in the elderly (Lund et al. 2013). ISHLT registry data demonstrate that with increasing age, death from graft failure, CAV, and acute rejection become dramatically less common. Instead risk of death from non-lymphoma malignancy, renal failure, organ failure, and infection increases (Lund et al. 2013). Moreover, metabolic diseases including hypertension, hyperlipidemia, and diabetes are more common in the elderly population. Despite possible age-related immunologic and pharmacologic changes, immunosuppression protocols are typically similar regardless of age. Choices of immunosuppressive regimen in the elderly population should be influenced by our knowledge of differential rejection risk, cause of death, and comorbid conditions.

Conclusion

Improved outcomes in cardiac transplant outcomes can be largely attributed to advances in immunosuppressive strategies. When formulating modern immunosuppressive regimens, one must recognize the changing landscape of outcomes including decreased mortality risk related to rejection and increased risk related to infection, malignancy, renal insufficiency, CAV, and metabolic disease. These conditions are impacted significantly by specific agents, and a patient-tailored, dynamic immunosuppressive strategy may prove advantageous.

Cross-References

- ▶ Complications of Immunosuppression
- ▶ Contemporary Survival in Heart Transplantation
- ▶ Induction and Maintenance Agents
- ▶ Malignancy After Transplant

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Infection Prophylaxis

18

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Abstract

Infectious complications remain a major cause of morbidity and mortality following heart transplantation. In addition to more targeted immunosuppression and effective treatment strategies, selective antimicrobial prophylaxis has led to the decline in overall incidence and mortality of infections in heart transplant recipients. Use of such prophylaxis remains a cornerstone to infection prevention in the post-transplant period.

Keywords

Heart transplant · Infectious complications · Screening · Prophylaxis · Outcomes

Introduction

Infection remains one of the most important causes for both early and late mortality following heart transplantation (Lund et al. 2015). However, since the first heart transplants were performed, the overall incidence of infectious complications has decreased substantially (Montoya et al. 2001; Haddad et al. 2010). This decrease is in part due to newer immunosuppressive strategies, improved diagnostics, and targeted antimicrobial chemoprophylaxis. Infectious outcomes following heart transplantation follow the traditional timeline for solid organ transplantation described by Fishman and Rubin (Fishman 2007). Bacterial and viral infections still predominate though risk for opportunistic pathogens persists in the peak periods of immunosuppression. And while infection risk decreases beyond the first year of transplant, the risk never normalizes for most individuals and can remain particularly high for a small percentage. Special considerations for the heart transplant recipient include sternal wound infections, mediastinitis, ventricular assist device (VAD)-specific infections, and cardiotropic parasitic infections. The balance between the need for immunosuppression to prevent allograft rejection while minimizing infections and permitting a meaningful life in a world of potential pathogens continues to challenge the practitioner and recipient. An overview of infections important to heart transplant recipients and approaches to their prevention will be discussed in this chapter.

Epidemiology and Risk of Infection Post-transplantation

Infections following heart transplantation in the current era are most commonly bacterial (52%), followed by viral (35%), less commonly fungal (13%), and rarely parasitic (<0.5%) (Haddad et al. 2010). Figure 1 highlights the changes in incident infections since the early 1980s, an era that predated antimicrobial prophylaxis and was characterized by use of high doses of steroids and lymphocyte-depleting agents (Hofflin et al. 1987). Incident infections have decreased substantially from 3.35 infections/person to 0.6 infections/person, ushered by calcineurin inhibition, steroid-sparing regimens, alternative induction agents, reduced doses of mycophenolate mofetil (MMF), and effective antimicrobial prophylaxis (Haddad et al. 2010). Overall, total infections have declined, gram-positive organisms account for a larger percentage of serious bacterial infections, cytomegalovirus (CMV) disease has decreased, opportunistic infections have decreased, and pneumocystis is now extremely rare. Risk for infection-related mortality is highest in the first year after transplant but also increases with advancing recipient age (Lund et al. 2015; Wever-Pinzon et al. 2017).

The risk for specific types of infection is characteristically dependent on the time from transplantation. Figure 2 highlights the risk for infection after heart transplantation and takes

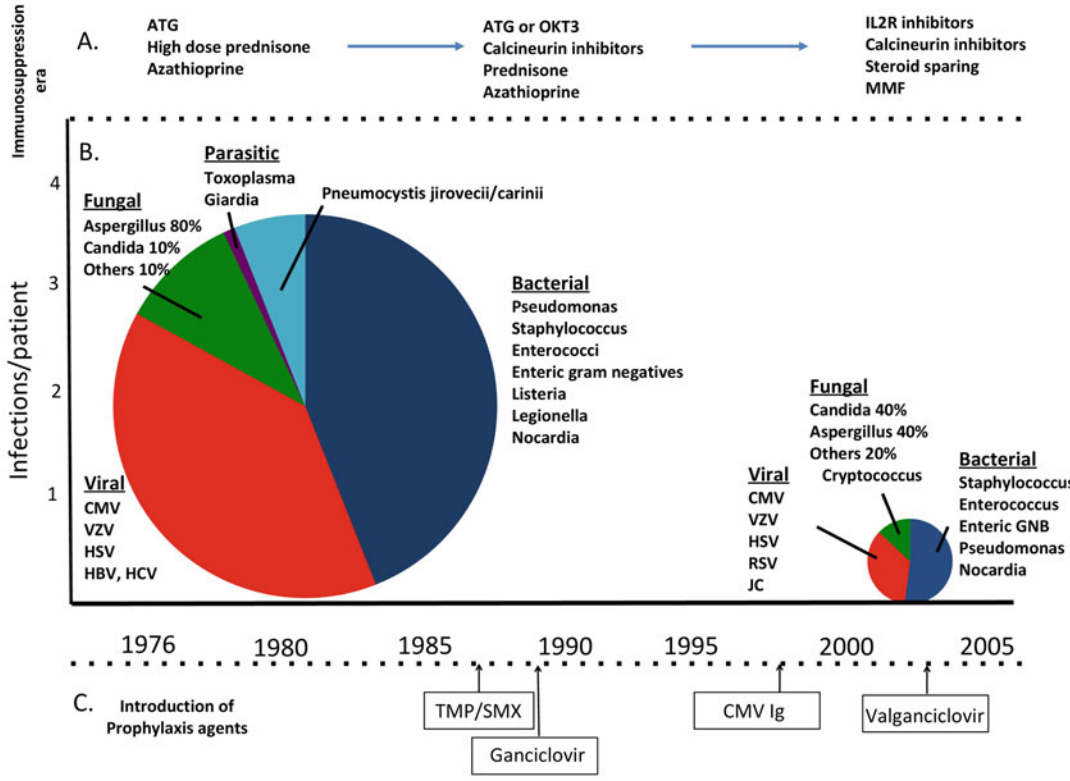

Fig. 1 Changes in infectious outcomes over different eras of heart transplantation. (**a**) Immunosuppressive combinations by era. (**b**) Height of pies indicates infection rate during the early time period and the more current time period. Pie wedges indicate distribution of infection class for indicated time periods. (**c**) Indicates timing of introduction of prophylactic agents to post-transplant care. (Adapted from Haddad et al. 2010; Hofflin et al. 1987)

into account both the expected degree of immunosuppression and likely epidemiologic exposures. There are three general time frames to consider – early (0–1 month), intermediate (1–6 months), and late (>6 months) post-transplantation periods (Fishman 2007).

Factors that determine the net state of immunosuppression include dose, duration, type of immunosuppressant, preexisting immunodeficiency, progressive immune senescence with age, the presence of infections with immunomodulatory viruses (CMV and HIV in particular), and metabolic effects associated with the transplantation procedure itself.

Several non-specific laboratory markers of immunity are available to the clinician and may indicate risk for infection. However, data on how such markers should impact clinical decisions are lacking. Total lymphocyte counts can be expected to be low with lymphocyte-depleting agents and may recover only over weeks to months. High tacrolimus levels will decrease T cell function and will temporally increase the risk for latent pathogen reactivation or de novo opportunistic infections. T cell function assays (ImmuKnow: Viracor-IBT Laboratories, Lee's Summit, MO) measure T cell response to mitogen stimulus and may in some circumstances allow for appropriate adjustment of immunosuppression (Kobashigawa et al. 2010). During periods of low T cell function, effective antimicrobial prophylaxis is of particular importance (usually in the first 3–6 months following transplant or after treatment of cellular rejection). Absolute neutrophil counts (usually <500 cells/ul) may be a marker of excess MMF or other underlying immunodeficiency and signal enhanced risk for bacterial and invasive fungal infections. Immunoglobulin concentrations (IgG <600 mg/dl) and some complement factors indicate a risk for bacterial or viral pathogens (Sarmiento et al. 2016). Despite some initial

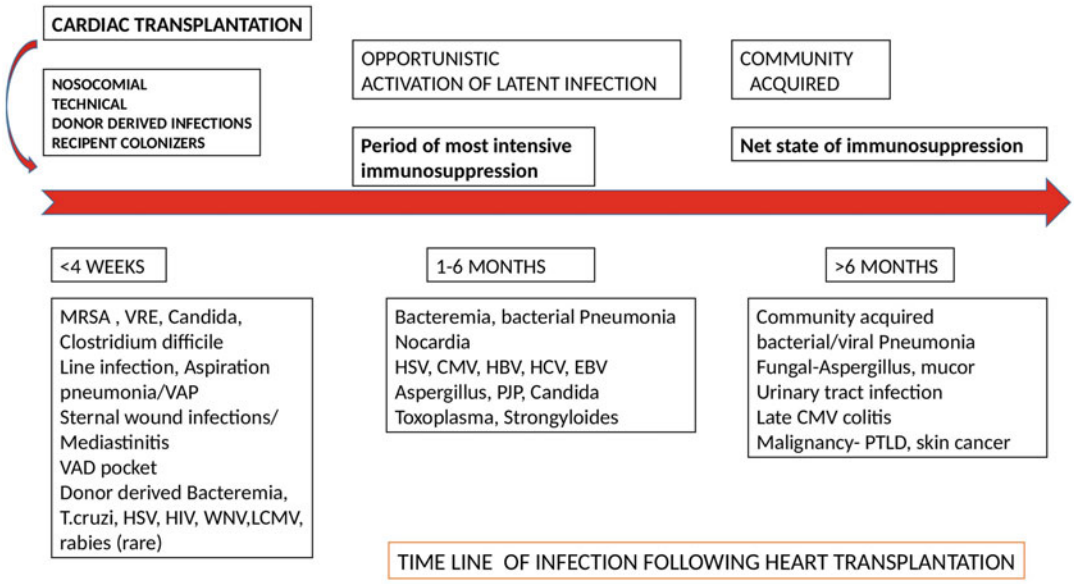

Fig. 2 Timeline of infection risk following heart transplantation. (Adapted from Fishman and Rubin 1998)

promising data, repletion with passive immunoglobulins in the solid organ transplant population does not consistently prevent subsequent infection and does not improve long-term survival (Carbone et al. 2012; Florescu et al. 2014).

In addition to the generally recognized risk of infection associated with commonly used immunosuppressants in heart transplantation, the association between some specific immunosuppressing agents and infection should be recognized by the transplant clinician. The following drugs have specific warnings related to infection risk. Rituximab, used for treatment of antibody-mediated rejection (AMR), has been associated with cases of progressive multifocal leukoencephalopathy (PML) due to JC virus infection (Carson et al. 2009). Devastating cases of this disease have been reported in the heart transplant setting following treatment with rituximab for AMR (Loyaga Rendon et al. 2013). Rituximab can also unmask latent hepatitis B infection. Before rituximab administration, all patients should have updated hepatitis B serologies, and those with evidence for past exposure to native virus (HBcAb+ in particular) should be referred to a specialist in hepatitis B management. Belatacept, currently used primarily in kidney transplant recipients, is associated with an increased risk for post-transplant lymphoproliferative disorder (PTLD) and is contraindicated for use in Epstein-Barr virus (EBV) seronegative patients (most donors are EBV seropositive). Eculizumab has also been used to treat AMR and targets complement protein C5, preventing formation of the membrane attack complex. It has been associated with life-threatening and fatal meningococcal infections. Meningococcal vaccination is recommended at least 2 weeks prior to the administration of the first dose of eculizumab. The benefits of any immunosuppressant must always be weighed against its potential risks.

Infection Prevention Strategies in the Pre-transplant Setting

The pre-transplant evaluation is designed to assess both usual and exceptional risks for post-transplant infection in the individual candidate. This evaluation includes a detailed history of infection, pertinent exposures, and existing immunity. It is also intended to reduce any identified risk during a time of relatively intact

Table 1 Pre-transplant evaluation

1. Recipient serologies	CMV IgG EBV VCA IgG HIV third- or fourth-generation serologic test Hepatitis B: surface antigen (HBsAg), core antibody (HBcAb), surface antibody (HBsAb) Hepatitis C RNA (with or without HCV IgG) Measles IgG Syphilis IgG (confirmatory testing with FTA Abs and RPR) TB screen (IGRA or PPD). Universal screening or targeted by risk group Toxoplasma IgG Varicella IgG If endemic exposure: *Trypanosoma cruzi* antibody *Coccidioides* antibodies (immunodiffusion and complement fixation) *Strongyloides* IgG
2. Immunizations	Refer to Table 2
3. Evaluation for the increased risk for tuberculosis	1. Persons who have immigrated from regions with rates of TB >25 cases/100,000 population 2. Close contact with person with active TB 3. High-risk groups: injection drug use, homeless persons, HIV infection 4. Person who work or reside with people who are at a high risk for TB in facilities such as hospitals, nursing homes, correctional centers, residential homes, homeless shelters
4. Assessment of geographic risk	Refer to Table 3
5. VAD-associated infections	Refer to Table 4
6. Education for risk reduction	1. Frequent hand washing 2. Avoid sick contacts 3. Strict dietary habits: avoid untreated water, undercooked food, unwashed produce, unpasteurized dairy products, soft cheeses 4. Avoid gardening and construction sites in the first year. If encountered or pursued at later times, gloves and masks may reduce the risk for soil, decaying vegetation, and dust-borne pathogens 5. Avoid animal excrement (particularly cat litter, bat and bird droppings) 6. Safe sexual practices 7. Ensure safe travel planning with directed vaccines and prophylaxis when required and travel medicine input when able 8. Mosquito and tick bite prevention

immunity. Table 1 outlines the standard evaluation for heart transplant candidates.

Serologies

Serologic status is used to risk stratify the recipient for common donor-acquired diseases including CMV, toxoplasmosis, or EBV-related PTLD or for reactivation of latent infection. Seropositivity is a marker of prior exposure and thus of effective cell-mediated control of these latent infections. Such patients are at a reduced risk for severe forms of acute infection with these pathogens should the donor organ be latently infected. Table 1 outlines serologic testing prior to transplant.

Vaccines

Serological results offer the opportunity to assess immunity to hepatitis B, measles, and varicella and to offer vaccination when needed. Other vaccines recommended in the adult guidelines are pneumococcal vaccine, tetanus with updated pertussis, shingles vaccine, and HPV vaccine for those <27 years of age. Table 2 includes the recommended vaccinations for adult candidates for heart transplantation (MMWR; Danziger-Isakov and Kumar 2013). Such

Table 2 Immunizations in heart transplant recipients

Vaccine	Pre-transplant	Post-transplant	Dosing schedule
Hepatitis A	Yes, seronegative	Yes, seronegative	0, 6 months
Hepatitis B 20 ug Engerix-B	Yes, seronegative	Yes, seronegative	Standard: 0, 1, 6 months Accelerated: 0, 1, 2 months
Hepatitis B 40 ug Recombivax HB	Yes, if HBsAb <10 mU/ml 1–2 months after standard series	Yes, based on the need, and if HBsAb <10 mU/ml 1–2 months after standard series	0, 1, and 6 months
Combined hepatitis A and B; Twinrix	Yes, seronegative both viruses	Yes, seronegative both viruses	Standard: 0, 1, 6 months Accelerated: 0, 7, 21 days
Pneumococcal (Pneumovax polysaccharide vaccine, PPSV; Prevnar conjugate vaccine, PCV)	Yes	Yes	PCV and then PPSV at >8 weeks or PPSV and then PCV at 1 year Second PPSV 5 years later
Influenza, inactivated High dose, age >65 Quadrivalent, others	Yes	Yes	Annually, fall or winter
Tetanus diphtheria acellular pertussis (Tdap)	Yes, if not yet given as adult	Yes, if not yet given as adult	Single dose and then Td every 10 years
Human papilloma virus (HPV)	Yes, age <27	Yes, age <27	3 doses – 0, 2, 6 months
Meningococcal vaccine (MCV4)	Yes (age <23, first-year college dorm)	Yes (age <23, first-year college dorm)	2 doses, 8 weeks apart
Varicella	Yes, if seronegative	No, contraindicated	2 doses, 4–8 weeks apart, if dose given within 4 weeks of HT offer, provide antiviral coverage at the time of HT
Zoster/shingles	Yes, age >50	No, contraindicated	1 dose, if given within 4 weeks of HT offer, provide antiviral coverage at the time of HT
Measles, mumps, rubella (MMR)	Yes, seronegative and <2 documented MMRs, and born after 1957	No, contraindicated	1–2 doses >4 weeks apart

vaccines should be encouraged prior to transplant to achieve the best immune response. Inactivated vaccines can be completed after transplantation and in general should not delay transplantation. An accelerated series of combined hepatitis A and B vaccine can be given to complete the series if transplantation is expected within 6 months. It should be acknowledged that patients with advanced heart failure (particularly Status 1 patients) may respond suboptimally to vaccination as demonstrated by reduced response to hepatitis B vaccine series (Foster et al. 2006). A booster vaccine or repeated vaccination series using standard or higher-dose HBV vaccine can be attempted, but additional series are not recommended. Live vaccines (MMR, Zostavax, Varivax) are generally not recommended in the post-transplant setting and should be completed prior to transplantation when possible.

Tuberculosis Risk

Since tuberculosis can reactivate in the setting of post-transplant immunosuppression, many heart transplant programs perform testing for latent tuberculosis in all transplant candidates. Such testing is most strongly recommended for those

at an increased risk for tuberculosis exposures as listed in Table 1. Testing can be performed using PPD or interferon gamma release assay (QuantiFERON). Patients with evidence for latent TB should be referred for possible treatment. Such treatment includes isoniazid (INH) for 6–9 months, INH + rifapentine for 3 months, or rifampin for 4 months and can reduce the risk for reactivation up to 90% (USPSTF 2016). While it may often be preferred to complete such treatment before transplantation when able, it is not required for transplantation to proceed and can often be completed even after the transplantation. However, both rifampin and rifapentine should be used with extreme caution after transplantation due to enhanced metabolism of tacrolimus and cyclosporine and resultant rejection.

Geographic Risk

Additional testing may be required with specific geographic and environmental exposures that may affect the risk for post-transplant reactivation or repeated exposures. Additional prophylactic strategies may be recommended based on test results. Table 3 offers some guidance on typical testing based on the country of origin or travel. Details on prophylaxis related to such risk are provided in subsequent sections. It is most appropriate to obtain infectious disease consultation to assess these and other geographic risks in the pre-transplant setting. This is also important in the acute setting when infectious diseases can be masked by signs of end-organ disease.

Table 3 Geographic risk factors

Geographic distribution	Pre-HT screening for endemic infections
South America, Central America, Mexico	Chagas disease, *T. cruzi* IgG
SE United States, Eastern Europe, SE Asia, Central and South America, sub-Saharan Africa	*Strongyloides stercoralis* IgG
Central and South America, Mexico, SW United States	*Coccidioides* IgG/CF
Ohio and Mississippi river valleys South and Eastern Europe, Australia, Africa, portions of India, and Central America	*Histoplasma* CF antibody if possible active infection (additional diagnostic tests may be required)
Middle East, Mediterranean Basin, Central and South America, Asia, Africa	*Brucella* serology if possible active infection
Parts of sub-Saharan Africa, Middle East, China, the Philippines, Indonesia, Laos	Schistosoma antibody (usually EIA)

Ventricular Assist Device (and Total Artificial Heart) Infection

Ventricular assist device (VAD)-specific infections require special attention in the pre-transplant setting but in general do not preclude transplantation. Outcomes for transplanted patients with existing VAD-specific infections have been shown to be similar to those without such infections (Tong et al. 2015). Similar, but less robust, data indicate that the same is true for infections with total artificial heart (Hidalgo et al. 2017). Ventricular assist device infections occur in 18–59% of patients following VAD implantation with the prevalence increasing with duration of device support (Koval et al. 2014; Tong et al. 2015). VAD-specific infections involve the driveline, the device pocket, or the pump components (Hannan et al. 2011). Table 4 includes the most likely involved organisms at each site of VAD infection. Since such infections are often associated with biofilm formation, it is rare to be able to eradicate the infection without device removal. The device can only occasionally be removed due to cardiac recovery. Unfortunately, there is limited success with device exchange without residual infection (Tong et al. 2015; Chamogeorgakis et al. 2012). Thus, once infection begins, ongoing infection management is required until transplantation, often with continuous or repeated antibiotics, and occasionally surgical drainage procedures. Since the likelihood of transplantation for those with VAD-specific

Table 4 VAD-specific infections

Site of infection	Distribution of organisms
Driveline	*Staphylococcus aureus* (20–44%)
	Pseudomonas aeruginosa (10–45%)
	Enteric gram-negative bacteria (13–30%)
	Coagulase-negative staphylococci (7–20%)
	Enterococcus spp. (<5–15%)
	Corynebacterium spp. (<2–15%)
	Candida spp. (0–8%)
Pump pocket	Coagulase-negative staphylococci (15–40%)
	S. aureus (20–30%)
	Enterococcus spp. (20–24%)
	Enteric gram-negative bacteria (5–25%)
	P. aeruginosa (5–19%)
	Candida spp. (10%)
Pump/ cannula	Coagulase-negative staphylococci (20–40%)
	S. aureus (20%)
	P. aeruginosa (8–20%)
	Enteric gram-negative bacteria (0–15%)
	Enterococcus spp. (0–30%)

References: Koval et al. (2013, 2014)

infection is not significantly different than those without infection, the duration of pre-transplant infection management can be prolonged (Koval et al. 2014; Tong et al. 2015). With infectious disease input, even some multidrug-resistant pathogens can be managed successfully through the heart transplant procedure. For patients with overt sepsis syndrome, with deep infections with fungi, or with organisms without sustainable antibiotic options, transplantation would be exceptionally high risk and may be prohibitive (Aslam et al. 2010). Perioperative antibiotic management should be planned in the pre-transplant setting when able, and infectious disease consultation should occur before or immediately after transplantation. Intraoperative cultures should be obtained from relevant component sites when the device is removed during the heart transplant procedure.

Risk Reduction

Transplant recipients should adhere to infection control measures in order to avoid environmental pathogens, particularly in the first 6 months following transplantation and during other periods of intensified immunosuppression (usually when treated for rejection). While patients may lower their guard somewhat beyond the first year, they should always be attentive to their ongoing immune impairment. Table 1 outlines some of the preventive measures to be followed.

Infection Prevention Strategies in the Early Post-transplant Period (0–30 Days)

The early post-transplant period is characterized by the risk for nosocomial and surgical site bacterial infections (Mattner et al. 2007). Most commonly patients experience hospital-acquired and ventilator-associated pneumonia, urinary tract infections, and intravascular catheter sepsis (Haddad et al. 2010; Montoya et al. 2001; Mattner et al. 2007; Rajagopal et al. 2008). Cardiothoracic surgical and postoperative ICU care guidelines pertain to all heart transplant recipients (Costanzo et al. 2010).

Surgical Site Infection Prophylaxis

Sternal wound, mediastinal, and infections related to existing VAD specific infections are of particular importance in the heart transplant recipient. To date there have been no trials comparing perioperative antibiotic regimens and heart transplant infection outcomes. Use of surgical infection prophylaxis is extrapolated in part from cardiothoracic surgery guidelines, which recommend a perioperative cephalosporin beginning within 1 hour of surgical incision and continuing no longer than 48 hours postoperatively. Vancomycin (with or without gram-negative coverage) substitution is

recommended in selected environments where MRSA colonization is likely or documented or for those with Beta lactam allergies (Engelman et al. 2007; Edwards et al. 2006). Dosing frequency should follow the American Society of Health-System Pharmacists (ASHP) guidelines (Bratzler et al. 2013).

Ventricular Assist Device Infection

For patients with VAD-specific infections, perioperative prophylaxis should be modified to cover the VAD-infecting organism(s). Often the patient has been chronically suppressed with such antibiotics at the time of transplantation, and a plan should be in place for perioperative management (see section "Infection Prevention Strategies in the Pre-transplant Setting"). Infectious disease consultation is recommended to assist in post-transplant care as there may be residual infection from VAD sites including the pump pocket, the subcutaneous tissues of the tunneled driveline, or the mediastinum. Median duration of post-transplant antimicrobials for VAD-related driveline infections is 15 days but can range from very short (no longer than 48 hours in the case of modest superficial driveline infection) to very long (up to 145 days for deep-seated mediastinal infections) (Koval et al. 2014).

Herpes Virus Infection Prophylaxis

The most common viral infection during the first month after transplantation is reactivation of herpes simplex virus (HSV) in seropositive individuals. However, the widespread use of antiviral prophylaxis has contributed to the reduced incidence of HSV infection. While CMV disease does not commonly manifest in the early post-transplant period, it is likely that replication from the allograft or the recipient can begin during this time and prophylactic strategies are traditionally begun as soon as possible after transplantation.

Donor-Derived Infection

Donor-derived infections may occur in a very small minority of patients during this period (<1%). While donor-derived infections most commonly include the expected cytomegalovirus (CMV) and hepatitis B virus (HBV), unexpected transmissions such as Chagas disease, Human Immunodeficiency Virus, Hepatitis C Virus, lymphocytic choriomeningitis virus (LCMV), rabies, West Nile virus, and *Mycobacterium tuberculosis* have also been reported (Ison and Nalesnik 2011). Use of preemptive monitoring and universal prophylaxis has lowered the transmissions of expected donor-derived infections. Table 5 lists the recommended donor screening testing.

Prophylaxis strategies in the early postoperative period include perioperative antibiotics directed at surgical site infection, known as VAD-specific infections, herpes viruses, and donor-specific infections. Consultation with infectious disease specialists is encouraged in the setting of the specific risk for VAD infection management and special donor risk situations. Standard infection prophylaxis for this time period is outlined in Fig. 3.

Infection Prevention Strategies in the Intermediate Post-transplant Period (1–6 Months)

Most heart transplant recipients remain highly immunosuppressed during the intermediate post-transplantation period (1–6 months). In the absence of prophylaxis, patients develop infections with diverse opportunistic pathogens such as CMV, EBV, *Pneumocystis jirovecii* (*PJP, previously P. carinii/PCP*), *Aspergillus* species, *Nocardia* species, *Toxoplasma gondii*, and *Listeria monocytogenes*. The introduction of high-dose immunosuppression can result in reactivation of chronic donor-derived allograft infections or certain latent infections in the recipient such as *Mycobacterium tuberculosis*, *viral hepatitis*, *Histoplasma capsulatum*, or

Table 5 Donor screening

Infections	Testing
Herpesvirus infections	CMV IgG EBV IgG
Human immunodeficiency virus infections	HIV third- or fourth-generation serologic test HIV nucleic acid testing (NAT) in CDC Increased risk donors
Hepatitis virus infections	Hepatitis B surface antigen (HBsAg) Hepatitis B core antibody (anti-HBc) HBV NAT Hepatitis C IgG Hepatitis C NAT (in deceased donor)
Syphilis	Syphilis testing, RPR
Miscellaneous	*Toxoplasma* antibody (not routinely performed by all procurement organizations) Blood and urine cultures in deceased donor
Optional	*Trypanosoma cruzi* antibody, *Coccidioides* antibody, *Strongyloides* antibody, *Histoplasma* antibody, tuberculosis (PPD or IGRA), and *Brucella* serology (depending on geographic risks)

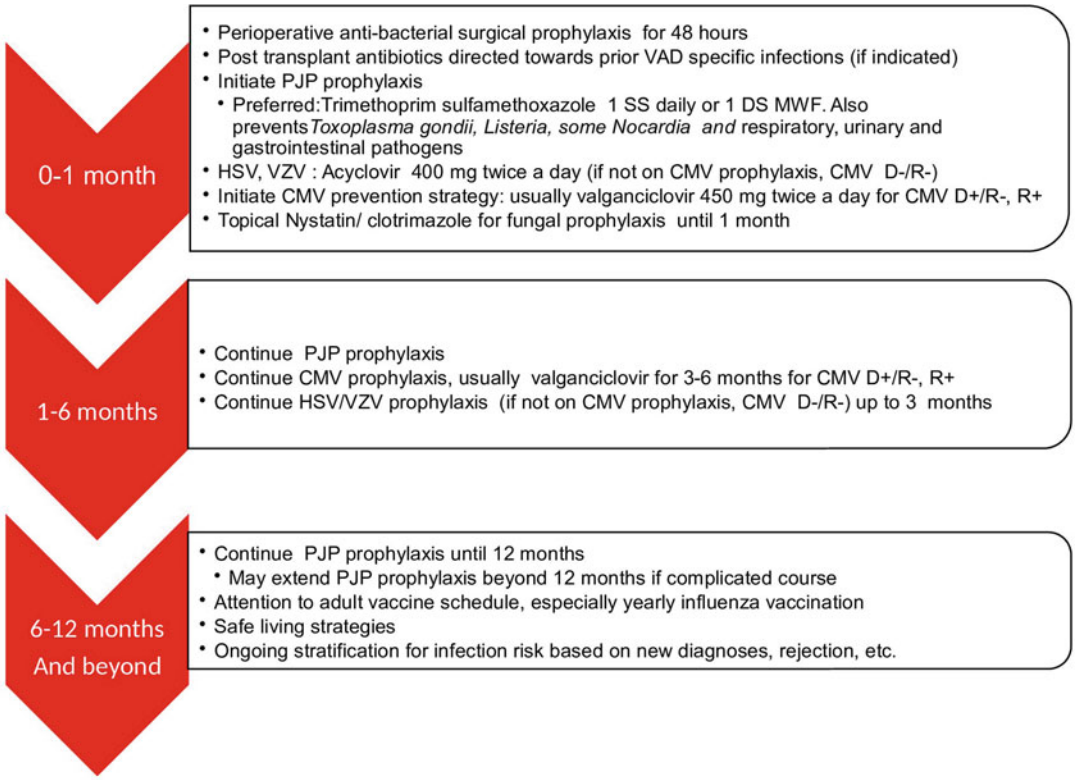

Fig. 3 Infection prophylaxis following heart transplantation by time from transplantation

Coccidioides immitis. Fungal infections of *Candida* and *Aspergillus* occur relatively early during this period. Environmental exposures may also play a role during this period and place patients at a higher risk for pathogenic fungi including *Cryptococcus*, *Histoplasma capsulatum*, *Coccidioides immitis*, or *Blastomyces dermatitidis*. Standard infection

prophylaxis for this time period is outlined in Fig. 3.

Infection Prevention Strategies in the Late Post-transplant Period (>6 Months)

In the late post-transplantation period (>6 months), most transplant recipients, if doing well, are on their lowest immunosuppression. Similar to the general community, they are susceptible to community-acquired pathogens such as influenza, parainfluenza, respiratory syncytial virus, adenovirus, human metapneumovirus, *Legionella* species, and pneumococcus. These patients however tend to have more prolonged and severe infections associated with higher mortality rates and increased risk for rejection. Chronic viral infections such as HBV or HCV can reemerge during this period causing allograft injury or malignant conditions such as post-transplantation lymphoproliferative disorder (PTLD) or skin cancer. However, prophylaxis during this period is limited to ongoing PJP prophylaxis for most programs. Monitoring for late CMV reactivation and infection remains important. Standard infection prophylaxis for this time period is outlined in Fig. 3.

Herpes Virus Infections

In the absence of an effective prophylaxis strategy, herpes virus infections, including herpes simplex virus (HSV), varicella zoster virus, and cytomegalovirus, occur commonly after heart transplantation and can account for serious morbidity and mortality. However, incidence of herpes virus infection has decreased nearly tenfold since the pre-CNI era (Haddad et al. 2010).

Cytomegalovirus (CMV)

CMV infection remains one of the most challenging infections to manage after transplantation. It requires effective T cell function (primarily T cell memory) to maintain control of latent infection in the case of seropositive recipients. It requires more adept T cell function (including expansion of a new T cell repertoire) to control acute infection from seropositive grafts. Thus risk factors for serious CMV infection include CMV Donor +/Recipient − status (D+/R−), thymoglobulin induction, high tacrolimus concentrations, and prolonged high doses of steroids. The greatest risk period for CMV is in the first 6 months following transplantation, coinciding with the period of greatest immunosuppression.

CMV acute infection or reactivation most often causes direct cytopathic effects, most commonly CMV syndrome (fever, cytopenias, malaise), but also can cause tissue-invasive disease including enterocolitis, esophagitis, pneumonitis, carditis, or hepatitis. Rarely does retinitis occur in the solid organ transplant recipient (as compared to patients with AIDS), and routine evaluation of the retina is not recommended unless the query of visual symptoms is met with a positive response. A variety of indirect effects have been associated with CMV infection thought to be due to the immunomodulating effects of the virus including acute and chronic rejection, other infections, PTLD, new-onset DM, accelerated coronary vasculopathy, and overall mortality (Potena et al. 2006; Petrakopoulou et al. 2004). Such effects have not been consistently demonstrated, however.

A preventive strategy for CMV is imperative in the first 3–6 months following transplantation. Prophylaxis involves a set duration of antiviral therapy (usually valganciclovir (VG)) during the peak period of prophylaxis. Breakthrough viremia is rare during the prophylaxis period (assuming antiviral dosing has not been compromised), but after cessation, CMV can still emerge. Since immunosuppression is less intensive by this time, the incidence of infection is diminished. However, late CMV can still be quite severe and may be more likely to be due to drug-resistant virus. Prophylaxis may prevent some of the indirect effects of CMV infection including CAV (Potena et al. 2009).

Preemptive therapy involves monitoring blood for early CMV replication with CMV DNA or

pp65 antigen detection assays and then initiating antiviral therapy to suppress detectable virus. Preemptive therapy requires detailed attention by the transplant team to initiate antiviral therapy as early as possible to prevent more serious manifestations of CMV infection. It helps with earlier control of the virus by the patient's recovering immune system and reduce costs associated with treating an active infection but challenges include the side effects of valganciclovir and drug resistance over time.

Prophylaxis and preemptive therapy are both valid options but have distinct risks and benefits, and often a hybrid approach is adopted at the programmatic level (a period of prophylaxis followed by monitoring and preemptive therapy). A pending study in solid organ transplant recipients comparing the two approaches is anticipated (clinicaltrials.gov/NCT01552369). Prophylaxis with valganciclovir may be preferred for 3–6 months in the highest-risk heart transplant recipients (CMV D+/R−) with the longer course reserved for patients with ATG induction or other more intensive immunosuppression regimens. For CMV R+ patients, either prophylaxis with valganciclovir for 3 months or preemptive therapy is a reasonable option.

CMV prophylaxis for D−/R− is not recommended, but patients must be counseled about the possibility of primary infection from a community source or from future blood products.

CMV immunoglobulin was introduced as prophylaxis in 1998 before the efficacy of valganciclovir prophylaxis was well established. Its use has been associated with improved survival, reduction in CMV disease, and CMV-associated deaths (Bonaros et al. 2008). There are limited data to support its use in the setting of available antivirals. However, some centers use it adjunctively.

Herpes Simplex Virus (HSV)

Impaired cell-mediated immunity results in herpes simplex virus type 1 and 2 (HSV-1, HSV-2) reactivation in 40–50% of heart transplant recipients. These can be more severe and prolonged than the normal host. Its most common clinical manifestations are mucocutaneous lesions or disease that can extend to the esophagus and airways. Herpes simplex pneumonia, hepatitis, and encephalitis can occur in transplanted individuals but are relatively rare in the current era. Antiviral prophylaxis is indicated in all heart transplant recipients during the peak period of immunosuppression (Miller and Dummer 2007). Acyclovir is effective, but famciclovir and valacyclovir are acceptable options. Ganciclovir or valganciclovir alone is indicated if the patient is otherwise getting CMV prophylaxis.

Varicella Zoster Virus (VZV)

Varicella zoster virus results in significant morbidity after organ transplantation and occurs in up to 25% of heart transplant recipients in the absence of antiviral prophylaxis. Disseminated and multidermatomal disease is common and can result in severe CNS involvement, severe postherpetic neuralgia, and cutaneous scarring. Occasionally visceral disease can manifest prior to cutaneous lesions (Miller and Dummer 2007). Acyclovir, famciclovir, and valacyclovir are recommended in the early post-transplant period for patients unless receiving valganciclovir for CMV prophylaxis. All patients age >50 should receive pre-transplant Zostavax (Table 6).

Pneumocystis jirovecii Pneumonia (PJP, Previously *P. carinii*/PCP)

Without prophylaxis, *Pneumocystis jirovecii* infection occurs in 6–20% of heart transplant recipients, though incidence varies depending on the intensity of immunosuppression and has diminished in the most recent era of immunosuppression. Most cases present with pneumonia, generally presenting with dry cough, hypoxemia, and pulmonary infiltrates. Onset is classically in the first 180 days following transplant but may occur later in certain high-risk patients (those with repetitive episodes of rejection or additional causes for immunosuppression). Mortality can

Table 6 Herpes virus prophylaxis

CMV serology	Drug	Dose, duration	CMV monitoring
D+/R−	Valganciclovir (VG)	450 mg BID × 3 months, consider 6 months if rATG	Weekly CMV PCR for 3 months after stopping VG and then biweekly for ≥3 months
D any/ R+	Valganciclovir	450 mg BID × 3 months	Weekly or biweekly CMV PCR for 3–6 months after stopping valganciclovir
D−/R−	Acyclovir or valacyclovir	400 mg BID or TID × ≥1 month 500 mg daily or BID	Not required

Table 7 Pneumocystis prophylaxis options

Drug	Duration	Comments
Trimethoprim/sulfamethoxazole 160/ 800 mg Mon, Wed, Fri	At least 1 year	Preferred, also prevents other important infections
Inhaled pentamidine 300 mg monthly	1 year	Respirgard II nebulizer (Marquest, Englewood, CO)
Dapsone 50–100 mg daily	1 year	Test for G6PD. Risk for methemoglobinemia and hemolytic anemia even if G6PD negative
Atovaquone 1500 mg daily	1 year	Costly, may not be covered by insurance

still be as high as 35% in the setting of appropriate therapeutic management, stressing the importance of early diagnosis. Diagnosis is typically by PJP PCR or specific stains of induced sputum or bronchoalveolar lavage fluid. However, diagnosis can be challenged by low organism burden in solid organ transplant setting (compared to HIV-infected patients) and may require lung biopsy to effectively rule it out.

There has been a dramatic reduction in *P. jirovecii* infection since the introduction of routine prophylaxis when begun in the first 3 weeks following transplant. Guidelines recommend pneumocystis prophylaxis for at least 1 year following transplantation though programs may adjudicate this based on the degree of immunosuppression for their patients.

Trimethoprim/sulfamethoxazole is the optimal prophylaxis agent being >90% effective when properly dosed (Carr et al. 1992). The extent of reported allergies or toxicities to trimethoprim/sulfamethoxazole is worth evaluating given its value at preventing not only PJP but also *Toxoplasma gondii*, *Nocardia*, *Listeria*, and common respiratory, urinary, and gastrointestinal pathogens.

In those with true allergies or significant toxicities to trimethoprim/sulfamethoxazole, dapsone, atovaquone, and aerosolized pentamidine may be used but are somewhat less effective (Bozette et al. 1995). It is important to recognize that dapsone at the standard prophylaxis dose of 100 mg daily has been associated with hemolytic anemia or methemoglobinemia in the solid organ transplant population even in the absence of glucose-6-phosphate-dehydrogenase (G6PD) deficiency (Lee et al. 2005) and at reduced doses is not reliably effective at prophylaxis (Souza et al. 1999). Atovaquone is costly and may not be covered by all insurance providers. Due to these issues, monthly aerosolized pentamidine is often used in those transplant recipients unable to tolerate trimethoprim/sulfamethoxazole (Table 7).

Toxoplasmosis

Attention to toxoplasmosis risk in the current era of solid organ transplantation (SOT) is controversial and may be outdated since clinically significant infection is rare. Routine serologic testing is no longer universally recommended (Derouin and Pelloux 2008).

Among solid organ transplant recipients, the risk of toxoplasmosis is highest in heart transplant recipients due to encystation of the parasite in the

striated muscle. Primary infection is of greatest risk among seronegative recipients that receive a heart from a seropositive donor (*Toxoplasma* D+/R−). In an era prior to the routine use of effective prophylaxis, clinical toxoplasmosis in sero-mismatches was reported in 25–75%. SOT recipients can also develop primary infection (R−) by oral ingestion or reactivation of *T. gondii* acquired prior to transplantation (R+). Reactivation is closely associated with the degree of immunosuppression but on the whole is unusual in SOT recipients.

Toxoplasmosis usually occurs in the first 3 months following heart transplantation and manifests as fever, pneumonitis, myocarditis, encephalitis, and disseminated multiorgan disease. When presenting with myocarditis, it can be confused with allograft rejection. Untreated *T. gondii* in the SOT patients have a mortality of nearly 100%. Diagnosis requires demonstration of the parasite or its DNA in the blood, CSF, bone marrow, BAL fluid, or tissue. Pyrimethamine in combination with either sulfadiazine or clindamycin or atovaquone or Bactrim alone for a minimum of 6 weeks followed by secondary prophylaxis – in which its duration is individualized on the basis of the patient's risk of reactivation and net state of immunosuppression.

The incidence of toxoplasmosis has decreased during the last 30 years and in general is very uncommon, particularly in the United States where seroprevalence is relatively low. This is in part due to the protective effect of prophylaxis but may also be due to changes in immunosuppression. Data from Stanford in 2001 demonstrate the effect of prophylaxis in OHT with 0/16 D+/R− recipients receiving prophylaxis compared to 4/16 (25%) without prophylaxis developing toxoplasmosis (Montoya et al. 2001). All four died from infection. More recent data from large US transplant centers that do not use prophylaxis specifically or even aim to identify a high-risk status demonstrate that the risk for toxoplasmosis is negligible when trimethoprim/sulfamethoxazole is used for PJP prevention. Some advocate daily dosing of trimethoprim/sulfamethoxazole for high-risk patients, but, in practice, standard doses used for PJP prophylaxis seem to be adequate (Baran et al. 2006). Although dapsone and atovaquone (used for prevention of *P. jirovecii* pneumonia) also have activity against toxoplasmosis, each of these may optimally prevent infection only when combined with pyrimethamine. Pentamidine has no activity against toxoplasmosis and would be ineffective for prophylaxis (Table 8).

Table 8 Toxoplasma prophylaxis

Serologic status	Recommendation
Toxoplasma IgG D+/R−	Trimethoprim/sulfamethoxazole 160/800 mg MWF or 160/800 or 80/400 mg daily. At least 1 year
	If unable to tolerate sulfa, can consider pyrimethamine 25 mg daily with dapsone, atovaquone, or clindamycin
Toxoplasmosis IgG R+	Routine PJP prophylaxis
All patients	Avoid cat litter, properly wash produce (avoid ingesting oocysts), ensure properly cooked meat (kill cysts)

Chagas Disease

Trypanosoma cruzi is a protozoa that causes American trypanosomiasis and is endemic to Central and South America. Transmission can occur through the bite of the vector; through blood transfusion, in utero; and by organ transplantation. Infection may be asymptomatic but in 33% causes chronic disease of the heart and intestine that only manifests decades later as heart failure and/or megaesophagus or megacolon. Chagas cardiomyopathy is the third leading indication for heart transplantation in endemic regions. Initially considered a contraindication for heart transplant, Chagas cardiomyopathy was shown to have better outcomes than other cardiac conditions and is now routinely performed. Post-transplant Chagas reactivation is expected (most likely from the adrenal glands or skeletal muscle) in 20–45%, and its emergence should be monitored with routine surveillance (Table 9) and managed. The risk of Chagas reactivation is related to the degree of immunosuppression, and, in general, immunosuppression should be run as low as

Table 9 *T. cruzi* management in heart transplantation (HT)

Time period	Recommendation	Comments
Pre-HT	*T. cruzi* IgG	HT candidates from endemic regions or born to mothers from endemic regions
	Screen for esophageal dilatation	Relative contraindication to HT
Transplant	Consider the need for induction immunosuppression	Avoid if able Basiliximab preferred over thymoglobulin
Post-HT	Minimize immunosuppression	Lower calcineurin inhibitor levels, azathioprine instead of mycophenolate mofetil, early weaning corticosteroids
	Parasite monitoring: PCR and blood smear	1st 2 months: weekly 2–6 months: every 2 weeks 6–12 months: monthly 13–24 months: every 3 months >24 months: every 6 months And if unexplained febrile illness or suspected rejection
	Treatment of documented viremia	Benznidazole 5–10 mg/kg/day for 60 days Nifurtimox 8–10 mg/kg/day for 60–90 days Both drugs available by IND from the CDC

Benatti et al. (2017) and Chin-Hong et al. (2011)

reasonably possible. Symptomatic reactivations can manifest as fever, myocarditis (mimicking allograft rejection), subcutaneous nodules, or rarely disseminated disease. Patients respond well to benznidazole or nifurtimox with clearance of parasitemia and resolution of clinical symptoms often after the first week of treatment. Neither drug is FDA approved for use in the United States but is available by IND through the CDC. The mortality rate related to reactivation of *T. cruzi* following heart transplantation is relatively low, around 0.9% (Fiorelli et al. 2011).

Fungal Infections

The incidence of serious fungal infections in heart transplantation has fallen substantially over time, from 0.29 events/patient in the era preceding calcineurin inhibitors to 0.08/patient in the most recent era (Haddad et al. 2010). Multicenter monitoring indicates a rate of 3.4% in the first year after heart transplantation (Pappas et al. 2010). Most invasive fungal infections (IFI) are due to *Candida* in 49% or *Aspergillus* species in 23% but can include *Cryptococcus*, other filamentous molds (mucorales, dematiaceous fungi), and dimorphic endemic fungi (*Histoplasma*, *Coccidioides*, *Blastomyces*). High-dose steroids, delayed chest closure, induction with OKT3, antithymocyte globulin, and post-transplant renal replacement therapy have all been identified as risk factors for early IFI in heart transplant recipients, chronic rejection, and renal failure with late IFIs associated (Rabin et al. 2015; Echenique et al. 2017).

Candida accounts for 30–40% of invasive fungal infections, usually occurring in the first 30–60 days after transplant and associated with critical illness conditions. Candidemia related to intravenous catheters or as a consequence of surgical site infections (sternal wound infections, mediastinitis) is most common.

Aspergillus infections were reported in greater numbers in earlier eras of transplantation but have declined in recent years. They can occur early <30 days or late >30 days with the median time of onset 46 days post-transplantation (Montoya et al. 2003). Disease is confined to the lungs in 40%. Patients present with fever, cough, abnormal chest imaging (classically single/multiple nodules with halo signs or cavitation; alveolar infiltrates without these classic findings can also occur). Disease

disseminates hematogenously from the respiratory tract to the brain or skin in 30%. Rarely, it infects the mediastinum. Early-onset disease may be impacted by inhaled amphotericin during the inpatient post-transplant course, especially if epidemiology indicates a local source.

Histoplasma capsulatum can be found worldwide but in the United States is endemic to the Ohio and Mississippi river valleys. After heart transplantation, infection is uncommon (0.48%), but there are regional variations in incidence. Disease can be confined to the lungs, but dissemination is common (presenting as fever, cytopenias, tissue-based granulomatous disease) occurring in 80% of those with organ transplantation (Assi et al. 2013). Detection of *Histoplasma* antigen on the urine and serum is highly sensitive. Diagnosis can also be made by growing *H. capsulatum* in the blood, sputum, body fluids, or tissue biopsy. Thirty percent of cases occur in the first year after transplant, with 10% mortality and relapse in about 6% of patients. Prophylaxis for histoplasmosis is not recommended in the heart transplant recipient even in endemic areas. *Histoplasma* is not characteristically latent and thus does not reactivate, so pre-transplant serologic testing is not routinely recommended. Old granulomatous nodules in a *Histoplasma* endemic area are not likely to be of clinical significance in the post-transplant setting.

Blastomyces is also endemic to the Mississippi and Ohio river valleys, as well as states bordering the Great Lakes and the Saint Lawrence Seaway. Similar to histoplasmosis, lungs are the primary site of infection, but the organism can disseminate to the skin, osteoarticular structures, central nervous system, and genitourinary tract. Antifungal prophylaxis is not recommended.

Coccidioidomycosis is endemic to the Southwestern United States, Northern Mexico, and parts of Central America. It can cause serious illness in solid organ transplant recipients presenting with severe pneumonia or dissemination to subcutaneous tissues, meninges, or bones with associated fungemia. Annual incidence ranges from 2% to 5% in regions of endemicity, with the highest incidence in the first year after transplant (Blair and Logan 2001). Disseminated coccidioidomycosis has been reported to be as high as 72% but in more recent years ranges from 0% to 25%, likely due to earlier recognition and less toxic antifungal therapies. Azoles have been recommended as primary prophylaxis for patients at a high risk for infection or reactivation after transplant (Galgiani et al. 2016).

Table 10 Antifungal prophylaxis

Fungal syndrome	Drug	Duration
Mucosal candidiasis, thrush	Nystatin swish and swallow	1–3 months
	Clotrimazole troche	1–3 months
Aspergillus, if inpatient risk	Inhaled amphotericin	During inpatient stay
Coccidioidomycosis		
Endemic	Fluconazole 200 mg daily	6–12 months
Seropositive	Fluconazole 400 mg daily	6–12 months

Routine use of systemic antifungal prophylaxis is not routinely recommended in cardiac transplant recipients. However, mucosal prophylaxis with nystatin swish and swallow or clotrimazole troche for a month following transplant is used in certain centers. Consideration for prophylaxis in patients with specific risks or in outbreak situations may be given (Table 10).

Increased Risk Donors

A CDC increased risk donor has a higher than average risk for HIV, HBV, and/or HCV infection but does not meet the criteria for the existing infection. Increased risk donors have about five times the risk for these blood-borne infections as usual risk donors (e.g., 0.5% HIV in usual risk but 2.5% in increased risk). This risk is markedly diminished by NAT and serologic testing of the donor at the time of donation, but there remains a very small chance of donors being in the 7-day window period if ongoing exposure risk is presumed. Transmission of blood-borne pathogens has been reported very rarely in these circumstances. Donors will be screened by the organ procurement organization for the increased risk

for HIV, HBV, and HCV by specified criteria. Potential recipients should be counseled about the relatively increased risk for these bloodborne pathogens and should be specifically consented prior to allocating these organs. Follow-up of the recipient for infection transmission is mandated by the UNOS and should include testing for HIV, HCV, and HBV at the baseline, at 1–3 months, and at 12 months to ascertain potential transmission (Seem et al. 2013).

Hepatitis B Virus

All patients should be tested for hepatitis B serology prior to listing and at the time of transplantation. Nonimmune organ transplant candidates should be vaccinated for hepatitis B with a three-shot series (Table 2). All donors should be tested for hepatitis B serology prior to organ donation. All recipients should be tested again for hepatitis B serology in the event of rituximab use.

Heart transplant candidates with chronic active hepatitis B should be evaluated by a hepatologist or infectious disease specialist with expertise in hepatitis B prior to transplant listing. Candidates with cAb positivity (sAg negative) and sAb+ are at a low risk for reactivation unless HBsAb is lost. Post-transplant monitoring of sAb every 3 months may be considered since loss of surface antibody usually precedes reactivation. In those with cAb+ only (sAb negative) and those receiving rituximab for AMR, prophylaxis with lamivudine and monitoring for sAg and HBV DNA every 3 months are encouraged. Consultation with a hepatologist or infectious disease specialist is recommended.

Hepatitis B transmission during transplantation occurs most easily in the setting of donor HBsAg positivity. While it is not an absolute contraindication to organ transplantation, organ donation from a donor with active hepatitis B is rarely performed deliberately in heart transplantation. Recipient vaccination, careful use of antiviral therapy, and passive HBIG immunotherapy can effectively prevent transmission to the recipient, and a careful management approach could be considered in urgent cases of heart transplantation (Levitsky et al. 2013).

On the other hand, the use of organs from HBcAb+ (HBsAg-negative) donors is acceptable and relatively common regardless of the HBsAb status of the donor. Only one episode of clinically significant de novo hepatitis B infection has been reported in 122 heart transplants from five studies of HBcAb+ donors (Huprikar et al. 2015). This single recipient was HBsAb negative and did not receive prophylaxis. Serologic conversion (sAb or cAb) in the recipient has been reported, and these could theoretically result in later HBV reactivation. Therefore, it is important to obtain informed consent for HBcAb+ donor organs and to consider the need for risk mitigation. Antiviral prophylaxis with lamivudine, entecavir, or tenofovir formulation may be considered for up to a year in susceptible heart transplant recipients but is not recommended in HBsAb+ recipients. Ease of acceptance of an HBcAb+ donor organ is the strongest indication to effectively vaccinating heart transplant candidates for hepatitis B in the pre-transplant setting.

Hepatitis C Virus (HCV)

In the 2000s, HCV donors were rarely used for cardiac transplantation owing to the increased risk of mortality and accelerated coronary allograft vasculopathy (CAV) (Haji et al. 2004; Gasink et al. 2006). The availability of curative direct-acting antivirals for the treatment of hepatitis C virus has enabled the use of otherwise good hepatitis C donors to expand the organ donor pool. Coincidently, the opioid epidemic has increased the availability of organs from otherwise healthy young donors with hepatitis C infections (Levitsky et al. 2017). The use of hepatitis C-positive donors in hepatitis C-negative transplant recipients is now occurring at many organ transplant centers and is the subject of a consensus statement by the American Society of Transplantation on their use in solid organ transplantation (Levitsky et al. 2017). The nucleic acid testing (NAT) for viral load was added to routine donor workup in 2015, helping to

discriminate the infectious donors (HCV antibody +/NAT+) from the noninfectious donors who had cleared HCV (HCV antibody +/NAT−). The largest case series of 12 HCV-naive recipients of heart transplantation from HCV-positive donors showed nearly universal infection with HCV post-transplant (from NAT + donors) but with complete viral clearance with DAA therapy (Schlendorf et al. 2018). Data recently available from a clinical trial of ten HCV D+/R− heart transplant recipients (USHER trial) with early post-transplant elbasvir/grazoprevir treatment for recipient HCV infection showed high cure rates and short-term acceptable outcomes (McLean et al. 2019). The long-term effect of HCV infection or DAA therapy on graft function, rejection, CAV, and renal and hepatic outcomes is yet to be known. In a setting of programmatic management of such donor/recipients with assurance of access to appropriate DAA therapy early after transplant, it appears that the benefit of HCV D+/R− may outweigh the risk for many patients on the heart transplantation waiting list (Moayedi et al. 2018). Additional data is anticipated in the coming years.

Conclusion

The incidence and impact of bacterial, viral, and fungal infections in cardiac transplantation have dramatically declined over the past 30 years owing to more advanced surgical techniques, better treatment strategies, and use of targeted antimicrobial prophylaxis. Advances in antimicrobial therapies (as with HCV) may continue to increase the donor pool. Improved strategies to individualize the patient's risk with selective prophylaxis and treatment strategies are required.

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Monitoring for Rejection

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Abstract

Survival following cardiac transplantation has improved over the last three decades, partly as a result of vigilant monitoring for immunologic intolerance. Early detection of rejection allows for the modulation of recipient immunity with immunosuppressive medications. These immune-modulating agents may have untoward side effects, thus underscoring the necessity for continued surveillance of rejection to enable minimal effective dose administration. Rejection monitoring has been synonymous with endomyocardial biopsy (EMB), the "gold standard" in rejection monitoring. Endomyocardial biopsy provides tissue that may help distinguish the type as well as the severity of rejection. Although rejection risk is time dependent and attenuates over time, it never completely disappears. This need for continued surveillance has led to a growing interest in alternative noninvasive techniques for monitoring rejection.

Keywords

Cardiac transplantation · Cellular rejection · Antibody-mediated rejection · Endomyocardial biopsy

Introduction

Cardiac transplantation is universally regarded as the most effective treatment modality for severe end-stage heart failure. This treatment strategy for heart failure is however limited by the finite organ donor supply that has remained stable over the decades, with about 3000 transplants in the USA per year. Fortunately, medical advances in the last three decades have improved patient survival following cardiac transplantation surgery. The impressive survival gains that have been realized in the current era of cardiac transplant have rested partly on the ability to mitigate the risk of allograft rejection with immune-modulating medications as well as the universal adoption of routine surveillance protocols for rejection in transplant centers. The median survival rate following cardiac transplantation is now greater than 80% at 5 years (Yusen et al. 2016; Stehlik et al. 2010).

Allograft rejection describes the recipient's immune response to the donor heart's human leukocyte antigen (HLA). Since the donor heart is genetically dissimilar as the host, an immune response of variable intensity is evoked. Reducing immunological variability between the donor and the recipient is critical to the prevention of acute rejections especially early on after surgery. The process of donor-recipient cross matching has significantly been improved since the time of the first heart transplant by Barnard and colleagues in 1967 to the extent that hyperacute rejection (triggered by preformed antibodies against the donor HLA epitopes) is now a rare phenomenon (Barnard 1967). Even with the most meticulous cross matching process, there will be an unavoidable host immunologic response of the recipient against the donor HLA. The risk of rejection is higher in the first year of transplantation, and for this reason, rejection surveillance and immune-modulating strategies tend to be more aggressive during this time period. Monitoring and detecting rejection allows for an early diagnosis and, when necessary, adjustment in immunosuppression medications so as to preserve allograft function.

The risk of cardiac allograft rejection emerges at the moment of transplant when the recipient immune cells interface with the donor allograft and in principle continues throughout the recipient's life span. The primary target cells in the allograft include endomyocardial and coronary endothelial cells. Rejection is attributed to a myriad of redundant immunological mechanisms

involving both the innate and adaptive immune pathways. Cardiac allograft rejection is classified in temporal terms as hyperacute, acute, or chronic rejection. Furthermore, it is also classified immunopathologically as cell mediated or antibody mediated based on the predominant immunological foreground driving the rejection process. Acute cellular rejection (ACR) is the commonest type of rejection and is primarily related to the mononuclear inflammatory response (specifically T cell immunity) directed against the donor HLA epitopes. Antibody-mediated rejection (AMR), also known as humoral or vascular rejection, is primarily related to the circulating antibodies or activated recipient B cell response to the donor antigens.

Mitigating the risk of rejection in principle begins in the pre-transplant phase of patient care. Meticulous attention to the cross matching process, by identifying the panel-reactive antibodies (PRA) and anti-HLA with flow cytometry, help predict which patients have a heightened risk of rejection (Nwakanma et al. 2007; Tambur et al. 2000). At the time of surgery, the newly transplanted heart is exposed to the host immune defenses that potentially compromise allograft function. As discussed earlier, modern cross-match techniques and clinical selection of donor-recipient pairs have led to a decline in the number of cases of hyperacute rejections. The "early" period, roughly defined as the first few weeks to the first-year post-transplant, encompasses the time of the highest risk for both ACR and AMR. Fortunately, the frequency of rejections has been on the decline over the last couple of decades. Although 75% of patients will have no rejection during the first year, about 25% will have some rejection, and about 12% will have rejection requiring immunotherapy modification (Stehlik et al. 2006). After the first 12 months, also referred to as the "late" period, rejection is significantly less common although there is still a small perennial risk (Kfoury et al. 2016). Further, it is notable that ACR and AMR can occur simultaneously in approximately 25% of cases of rejection (Taylor et al. 2000). Mortality from acute rejection is highest in the first year, accounting for 4–9% of deaths (first 30 days and 31 days to 1 year, respectively) (Stehlik et al. 2016). Monitoring for rejection is particularly important in this early time period and has a bearing on the ability to fine-tune immunosuppression medications so as to maintain a critical balance between the prevention of rejection and the avoidance of adverse effects of immunosuppression medication (such as renal dysfunction, malignancies, and opportunistic infections).

This chapter will provide an overview of techniques commonly employed in monitoring rejection, the associated and historic background, as well as the promising noninvasive rejection surveillance modalities.

Physical Exam for Monitoring of Cardiac Rejection

As in all of medicine, the foundation of rejection monitoring is a history and physical examination. The complexity of a transplant patient's medical history, immunosuppression, denervation, and adaptive hemodynamics can mask certain symptoms making clinical ascertainment challenging. Any new symptom or concern by the patient should prompt further evaluation. Consideration of clinical risk factors can be helpful in the monitoring of rejection. Younger recipient age, female gender, previous episodes of rejection, high donor-specific antibody (DSA) levels, and non-compliance to immunosuppression medications may signal patients at greatest risk for rejection. There are also socioeconomic and demographical factors that are predictive of rejection. For instance, low socioeconomic status may influence medical adherence and by extension rejections (Denhaerynck et al. 2005). Higher rates of rejection have been documented in African American cardiac transplant recipients (Singh et al. 2011). The risk of rejection in the first year is highest among African Americans and Hispanic-Latinos, while Asians had less risk than Caucasians (Kilic et al. 2012).

Rejection can be largely asymptomatic and subclinical, yet vigilance in clinical history taking may reveal early clinical manifestations of rejection. The immune-mediated inflammatory

response of rejection results in edema and eventual fibrosis of the allograft and functional impairment. Diastolic dysfunction can result in a return of congestive heart failure symptoms such as paroxysmal nocturnal dyspnea, orthopnea, and edema. A decrease in exercise tolerance may result from congestion, decreased cardiac output, or arrhythmias. Jugular venous distension may be present. Importantly, vagal denervation in transplant patients results in a higher resting heart rate of approximately 100–110 bpm. Changes in heart rate (bradycardia or pronounced tachycardia/arrhythmia's) and in some cases syncope may signal a rejection episode (Shah et al. 2013). Symptoms of rejection can also parallel those of a multitude of infections in an immunocompromised host and warrant early consideration of both in order to achieve a good clinical outcome. There are important limitations of relying heavily on history to diagnose rejection as it can be subclinical; therefore complimentary testing combined with clinical judgment is necessary.

Electrocardiographic Monitoring for Rejection

The electrocardiogram (ECG) is a familiar, widely available, and inexpensive tool for cardiac evaluation and diagnosis. Rejection may be diffuse, involving surrounding myocardium and the conduction system, or isolated to the conduction system (Knight et al. 2010). Thus changes in ECG can provide important components to the evaluation of rejection. The utility of ECG in monitoring rejection should be centered around documentation of new arrhythmias which may accompany an acute rejection episode. Low voltage signals may also be present in some patients with diffuse edema surrounding the cardiac myocytes. There has been a report of ST elevation related to combined cellular and antibody rejection which may be related to intense inflammatory process from combined rejection (Vlismas et al. 2015).

Post-transplant intraventricular conduction delays are not uncommon after cardiac transplantation, with 73% of patients having RBBB on first post-transplant ECG (Leonelli et al. 1994). Development of a RBBB morphology on ECG is significantly related to a higher transpulmonary gradient prior to transplantation, spatial orientation of the new heart in the mediastinum, and pressure overload and in some cases due to acute rejection. Right bundle branch block in isolation, however, is not related to overall prognosis (Ferretto et al. 2017). For the 27% of patients with a normal ECG, they continued to have a normal ECG (Leonelli et al. 1994).

The relationships between atrial fibrillation/flutter signaling a rejection episode have yielded variable results. In a study by Dasari et al., of the 34 patients with atrial fibrillation or flutter, only 1 had a grade 2 or greater ACR (Dasari et al. 2010). Similarly, the development of atrial fibrillation or atrial flutter, ectopic atrial tachycardia, and supraventricular tachycardia following OHT was not strongly associated with rejection (Pavri et al. 1995; Romhilt et al. 1982). In a large study (892 OHT patients), 22 of 69 atrial fibrillation episodes and 10 of 20 atrial flutter episodes occurring in the first 2 weeks also had the diagnosis of rejection. In the same study, all 41 episodes of atrial flutter after 6 months were associated with cellular and humoral rejection or CAV (Cui et al. 2001). In clinical practice, however, the development of new atrial arrhythmias may be an ominous sign for rejection.

PVCs commonly occur in the early postoperative period and decrease in frequency with time (Jacquet et al. 1990). Late, sustained ventricular arrhythmias such as NSVT and VT are associated with graft failure, CAV, and allograft rejection.

Sympathetic reinnervation can occur in a minority of patients and is dependent on the time lag from surgery as well as the surgical technique. Reinnervation will result in an increase in heart rate variability and response during exercise, but it is not associated with bradycardia (Wilson et al. 2000; Gallego-Page et al. 2004). Bradycardia and syncope are ominous findings that should raise concern for rejection. A case series of six patients presenting with bradycardia and syncope, 11–83 months (42.5 $\pm$ 26.5) post-transplant, four with previous cellular rejection, were described relative to pathologic findings. Four surviving patients had ISHLT grade 0 ($n = 3$)

and grade 1A ($n = 1$). One of the two patients that did not survive was found to have ACR predominantly involving the conduction system with only mild changes in the working myocardium (Knight et al. 2010). Chan et al. described a 15-month-old OHT recipient that 6 weeks post-transplant developed bradycardia and died. Severe ACR involving primarily the conduction system was found on autopsy (Chan et al. 2006). Other autopsy studies of OHT hearts from non-cardiac death or retransplanted patients found no significant increased rejection of the conduction system compared to the surrounding myocardium (Stovin and Hewitt 1986).

Ventricular-Evoked Response

Analysis of ventricular-evoked response (VER) has been utilized for detection of rejection early after surgery. The technique utilizes ventricular monitoring via two unipolar screw-in leads, one in each ventricle. Intramyocardial electrograms were recorded from telemetric pacemaker, and trends in electrical conduction can be followed (Schweiger et al. 2005). Although effective, the invasive nature of the procedure and complexity of data interpretation have likely slowed clinical adaptation.

ISHLT Class IIa recommendations for VER (Costanzo et al. 2010):

- In centers with proven expertise in VER monitoring, intramyocardial electrograms recorded noninvasively with telemetric pacemakers can be used for rejection surveillance in patients at minimal risk for rejection.

Biochemical Testing for Monitoring of Rejection

Brain natriuretic peptide (BNP) elevations have been observed in heart transplant recipients experiencing rejection (Geiger et al. 2008). Serial BNP testing has been predictive of rejection and has demonstrated a high specificity and negative predictive value (Damodaran et al. 2012). Similarly, high-sensitivity troponin I have demonstrated a high negative predictive value (99%) to rule out acute rejection (Patel et al. 2014). Although these studies illustrate the usefulness of biochemical markers, further studies are necessary prior to being widely accepted to monitor rejection.

Echocardiographic Monitoring for Rejection

A decrement in cardiac function always warrants further investigation of cardiac transplant compromise. Early diagnosis and anticipation of acute cellular rejection even prior to EMB allow for prompt therapeutic adjustment. Invasive procedures such as endomyocardial biopsy (for rejection) and cardiac catheterization (for CAV) can be judiciously scheduled based on noninvasive echocardiogram studies. An early signal of acute rejection is the presence of diastolic dysfunction, albeit with low sensitivity and specificity (Yoshida et al. 1998; Palka et al. 2005).

Adaptation of the donor heart to the unfamiliar environment, different surgical techniques, and normal postsurgical changes present a challenge to obtaining early echocardiographic images. Depending on the implantation technique, the atrium may be enlarged and with a suture line mid cavity. If recipient pulmonary pressures remain elevated, the RV may be enlarged. The septal motion is often exaggerated and paradoxical as often seen post-cardiac surgery (Gorcsan et al. 1992). Transesophageal echocardiogram (TEE) is routinely conducted during implantation and in the early postoperative time when transthoracic echocardiogram (TTE) is unable to obtain adequate evaluation due to postsurgical changes.

A transient reduction in myocardial contractility for the first 12–24 hours may result from reperfusion injury from prolonged cold ischemia time (>4 hours) (Appleyard and Cohn 1993). The most concerning cause of perioperative LV dysfunction is hyperacute rejection. Fortunately, rate, hyperacute rejection is the catastrophic cardiac collapse resulting from global ischemia as recipient preformed IgM and IgG bind to donor endothelial cells. Although most often abrupt, hyperacute

rejection may be seen any time in the first 24-hours post-surgery (Trento et al. 1988).

The frequency of echocardiography in the years following transplant is not protocolled; nonetheless they are frequently helpful in clinical management. Acute cardiac rejection should be suspected with any change in wall motion or decrement in right or left cardiac ejection fraction in the first few years post-transplant. Later, rejection is always a risk; however CAV becomes more of a consideration.

Tissue Doppler mitral annual velocity, speckle tracking strain imaging and strain rate have demonstrated promise in detecting allograft rejection; however these ultrasound technologies have not been able to reliably predict significant rejection ($\geq$ 2R). GR can involve small segments of the LV explaining the normal global LV systolic function yet the continued presence of rejection on EMB. Global longitudinal peak systolic strain (GLS) is frequently reduced in acute GR despite an often normal LVEF.

Endomyocardial Biopsy

Endomyocardial biopsy (EMB) has been the cornerstone for monitoring cardiac allograft rejection. The EMB is conducted through a central venous access most often obtained via the right internal jugular or femoral veins. Small endomyocardial samples are taken from the right ventricular septum; usually four to six separate samples are obtained with the use of a bioptome for immunohistopathological analysis.

Tissue biopsy of transplanted solid organs for signs of rejection had their start with needle biopsy of liver and kidney transplant. The needle biopsy of a solid organ with no dynamic motion or significant pressure changes as seen in liver and kidney biopsies is safe. Unfortunately, a similar technique of needle biopsy for the monitoring of cardiac allograft rejection proved difficult and with significant risk, likely due the various hemodynamic pressures and constant cardiac motion (Kent et al. 1956).

The first resemblance of the modern flexible forceps bioptome was the Konno-Sakakibara bioptome described in 1962 and the first to utilize a venous approach (Sakakibara and Konno 1962). Their bioptome was utilized in the diagnosis of unknown cardiac conditions predating the era of cardiac transplantation. With five patients, they obtained ten biopsies reporting only two PVCs and had no "untoward effect." The technique of obtaining a small piece of endomyocardium and myocardium with small forceps continued to be utilized for cardiac transplant patients. A decade later a percutaneous access EMB procedure was described utilizing the internal jugular vein (Caves et al. 1974). Instrumentation and a technique for femoral vein access EMB was described in 1984 (Anderson and Marshall 1984). These two techniques are largely unchanged since their inception, and EMB remains the "gold standard" for monitoring cardiac rejection.

Spiegelhalter and Stoven used a statistical model to help determine the number of biopsies that increases the diagnostic accuracy for acute rejection. In general, obtaining only 3 EMB samples have a 5% probability of inadequate sampling. That chance is reduced to 2% with four samples (Spiegelhalter and Stovin 1983). It has been demonstrated that if mild rejection is present in three of four biopsies, the risk of a moderate-severe rejection is high (Sharples et al. 1992). The veracity of the diagnosis of rejection can be attenuated by the presence of sampling artifacts, such as samples obtained from a contraction band that formed along the RV septum as a result of repeated biopsies of that site. Therefore, the acute cellular rejection grading scheme for the International Society of Heart and Lung Transplant (ISHLT) requires at least four endomyocardial tissue specimens free of significant artifact to improve diagnostic accuracy (Cunningham et al. 2006).

The EMB is generally as a safe procedure in experienced hands. Complications although rare are known to occur. Complications can include pneumothorax, hemothorax, cardiac perforation, cardiac tamponade, coronary ventricular fistula, heart block, tricuspid valve damage, or death. Fortunately, the risk of major complication is reported as $<$1%. A large retrospective study at a single center reviewed 2117 biopsies (77.1%

femoral access) finding a cumulative complication rate of 0.71% (Saraiva et al. 2011). A retrospective study over 28 years reviewed 3068 RV biopsies from a femoral vein approach, finding an overall major complication rate of 0.45% (Chimenti and Frustaci 2013). Deckers et al. reported 546 biopsies (96% internal jugular access) with a 6% rate of any complication, including what other studies would term minor complications. The risk of major complication in their study was similar with possible or definite perforation occurring at a rate of 1.2% (Deckers et al. 1992).

The risk of tricuspid valve regurgitation, as a complication of EMB, rises incrementally with each sequential EMB procedure. In a study of 101 patients with EMB, 25% had developed severe tricuspid regurgitation with the rest having non-severe tricuspid regurgitation. The risk of severe TR was directly related to the number of EMB procedures; the authors proposed 31 EMB procedures as the inflection point where the risk of severe TR is highest (Nguyen et al. 2005).

Cardiac transplant patients are often scheduled for EMB more frequently in the first year, and depending on risk factors and episodes of rejection, EMB is done less frequently over time. There are individual variations among institutions in surveillance protocols but generally follow the timeline illustrated in Table 1. When episodes of rejection are noted or new symptoms develop, EMB is scheduled as determined necessary.

A study by Chi et al. evaluated EMB on a scheduled protocol compared to EMB in the event suspected rejection. Most rejection episodes (86.4%) were observed within 2 years; at 3-year time point from transplant surgery, rejection was observed in only 2.1%. For both the scheduled EMB and event EMB groups, 10-year survival was 64 and 53%, and 10-year freedom from rejection was similar (Chi et al. 2012). There is therefore no convincing evidence that EMB after 5 years changes survival or detection of rejection (Stehlik et al. 2006).

Consensus guidelines have been published (Costanzo et al. 2010) and are summarized below:

- The standard of care for adult HT recipients is to perform periodic EMB during the first 6–12 postoperative months for surveillance of HT rejection.
- The standard of care in adolescents should be similar to that in adults, including surveillance EMB for heart allograft rejection for 6–-12 months after HT.
- After the first postoperative year, EMB surveillance for an extended period of time (e.g., every 4–6 months) is recommended in HT recipients at higher risk for late acute rejection, to reduce the risk for rejection with hemodynamic compromise and the risk of death in African American recipients.

Acute Cellular Rejection

Acute cellular rejection (ACR) is the most frequently encountered type of rejection. The scheduled biopsy protocols observed at most transplant centers are based on the frequency and risk of ACR based on and temporally related to the time from transplant surgery. ACR is most common in the first month and then tapers off in the ensuing months.

Table 1 A typical schedule for protocolled EMB following transplant

Post-transplant	Frequency of EMB	Other considerations
Month 1	Weekly	
Months 2–3	Every other week	More frequent if clinical concern
Months 4–6	Monthly	
Months 7–12	Every other month	Consider AlloMap
Year 1–2	Every 6 months	
Years 2–5	Yearly	
After 5 years	Not scheduled	EMB if there is concern for rejection

Acute cellular rejection is primarily a lymphocytic or T cell infiltration of the myocardium that is best diagnosed by EMB and light microscopy. The cells stain positive for CD4 and CD8. The infiltration of lymphocytes often accompanies myocyte injury and necrosis. The degree of cellular infiltrates and damage mirrors the severity of rejection. Hemodynamic compromise is rare and not often associated with lower grades of ACR. In rare cases, however, more advanced grades of ACR necrosis and diffuse cell injury will lead to compromise in the cardiac function.

Grading criteria for ACR were first published by the ISHLT in 1990 in an attempt to standardize the nomenclature and was then subsequently revised in 2004 (Stewart et al. 2005). Both the 1990 and 2004 have a grade 0 indicating no rejection. As the grade of rejection increases so does the severity of rejection. The 1990 criteria included grades 1, 2, 3 and 4; grades 1 and 3 included A and B subcategories for focal and diffuse. The 2004 nomenclature simplified the designation and is in current use today. Grades 0R, 1R, 2R, and 3R are the current designations. The "R" represents "revised." Grade 0 is no rejection, 1R is mild, 2R is moderate, and 3R is severe (Table 2).

Acute cellular rejection grade often informs the intensity of immunosuppression therapy recommendations. ACR Grade 0R is synonymous with normal cardiac myocardium as there is no finding of rejection (Fig. 1a, b). ACR Grade 1R is diagnosed when there is mild rejection depicted by a single focus of myocyte damage or focused perivascular infiltrate (Fig. 2a, b). Grades 0R and 1R are common and do not prompt a change in immunosuppression. Grade 2R is similar to Grade 1R but with at least two regions of myocyte damage (Fig. 3a, b). Grade 2R without hemodynamic compromise often prompts a brief increase in immunosuppression therapy, usually an increase in steroid dose, and repeat EMB in the near future. With diffuse perivascular infiltrates and multiple regions of myocyte damage and associated edema, Grade 3R is diagnosed (Fig. 4a, b). Grade 2R with hemodynamic compromise or Grade 3R is treated with robust immunomodulatory therapy, such as antithymocyte globulin and intravenous steroids.

Acute cellular rejection grading has been reported to have variability when Quilty lesions are present. Quilty lesions are nodular endocardial infiltrates comprised of plasma cells and B lymphocytes with surrounding T lymphocytes (Marboe et al. 2005). Quilty lesions generally do not portend adverse prognosis, and they are not reason to change immunosuppression therapy (Fig. 5a, b).

Acute cellular rejection often responds to a brief augmentation of immunosuppression in

Table 2 Nomenclature of ACR established in 1990 and revised in 2004

1990		2004	
Grade 0	No rejection	Grade 0R	No rejection
Grade 1, mild A – Focal B – Diffuse	A – Focal perivascular and or interstitial infiltrate without myocyte damage B – Diffuse	Grade 1R, mild	Interstitial or perivascular infiltrate with one focus of myocyte damage
Grade 2, moderate (focal)	One focus of infiltrate with associated myocyte damage	Grade 2R, moderate	Two or more foci of perivascular infiltrate with associated myocyte damage
Grade 3, moderate A – Focal B – Diffuse	A – Multifocal infiltrate with myocyte damage B – Diffuse infiltrate with myocyte damage	Grade 3R, severe	Diffuse infiltrate with multifocal myocyte damage, edema, hemorrhage, vasculitis
Grade 4, severe	Diffuse, polymorphous infiltrate with extensive myocyte damage, edema, hemorrhage, vasculitis		

Stewart et al. (2005)

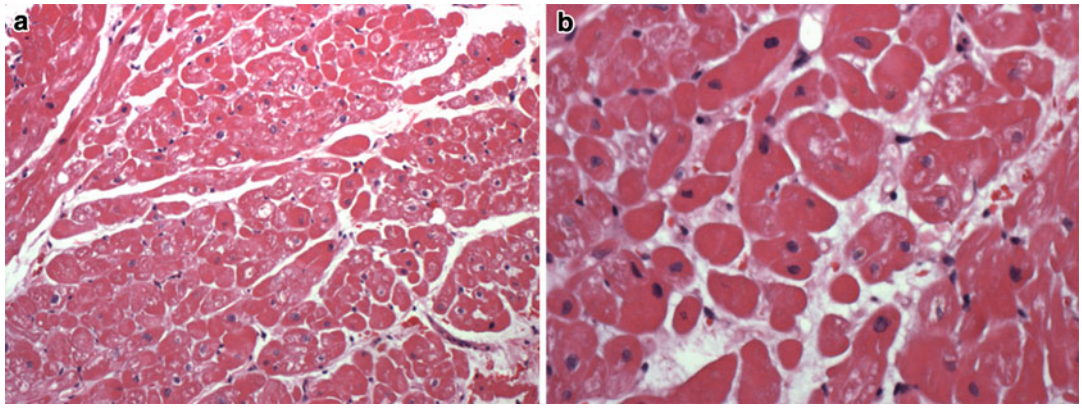

Fig. 1 Endomyocardial biopsy demonstrating acute cellular rejection (ACR) Grade 0R (**a**) low power and (**b**) high power. Normal myocardium with no evidence of rejection

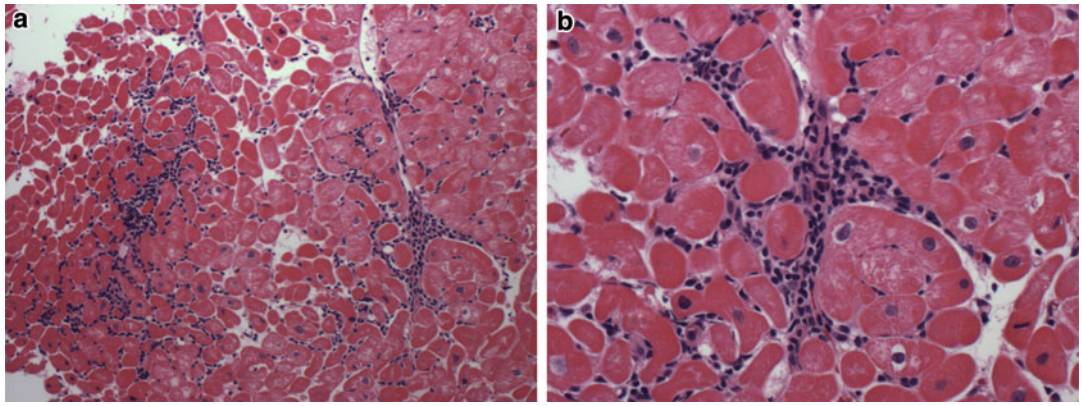

Fig. 2 Endomyocardial biopsy demonstrating acute cellular rejection (ACR) Grade 1R (**a**) low power and (**b**) high power. Mild (ACR 1R) rejection demonstrating one focus of interstitial infiltrate within the myocardium

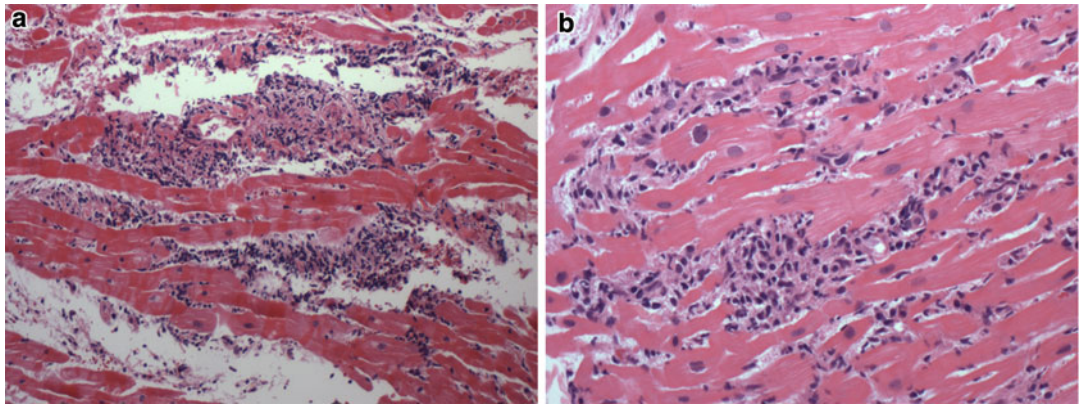

Fig. 3 Endomyocardial biopsy demonstrating acute cellular rejection (ACR) Grade 2R (**a**) low power and (**b**) high power. Grade 2R is similar to Grade 1R but with two foci of interstitial infiltrate and myocyte damage

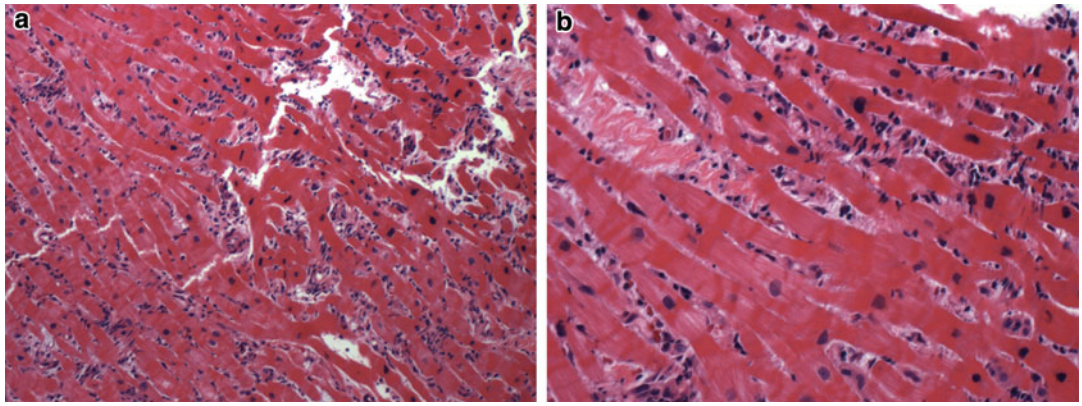

Fig. 4 Endomyocardial biopsy demonstrating acute cellular rejection (ACR) Grade 3R (**a**) low power and (**b**) high power. Grade 3R with multiple infiltrates with myocyte damage and vasculitis

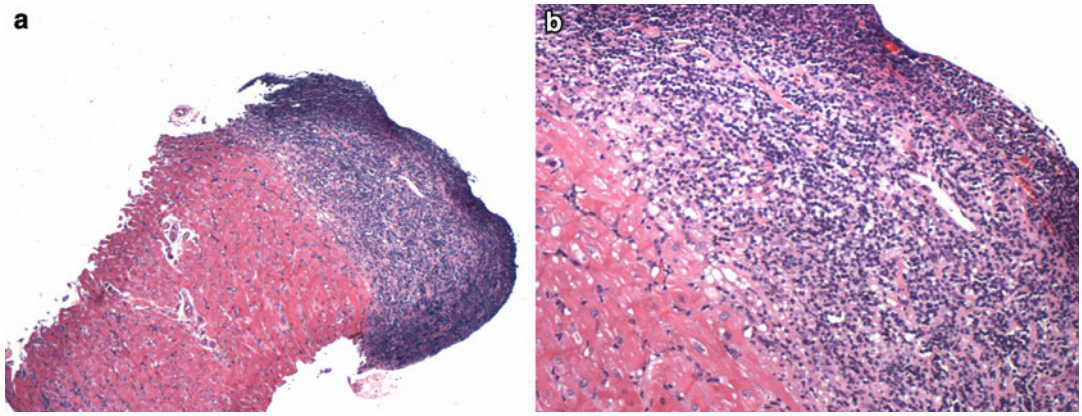

Fig. 5 Endomyocardial biopsy demonstrating a Quilty lesion (**a**) low power and (**b**) high power

nearly 90% of cases (and the correction of the underlying cause such as nonadherence). This ability to capture rejection early even when it is asymptomatic has greatly contributed to the success of cardiac transplantation in our modern era.

Antibody-Mediated Rejection

While contemporary immunosuppression regimens as well as the universal adoption of EMB-based surveillance protocols have attenuated the incidence of acute cellular rejection (ACR), this, however, has not been the case for antibody-mediated rejection (AMR) (Kobashigawa et al. 2011a). The diagnosis of ACR was well defined more than three decades ago; however, over the same period, there has been considerable debate regarding the existence of AMR (now widely accepted), development of criteria for AMR, and how to monitor for AMR. This occurred in part because the immunosuppression that allowed for a rapid increase in OHT survival in the 1990s has largely focused on T cell-related immunity, the main component of ACR. AMR is considerably more complicated involving primarily the B cell response, Ab production, antigen presentation, and in many cases activation of T cells (ACR and AMR have been reported to occur simultaneously) (Zeglen et al. 2009).

AMR is most often the result of circulation of antibodies directed at HLA class I and II antigens from the donor, non-HLA antibodies against endothelial cells, vimentin, or cardiac myosin

chains (Kobashigawa et al. 2011a). Vessel endothelial cells are the first cells exposed to circulating antibodies that initiate complement and the attraction of macrophages and neutrophils. It is therefore not surprising that AMR was first described as a rejection resulting from an arteriolar vasculitis by Herskowitz et al. in 1987 as J Heart Transplant (1987;6:127). The risk of AMR is higher among patients with previous LVAD, transfusion, previous pregnancies, elevated donor-specific antibody (DSA) development after transplant, higher panel-reactive antibodies before transplant, CMV positivity, and a prior transplant (Kobashigawa et al. 2011b).

The ISHLT first published diagnostic criteria for AMR (Reed et al. 2006). The ISHLT criteria for AMR as revised in 2013 are listed in Table 3.

EMB is recommended at established intervals based on the time from transplant; however that recommendation was traditionally based temporally on the risk of ACR. The EMB protocol is not specifically designed for monitoring AMR. Further, since AMR can occur early or late, a protocol design may not be practical. The highest risk for Ab development, and AMR, is early after transplant. Late AMR, years after transplant, has an increased risk for CAV and mortality at 1 year compared to early AMR. The difference in outcomes with early versus late AMR may be related to early diagnosis of AMR (early AMR) that is incidentally found during routine evaluation for ACR. Later, when ACR is not as likely and EMB is infrequent, AMR may develop and progress through a subclinical phase of an unknown duration.

Donor-specific antibodies (DSA) increase the risk of ACR, AMR, and CAV. Until 2010, DSA were required to diagnose AMR; however it is now realized that AMR can occur without significant DSA levels. In evaluating 221 heart transplant patients, Clerkin et al. reported 69 patients with DSA and 74 episodes of pAMR in 38 patients. In their study DSA were inadequate for the diagnosis of pAMR; however the presence of DSA increased the risk of graft dysfunction during pAMR (Clerkin et al. 2017). Novel noninvasive imaging modalities with cardiac MRI have been reported to be useful in detecting AMR particularly in EMB-negative biopsies (Butler et al. 2015).

Monitoring Donor-Specific Antibody

Prior to transplant a potential recipient has serum tested for existing antibodies. This panel of antibodies is termed the PRA or panel-reactive antibody. The PRA tests serum for existing antibodies against HLA (human leukocyte antigen) using lymphocytes in a panel created from approximately 100 blood donors. The higher the number (PRA%), the more difficult it will be to find a donor match. For example, if the recipient's PRA% is 30, then 3 out of every 10 donors will not be a suitable match for the recipient due to the risk of immunologic rejection. This is the general principle of recipient-donor matching; however PRA has further been refined. We all have a unique HLA panel that is mostly inherited. The PRA% will be representative of the HLA reaction

Table 3 Pathology definitions of pAMR

Pathologic antibody-mediated rejection (pAMR)		
pAMR 0	Negative for AMR	Histopathologic and immunopathologic negative
pAMR 1 (H+)	Histopathologic AMR alone	Histopathologic findings present **and** immunopathologic findings negative
pAMR 1 (I+)	Immunopathologic AMR alone	Histopathologic findings negative **and** immunopathologic findings positive; that is, CD68+ and/or C4d+ for IHC and C4d+ with or without C3d+ for IF
pAMR 2	Pathologic AMR	Histopathologic **and** immunopathologic findings are both present
pAMR 3	Severe pathologic AMR	Interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis, and/or karyorrhexis and marked edema **and** immunopathologic findings are present

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to numerous antigens that can be quantified. When an antigen, such as a virus, is presented on the surface of the cell, they are stimulating major histocompatibility complex (MHC) Class I. That family of antigens are labeled with A, B, or C (major antigens) or E, F, or G (minor antigens). HLA that are presented on the surface of the cell stimulate MHC Class II and are labelled as DM, DQ, DP, DR, DOA, or DOB. Any human serum tested for PRA will have reactivity to numerous antigens, and they will have variable clinical significance. The antigens listed by letter/letters and a number (such as B27 or DR4) are then entered into a database that will be able to account for the likelihood that a donor and recipient will match with a low risk of rejection.

HLA antigens do not change appreciably except for a few exceptions. A previous transplant has the highest risk of development of HLA antibodies (donor-specific antibodies). Pregnancy, especially with three or more pregnancies, may result in the development of new HLA antibodies. Blood transfusions have historically increased the risk of sensitization, but new filter techniques have lowered the risk (Bray et al. 2006; Nwakanma et al. 2007).

Although there is significant variability in the practice of monitoring DSA in the post-transplant period, the ISHLT guidelines recommends following DSA at 1, 3, 6, and 12 months postoperatively in all patients and in any patient who presents with evidence of graft dysfunction. After the first year, there is not strong data to support routine monitoring in patients who are at low risk, although most centers will continue to do so on an annual basis. Sensitized patients should continue to be monitored at more frequent intervals. Asymptomatic DSA does not warrant treatment, but should trigger closer evaluation of graft function and more frequent follow-up monitoring. If $C1q^{+}$ antibodies, graft dysfunction, or restrictive physiology are present, antibody treatment should be initiated (Kobashigawa et al. 2018).

Post-transplant desensitization protocols are similar to pre-transplant ones and are aimed at eliminating circulating antibodies in order to improve post-transplant outcomes. Common treatments include IVIg, plasmapheresis, immunoadsorption, and rituximab. IVIg appears more effective and better tolerated from an infection standpoint than plasmapheresis (John et al. 1999). Rituximab has been used successfully in combination with IVIg, with or without plasmapharesis (Kobashigawa et al. 2011c). Most recently bortezomib, a proteozome inhibitor initially developed for treatment of multiple myeloma, has been successfully used in reduction of alloantibodies in patients refractory to combination therapy of IVIg and rituximab (Patel et al. 2011). The utility of all desensitization protocols is limited by infectious complications and adverse side effects which should be carefully weighed against the benefits prior to initiating therapy.

Gene Expression, AlloMap

Gene expression profiling is a reliable option for noninvasive monitoring of acute cellular rejection (ACR) in patients at minimal risk for rejection starting 6 months post-transplant. The commercially available gene expression profile test, known as AlloMap, derives its strength from a high negative predictive value that essentially "rules out" acute cellular rejection in select patients. AlloMap is a noninvasive serum-based test of recirculating peripheral blood mononuclear cells (PBMC) that measures genes that are transcribed in the process of acute cellular rejection and myocyte injury. As there are numerous genes expressed at various levels during the cellular rejection process, and no single gene studied can predict rejection, AlloMap relies on measurement of a panel of genes. However, it cannot quantify the degree of rejection.

The Cardiac Allograft Gene Expression Observational Study (CARGO) evaluated gene expression in PBMC samples of cardiac transplant patients to discriminate between ISHLT grade 0 and ISHLT $\geq$3A (1990 nomenclature). From 252 candidate genes, the investigators developed a gene profile test utilizing 11 genes identified to distinguish between normal and allograft rejection; the profile also includes 9 genes for normalization and control. Those 11 informative genes code for many immune mechanisms of

upregulation and downregulation of cells to include T cells, NK cells, platelets, neutrophils, and monocytes. From clinical application standpoint, the gene expression assays are translated to a numerical score system ranging from 0 to 40. A high negative predictive value (99.6%) for grade 3 A rejection (2R by 2004 revised nomenclature) or higher was established with a score of <30 (Deng et al. 2006).

The Invasive Monitoring Attenuation Through Gene Expression (IMAGE) trial compared AlloMap testing to routine EMB in 602 patients transplanted between 6 months and 5 years. Where the CARGO study compared EMB findings to AlloMap score, the end point of the IMAGE study was allograft dysfunction, death, or retransplanation at 2 years. The cumulative end point was 14.5% with AlloMap and 15.3% with EMB, thereby demonstrating non-inferiority of AlloMap testing in patients at low risk for rejection more than 6 months post-transplant (Pham et al. 2010).

AlloMap was approved by the FDA in 2008 largely based on the CARGO study. The FDA has approved the test for patients 15 years of age or older at least 2 months post-transplant. Gene expression profiling is approved for the evaluation for ACR in patients with a low probability of moderate-severe ACR; the study is however not FDA approved for the evaluation of AMR. In a study of patients in the CARGO study, the performance of AlloMap was not influenced by the level of the most common immunosuppressive medications, cyclosporine, tacrolimus, and sirolimus (CARGO). Since the CARGO study excluded patients that received rejection therapy in the previous 21 days or a transfusion in the previous 30 days, the effect of those therapies on AlloMap score is not known. Starling et al. found that ≥20 mg of daily prednisone may artificially decrease the AlloMap score. The variability of a person's AlloMap score can predict future clinical events (Deng et al. 2014).

ISHLT Class IIa recommendations for AlloMap (Costanzo et al. 2010):

- Gene expression profiling (AlloMap) can be used to rule out the presence of ACR of grade 2R or greater in appropriate low-risk patients, between 6 months and 5 years after HT.

MicroRNA and DNA Testing for Rejection

Circulating microRNA molecules specific to cardiac rejection using serum analysis hold promise as an alternative to EMB. Ribonucleic acid (RNA) is a primary part of genetic expression. There are coding RNAs (messenger RNA) and many noncoding RNAs, such as microRNA (miRNA). miRNA originates in single-stranded RNA and forms a hairpin secondary structure that regulates posttranscriptional gene expression in target gene. The hairpin structure is approximately 70 nucleotides long and is enzymatic processed to the mature microRNA of approximately 22 nucleotides. MicroRNA was first discovered in 1993 by Lee et al. at Harvard University and further described as important regulator of cellular development and in metabolic regulation (Lee et al. 1993). One microRNA can potentially be related to hundreds of messenger RNAs and thereby responsible for phenotypical variability.

Gene expression, and thereby microRNA expression, is the earliest step in cardiac rejection and has the potential to diagnose rejection at its earliest signal. Van Huyen et al. studied 113 heart transplant patients and discovered microRNA expression identifying allograft rejection. Their study identified four microRNAs with serologic expression that strongly discriminated between normal and cardiac allograft rejection as diagnosed with traditional EMB. The microRNAs of interest for heart transplant rejection included genes expressed for endothelial activation (miR-92a), cardiovascular remodeling (miR-31), and inflammation (miR-92a and miR-155). Further, these genes identify cellular rejection and antibody-mediated rejection, as well as early and late rejection (Duong Van Huyen et al. 2014). Along these lines other noninvasive tests for rejection surveillance using blood marker have emerged. For instance, circulating donor cell-free DNA to total cell-free DNA ratio has been evaluated as a promising biomarker for rejection

monitoring (Pham et al. 2010). A high ratio of circulating donor cell-free DNA to the total cell DNA, at least 2 weeks post-transplant, is highly associated with rejection (Kobashigawa et al. 2014). Both miRNA and cell-free DNA testing can be used for AMR as well as ACR.

With further refinement and validation, these biomarkers for rejection have the potential to non-invasively diagnose rejection with greater accuracy than EMB.

Computed Tomography Monitoring for Rejection

Computed tomographic coronary angiography (CTA) does not have a role in the evaluation of cardiac rejection. The high heart rates that are often present in cardiac transplant patients preclude optimal CTA imaging techniques except in newer dual-source systems. In OHT patients, CTA will best be utilized for the evaluation of coronary artery vasculopathy (CAV) (Wever-Pinzon et al. 2014). If echocardiogram views are limited, CTA can also help evaluate RV and LV function but carries significant ionizing radiation exposure.

MRI Monitoring for Rejection

Cardiac magnetic resonance imaging (CMRI) is a noninvasive and non-irradiating imaging modality that can potentially detect the cellular changes associated with rejection. Although EMB is currently the gold standard for rejection monitoring, it has some pertinent limitations such as invasiveness and patient comfort. Furthermore, it only samples the right ventricle and may miss foci of rejection. On the other hand, CMR has the advantage that it is noninvasive and can in principle evaluate the entire heart. CMRI has been helpful in the diagnosis of myocarditis and stress cardiomyopathy (Takotsubo) (Abdel-Aty et al. 2005, 2009). A promising CMR modality for detecting rejection is the use of T2 quantification (relaxation time), which can be used to measure myocardial tissue contrast based on the relaxation time decay after an excitatory pulse. Longer T2 relaxation time is associated with acute rejection (Butler et al. 2009). A longer T2 time has a high negative predictive valve (97%) for detecting ACR grade 2 (Taylor et al. 2010). When CMRI was compared to EMB in 60 patients, the presence of ACR $\geq$ 2 or AMR, CMRI had a high sensitivity and negative predictive value in predicting biopsy-proven rejection. The indicators of rejection by CMRI, T2 relaxation time (detecting edema), and RVEDVI may be helpful in diagnosing rejection in otherwise biopsy-negative rejection (Butler et al. 2015).

Conclusion

Cardiac allograft rejection is common especially early on after transplantation. In contrast to antibody-mediated rejection, the incidence of acute cellular rejection has been decreasing although still remains the commonest form of rejection. While rejection is a perennial risk, it is however time-dependent, attenuating over the years. Rejection can lead to allograft dysfunction including the untoward downstream acceleration in the development of allograft vasculopathy. It is thus imperative to monitor for rejection to preserve allograft function. Endomyocardial biopsy still remains the gold standard test for rejection surveillance. There are however promising novel, noninvasive, rejection monitoring modalities that are emerging and increasingly being incorporated into clinical practice.

Cross-References

- ▶ Chronic Rejection
- ▶ Contemporary Survival in Heart Transplantation
- ▶ Matching Donor to Recipient
- ▶ Pathophysiology of Heart Failure

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Part X

The Contemporary Successful Heart Transplant Program

Regulatory Agencies

20

Nicole A. Pilch

Contents

Abstract

"Regulatory Agencies and Heart Transplantation" provides an overview and history of the evolution of regulatory oversight. Specifically, this chapter will focus on OPTN/UNOS and CMS and provide navigation through these regulatory bodies and identify areas in which heart transplant team members should focus their understanding. Discussion about the UNOS Membership and Professional Standards Committee, the Scientific Registry of Transplant Recipients will also be detailed. An overview of for-cause and on-sight surveys will provide the reader insight into the regulatory world. Common methods to prepare for site surveys and a general overview of regulatory inquiries are provided. The reader will also find a detailed discussion of UNOS and CMS required quality assurance performance improvement (QAPI) programs which includes common methods to obtain data. Finally, this chapter provides a list of common regulatory resources that can be accessed quickly to facilitate regulatory oversight of heart transplantation in a single center.

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Organ Procurement and Transplantation Network (OPTN) · National Organ Transplant Act (NOTA) · Health and Human Services (HHS) · Scientific Registry of Transplant Recipients (SRTR) · United Network for Organ Sharing (UNOS) · Centers for Medicaid and Medicare (CMS) · Quality Assessment Performance Improvement (QAPI) · Membership and Professional Standards Committee (MPSC) · Performance Analysis Improvement Subcommittee (PAIS) · Policy Compliance Subcommittee (PCSC) · Health and Human Services Health Resources and Services Administration (HRSA)

Introduction

Solid organ transplant, including heart transplant, is under significant governmental oversight. There are several governing bodies which regulate every nuance of heart transplant from the evaluation of a potential candidate through their posttransplant care. The next several sections will discuss the general regulatory oversight of all of solid organ transplant and then identify specific issues and resources for heart transplant. The regulatory landscape within transplant is constantly changing with new policies, bylaws, federal regulations, and their revisions. As a consequence, this chapter will not address the specifics but will provide a roadmap to identifying which resources are needed for new or established heart transplant programs.

The Final Rule

On October 19, 1984, the landscape of transplant became more solidified with the passage of the National Organ Transplant Act (NOTA) (42 USC 201) (National Organ Transplant Act 1984). This act established a task force to look at all facets of organ transplantation from ethics to cost of each phase of transplant including donation. This act also established an Organ Procurement and Transplantation Network (OPTN) and oversight of this network by the Secretary of Health and Human Services (HHS) was established by the OPTN final rule (National Organ Transplant Act 1984) (Organ Procurement and Transplantation Network: Final Rule 2005). The OPTN was required to be a private, non-for-profit entity which was charged with creating and overseeing policies that establish several things including (but not limited to): (1) the composition and minimum education/experience requirements for members of the individual transplant center's team, (2) testing/laboratory requirements for candidate evaluation/listing and listing certification to establish disease state severity, (3) organ allocation/placement and continual evaluation of organ allocation based on geography, disease state severity to maintain equity congruent with the Final Rule, (4) posttransplant follow-up and outcomes requirements and oversight as a means to also maintain equity and appropriate use of organs, (5) procedures and reporting to maintain patient safety and public health, and (6) education about organ transplantation (National Organ Transplant Act 1984; McDiarmid et al. 2008). However, most importantly, NOTA established that the OPTN create and oversee the national transplant registry to facilitate organ matching (Leppke et al. 2013). The goal was to have an OPTN that was free from political bias and would independently work to ensure organ transplantation was fair and equitable over time. The current contracted private entity that serves as the OPTN is the United Network for Organ Sharing (UNOS). Interestingly, OPTN rules are not laws and cannot be enforced. However, in 2007, the Centers for Medicare and Medicaid put forth their conditions of participation for transplant centers which allowed OPTN rules to be enforceable if a center wanted to transplant Medicare patients (Cameron and Sullivan 2013). These conditions indicated that in order to meet the CMS conditions of participation, the center would have to be a member of the OPTN in good standing, therefore making OPTN/UNOS bylaws a requirement (Cameron and Sullivan 2013).

UNOS as the OPTN

The OPTN bylaws (https://optn.transplant.hrsa.gov/governance/bylaws/ [accessed 1/4/19]) are required to be followed by UNOS and drive UNOS policy development and revisions. The OPTN bylaws outline the membership requirements for various entities including the transplant hospital and prescribe what services and affiliations they must have to perform transplants. The bylaws also single out individual organ transplant programs and their membership and personnel requirements. Appendix H of the bylaws provides the membership and personnel requirements for heart transplant programs. The bylaws provide pathways for the primary heart transplant surgeon and physician to oversee heart transplant at their center. Each center is required to identify and designate a primary heart transplant surgeon and physician. Individuals designated as the primary surgeon and physician are responsible for compliance with the bylaws and therefore adherence to UNOS policies (Organ Procurement and Transplantation Network (OPTN) bylaws 2018).

The Membership and Professional Standards Committee (MPSC) is a standing OPTN committee made up of a transplant professional peer team. The MPSC is further broken down into two standing functional areas: (1) the Performance Analysis and Improvement Subcommittee (PAIS) responsible for reviewing member performance metrics such as post-heart transplant 1-year patient and graft survival and (2) the Policy Compliance Subcommittee (PCSC) responsible for reviewing member compliance with OPTN bylaws and policies (Organ Procurement and Transplantation Network (OPTN) bylaws 2018). Once cases are reviewed and due process is completed as delineated by the bylaws, the MPSC can make recommendations to the OPTN Board of Directors about the member (Organ Procurement and Transplantation Network (OPTN) bylaws 2018). Historically, these committees functioned as true committees and members of the MPSC would be on either of the committees. As of summer of 2019, these committees were functionally dissolved meaning that all members of the MPSC review cases that are PAIS or PCSC related. To understand the implications of the OPTN/UNOS MPSC function and how it relates to the transplant center, we will explore its functionality further.

UNOS MPSC

It is important to have an understanding of UNOS and the MPSC. The MPSC works to improve the culture of safety and high reliability within transplant programs through a peer review process (McDiarmid et al. 2008). Centers are encouraged to report errors and help other centers identify areas of opportunity to prevent future events. Without reporting and self-reporting, systems of care cannot be corrected. Therefore, reporting to UNOS should be done without fear of UNOS actions. The MPSC is also charged with ensuring that public safety is considered when reviewing cases involving patient safety or policy/bylaw violations (McDiarmid et al. 2008). UNOS policies and bylaws are constantly evaluated and must be modified to keep pace with the ever changing landscape within organ donation and transplant (McDiarmid et al. 2008). As such the activities of the MPSC are constantly changing along with potential adverse actions.

The MPSC peer team is primarily responsible for: reviewing new program or programmatic leadership applications, conducting ongoing, confidential peer review of UNOS policy and bylaw violations, as well as evaluating programmatic outcomes based on flagging criteria (McDiarmid et al. 2008). The MPSC meets three times per year and holds monthly or as needed conference calls (McDiarmid et al. 2008). The membership consists of 33 members of the transplant community which represent all facets and aspects of transplant including the patient perspective (McDiarmid et al. 2008). The MPSC considers applications to ensure that the center is meeting UNOS policies and bylaws, and when anomalies arise, they reach out to the center for clarification or explanation. The MPSC also considers findings from routine and MPSC-directed on-site surveys. In the event

of a concern for noncompliance, the MPSC conducts a confidential peer review. Several actions can be taken and are prescribed in the UNOS bylaws. The MPSC facilitates due process and attempts to engage the member in the peer review process. If the MPSC decides to take an adverse action that impacts the ability of the center to perform organ transplants, the action needs to be approved by the UNOS board of directors and a recommendation made and approved by the secretary of HHS (McDiarmid et al. 2008). If a center is put on probation or becomes a "Member Not in Good Standing," this is a public announcement that goes to the press, patients, and other federal bodies such as CMS (McDiarmid et al. 2008; Organ Procurement and Transplantation Network (OPTN) bylaws 2018). These actions require the member to put corrective action plans in place and are frequently subject to external on-site reviews. The outcome of these adverse actions often has a "waterfall effect" in which other payers, referring providers, and potential candidates may avoid the center. Centers have the option of voluntarily inactivating their transplant program to avoid these adverse outcomes.

New members of a heart transplant team should be encouraged to review the relevant UNOS policies and bylaws (https://optn.transplant.hrsa.gov/governance/policies [accessed 2/13/19]) which provide a framework for each center and should be used as a blue print for internal policy and workflow development. In addition, UNOS prescribes requirements for who can be a primary heart transplant surgeon and physician. There are several pathways to obtain approval from the MPSC to oversee the program.

It is not uncommon to wonder how or why a center would receive a letter from the MPSC and how the center should respond. Letters from UNOS may or may not be from the MPSC; they could simply be inquiries about potential policy violations. For example, if a center is allocated a heart for the patient at sequence 1 and the center places the organ at sequence 6 without adequate explanation in records submitted, UNOS may inquire why the organ was placed out of sequence. The center would need to explain why and frequently there is a good reason and not a policy violation. In the event that there is a policy violation, the center would receive a letter from UNOS and be required to submit details about the violation and an action plan detailing how you will prevent this event from happening again. Policy violations that are frequently occurring across the country will trigger the MPSC to look at the policy and or determine if alternative actions need to be implemented. Alternatively, a center may fall into a PAIS review for outcomes. The PAIS review will require several items to help the committee understand the status of the program, what improvements have been made, and what the center intends to do to improve outcomes or volume. These responses do take time to collate; however, the idea is that the center is aware of outcomes or volume anomalies and has been proactive based on their Quality Assurance Performance Improvement Program (QAPI) to implement action items (see specific section). For centers that have not set up this infrastructure, creating and implementing a QAPI program is frequently part of the action plan. The MPSC is geared towards helping the center improve through the peer review process and prevent the center from entering into a scenario in which they lose the ability to perform organ transplants by action or design.

Scientific Registry of Transplant Recipients (SRTR)

When NOTA was passed in 1984, there was also a provision that mandated that a scientific registry of all transplant recipients be established (Leppke et al. 2013). The development of the SRTR was a remedy to that requirement with the goal to evaluate all solid organ transplant candidates, donors, and recipients and ensure ongoing evaluation of the status of organ transplant (Leppke et al. 2013). The SRTR was initially managed by UNOS but has moved to several entities overtime. Currently, SRTR is managed by the Chronic Disease Research Group of the Hennepin Healthcare Research Institute under contract from the US Department of Health and Human Services Health Resources and Services Administration or HRSA

(Leppke et al. 2013). All transplant programs are required to submit patient and donor level data to UNOS who in turn collaborates with the SRTR to provide publically available data on each transplant program on a continuous basis (Leppke et al. 2013; Kasiske et al. 2016). The formation of a national, mandated registry is relatively unique to solid organ transplant. This registry is required to allow for analysis of program specific outcomes. Programs that do not supply the data accurately or timely can be cited by CMS as out of compliance with the conditions of participation for data submission (https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/downloads/SCLetter08-25.pdf2008, accessed 2/12/2019). The overall intent of establishing an entity that would oversee transplant data was to ensure that equity and oversight of transplant was ongoing (Cameron and Sullivan 2013).

Outcomes must be reported at least twice a year per the HHS final rule from March of 2000, and therefore, the SRTR provides program-specific reports (PSRs) every 6 months (Leppke et al. 2013). Data is provided from the OPTN/UNOS monthly (Leppke et al. 2013). Data that will be analyzed in the PSR is made available to each center during a "data integrity" period which occurs 2 months prior to the secure report release. This period occurs 1 month before the data lock of the next report. Reports are published to the public every January and July but securely released the month before to each center in December and June. It is extremely important for centers to evaluate the data that is going to be considered during the data integrity periods (October and April). The SRTR releases a report and flags missing values and outliers to centers on their secure site (https://securesrtr.transplant.hrsa.gov/ [accessed 2/13/19]). Since the data from the center is frequently manually entered or validated in the "Transplant Information Electronic Data Exchange" or TIEDI, which is the electronic platform established in 1996 to capture transplant center and organ procurement organization data, it can be prone to error. Program directors need to provide oversight to make sure the appropriate variables are captured to ensure that the SRTR risk model best predicts the expected number of events for their program. The risk models are also published on the SRTR website (www.srtr.org), and the variables for heart transplant patient and graft survival are available for review. So how does data integrity impact a center? Centers are judged based on the risk model's prediction of the expected number of patient deaths and graft losses.

Most centers who continuously evaluate their data will be able to anticipate if their outcomes are close to the UNOS flagging threshold. However, if they do not have a system internally to help them review their outcomes to anticipate flagging, the SRTR has some tools. Specifically, each secure report has a tool embedded within the raw excel data file available to each program in which you can enter anticipated outcomes and identify if the center will be flagged. In addition, each secure report contains a CMS/UNOS flagging report that allows the center to anticipate if they will be flagged with the release of the next PSR. The SRTR also provides a CUSUM chart or cumulative sum to aid centers in tracking their performance between reports. The CUSUM tool is best used to illustrate spikes in untoward outcomes which may lead to outcomes flagging (Snyder et al. 2014). This tool is available monthly on the center's secure SRTR website and has a detailed explanation of the tool methodology and caveats to its use. It is important to recognize that the CUSUM is only as good as the data SRTR has therefore if all the data has not been reported for a patient or allograft loss or all the risk elements are not captured the signal may not be accurate (Snyder et al. 2014). CUSUM should be considered another mechanism for outcomes tracking in conjunction with other tools.

Every transplant program is required to provide their SRTR outcome to prospective patients and confirm that the patient understands the outcomes of the program before transplant (https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/downloads/SCLetter08-25.pdf2008, accessed 2/11/19). The PSR details information about the individual center's waitlist, including potential recipient characteristics and waitlist mortality as well as organ acceptance and transplant rates in

conjunction with the center's 1- and 3-year allograft outcomes.

The traditional focus has always been on 1-year patient and allograft outcomes as these outcomes are scrutinized by CMS. Failure to meet outcomes requirements may lead to condition level deficiencies which could trigger loss of Medicare funding for a program. Each PSR contains 2.5-years' worth of transplant outcomes for each individual program which consists of five 6-month cohorts (Table 1) (Kasiske et al. 2016). There are some caveats to note about the reports. It is important to understand that the data appears delayed, but this is to ensure the appropriate follow-up time. For example, the July 2019 SRTR PSR will include patients transplanted from 1/1/2016 through 6/18/2018 for analysis of 1-year outcomes (Table 1). Patients transplanted in the last 6 months of the cohort of the final reporting period will only have observations in the report up to 180 days. Therefore, a patient in cohort 5 (Table 1), who ended up having a graft loss or experienced death at 182 days, would not have their outcome counted until the next reporting period. Each section of the PSR has a detailed explanation of the technical methods and is available to the public at www.srtr.org [accessed 1/15/19].

The UNOS PAIS subcommittee of the MPSC will evaluate programs that demonstrate lower than expected 1-year patient or graft survival but they have a lower threshold for reviewing programs versus CMS. UNOS bylaws evaluate programs in which the: "(1) probability is >75% that the hazard ratio is >1.2 or (2) probability is >10% that the hazard ratio is >2.5."[1] Centers identified for review will be asked to submit and confirm their data, discuss why they have outcomes anomalies, and elaborate what they have done or plan to do to improve their outcomes. The intent of UNOS is to flag centers earlier and provide support to help them improve their outcomes and avoid CMS condition level flagging.

Table 1 Program-specific report July 2019 SRTR PSR five cohort examples

Cohort	Transplant dates
Cohort 1	1/1/2016–6/30/2016
Cohort 2	7/1/2016–12/31/2016
Cohort 3	1/1/2017–6/30/2017
Cohort 4	7/1/2017–12/31/2017
Cohort 5	1/1/2018–6/30/2018

SRTR upcoming reporting can be found at https://www.srtr.org/reports-tools/psr-reporting-timeline/ [accessed 1/15/19]

Prior to December 2017, the CMS flagging criteria evaluated 1-year patient and allograft outcomes and would cite the center at a standard level if the following three criteria were met: (1) the observed outcomes – expected outcomes >3, (2) the observed outcomes/expected outcomes >1.5, and (3) one-sided p-value <0.05 (Kasiske et al. 2016). This would move to a condition level if these three criteria were met in at least two of the last five consecutive PSRs (Kasiske et al. 2016). The challenge to this strategy is that centers were being flagged based on very old data which may have come from distinctly separate cohorts of patients. On December 16, 2016, CMS released an updated memo which changed the flagging thresholds (https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Downloads/Survey-and-Cert-Letter-17-13.pdf [accessed 1/18/19]). A standard level deficiency would stay the same. However, to be flagged at a condition level, the following criteria would now need to be met: (1) observed events-expected >3, (2) observed/expected >1.85, and (3) one-sided p-value <0.05 (https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Downloads/Survey-and-Cert-Letter-17-13.pdf [accessed 1/18/19]). Also instead of CMS looking backwards at previously reported cohorts, they will evaluate performance going forward and identify if the program continues to trend in the wrong direction. The memo indicates that if continued outcomes anomalies are noted on subsequent reports, then CMS would consider the center to be out of compliance at a condition level and this may trigger and on-site survey (https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Downloads/Survey-and-Cert-Letter-17-13.pdf [accessed 1/18/19]).

The outcomes thresholds have been a significant point of contention among transplant

programs. Private payers are also holding centers to outcomes requirements that are at times more stringent than CMS. Private payers request information from the centers and use outcomes data to identify certain centers as "centers of excellence" (Kasiske et al. 2016). If this designation cannot be obtained, the transplant center is in jeopardy of not being able to perform transplants in those beneficiaries or plea on a case-by-case basis. In addition, if a center loses CMS certification for outcomes, most private payers have a provision that indicates that in order for their beneficiary to have a transplant at a specific center, the center must be approved by Medicare. The ripple of effect of poor outcomes can last several years for centers, and it is essential to be proactive to ensure outcomes are analyzed and that all the risk model variables are captured.

It is interesting that the Trump administration (2018) put out a proposal to deregulate transplant. The "Medicare and Medicaid programs; regulatory provisions to promote program efficiency, transparency and burden reduction" proposed removing outcomes and volumes thresholds for program reapproval (https://www.federalregister.gov/documents/2018/09/20/2018-19599/medicare-and-medicaid-programs-regulatory-provisions-to-promote-program-efficiency-transparency-and [accessed 1/18/19]). As of September 30, 2019, there was an announcement to remove outcomes and volumes requirements for reapproval of transplant programs as part of the "Omnibus Burden Reduction Final Rule" (https://federalregister.gov/d/2019-20736).

Centers for Medicare and Medicaid

CMS is the largest payer in solid organ transplantation (Hamilton 2013). In order for a heart transplant center to accept Medicare and Medicaid, they must meet the conditions of participation set forth for transplant hospitals. The Centers for Medicare and Medicaid Services (CMS) final rule was published on Friday, March 30, 2007, and set the conditions of transplant hospital participation. In simplified terms, if centers do not meet the conditions of participation based on site survey findings or from the SRTR prescribed outcomes, they are in danger of losing CMS funding for that program. If the center does not meet the outcomes or volumes thresholds and are flagged by CMS at a condition level, they can apply for "mitigating factors." What are mitigating factors? Simply speaking, the center must tell a prescribed "story" utilizing the framework set forth by CMS to articulate why the SRTR model did not predict the outcomes of the center appropriately, or that the center has put systems in place that are not reflected in the SRTR outcomes. For example, if a heart transplant center was flagged at a condition level for outcomes and they are not showing any improvement, they would need to explain the factors behind the SRTR model's inability to predict their data appropriately. Perhaps the center is taking on more highly sensitized patients and desensitizing them but unfortunately experiencing a higher degree of graft loss. The risk model does not consider this high-risk group, and if you remove them from the data and rerun the SRTR model, the center may be able to demonstrate that their innovation is not represented by the model. Alternatively, a center could be using an experimental, post-harvest heart pump to preserve heart tissue longer and enable longer cold ischemia times; however, early in its use, there was a high rate of primary graft dysfunction which required a higher than expected number of re-transplants. The mitigating factor has to occur before the data is released and the center must demonstrate that they are improving (Cameron and Sullivan 2013). The center has 210 days for mitigating factors to be evaluated which allows for additional programmatic outcomes to be considered (Hamilton 2013). If CMS does not accept the mitigating factors application, then the center has three options: (1) voluntary closure, (2) involuntary closure, or they may be offered a (3) systems improvement agreement (Cameron and Sullivan 2013). The system improvement agreement or SIA is a legal contract between the center and CMS. The center enters into a probationary period and must notify all of its patients of its status (Cameron and Sullivan 2013). During an SIA, frequently CMS requires external consultants to come to the program and evaluate everything

from policies and procedures to staffing and their quality assessment and performance improvement program. The external reviews and all programmatic improvements that CMS requires must be completed and are at the expense of the center. If the program fails to meet the requirements of the SIA, they are closed and they cannot appeal the decision (Cameron and Sullivan 2013). Anecdotally, programs that have gone through mitigating factors process or been subject of an SIA indicate that it does lead to sustained improvements in the program and does foster more internal oversight of policies, procedures, and analysis of quality outcomes. The Omnibus Burden Reduction Final Rule changes have quickly modified the landscape in transplant as mitigating factors and system improvement agreements are no longer needed for reapproval since the outcomes requirements have been removed (https://federalregister.gov/d/2019-20736). Mitigating factors and system improvement agreements are still options for initial approval of programs or for programs that are restarting. A working knowledge of the history is needed as true employment of the changes has not been fully realized and the transplant community is still held to outcomes from a UNOS/MPSC perspective.

Quality Assessment and Performance Improvement (QAPI)

Each transplant program is mandated by CMS conditions of participation and the UNOS bylaws to have a QAPI program (Hamilton 2013). This program is responsible for ongoing evaluation of data within the program. The goal is that each transplant program is proactive and is able to identify anomalies that may contribute to lower than expected volumes or outcomes before they become subject to flagging by UNOS or CMS. Each program is required to develop a QAPI policy which details who leads the QAPI, how metrics are identified, and how data is evaluated. Also, centers are required to have a process and outcome measure in each phase of transplant (pre, peri, post) along with analysis of performance. Table 2 illustrates potential process and outcomes

Table 2 Example process and outcome measures by phase that may be used for QAPI

Category	Process	Outcome
Performance	Time from listing to transplant Time from referral to evaluation Time from evaluation to selection Time from selection to listing	Transplant volume Referral volume Selection volume Listing volume Number of bridge to transplant left ventricular assist devices performed
Pretransplant	Time from listing to non-transplant outcome (death, delisting) Policy related – Listed and notified within 10 days Policy related – ABO verification correctly done at listing per center policy	Waitlist mortalities Outreach event and new referral obtained Financial clearance obtained within 10 days of selection committee approval
Perioperative	ABO verification in the OR Cold ischemia time Organs declined and transplanted at other centers	Blood product use in the OR Need for extraordinary measures (ECMO, RVAD) Incidence/ severity of primary graft dysfunction
Posttransplant	Length of stay outliers 7-, 14-, or 30-day post-discharge readmission Time within therapeutic range for immunosuppression Time to first readmission	Incidence/ severity of rejection Incidence/ severity of opportunistic infections Protocol adherence Surgical complications Medical complications
Overall	Patient/graft survival	Patient/graft survival

measures that could be tracked. It is important to define these metrics to ensure that a process and outcome measure exists in each phase. Frequently, process and outcome can be interchangeable. Therefore for consistency, it is beneficial to designate the category of the metric and the specific tool (scorecard, dashboard, etc.) used to track them. The center must be able to articulate how they choose metrics (**QA**PI) and what process improvement (QA**PI)** methods they use when metrics are not meeting goals. Each program must also detail what their definition of an adverse event is, what is done to review it, how these events are tracked, and how actions to prevent a repeat of the adverse event are implemented (Reich 2013). There are many ways to implement these regulations. Some centers meet weekly for a short period of time to review data whereas others wait for quarterly meetings. The key is that the center's actions are the same as what they said in their policy. Also, that QAPI activity and meetings are not stagnant. For example, if the team notes a recent increase in the number of poor patient outcomes, the center's quality/clinical/operational leadership should increase the frequency of meetings and data review. It is also beneficial to select metrics thoughtfully. For example, a common metric identified for pretransplant could be waitlist mortality. However, if a center only had one in the past 12 months, is this meaningful to track? The metric should provide value to the patient, team, and organization (Mathur and Talwalkar 2018). The QAPI program must have bidirectional flow of information meaning that the transplant program must have a method to communicate all the way up to the board of directors and the information must flow back down to the program as well. The intent is to ensure that transplant programs have enough hospital oversight and support to maintain positive outcomes and utilize organs in a judicious way.

How should a center acquire data for QAPI? This is a common and dynamic question. There are several resources available simply by completing the required data submission to UNOS. Each center has access to waitlist metrics, organ offers, and transplants performed at their center. The Standard Transplant Analysis and Research (STAR) report is available for each organ, and field descriptions are also available in the files. This is an exceptionally powerful tool that allows tracking your center's data and keep up on patient and allograft losses as long as the center is reporting as prescribed. UNOS also has reports about specific organ procurement organizations, and organs offered to you, and what happened to them if you turned them down. Beyond individual center reports, there are reports about each center's waitlist and how the center compares regionally and nationally. These data are published monthly and available in the "data services" section of the center's UNET (UNOS's secure enterprise) profile. SRTR also has several tools that allow centers to look at their data during the secure release and with the public release. The SRTR section contains links to the SRTR website and time spent navigating the site is well spent to secure understanding of risk model elements and the methodology behind the reports that are published. Internally it is helpful if the center's medical record can identify transplant recipients and be able to pull additional data from them. However, using data from the SRTR files to go back to the center's records, either manually or with the use of analytics, can also help centers identify and track their transplant patients. Most centers have the infrastructure in place to identify transplant patients for Medicare cost reporting purposes which aids in covering some of the pretransplant expenses. Electronic medical record systems across the country have also been leveraged to find transplant data. Queries to other centers, using the same system, can help with report building and patient identification to minimize the need for manual chart abstraction as much as possible.

What Happens During a Survey?

There are several survey experiences that a heart transplant program may encounter. The three main regulatory bodies that the heart transplant team will interact with during their tenure of practice would most likely be CMS, UNOS, and the Joint Commission.

CMS will visit a program for initial certification, recertification (every 5 years https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Downloads/QSO-19-11-Transplant.pdf [accessed 2/13/20]), and for cause. These surveys are unannounced but likely expected if the center applies for a new program or they know where they are on the recertification cycle. The CMS survey involves the surveyors entering the center and indicating the intent of the survey. Most centers have an infrastructure and alert system to indicate when surveyors are here. The surveyors will initially ask for a set of documents which includes lists of patients and policies. The list of required documents is published online and is usually kept in a location (physically or electronically) where they can be accessed quickly for the surveyors (https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/SurveyCertificationGenInfo/Downloads/SCLetter09-09.pdf, accessed 1–19-19). Leading up to an expected survey, it is important that all policies and procedures are reviewed. Practice and workflows should reflect internal policy and compliance with UNOS and CMS policies. The CMS interpretive guidelines help centers discern what CMS requires and what the CMS surveyor will be looking at. The CMS unannounced survey will generally last 1–2 days for single programs and up to 5 days for a full center survey. The more prepared the center is in turning over documents to the surveyor, the quicker they can conduct their survey activities. The surveyor will trace patient records to ensure compliance with internal policies and examine internal policies to ensure that they are compliant with UNOS and CMS. The CMS survey particularly focuses on the multidisciplinary team. They want to ensure that each person serving in the designated role has the appropriate level of training and is truly a member of the multidisciplinary team. Specifically, that each team member is integrated into each phase of care and that the team member can articulate it during an interview with the surveyor. Also, there should be evidence of the team member's involvement in each phase of transplant within the medical record. Surveyors will try to visit every aspect of care in person from the clinic to the wards and intensive care unit. They will also attend QAPI meetings and patient selection meetings if they occur while they are surveying the center. CMS surveyors will also reach out to patients in person or if unavailable, they will talk to patients who are not currently in the facility but are on their roster of patients selected for the audit. They want to ensure that their beneficiaries are receiving optimal care and communication from the transplant team. Oftentimes this is a shining moment during the survey and illustrates the hard work of the multidisciplinary team. Some example questions that are asked during a CMS survey that can be used for "just-in-time" training are listed in Table 3. Several of these questions can be used to educate the multidisciplinary team about the transplant centers policies and how they are aligned with UNOS and CMS policies.

The CMS surveyors can also come for a focused QAPI survey and simply evaluate the QAPI program (https://www.cms.gov/Outreach-and-Education/Outreach/OpenDoorForums/downloads/qapiworksheet9810.pdf, accessed 1–16-19). The QAPI program, as discussed, is a requirement for each center to demonstrate how they evaluate and track outcomes and use this information for process improvement. This survey also focuses on evaluating the process the center uses to identify adverse events and prevent them from happening again. It is important that the QAPI program keeps consistent minutes and attendance logs to demonstrate the nuances of the meetings and that the attendees are a representation of the multidisciplinary team. Surveyors will want to see examples of the multidisciplinary team's involvement in identifying areas of opportunity and how they use the metric information to improve processes.

UNOS can have MPSC-directed site visits or routine site survey visits. MPSC-directed site visits look and feel more like CMS visits. They can be announced and typically involve a review of all aspect of the program in question. In contrast, UNOS site recertification surveys are announced. UNOS will typically notify the center in advance and provide a list of patients and items they will be reviewing. This allows time for the center to review the records and have them ready for the surveyor.

Table 3 "Just-in-time training": potential CMS surveyor questions during initial and recertification visits

Informed consent process	Tell me about your informed consent process used during the transplant evaluation? How are patients consented for the heart transplant procedure?
Selection and wait-listing	How is it communicated to patients that are deemed not a candidate by the selection committee? What happens when patients are too sick for transplant? What is the notification process for taking them off the list? Tell me about your process for referral to selection What are patients told about CMS certification at your center?
Organ verification in the OR	How is organ verification performed in the OR?
Referring providers	How does your center interact with referring providers? What happens after a patient is transplanted? Is there a process to notify referring providers? How are referring providers educated about transplant and the process at your center?
Multidisciplinary team education	How do the physicians educate the nursing staff and other multidisciplinary care team members? How to the staff taking care of patients at the bedside and the multidisciplinary team keep up on education?
Onboarding/orientation of multidisciplinary team	What is the onboarding process? What competencies are completed?
QAPI	Tell me about your QAPI meetings. Who attends, what do you do there? What do you use to track quality assessments? What happens if there is an adverse event? How is it tracked? What process improvement projects are you currently working on?

This focus of the routine site survey is to ensure that the center is following UNOS policies. For example, appropriately removing patients from the transplant waitlist once transplanted. All the center elements are collated and elements that cannot be verified will be deemed unverified. Centers are then given clinical and administrative score based on the total number of elements evaluated. The scores and survey findings are communicated to the MPSC PCSC. The PCSC will review the findings and provide a recommendation about additional actions. High clinical and administrative scores will release the center from further monitoring in most cases. Lower scores may cause the center to be subject to further monitoring. Any unverified element will require an action plan to alleviate further errors.

Finally, the Joint Commission will perform reviews most often at a center level unless there is a specific complaint filed about a transplant patient. During a Joint Commission visit, the surveyors may review disaster preparedness policies and review plans for organ transplant during a natural disaster. Joint Commission surveys are typically focused on evidence of hospital-wide compliance with Joint Commission standards based on area. Patient tracers may include transplant patients. Table 4 provides some helpful resources for heart transplant regulatory oversight.

Table 4 Resources for heart transplant regulatory oversight

Online resources	
UNOS	https://unos.org/
OPTN bylaws	https://optn.transplant.hrsa.gov/governance/bylaws/
UNOS/OPTN evaluation plan	https://optn.transplant.hrsa.gov/governance/compliance/
UNOS/OPTN policies	https://optn.transplant.hrsa.gov/governance/policies/
SRTR	SRTR.org
SRTR secure site	https://securesrtr.transplant.hrsa.gov/
CMS transplant	https://www.cms.gov/Medicare/Provider-Enrollment-and-Certification/CertificationandComplianc/Transplant.html

Conclusion

Regulatory oversight of heart transplantation is ever-changing. Continual review and understanding of current OPTN/UNOS and CMS regulations is paramount to allow for continued funding of individual transplant programs. Regulatory oversight, although at time burdensome, provides the transplant community and patients confidence in the equity of organ disposition. Regulatory oversight ensures that all transplant centers are playing by the same set of rules and provides a framework for preventing centers with inadequate resources or skills to continue heart transplantation without intervention. Every individual involved in heart transplantation will encounter interface with a regulatory body. It is important to remember why oversight exists and encourages constant vigilance and high reliability.

Cross-References

- Contemporary Survival in Heart Transplantation
- Current Listing System
- Matching Donor to Recipient
- Recent Changes and Future Challenges in the Heart Allocation System
- Retransplantation

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Quality Assurance and Process Improvements

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Abstract

The emphasis on quality assurance and process improvement (QAPI) has evolved in transplant programs since 2007 with implementation of the Centers for Medicare and Medicaid Conditions of Participation (CMS CoPs). Since release of the CMS CoPs, private insurers, as well as CMS, are focused on transplant center outcomes reported by the Scientific Registry of Transplant Recipients (SRTR). Programs have expanded staffing to include professionals whose knowledge and expertise is in quality. Most transplant programs now include quality managers, data coordinators, and analysts to help ensure data integrity and quality outcomes are compliant with required expectations. Larger transplant programs may have a statistician on board while others have access to a statistician to address the complexities of data analysis. The development and management of a QAPI program for transplantation requires special skills and knowledge that most transplant professionals have not received in undergraduate or graduate studies. In this chapter, readers are provided with tools for developing scorecards, performance measures, and a quality plan that is structured on the CMS QAPI recommendations. Examples specific to heart transplantation are provided. Special attention is given to methods for ensuring data integrity and analysis for adult transplant programs.

Keywords

Quality · Performance improvement · Data · Performance measures · QAPI · Analysis · SRTR

Introduction

In 2007, the Centers for Medicare and Medicaid (CMS) issued the CMS Conditions of Participation (COPs) for Transplant Programs in the United States. At that time, most transplant programs did not have dedicated data teams or quality managers. Over the next 10 years, transplant programs added personnel to specifically address the regulatory and quality requirements outlined in the CMS Conditions of Participation. Although the Conditions of Participation discussed the development of transplant quality programs, most consisted of a Quality Assessment and Performance Improvement (QAPI) Policy, QAPI Plan, and a transplant administrator trying to carve out time for a QAPI program. Initially, the focus on data entry and data integrity was minimal until the Scientific Registry for Transplant Recipients (SRTR) began public releases describing outcomes of each transplant program. Private insurers plus CMS were now focusing on transplant center outcomes and programs began to question their data. This new attention to

transplant program outcomes resulted in the development of transplant specific quality programs and a focus on hiring and educating staff to meet the demands of an effective quality program.

Soon after the release of the CMS COPs, several programs received a warning from CMS that their outcomes were not in compliance with CMS requirements. Transplant program leaders were beginning to understand the new rules whereby outcomes out of compliance were flagged. Initially, being flagged twice, within five SRTR releases, identified programs in jeopardy of receiving a Systems Improvement Agreement (SIA) from CMS. The first flag was a signal to transplant programs to review their outcomes and develop a plan for improving their outcomes or improve the quality of data being submitted. Many programs were not prepared to understand the seriousness of the COPs. Most programs did not have a quality professional assigned to review outcomes or to evaluate the integrity of data being submitted. By 2012, 127 of the 330 US transplant programs had flagged twice in five SRTR releases for outcomes or volume related issues (Hoopes, 2015). Being flagged meant that a program's graft or patient survival rates were not acceptable if:

- Observed minus expected graft failures or patient deaths were greater than 3.
- Observed graft or patient survival divided by the expected graft or patient survival was greater than 1.5.
- The one-sided p value was >0.05.

Thirty-five transplant programs entered into a Systems Improvement Agreement (SIA) with CMS and 16 programs discontinued transplantation rather than incur the costs being reported by colleagues across the United States. Costs associated with an SIA for each solid organ transplant program has been reported as 1.2 to 1.5 million dollars in indirect costs and over $800,000 in direct costs (Hoopes 2015; Hawryluk 2014). The greatest expense was in loss of referrals as transplant programs lost their Centers of Excellence status with insurers. Many programs became risk averse with patient selection being carefully scrutinized to avoid patients who may not survive the complexities of transplantation. Programs became more stringent in donor selection. Caution with both patient and donor selection often resulted in a decrease in volume for a program. The shrinking denominator would now enter the equation to analyze data and outcomes, potentially making it more difficult for a program to demonstrate improvements.

As part of the CMS SIA, an Independent Peer Review Team (IPRT) was required to visit each transplant program for several days to identify program specific problems and report them to CMS. Independent Peer Review Teams consisted of organ specific transplant professionals including a surgeon, physician, quality specialist, transplant administrator, social worker, transplant coordinator, and, often, a statistician. The report from the IPRT led CMS to issue requirements for the program to develop a Corrective Action Plan (CAP) that was submitted to CMS for approval or revision. Programs were given a timeline of up to a year to make the required changes outlined in the CAP. A quality professional was assigned to be on site with the team at least 4–5 days a month with monthly phone calls with CMS, transplant team members, and hospital leadership to report on progress or to identify problems with meeting the goals of the Corrective Action Plan. Programs who were unable to fully meet the demands of the CAP could request an extension. If the extension was not granted, the program could lose CMS certification.

Problems identified at many of the IPRT visits included patient selection and a need to focus on data integrity. It was clear there was a lack of sufficient staffing educated on ways to ensure the accuracy and integrity of data being reported in TIEDI forms. It was also clear that many transplant programs did not initially take CMS seriously (Hoopes 2015). Few transplant professionals were knowledgeable about the intricacies of quality and performance improvement. And few understood how to use the tools such as risk adjustments and hazard ratios provided by SRTR.

Evolution of Transplant Quality in Hospitals

In 2013, CMS announced Pilot Focused QAPI Surveys for transplant centers "to enhance assessment of Transplant Program Quality Assessment and Performance Improvement" (CMS 2013 f-QAPI). The letter released by CMS promised this pilot survey would be educational and would be performed in several hospitals before becoming a regular survey of transplant programs. Transplant programs began to feel the pressure of frequent oversite with UNOS surveys, CMS surveys that addressed the COPs, and, with this new announcement, a separate focused QAPI survey. Needless to say, the need for quality personnel became an absolute necessity in programs as did the need for a focus on the integrity of data being entered in the TIEDI forms.

Webinars on quality and regulatory issues were made available through the American Society of Transplantation (AST) and the American Society of Transplantation Surgeons (ASTS). A webinar series on quality was provided by CMS in 2015. Topics in that series included:

- Demystifying the FQAPI Process and the New Mitigating Factors Regulation
- Introduction to Transplant QAPI
- FQAPI Worksheet Overview
- Comprehensive Program and 5 Key Aspects of QAPI
- Objective Measures – Monitoring and Evaluating Services
- Performance Improvement Projects: Tools and Methods
- Adverse Events
- Transplant Adverse Event Thorough Analysis:
- QAPI Tools 1
- QAPI Tools 2
- Data Display – Tools and Methods
- Writing an Effective Plan of Correction

That same year, the Transplant Quality Institute (TQI) was formed to provide annual educational programs about CMS regulations, UNOS standards, and reports from the SRTR. In addition, participants have been provided with quality specific education that includes instructions on improving data integrity, scorecard development, and methods for evaluating performance. Since its inception, TQI has been sponsored by the American Foundation for Donation and Transplantation (AFDT) in Richmond, VA. Following the first TQI meeting, a list serve was developed to provide opportunities for sharing thoughts, ideas, and best practices with transplant administrators and quality personnel across the United States. Announcements on the quality list serve of CMS surveyor arrival at a specific program results in supportive responses and well-wishes from members of the list serve. Soon after the surveyors leave, a summary of the visit from the quality professional at the program often appears on the list serve to provide colleagues with information about CMS activities during the 3–4 days survey. This sharing of information and support from colleagues has led to over 600 members participating in the list serve.

Today, the focus on quality is included in a CMS Conditions of Participation survey as opposed to the original plan to have a separate CMS quality survey of transplant programs. There is no reference to F-QAPI in the new guidelines. In addition, CMS has changed its observed to expected ratio to 1.85 rather than the more stringent 1.5. A program still has to cross all three thresholds to be non-compliant with CMS outcome requirements for those recipients who were transplanted 1 year ago:

- Observed minus expected remains at <3
- The one-sided p value <0.05
- O/E increased to <1.85

However, the UNOS Membership and Professional Standards Committee (MPSC) continue to hold transplant programs to the original requirements with the O/E ratio at 1.5. Today, all three thresholds must be crossed in two consecutive SRTR releases. This is much more stringent than the original two out of five SRTR releases. With the previous requirements, a program could

implement a CAP that may allow the program to improve enough to avoid a letter from the MPSC or probation from CMS. Not achieving compliance in two consecutive SRTR releases makes it more challenging to implement performance improvement projects that result in sufficient progress to avoid interventions from the MPSC or CMS. Programs must focus on 30-day outcomes since transplants in that cohort will move into to the 1-year cohort with the next SRTR release.

Components of a Quality Program

The foundations of a firmly structured quality program begin with a quality policy and a quality plan. Both documents must reflect the quality policy and plan of the institution and should be transplant specific documents. In other words, a transplant program should have its own separate quality policy and quality plan but should clearly reflect and reference the hospital's policy and plan for quality. The policy provides an overview of the purpose of quality and defines elements of the quality program, whereas a quality plan is a detailed document that describes how the plan is implemented with meetings, data analysis, and identifies roles for leadership and participants in the program.

Key components for a quality program in transplantation include:

- A quality plan
- A quality policy
- Orientation programs focused on data and quality managers
- New staff orientation to CMS, UNOS, SRTR
- An adverse events policy
- Job descriptions that include quality for each team member

An effective QAPI program requires leadership that has the power to affect change and a strong belief in the culture that quality brings to a program (Reich 2013).

Designing a QAPI Plan

When CMS surveyors evaluate a transplant program for regulatory compliance, one of the documents they request is a written copy of the program's QAPI Plan/Program. They also request any QAPI reports and minutes of QAPI meetings. In addition, surveyors may request an adverse events log and the program's adverse events policy. Having a specific transplant adverse events policy helps to further describe the processes involved in identifying and analyzing adverse events.

The QAPI Plan, as outlined by CMS, should have five key elements that lay the foundation of the plan:

- Design and Scope
- Executive Responsibilities/Governance and Leadership
- Feedback and Data Systems
- Analyses
- Performance Improvement Interventions/Activities

Surveyors use a QAPI worksheet. Question 2.3 asks if the QAPI Plan contains the five key elements of a quality structure. Thus, using these five topics as a template or outline for the structure of a QAPI Plan is advisable. Surveyors will not have to ask a lot of questions if a QAPI Plan describes a transplant quality program using these five key elements. It is important to note that a transplant QAPI Plan covers all organs transplanted in a program. Specific organ performance measures are identified in the QAPI Plan and in the individual organ-specific program scorecards. A QAPI Plan is updated annually and must be reviewed by both transplant and hospital leadership on an annual basis.

Design and Scope

The Design and Scope of the QAPI Plan should describe the bidirectional flow of transplant quality outcomes to the hospital quality department

and upwards to the Board of Directors. In a continuation of the bidirectional flow of quality outcomes, transplant outcomes should be reported to staff such as the operating room, ICU, catheterization laboratory, and to the step-down units where staff care for transplant candidates and recipients. Also included in the Design and Scope section should be a description of how outcomes are communicated with any contractual agreements such as the immunogenetics laboratory and Organ Procurement Organization. These contractual agreements should have a bidirectional flow of information on performance measures based on the contracts. This will allow each entity to evaluate the effectiveness of the contract and to identify areas in need of performance improvement.

In this section of the QAPI Plan, it is important to discuss and describe aspects of clinical care through the phases of transplantation starting with the referral to listing process, the transplant or perioperative phase, discharge, and post-transplant follow-up phases.

Executive Responsibilities

Keeping the hospital's executive leadership informed on transplant activities and outcomes helps leadership understand the resources needed to achieve survey readiness for CMS and UNOS surveys and for The Joint Commission surveys for our Mechanical Circulatory Support Devices. The potential for having three surveys in 1 year requires appropriate resources to ensure success with these surveys. Having appropriate resources also helps to ensure the most optimal patient outcomes. Inviting hospital leadership or hospital Quality personnel to transplant QAPI meetings is a way to provide a real time view of the complexities of transplantation. Currently, the collection and analysis of data in transplant programs is not associated with reimbursements. It is strictly a cost that is incurred by each transplant program (Roberts et al. 2003).

It is important to describe the data-driven aspects of a transplant quality program. Providing a comprehensive orientation program for data managers is the first step in ensuring the integrity of data. Most programs in a hospital do not have the focus on data submission requirements that result in the outcomes being reported publicly twice a year. This is important to detail in the QAPI Plan and to communicate clearly to hospital leadership. Ensuring this is communicated to hospital leadership should be addressed clearly in the transplant QAPI Plan.

Feedback and Data Systems

Transplant programs must be data driven to provide the most meaningful evidence on performance. Ensuring the evidence is reliable requires data accuracy and integrity. Defining how data is collected and measured is a key point. Programs with definitions of data and education for the data collection personnel help to ensure the accuracy. For example, the transplant program may define length of stay from transplant surgery date to date of transplant discharge; however, hospitals calculate length of stay from date of admission to date of transplant discharge which may be substantially longer especially for heart recipients who may be in the Intensive Care Unit prior to transplant. Therefore, it is important to define quality performance measures and the data sources. Determining the diagnosis of a patient should not be left to the data personnel entering information on TIEDI forms. Diagnoses are often calculated in the risk analysis established by the SRTR. Thus, the diagnosis should be clearly determined in the patient selection committee meeting and communicated in writing to the data coordinator entering that data. Lack of adequate resources to collect data can negatively impact the outcome of data gathering and observance of findings.

Communicating transplant outcomes to hospital leadership and to the staff on units where patients are cared for is an important aspect of providing feedback to those who need to know. Communication to hospital leadership is usually accomplished through written submission of program outcomes as well as annual or semiannual presentations at hospital quality meetings. Communicating outcomes to staff caring for

transplant patients is not only important but also very much appreciated. Staff enjoys hearing about how their work has impacted on patient outcomes and helps to better understand their role in supporting and improving care. Length of stay, infection rates, patient satisfaction, and patient-reported outcomes are all measures that can be greatly influenced by those who have direct patient care responsibilities. Providing SRTR outcomes twice a year at staff meetings along with data demonstrating organ specific performance measures allows staff to identify areas for celebration as well as those in need of improvement. When data is presented to staff, they can better understand their role in participating with the transplant teams to achieve goals and improve outcomes.

Twice a year transplant programs have an opportunity to review SRTR data on their secure site for the Registry prior to final analysis and public release. It is important for transplant programs to review and correct any errors during this time period. Included in this review is data entered by the OPO that may impact on outcomes. Reviewing this data is a tedious process and requires tremendous effort and resources, but it is a task every program should take seriously.

Analyses

Once data is collected, it must be analyzed to provide transplant teams with significant evidence of program outcomes. Few transplant programs have access to statisticians to assist with the analysis of data. However, it is possible to consult with a statistician when data analysis requires more complex testing or examination. Analysis of data requires specialized quality and performance measurement tools and formal processes to fully assess and explore the information being collected. Most clinicians have not been educated in use of tools for data analysis and often require education to determine which tools are most appropriate for analyzing specific data. The CMS Webinars in 2014 addressed quality tools and these tools are always presented at the Transplant Quality Institute meetings each year. However, this is truly a learning process that requires both education and collaboration.

To be meaningful, data must be analyzed and communicated to team members to impact and improve processes. If data is simply reported without a further analysis into its significance, then there may be a missed opportunity into understanding, for example, why the length of stay this month was higher than the previous month. By analyzing the data and communicating it to the transplant staff, the multidisciplinary approach may uncover some findings such as that the LOS was higher because more patients developed post-op complications due to an environmental issue in the OR. That can then lead to improvement processes such as an investigation and mitigation of the physical environment of the OR. Meaningful data can be tracked on quality scorecards for distribution to transplant and or hospital leadership.

Analyzing the data and demonstrating this information in bar or line graphs, pie charts, or surface charts provides a visual presentation that assists the presenter in telling the story of transplant outcomes. It is most effective when presenting data over time to demonstrate trending upward or downward. This visualization provides staff with opportunities to develop strategies for performance improvement.

Performance Improvement Interventions

Once problem-prone areas of high risk, increased volume, or poor performance have been identified, it is time to develop improvement projects. Transplant programs should have several improvement projects completed and several in progress at any given time. Engaging staff in these projects is very important. However, clinicians have a responsibility to prioritize time to patient care. Setting aside time for performance improvement (PI) projects in a busy transplant program is not an easy task. Often, staff thinks that PI projects and quality assessments are the responsibility of quality staff. Quality is a team process and leadership must convey this

expectation and requirement to staff. One way to do this is to include quality and PI projects in each team member's job description. By adding PI projects to competencies is also an effective method for clinician involvement. To do this, transplant leadership must plan time for clinicians to participate in quality and PI activities. If quality participation is going to be an expectation and included in job descriptions, then leadership must provide focused time for this teamwork.

Following the implementation of the CMS Conditions of Participation and Transplant Focused QAPI, surveyors found that many programs did not have mechanisms to handle problems in need of being resolved. In other words, transplant professionals were not aware of performance improvement processes. Surveyors also noted that transplant QAPI Plans did not include any processes to monitor actions that were taken to make improvements in programmatic problems identified. The QAPI Plan did not address how improvement measures were evaluated or whether changes were sustainable. Some programs began their education by reaching out to hospital quality departments for guidance on activities to examine and improve care as well as tracking and documenting improvements. Bidirectional reporting for such activities promotes the culture of continuous learning and improvement (Ballard and Wiley 2015).

Performance Improvement is the result of analyzing high volume, high risk, and clinical activities, as well as from benchmarking and program goal setting. Additional opportunities for making improvements in a transplant program's performance may evolve from risk assessments, adverse events, a regulatory survey or a gap analysis. Writing a corrective action plan following a regulatory survey provides a program with the opportunity to prioritize performance activities.

QAPI Meeting Structures

The transplant QAPI Plan should outline the QAPI reporting structure as well as the meeting structure for the transplant program. Programs that transplant a single organ system will likely have one QAPI meeting monthly that reports data and outcomes. If the program is low volume, meetings may be quarterly or semiannually, based on volume and any outcome issues. Most transplant programs also have a quality leadership committee as part of its structure. This committee is often called the Transplant Quality Steering Committee. Meetings may be monthly, quarterly, or semiannually depending on the roles defined for this group. A Steering Committee is usually composed of transplant leadership which would include the administrative director, surgical and medical directors, quality manager, and representatives from one or more of the patient care areas. The roles for this program are outlined in a Charter or Policy. Often, this leadership group assumes the role of oversight for policies, PI projects, and overall quality of the program. In the meetings, SRTR outcomes are reviewed prior to public release, PI projects are reviewed for their effectiveness, new PI projects may be recommended, and new performance measures may be defined for various phases of the transplant scorecard.

For programs with more than one organ system being transplanted, each program should have a transplant quality committee where data is presented on a monthly, quarterly, or semiannual basis which is determined by volume or problem prone areas in need of additional scrutiny. For programs with heart, lung, liver, and kidney programs, each organ system would have a meeting where outcomes are displayed and discussed by team members. Heart transplant quality committees may include outcomes evaluated for mechanical circulatory support devices such as Ventricular Assist Devices or Extracorporeal Membrane Oxygenation (ECMO) as well as those for transplantation. If both programs are large volume, they may need to be separated to ensure outcomes are reviewed optimally.

Quality Committee membership is important to ensure communication is provided to area of the hospital where staff care for this complex patient population. CMS CoPs mandate that each specific organ transplant program develops and maintains

a QAPI program with a multidisciplinary team approach. Heart Transplant Quality Committees may include the following members:

- Transplant administrative director
- Transplant surgeons
- Transplant cardiologists
- Posttransplant nurse practitioners/coordinators
- Pretransplant coordinators
- Ventricular assist device (VAD) coordinators
- ECMO coordinators
- Social workers
- Pharmacists
- Dietitians
- Financial coordinators
- ICU nurse manager or quality manager
- OR nurse manager or quality manager
- Nurse manager or quality manager from post-anesthesia care unit (PACU)
- Nurse manager from step-down unit
- Director of hospital quality committee
- Nurse or quality manager from specialty units where VAD patients receive care
- Other areas may be invited as outcome specific measures are evaluated such as:
  - Cardiac catheterization personnel
  - Pathology personnel

Adverse Events Policy

Each transplant programs should have a transplant specific adverse events policy that defines what events would be considered adverse and how events are analyzed. Most heart transplant programs may identify the following events to be adverse:

- Serious complication or death caused by the transplant process
- Unintentional transplantation of a heart of mismatched blood type
- Heart transplanted into an unintended recipient
- Unintended transmission of infectious disease or malignancy to a recipient
- Loss of a transplanted heart within 1 year
- Patient death within 1 year after transplantation

The adverse events policy should reference and reflect the hospital adverse events policy. Near misses should be addressed in the policy with a process identified for reviewing a near miss. In addition, the adverse events policy should describe how and when the event is reported through the hospital's patient safety system.

Adverse Events Analysis

The Transplant QAPI Plan should identify the process and timing for adverse event analysis. Adverse events are defined in the transplant program's adverse events policy which should be a separate document from the hospital's adverse events policy. The policy must address the processes for identifying, reporting, and analyzing an adverse event. The corrective action plan developed from the analysis of the event must be tracked to determine effectiveness. If outcomes are not demonstrating an effective intervention, this action plan must be revised, and tracking should recommence with the changes. The goal of a corrective action plan is to prevent the event from reoccurrence. Thus, if the changes planned and implemented are not being effective in preventing a reoccurrence, the changes must be revised with tracking to evaluate improved effectiveness.

Adverse events must be maintained in a log. The adverse events policy describes the time in which an event is analyzed and how it is analyzed. Starting an adverse event analysis with a timeline is a practice that works well for heart transplantation. Because heart failure is often a chronic condition, events may develop during the treatment phases that can impact on the outcome following a heart transplant. Patients awaiting transplantation on ECMO, VADs, or total artificial hearts (TAH) may develop bleeding or clotting disorders or may develop infections. Having a timeline to review the events leading up to the adverse event is often helpful in the final identification of a root cause. A timeline can be developed by the quality

manager or director and is followed by review with those involved in the case. This review with clinicians helps to further identify problems.

In organizing a team to review the adverse event, inviting only those involved as well as an individual from the hospital risk department is wise. It is best to keep this process within the small group involved in the case to best manage the process. In performing a thorough or root cause analysis, it is important to focus on systems issues and not to blame an individual or group on the problem. Evaluating systems issues that can be changed or modified to protect clinicians in their clinical practice and protect the safety of patients is the best approach to reviewing an adverse event. Once an adverse event begins to assert blame, the process may well deteriorate to a point of ineffective outcomes and impact on the group's ability to develop a viable corrective action plan. The goal is to review systems to protect patient safety and clinical practice.

Orientation Programs for Quality Personnel

Because most transplant professionals have not studied quality, it is important to provide new staff with quality methods as part of the orientation. Spending a day with a quality professional in the hospital quality department could be beneficial as part of the orientation program. An example of an orientation program for transplant managers hired to work in quality is in Table 1. Programs that are fortunate to have hired a quality professional to manage a transplant. QAPI program will have the challenge of orienting the new personnel about CMS Conditions of Participation, Interpretive Guidelines, TIEDI forms, UNOS, SRTR, and the intricacies of transplantation. Much of the orientation program for quality managers would be applicable for either a transplant professional joining the quality team or a quality professional joining a transplant program.

Orientation for data coordinators is very important since this job was often given to assistants to enter data. With the focus now on data integrity, many programs are hiring data analysts or clinical professionals to enter data on TIEDI forms. These forms require data that will be analyzed by the SRTR to provide outcomes reports to the public and to insurers. Thus, it is important to ensure accuracy of data. The data may be as simple as a date of birth for a patient or it may be more complex such as determining the ischemic time. Ischemic time involves cross clamp times in donors and recipients, but calculations should also include time zones. How often does the data coordinator consider time zone calculations when a kidney from California is implanted in a recipient in New York? This should be part of the orientation to data entry for data coordinators. When looking at the SRTR risk adjustment scores, it is clear that diagnosis of a transplant candidate can carry considerable weight. This is a data point that should be determined and documented in the patient selection meeting and communicated clearly to those who are entering data in TIEDI forms. Table 2 is an example of an orientation program for a data coordinator.

Tools for Monitoring Quality

Scorecards and Dashboards

Often people use scorecard and dashboard interchangeably. A scorecard is a data collection tool that provides a program with performance measures, benchmarks, and data collected in specific time periods. In transplantation, programs collect data on a monthly or quarterly basis, using a red, yellow, and green schematic similar to a stop light. Green indicates all is going well in that area being measured. Yellow indicates there may be a problem that needs to be evaluated more in depth with a performance improvement project, especially if the yellow is persistent. Red indicates a problem that usually requires a performance improvement project.

Scorecards are often called report cards, and, similar to a report card demonstrates performance in a specific subject. A student may be doing very well in English but struggling with Math. This is indicated by the grade in each class. Similarly, a heart transplant program may be doing well with

Table 1 Orientation program for quality manager

Learning objective	Reference materials	Education	Comments
Weeks 1			
Discuss roles and responsibilities of a quality manager	Competencies and job description for QAPI manager Review CMS Conditions of Participation Interpretive Guidelines	1. Review job description and competency expectations 2. Review CMS CoPs 3. Review CMS Interpretive Guidelines 4. Regulatory bootcamp UNOS, CMS overview of each	
Describe transplant regulations related to quality	UNOS Policy on data submission UNOS heart allocation policy CMS quality regulations	1. UNOS by laws and policies 2. Review UNOS requirements for primary surgeon and primary physician for heart transplant program 3. Review requirements for process and outcome performance measures in phases of transplantation: pretransplant, perioperative, discharge, and postoperative follow-up phase	
Discuss CMS Conditions of Participation 2007 and Interpretive Guidelines	CMS quality regulations Program and hospital QAPI plans Transplant adverse events policy	Review QAPI plan: hospital and transplant Review adverse events for heart transplantation Review adverse events log Review thorough analyses completed in last 3 years	
Week 2			
Review scorecards Discuss performance measures for scorecard	CMS QAPI surveyors worksheet Benchmarks: ISHLT, SRTR, AHRQ	Review definitions, performance measures, explain benchmarks Access ISHLT website Access ISHLT clinical guidelines Access SRTR site Access www.ahrq.gov for evidence-based articles	
Review SRTR hazard ratios and Risk Adjustment Scores	www.srtr.org	Review heart transplant risk adjustment and hazard ratios	
Develop agendas for committee meetings	Minutes and agendas from past year	Review QAPI meeting agendas for past year Review agendas for QAPI Steering Committee meetings	
Demonstrate management of tools used in QAPI	Kelly DL (2011) Applying quality management in healthcare: a systems approach, 3rd edition. Health Administration Press: Chicago	Thorough/root cause analysis Corrective action plans Scorecards Fishbone 5 Whys FMEA	
Week 3			
Describe SRTR tables and CUSUM reports on program-specific secure site	https://secure.srtr.org	Review program-specific reports Review elements included in risk calculations Review CUSUM reports	
Identify resources for developing	www.ishlt.org http://optn.transplant.hrsa.gov/	Demonstrations Review of websites	

(continued)

Table 1 (continued)

Learning objective	Reference materials	Education	Comments
benchmarks Identify resources for developing quality indicators Review patient safety indicator site (PSIs) Review inpatient quality indicators (IQI)	https://qualityindicators.ahrq.gov/Modules/default.aspx		
Review CMS QAPI surveyor worksheet	CMS QAPI worksheet	Review worksheet	
Demonstrate development of graphs from Excel spreadsheets	Take excel training http://office.microsoft.com/en-us/training-FX101782702.aspx		
Attend Transplant Quality Institute meeting	www.amfdt.org		

unplanned return to the operating room and ABO verifications as demonstrated by the green indicator in the scorecard. However, the length of stay consistently remains above the 7–10-day benchmark as demonstrated by a yellow or red indicator. Drilling down to determine why the length of stay is always yellow or red will be important to change clinical practice and allow patients to be discharged within the benchmark timeline.

Scorecards for transplant programs collect data in phases of the transplant process. This includes preoperative, perioperative, discharge, and post-transplant phases. Benchmarks provide programs with goals to reach with the data being collected for each performance measure. Benchmarking can be accomplished by establishing goals based on previous data from within the program or can be based on SRTR or OPTN data, Vizient (formerly United Healthcare Consortium) data, or systematic reviews reported in the literature. The Agency for Healthcare Research and Quality is an excellent resource for systematic reviews and quality indicators and can be accessed at www.ahrq.gov. Performing a literature search on PubMed may also assist programs in finding literature on which to identify benchmarks. This site can be accessed at www.pubmed.gov. Multicenter prospective trials provide excellent resources for benchmarking.

A dashboard is a tool that reports analyzed data in graphs or charts where it is presented to staff and hospital leadership (Pugh 2011). Comparing the quality dashboard meaning with the tool used in a car or airplane that is also called dashboard may be helpful. Looking at the speedometer provides a driver with a visual tool of whether the driver is compliant with the speed limit or whether a change in performance is needed to meet the speed limit requirement. The speed limit is an indicator or goal to keep a driver in compliance with a law for driving safety. The same is true of a low gas gauge that clearly indicates it is time to obtain gas. The care dashboard provides a visual tool for determining when a stop for gas may be wise. A benchmark may be an indicator or goal to keep clinicians in compliance with patient safety. In either case, a dashboard provides a visual tool to help evaluate compliance or to indicate a need for intervention or change.

Components of a Scorecard

While scorecard components may vary from one program to another, most programs use the following elements or terminology in a transplant scorecard: performance measures or quality indicator, goals or benchmarks, definitions,

Table 2 Orientation program for transplant data team members

Learning objective	Reference materials	Educational classes	Comments
Weeks 1–2			
Discuss roles and responsibilities of a data coordinator	Review competencies, Job descriptions	Review job description and competency expectations	
Describe transplant regulations related to data requirements	**UNOS Policy 3.4.8.2** **CMS Interpretive Guidelines**	Resource navigation on Web **Regulatory bootcamp** UNOS, CMS overview of each	
Discuss data required for various TIEDI forms	www.unos.org	Meet with transplant coordinators to discuss forms	
Review TNBM transplant list in UNet	**UNet**	Education with transplant coordinators	
Describe SRTR tables on center-specific outcomes	www.srtr.org	Education on program-specific reports Education on elements included in risk calculations	
Discuss relationship between TIEDI forms and SRTR data	**Demonstration**	Meet with QAPI manager	
Orient to program database	**Program database**	Training	
Describe the observed and expected events being reviewed by CMS	CMS Interpretive Guidelines Review with QAPI manager	CMS Interpretive Guidelines Review with QAPI manager	
Review six medical records, identify source documents			
Reviews QAPI scorecard	Overview of QAPI scorecard	QAPI manager education	
Week 3–4			
Begin training in UNet	Website recorded education	**UNet class online**	
Observe the listing process with UNet.	UNet	Information on TIEDI forms	
With guidance enter referrals into database	OTTR entries	Work with QAPI manager	
Enter data into UNet	UNet	Work with transplant coordinators who enter data into TIEDI	
Review policies on data, quality, safety	Policies	Review with QAPI manager	
Education on scorecards	Review definitions, performance measures, explain benchmarks	Review with QAPI manager	
Education on use of Excel spreadsheets	Take excel training	Online through Microsoft	
Review DonorNet	On UNet site	Review with on call coordinators	
Begin the process for INTERMACS training	http://www.intermacs.org/membership.aspx		
Attend Transplant Quality Institute	www.amfdt.org		

(continued)

Table 2 (continued)

Learning objective	Reference materials	Educational classes	Comments
Describe long-term complications of transplantation: diabetes, HTN osteoporosis, infection, renal insufficiency, and malignancies	Articles, chapters in Transplantation Nursing Secrets, AST book		
Maintain communication with referring physicians and other healthcare providers	Form letters		

transplant phase, and type of indicator. Each of these terms or elements is described below.

Performance measures or quality indicators are measures to evaluate a center's transplant performance. According to CMS standard §482.96 (a) Components of a QAPI Program, "a transplant program must use objective measures to evaluate performance with regard to transplantation activities and outcomes" (Federal Register 2007 p. 15204). CMS further defined objective measure in the focused QAPI surveyor worksheet by stating the objective measures should be based on internally identified high risk, high volume, or problem-prone issues. Specifically, CMS states in this worksheet that the objective measures should NOT be those required by regulation or those that are financial (CMS 2013a). Thus, the objective measures should be those a program identifies for each phase of transplant that have a clinical focus as opposed to a regulatory or financial focus. Table 3 provides an example of performance measures in a scorecard along with benchmarks and references.

Most transplant programs use the term performance measure or quality indicators to identify objective measures being tracked on scorecards. These objective measures are identified by transplant team members, often at QAPI meetings. Over time, the measures may change as new indicators are identified or old indicators are removed. The reason for removing an indicator is often the result of consistently meeting the benchmark or goal for a year or more. Auditing the indicator quarterly for another year is a good idea to ensure the process continues to meet the benchmark.

Types of Indicators

Process and outcome goals or indicators are selected for each phase of transplant and should reflect the complexities and problem-prone areas of services within a program. A process measure is one that includes steps to complete a task (Ransom et al. 2011). An example of this is ABO verification in the operating room. An outcome measure is one that relates to the results. Length of stay is an example of an outcome measure. Good question to ask when selecting performance measures or quality indicators include: What does the team want to accomplish with each goal? Is the goal within the team's scope of control? Is this goal within a team's sphere of influence? Taking the SMART approach is a good idea when selecting performance measure. SMART indicators are **s**pecific, **m**easurable, **a**ttainable, **r**elevant, and **t**ime-bound.

Structure is an indicator that is rarely used in transplant scorecards. Structure indicators relate to the providers of care, tools and resources of the providers, and the settings in which they work (Kelly 2011).

Definitions

Defining the indicators or performance measures is important to ensuring everyone is collecting data using the same parameters. Length of stay, ischemic time, or return to the operating room (OR) are all areas where definitions help to determine the calculations of data collected. Some programs want to collect only cold ischemic time whereas others may combine warm and cold ischemic times for a total ischemic time. If one data team member is combining cold and warm times while another is collecting only cold ischemic time, data will not be accurate or consistently reported. Further defining return to the operating room as *unexpected* return to the operating room prevents the inclusion of patients returning to the OR for planned follow-up care such as a chest closure following heart transplantation.

Table 3 Example of heart transplant performance measures for scorecard

Performance measures	Suggested benchmark	Reference
Pretransplant		
Letter is sent to the patient and referring physician within 10 business days of the multidisciplinary decision stating the patient is being listed or not listed for heart transplantation.	100%	UNOS Policy 3.5 Patient Notification
Patient death after being listed for heart transplant will be <15% annually	<15%	Trivedi et al. 2016
Consent for transplant evaluation is signed	100%	Federal Register CMS 2007
Perioperative transplantation		
Length of stay in ICU will be <24 h	<24 h	Program data
LOS during transplant admission will be <10 days	7–10 days	www.srtr.org
Unplanned return to the OR will be <5% annually	<5%	Program data
Development of sternal wound infection will be <10% annually	<10%	Reineke et al. 2017
Immediate graft dysfunction will be <30%	<30%	Avtaar et al. 2018; DePasquale and Ardehali 2018; Nicoara et al. 2018
Discharge measures		
Education with patient and support person will be documented prior to discharge	100%	Program policy
Patient and support person will each achieve 90% or greater on pre discharge written test	100%	Program policy
Patient and support person are able to identify each medication and its purpose prior to discharge.	100%	Program policy
Posttransplant		
Readmission within 30 days will be <30% each month	<30%	McAdams-DeMarco et al. 2012
Graft loss within 30 days	<30%	Nicoara et al. 2018
Graft loss within 1 year	>93%	ISHLT Registry Data 2018

A transplant program or institute that has more than one solid organ transplant program requires a separate scorecard for each organ system in the program. Pediatric scorecards are maintained separately as are living donor scorecards. Thus, a transplant quality team may have 8–10 scorecards to maintain and committees to which reports must be provided on a monthly or quarterly basis. Having a physician champion for each organ system, including adult, pediatric, and living donors, helps the quality team in determining methods for data analysis, definitions of performance measures, and developing agenda items for each meeting.

Benchmarks

Benchmarks are goals or targets established by each team and are based on processes or outcomes of similar organizations. The QAPI team manager often locates articles or guidelines reporting on benchmarks that could be used for various performance measures. The articles or guidelines can be reviewed with the physician champion prior to the team meeting to ensure support for specific goals to be recommended. The team may review the reports or hear a summary of the reports at the QAPI meeting and decides if the benchmarks are appropriate and achievable for this team.

Phases of Transplant

Pretransplant Phase

Pretransplant phase is the time from referral to transplant. Some programs may define this phase as from the time of listing to the time of transplantation but the entire evaluation process should be captured in this definition. Most programs measure the time it takes for a patient to move

from referral to first appointment or referral to listing. This is a process measure since it evaluates steps to reach a certain point. Recently, programs have begun to measure deaths after a patient is listed for transplant and dies prior to receiving a transplant. The SRTR refers to this as the waitlist mortality rate which they define as how frequently patients listed for a transplant at a program die before receiving a transplant (SRTR 2018).

Perioperative Phase

Perioperative phase of transplant is the time the patient enters the hospital for surgery or the time the patient enters the operating room. This definition must be defined clearly by the program. For example, if the heart candidate is already admitted to the hospital and is on a mechanical support device or numerous inotropic agents, is that the same time period as a patient who is admitted for a heart transplant from home? Definitions such as this provide data collection teams with information to determine a time period. If a team decides to consider the perioperative period as that when the patient arrives in the operating room that is clear for both groups of patients. However, if anesthesia has not yet been induced and the heart transplant is cancelled, how is that perioperative period defined in a transplant program? Some may state the perioperative period is from the first anastomosis. The perioperative period must be defined.

Discharge Phase

The Federal Register (2007) states that the transplant center must have patient discharge planning included as part of the phases of transplantation. Tag X091 in the 2008 CMS Interpretive Guidelines states that multidisciplinary patient care planning must be documented during the discharge planning period (CMS 2008). Thus, adding a process and outcome performance measure during this period is a best practice that is sure to be reviewed by CMS surveyors.

Postoperative Phase

This is usually described as the time after a patient has been discharged from the hospital. Heart transplant recipients may be discharged to a rehabilitation unit to improve their strength and physical abilities. Therefore, it is important to define exactly when the postoperative phase begins. This is especially confusing for data team personnel who reads in the chart that the patient is still at the same facility but has been discharged from transplant unit to the rehabilitation program. A definition of the time a postoperative period begins is important to ensure the accuracy of data reported to QAPI teams and, especially, on TIEDI forms.

Tools for Monitoring Performance Improvement

Performance Improvement Projects

Collecting and analyzing data provides us with information about what is going well or areas where we may need to make improvements. Once we know where improvement is needed, we then decide on tools that will provide us with the best method for approaching an improvement project. Many hospitals provide staff with templates of tools for use with performance improvement projects. With today's focus on quality, hospitals are also providing employees with educational programs on quality such as lean six sigma. Some are even providing key leadership personnel with courses leading to a Black Belt in Six Sigma. When hospitals integrate quality and improvement projects into their culture, quality becomes engrained in staff as part of daily activities and thinking.

Tools for Performance Improvement

Using a tool to identify and understand the factors involved in a problem provides structure to the processes. Using tools such as process

mapping or a fishbone helps to visualize the problem and pathways to focus on in making changes to a process or a problem. Some tools are most helpful in the planning stages of a performance improvement project while others will assist in implementation of the project. A brief description of each tool is provided.

Process Maps

A process map is a visual tool that helps identify steps along a pathway to complete a project. It describes the sequence of events that is currently being used to accomplish a task or tasks. A process map helps visualize gaps in a pathway or steps where there are roadblocks or problems. A process map allows us to document the way we work while also allowing us to analyze areas in need of repair or improvement. There are symbols that can be used in mapping out a process. See Fig. 1.

Fishbone Diagram

A fishbone diagram is a tool to identify and organize factors involved in an identified problem. This is a good tool to use when brainstorming with a group. The diagram actually resembles a fish with the head being the identified problem and the bones representing various factors that you can identify with labels or categories. Figure 2 demonstrates how a fishbone was used in a transplant-related problem whereby the head represented the problem identified in this case as a prolonged period for a patient to be scheduled for transplant evaluation once he or she was referred. The bones were factors that the PI team identified as potentially problematic in causing the problem. The categories identified in the bones were: Space, which included exam room space, waiting room and conference room space for patient education. Also included in the category labels of the bones were staffing, leadership, processes, and policies such as those impacting on scheduling.

Pareto Charts

When analyzing the fishbone or the process map, it is easy to see that not all factors impact on the problem equally. In determining the next steps in improvement interventions, it is key to use the data extracted from the fishbone or process map. A Pareto chart is a bar graph that displays data in descending order from most frequent to least frequent. Thus, if you take information obtained from the fishbone in this case, you would determine that staffing is the most frequently identified factor followed by leadership and scheduling issues. The leadership in this case had changed so frequently in the past year that individual staff members were making decisions with the result of inconsistent and ineffective processes. By identifying the problems deemed to be most impactful on the problem, the PI team was able to select the areas in need of improvement.

Five Whys

This is a question asking method that explores the cause and effect relationship. It is another tool that can be used in a group situation to identify potential causes or factors involved in an identified problem. It is not useful in identifying a root cause but may help to identify factors involved.

Tools to Demonstrate Data

Run Charts

Run charts can be used to graphically identify trends and to measure change in performance following a change in process. When looking at trends, it is best to track the data over a long period of time.

Forming the Performance Improvement Team

When starting a performance improvement project, it is wise to select stakeholders as the major players. Those who are familiar with the problem

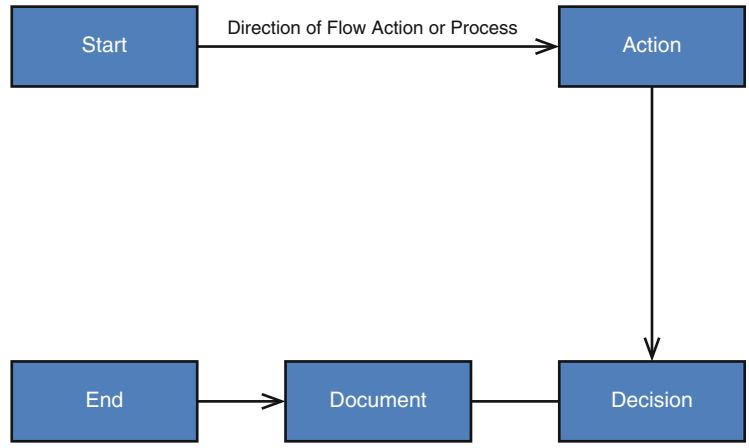

Fig. 1 Symbols used in process maps

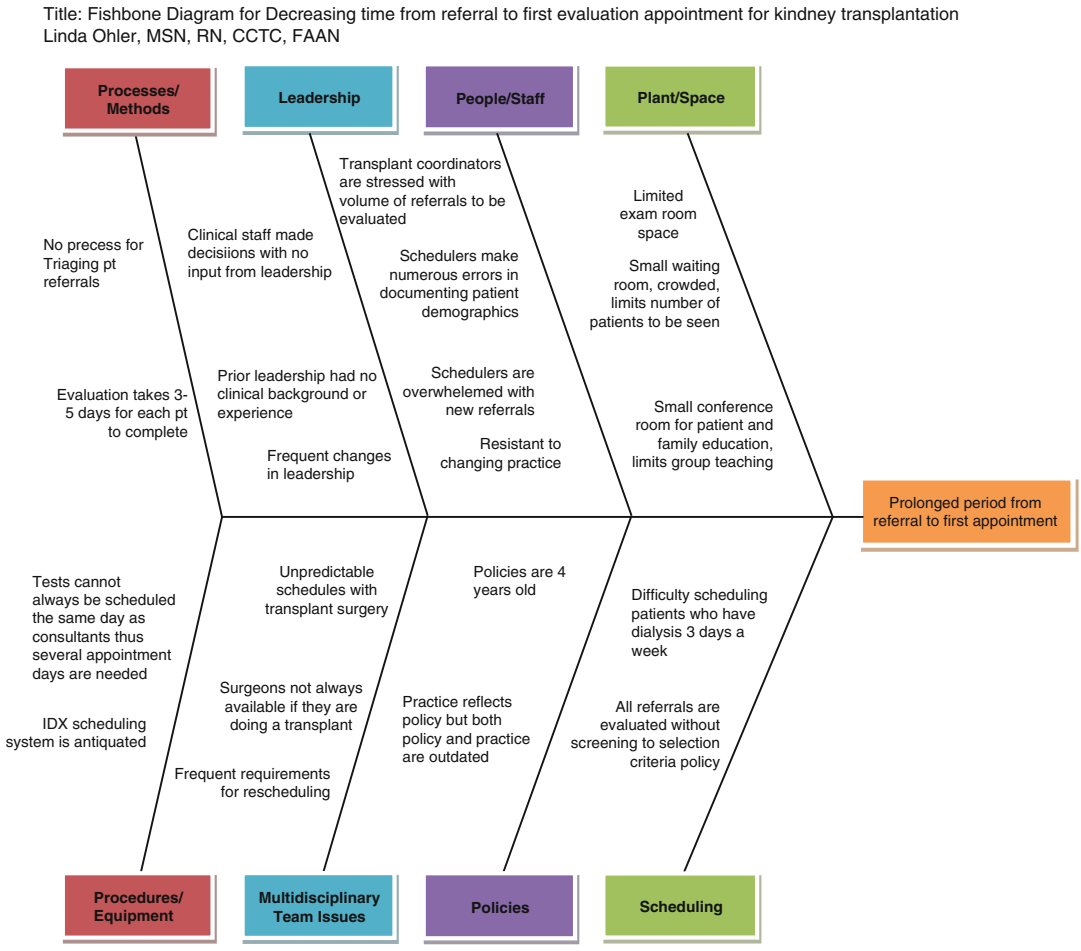

Fig. 2 Example of fishbone diagram

or are impacted by the outcomes are most likely to make time to work on the project. Using a fishbone is helpful in developing a team in that everyone has an opportunity to identify factors that are impacting on the identified problem.

Orientation to quality includes understanding the performance measure in pretransplant, perioperative, discharge, and posttransplant follow-up phases of transplantation. Understanding SRTR risk adjustments, observed to expected outcomes and hazard ratios should be part of every new clinician's orientation program. This ensures the clinicians understand the importance of quality to a transplant program and to our patients. Assigning a clinician to a performance improvement project in their area of focus is important for gaining expertise in quality processes. Clinicians are expected to provide an overview of their participation as well as reported outcomes of projects during their annual competency reviews.

Finding physician champions may also require initial education about performance measures, process improvement, root cause analysis, and benchmarking. Most physicians are focused on data and want to ensure data integrity in their programs. However, many physicians are not aware of the depth and detail of data requirement for TIEDI forms. Discussions that describe the relationship between data entered in TIEDI forms and SRTR risk adjustment models often leads physicians to developing a role in ensuring the accuracy of this data to be entered. A focus on data often ensures physician champions for quality.

Performing a Root Cause or Thorough Analysis

There are various methods for performing a root cause analysis. Often each facility has a method used by the hospital's risk department. Using the same tool will help with communicating with the hospital's risk department about the results obtained in the transplant root cause or thorough analysis. The Joint Commission has a process that has been effectively used in analyzing a transplant adverse event. When an adverse event is identified, the team must determine what systems need to be improved upon to prevent this problem from impacting on clinical practice and patient safety again. This is accomplished by performing a thorough analysis of the event. Heart transplant candidates usually have a history of chronic heart failure, possibly a ventricular assist device or total artificial heart prior to the transplant surgery. Thus, starting with a timeline that begins at the onset of disease can often identify factors that may have triggered or contributed to the adverse event.

Following the timeline, you can identify factors most likely to have an impact on the identified problem. Using a fishbone diagram can help identify the most impactful factors. Once the factors are identified, the use of a pare to chart can identify the top factors involved. Once identified, you can use Plan-Do-Check-Adjust to develop a corrective action plan. The corrective action plan can be tracked over time and demonstrated with a run chart to exhibit any improvements or areas where the plan may need additional changes. The run chart can also demonstrate sustainability of processes that were implemented as a result of the corrective action plan. Surveyors will usually request the adverse event log and will request a document demonstrating at least one thorough analysis.

Conclusion

Transplant programs are highly regulated by CMS Conditions of Participation and UNOS By-Laws and Policies. However, outcomes of the surveys have provided transplant professionals with an opportunity to standardize care and increase safety for both patients and clinicians. Corrective action plans have been implemented by every program as required after a survey. It has been a struggle to adjust to the oversight with frequency of surveys, changes in policies, and various interpretations of requirements. The evolution of transplant data teams and quality leaders has added a dimension of safety that cannot be overstated. The learning curve for transplant professionals

continues to grow but not as rapidly as it did over a 7-year period between 2007 and 2014. Programs are acutely aware of how important data entry has become and how this data is analyzed and reported publicly by the SRTR. Terms such as hazard ratios and risk adjustments are used almost daily in transplant programs. It has been a struggle, but the results of the struggles are proving to have a positive impact on our clinical practice and patient outcomes. We now have the tools to analyze our programs and staff who collaborate to ensure the accuracy of data collection and entry.

Cross-References

- ▶ Regulatory Agencies
- ▶ Surgical Complications

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Administrative Support of the Program

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Contents

Abstract

Heart transplant program management involves unique issues and challenges regardless of the particular organizational structure that program may reside within. Various administrative structures exist that provide oversight for transplant programs and each has its particular benefits and shortcomings relative to each individual organization and the structure of not only the heart transplant program but the overall cardiac and cardiothoracic services provided at the particular organization. There are numerous factors that impact how such programs were initiated, subsequently structured, and potentially restructured based on internal assessments of how services should be organized to best meet the needs of both the faculty and organization in providing services to the patient population served. There are different combinations in place that serve various needs of individual organizations or health systems within which a heart transplant program will exist. The service line concept is commonly utilized to align similar clinical services to gain efficiencies, some economies of scale and reduce costs and redundancies.

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Introduction

A frequently made comment about transplant programs is "..if you have seen one transplant program, you have seen **one** transplant program.." Despite there being hundreds of transplant programs across the country and the world, there are numerous iterations of administrative structures for each of these programs. What should be clear is that all transplant programs require oversight by a knowledgeable administrator who has responsibility to ensure the successful operational, fiscal, strategic, and regulatory functioning of that program or programs. Transplant programs have evolved to become complex organizational units that have significant strategic value and fiscal impact on the hospitals and medical departments within which they are embedded.

Simultaneously, the external environment governing transplant (United Network of Organ Sharing aka UNOS) and CMS (also called Medicare) has continued to develop numerous and increasingly complex regulations that impact operations, organ allocation, and therefore resources, volume, and costs of the program. It is critically important for this regulatory development to be monitored and there be participation in the review process; commenting on new programmatic proposals, participating in the transplant community discussion about such proposal impact; to be part of the administrative oversight role. The related regulations and compliance with them need to be ensured because lack of such compliance can impact program certification. CMS Conditions of Participation must be maintained since loss of said certification will result in either program censure via an SIA (services improvement agreement), program closure, and/or loss of Medicare/Medicaid funding. Any of these scenarios are damaging to the reputation of the program and organization, and may result in considerable financial losses.

The larger volume of transplant programs involve abdominal programs such as kidney, pancreas, and liver (kidney transplant has the highest volume of programs) and often have an administrator assigned to oversee them. In organizations that have only a kidney transplant program, the individual who provides administrative oversight may also be tasked to provide administrative oversight to other areas such as dialysis or some other related clinical areas. It is a matter of scope of work responsibility and workload distribution relative to others in the organization with comparable titles and/or responsibilities.

Increasingly there are a variety of combinations of organizational structures that may have an administrator that is asked to assume additional responsibilities (beyond that of the transplant programs) or may have responsibility for multiple transplant programs. Frequently organizations that have both abdominal and thoracic transplant programs evolved to have a combined organizational structure with one administrator that is responsible for all transplant programs regardless of where the faculty reporting structure resides. The administrative structure of the transplant programs more often, at this time, resides under the hospital administrative structure since the programs are certified as hospital services and are reviewed by CMS as such. Generally, the bulk of the funding or budgetary dollars involved in the transplant budget are also considered hospital dollars rather than Department of Medicine or Surgery dollars.

For the past 20 plus years, many academic medical centers, where the predominance of thoracic transplant programs exists, have evolved into organizational structures called a "Center" (Heart and Vascular Center, Cardiovascular Center, a Heart Center). What this particular named structure is meant to denote or combine will vary from organization to organization and will vary somewhat in scope as to what the Center has within its span of control over positions, funding, clinical operations, and faculty.

Each organization may have a somewhat different combination of divisions and services combined under this particular "Center" title. This "Center" may include some subset of the

Department of Medicine, Surgery, and/or Cardiothoracic surgery coming together for some functional, operational, as well as economic purpose.

That purpose and the politics behind the development of the Center will guide and define the decisions behind how certain administrative structures are put in place and where the heart transplant program may fit into that structure.

The size of the heart transplant program may or may not be a guiding element in the decision of how that program is organized and the decision of who serves as the administrator over those transplant programs. Often one needs to look at the history of the various departments involved in how the transplant programs first evolved and who were the driving forces behind the programs genesis and development and similarly what was the rationale behind the development of the Heart/Cardiovascular Center.

Often, the rationale behind the development of such centers is looking at the commonalities behind the mission and focus of the core personnel involved in the services being delivered, how resources are planned for and costs are monitored relative to the revenue being generated. As well as looking at the key players involved, such as cardiothoracic surgeons or cardiologists and where their activities and effort is primarily focused. This falls under the "service line" concept.

As stated earlier, there are many ways to organize the oversight of a heart transplant program and it would be difficult to define a "best practice" model, but there are key elements that should be addressed for that heart transplant program to be appropriately supported and hopefully allowed to flourish.

Transplant, Regulations, and Resources

Transplant programs, regardless of size, are labor intensive endeavors. This field of healthcare is one of the most regulated. No other specialty has as much regulatory definition regarding how patients are referred, evaluated, what data is collected, who must see the patient as part of the evaluation, how patients are educated about transplant as an option down to specific verbiage that must be used and documented about the educational content and process. Specific verbiage and timing about communication letters to patients concerning their status on or off waiting lists, specific criteria that must be met in order for a patient to be classified a certain "status" level on the waiting list, documentation that must be identified in the chart that must be available to support that classification beyond a note by an MD; to name just a few of the elements that must be adhered to in order to be compliant with both OPTN/UNOS and CMS rules. In order to successfully manage such programs, those providing administrative oversight and directing workflow and resources need to be aware of these regulations and be cognizant of how they impact workflow, resource needs, and overall operations in order to maintain compliance and simultaneously allow the program and staff to thrive.

Whether the heart transplant program is managed within the "Transplant Center" as part of a multiorgan transplant service line or resides as a component within an alternate structure such as a "Heart/Vascular Center"; resources need to be identified, workflow defined, quality metrics developed and monitored; revenue and costs allocated to appropriate accounts. Someone needs to facilitate and potentially lead such efforts and be able to understand the needs of the transplant program and how these personnel needs and workflow issues may overlap with divisions such as Heart Failure or Mechanical Circulatory Assistance/Ventricular Assistance Device (MCS/VAD) programs. How those sections are organized will directly or indirectly impact how the heart transplant program is organized.

The challenge comes in managing all these efforts and personnel within the particular work sections and recognizing that there will be multiple overlapping areas with other divisions and departments. When looking at resource needs, efficient workflow, the use of shared space such as inpatient beds, ICU beds, outpatient clinics, and diagnostic testing time and space, these competing requests and needs must be factored into any equation.

As heart transplant programs have evolved, so have a variety of combinations of work distributions that impact how resources are allocated. One of the most common areas of overlap for heart transplant programs is personnel and resources involved in the management of MCS/VAD patients along with the heart transplant population. The two work units are highly integrated in terms of patient referrals and assessment, since so many heart transplant patients are also candidates for bridging MCS/VADs. It is not unusual for some programs to combine services and have the heart transplant coordinator provide care to the patients during their various transplant phases but also assume responsibility for managing the patient pre- and post-MCS/VAD implant since that care is so integrated with their transplant candidacy maintenance. The phrase "bridge to transplant" MCS/VAD description infers that obvious integration and overlap in care coordination.

However, one can equally argue that those nurses who manage the "advanced heart failure" patient who may or may not proceed to transplant could also manage the VAD population including not only the "bridge to transplant" (BTT) patient but also the "destination therapy" (DT) population who presumably is not being considered for transplant. Though there are ample times that the DT patient, at some juncture, may convert to a BTT category and vice versa as clinical circumstances evolve. Both categories of patients can fall under the umbrella of "advanced heart failure" care and be managed by both those nurses and the particular cardiologists, who in some facilities may be involved in managing the transplant population along with the heart failure population and in other programs might be managed by a different set of cardiologists and/or surgeons.

Some Heart Centers may be large enough to offer a variety of specialized physician teams to focus on particular service subsets within Cardiology, concentrating on general cardiology, electrophysiology, advanced heart failure, heart transplant, VAD/MCS management, pulmonary hypertension, invasive diagnostics therapy, ECMO, perfusion services, critical care management, etc. In such instances, there can be a substantial variety within the center of how heart transplant program personnel are organized and subunits, with their resources, overlap even more and managing growth in several of these sections with the Center becomes even more of a challenge since growth is not equal in each section, nor at the same pace. Often this results in partial personnel needs (less than a full time equivalent staff member); then the challenge becomes how to share such resources between work units since a full time staff member may only be able to be justified based on the growth demonstrated in two or more separate work units or sections.

Such complexity of services and the various resources that are required for each organizational unit become a more complex system to manage when looking at resources needed. Resources include personnel full time equivalents (FTEs), space, supplies, and support staff needed to both sustain the unit and facilitate growth, if there is desired growth. Often, when programs are in growth phases, leadership must look at opportunities to find means to leverage resources across work units to manage the workflow until a critical mass is achieved that can justify additional resources. Regardless of where the heart transplant program resides administratively, the request for additional resources goes to central hospital administration for FTEs and funding support.

This competition for resources and how any organization chooses to structure such decisions or service lines will often impact the decisions about what the administrative structure might be that is providing oversight for the heart transplant program. Few individuals outside of the transplant arena appreciate the complexity of the regulatory environment that governs the transplant world which reinforces the need for oversight by someone that has that knowledge.

Most healthcare organizations deal with some measure of regulations and requirements from The Joint Commission, CMS (Medicare), and the respective State Health Department's requirements along with the pressures of reimbursement concerns from shrinking Medicare/Medicaid payments, managed care contracts, new bundled services payment structures, and any number of

combinations of payment methodologies as well as the vagaries of whatever may be occurring in the legislative arena in one's State or nationally.

Transplant has all these pressures along with numerous specific regulations from CMS and OPTN/UNOS that guide a variety of workflow processes. Organ allocation decisions made by OPTN/UNOS can quickly impact not only program volume but costs and therefore program survival. CMS mandated QAPI (Quality Assurance, process improvement) requirements and outcome expectations that are monitored regularly by external agencies and are provided publicly every 6 months so the public and insurance companies have ready access to such outcomes and volume comparative data on any program in the United States and potentially use this data to make decisions about program selection, to name some of the most obvious regulatory items.

In order to adequately manage a heart transplant program, or for that matter any transplant program, one needs to balance all of these functional elements and data in order to strategically plan for the programs continued survival, growth, and economic viability. This goes back to the earlier statement of the need for someone who is knowledgeable about current OPTN/UNOS and CMS regulations governing transplant to be managing the heart transplant program. It would also be highly advisable for this individual to be familiar with some of the unique transplant fiscal rules and regulations that govern use of the Medicare Cost Report; managed care issues with contract terms structure and reimbursement levels that need to be adjusted as organ acquisition charges and organ allocation rules changes impact costs. It is a challenge to identify someone that is very familiar with all of this unique transplant information that is operational, regulatory, and fiscal in nature and also be well versed at the challenges and issues involved in the overall management of a Heart/Vascular Center with all its own particular operational, fiscal, and regulatory issues that also need to be addressed. In many circumstances, there are competing priorities within the organization and determining what is the administrative structure that best addresses such disparate but overlapping strategic priorities and goals is critical to the successful development of both the heart transplant program as well as the overall cardiac/cardiac surgery aspect of the organization.

Center Structures and Models

Some of the different administrative structures that can be found in any number of medical centers are as follows, and this is not meant to be an all-inclusive list but a sample of some of the more common combinations seen.

Heart Transplant Program Embedded Within the Department of Surgery or Department of Cardiothoracic (CT) Surgery

A structure that was more common 20 plus years ago often because the individuals that may have fostered the start and development of the heart transplant program were surgeons. In this structure, the program was a section or division within the Department of Surgery or Cardiothoracic Surgery and staff to support the program were then hired either by the department or were assigned to the program. Transplant Coordinators may have been employees of the Department of Nursing with a Nursing supervisor who may or may not be transplant knowledgeable. Support staff such as social workers, clerical staff, IT staff, financial counselors, dietary staff would all be based out of their "home" departments and may be assigned to transplant as part of their duties and any increase in need for time and FTEs must be negotiated with a myriad of department heads from these various specialties. The administrator may be the same person who manages the Department of Surgery or CT Surgery and often may not be that transplant knowledgeable and will be highly dependent upon the information provided to them by the physician lead in the department as well as input from cardiologists involved with the program but who are under a different department, usually Medicine, in the Division of Cardiology. Often there may be competition for coordinator and

support staff time between Surgery and Cardiology as well as concern about who can direct the work of the staff since they are often seen as being within a particular department rather than "programmatic" staff. Fiscal management of the program may be seen from a more limited focus, that focus being surgeon reimbursement and RVU generation since most often heart transplant case volume, with or without MCS/VAD implants, is not the predominant volume activity that generates that surgeon's activity level and income. This particular structure is no longer predominant as transplant programs have evolved and are increasingly supported by hospital dollars and hospital administration takes a greater interest in such program structure and management. Many have transitioned into some alternate format as described further in this chapter.

Heart Transplant Program as Part of a Multi-organ Transplant Center

In this structure, there is the highest likelihood that the administrator assigned would either be a transplant experienced professional or else the expectation would be that the individual hired into this role would be expected to gain that knowledge and expertise as part of their orientation and growth in the role. Here some of the challenges may be whether the Transplant Center is organized as merely a collection of programs with personnel all residing in their various home departments and FTEs are all "borrowed" by the Transplant Center or whether the transplant budget actually contains the pertinent personnel and dollars so those resources are clearly allocated and accounted for within that Transplant structure. This would include faculty time and effort in support of the transplant programs under this "Center" umbrella. Or if the Transplant Center is a true "Center" with a budget that reflects commitments and FTEs, as well as funds in their budget that define the positions and personnel that are needed and have been negotiated to support the respective programs along with having the revenue generated by these activities and billing providers allocated back to the Transplant Center and it be recognized not only as a Cost center but as a Revenue center.

In such a "Center" structure, while personnel such as transplant coordinators or social workers may be hired through their home departments, their position and dollars as well as the staff themselves reside within the Transplant Center budget and ideally within the physical space. Usually even the hire of such personnel if facilitated from within the Transplant Center. This applies to personnel that are identified as "core" program personnel and needed for the effective functioning of the program. Personnel FTE percentage or time is essentially "purchased" by the Transplant Center in support of the programs needs and having that expense reflected on the Transplant Cost Center is a more accurate reflection of true expenses involved. It also allows for easier data capture and allocation of pretransplant expenses onto the Medicare Cost Report. The personnel can be matrixed to reflect their reporting to not only their "home department" for certain regulatory purposes such as nurses to the Nursing department (often Magnet issue), social workers to a social work supervisor, IT personnel to IT department supervisory structure but also reflect a direct reporting relationship to the leadership of the Transplant Center.

Faculty resources can also be part of this Center structure with faculty FTEs and time purchased as well and allocated to the Transplant Center budget along with the related revenue to offset the expense. This Commitment of faculty FTEs involves a major commitment by both the Departments of Surgery and Medicine and again can be used to more accurately reflect the time and effort involved to support any programs functioning and growth needs. This is also a good mechanism to reflect the actual faculty support needed for the program and allow tracking of respective RVUs, clinic time, and case volume that is generated related to the program both directly and indirectly. This would include not only faculty such as surgeon and cardiologist, in the case of the heart transplant program, but related personnel that may spend a substantial portion of their time in support of the

program. This could include infectious diseases, pulmonology, nephrology, psychology or psychiatry, palliative care, and others. Often within a multiorgan transplant center, the core specialists in one program such as nephrologists in the renal transplant program are the primary renal disease consultants for the heart program or the pulmonologists in the lung transplant program will be the primary lung disease consultants to all the other transplant programs because of their familiarity with transplant specific evaluation and posttransplant concern, immunosuppressive regimens, and many other related issues that cross all transplant programs.

In many instances, the VAD/MCS program personnel are an extension of the heart program and will reside under this Transplant Center umbrella and in other instances this is where some of the divergence begins with the MCS/VAD program and personnel residing under CT Surgery or Cardiology divisions or under a "Heart Center" model. This will then involve negotiation between administrators and managers about how workflow handoffs occur and how staff, especially MCS/VAD coordinators, are used most efficiently and effectively, especially when there are position vacancies or there is program growth. Being on-call and having enough personnel to handle this function without burning out staff, especially if they need to come into the office after being on call the night before, can be another challenge. Some on call functions are easier to share, such as call between heart and lung transplant programs. However, they do not cross cover as readily between heart and liver or kidney transplant programs. This may then create challenges when there are vacancies in heart and the Center does not have a lung transplant program. Then it may be necessary for the Transplant Center leadership and the Heart Center leadership to negotiate some form of cross coverage, if feasible. If the MCS/VAD program is under the Heart Center, this may be one option for temporary support. Or else alternate means of on-call coverage may need to be pursued with a third party. The bottom line is that in any instance, there may not always be enough resources available within the Transplant Center to meet all the needs of the Heart program and some negotiation with the Heart Center would be inevitable.

More than likely these types of negotiations and collaborations would need to be occurring on a regular basis because it would not be unusual for the surgeons and cardiologists to be practicing in the same inpatient and outpatient space and facilities as the balance of the cardiologists and CT surgeons within the organization. So as there is competition for bed and clinic space, as well as time slots for diagnostic services such as cardiac catherization or stress testing, etc., so there would need to be a collaborative relationship established between the administrative leaders of both Centers (Transplant and Heart) for the ultimate benefit of all the patients involved.

Heart Transplant Program Resides Within a Heart, Cardiovascular, or Heart and Vascular Center

As noted earlier, many academic medical centers now have some form of a Heart and Vascular Center or Cardiovascular Center. The names vary somewhat from organization to organization. But as noted earlier there is some combination of clinical divisions, usually involving Cardiology and Cardiothoracic surgery (sometimes includes vascular surgery as well), clinic space, inpatient beds, an ICU especially if there is a dedicated cardiothoracic ICU and/or Cardiac ICU. This frequently includes many cardiac diagnostic services that are aligned with the faculty associated with the Center such as the Cardiac Catherization suite, cardiac stress testing, electrophysiology, EKG testing, to name a few. There are often numerous smaller subunits within this center that reflect various interests or specialties within Cardiology and CT surgery. These are common sections such as heart failure management, pulmonary hypertension, general cardiology, cardiac interventions, possibly pediatric cardiology, and/or surgery; TAVR, VAD/MCS, heart and lung transplant to name just a few. This is not an all-inclusive listing of potential combinations; as stated earlier, this may vary

from organization to organization based on the services they provide and decided to include in the particular "Center" model.

In such a structure, size may matter for transplant. It would not be unexpected in such a heart center structure to have the administrator be focused more on the overall cardiovascular (nontransplant) structure and organization of the center. Clearly, this is an organizational entity that can generate a great deal of revenue, cases, RVUs, and overall billable encounters as well as have a significant number of FTEs and considerable expenses. So the likelihood that this center administrator would also have significant transplant specific knowledge and experience is less likely, though possible. Now as to the earlier comment about "size matters" for the transplant program. If the transplant program is of a substantial size and therefore seen as a significant work unit (likely generating substantial revenue and contribution margin) within the center, it could have a manager or assistant administrator assigned to it that could be transplant knowledgeable and have both operational and fiscal accountability for the particular work unit within the "Heart Center." If they also supervise the MCS/VAD work group, which logically should have a close working relationship with the heart transplant staff, this could make for some well-integrated work units within the "Center" structure.

This could be another way for the transplant program to receive the needed attention from an appropriately knowledgeable individual who has access to needed resources and support for the program. In such a structure, the transplant program could potentially tap into resources available in other work units within the "Center" to facilitate sharing of resources at times of growth where critical mass has not been reached that justifies certain additional resources or for managing temporary vacancies such as maternity leaves or resignations/transfers. There is still negotiation involved here since each work unit wants to preserve its own resources and sharing is not always readily facilitated. However, when all these resources reside within one Center or Department, it does make it somewhat easier to facilitate such sharing with leadership support.

However, when the transplant program is smaller and not seen as a major work unit, then it likely will not be assigned a separate manager to oversee it and if there is a manager assigned, they may have transplant and other work units to supervise and this decreases the likelihood that this person would be transplant knowledgeable. This then reduces the likelihood that the transplant program will have the appropriate oversight not only for daily workflow issues and efficient deployment of staff but managing the fiscal and regulatory aspects of the programs including being cognizant of the previously mentioned UNOS and CMS regulations and requirements for QAPI programs.

Another possible iteration on managing this issue would be for the Heart Center to retain or pay for a certain amount of time from the organizations Transplant Administrator, assuming there is one in the facility. In such a manner, the Heart and Vascular Center or Heart Center retains its administrative structure and its control over the costs and resources of the programs under that Center structure but acknowledges their lack of expertise in the transplant specialty specifics such as OPTN/UNOS and CMS rules, aspects of managed care contracting and site visits, regulatory audits and their management, interacting with the Organ procurement organization (OPO), assessing the programmatic impact of changes in organ allocation rules to name just a few.

While this is a way to address some of the oversight issues and engage transplant specific expertise, assuming that there is a transplant administrator within the organization and they have the bandwidth to assume this supplemental responsibility as well as the desire to enter into an administrative "consulting" arrangement. One of the concerns in such an arrangement is whether this structure provides the transplant administrator direct responsibility for the staff involved in transplant or if their role is purely oversight of operations outcomes and consultative in terms of suggesting changes based on new UNOS or CMS regulations; contractual issues, OPO changes relative to pricing or organ allocation and QAPI program management. In this situation the Transplant administrator and the Heart Center administrator will need to develop a collaborative relationship for this arrangement to work effectively. This will take time and the staff and MD's

involved will periodically feel some confusion about where they should be directing their questions or requests for support or resources. There should be some mechanism established to regularly discuss process issues along with resource concerns for the program so that staff and faculty can be apprised of the mechanism to discuss and forward requests as well as hear back about such requests in a reasonable time frame. Some of the other challenges here is how resource needs are identified and addressed. The Transplant Administrator may be approached about supporting the need for more personnel in the transplant or the MCS/VAD program and while some justification can be developed and discussed, if the Transplant Administrator does not have access to the Center; and therefore heart transplant/MCS/VAD program financial reports, it may be difficult to have solid enough argument developed to support such additional resources within the appropriate context. This reinforces the need for the Transplant Administrator and the Heart/Cardiovascular/Heart and Vascular Center Administrator to have a strong collaborative relationship since they would need to work together to provide the justification for these additional resources. Logically the Center administrator will not want the request for additional resources for the Heart transplant program to result in other work units within the Center to not receive their requested resources. That competition within the Heart/Cardiovascular/Heart and Vascular Center itself needs to be addressed and negotiated in a manner that still provides support for the heart transplant program and MCS/VAD program. But we all know that these various competing requests and priorities present challenges when there may be limited dollars and all requests simply cannot be approved. This is where it becomes acutely obvious how important it is to have an overarching strategic vision and goals that have been effectively communicated to various team members. When such decisions about resources need to be made, they should rationally support the overall strategic goal of the Center and ultimately all the pertinent work units, as well as the heart transplant program.

There must also be a mechanism to address any quality concerns that occur within the transplant program, identified via its QAPI program process, that overlap into other components of the Heart / Cardiovascular/Heart and Vascular Center such as the diagnostic areas or inpatient units. Ideally there should be some mechanism to integrate the quality program for the transplant program with whatever quality program is in existence for the overall Heart /Cardiovascular/Heart and Vascular Center. In such a manner all aspects of the Heart/ Cardiovascular/Heart and Vascular Center would benefit from a comprehensive approach to problem solving issues identified. Details about the QAPI program needs of a heart transplant program are expanded upon in another chapter but how that program is managed and integrated into the overall management of the heart transplant program as well as the overall Center structure, regardless of which structure exists, is important to the operational effectiveness of the program and its ultimate outcomes and program development and successful growth.

There may be other combinations of structures within any given organization and as stated at the beginning of this chapter, "..if you have seen one transplant program, you have seen ONE program..". This is very true because of all the myriad of ways that these programs were started, how they evolved in their respective organizations and the various personnel; administrative and clinical; that have provided oversight and direction for the programs evolution. Preferentially the structure for the program management should be such that faculty and staff have clear direction as to where to direct questions and requests for program resources and overall management while the administrators of the Transplant programs and Heart/Cardiovascular Center work collaboratively to negotiate resource requests and overlapping program needs and strategic development.

Elements of Transplant Management

The primary issue to focus upon is that the heart transplant program, as all transplant programs, need to have someone with specific knowledge and skills in place or else be willing to develop them quickly, in order to adequately support the

heart transplant program in its daily operations and long-term development and growth. This includes personnel management, regulatory oversight and fiscal management. To broadly summarize the major categories of knowledge and functions that a Transplant Administrator needs to be familiar with and be responsible for to a large degree, the following would be a listing of the majority of such categories:

- *CMS Conditions of Participation (CoP's) and United Network of Organ Sharing (UNOS) regulations*
  1. Being familiar with regulations and knowing how they impact operations.
  2. Preparing for audits and ensuring appropriate preparation for planned and unplanned surveys.
  3. Knowing the impact of non-compliance with CoP's.
  4. Internal monitoring to ensure programmatic compliance is maintained.
- *Organ Procurement and Transplant Network (OPTN) Framework and oversight Structure-*
  1. Being familiar with what OPTN is and does.
  2. Participating in UNOS regional meeting, committees, commenting on policy proposals that may impact the transplant community and the specific program.
- *UNeT as a data collection and repository tool. Resources that reside within UNeT*
  1. Data integrity of the program, who collects that data, how is it collected.
  2. What is audit mechanism to ensure accuracy of data submitted? This data impacts program Outcomes reported publicly.
- *QAPI Program development and maintenance*. Requirements that must be met for Medicare (CMS)

  Certification including integration with the hospital quality program and root cause analysis (RCA) Process
  1. What are the components of such a program.
  2. Does the program have the needed personnel to manage this function for the program.
  3. Is their Faculty support for the program.
  4. Is there a solid process in place to effectively review and address any outcomes concerns.
  5. Is there solid integration with the hospital's overall Quality program.
- *Medicare Cost Report usage and data collection- reimbursement impact*
  1. Who manages this process.
  2. How are charges identified and tracked in order to move to the Cost Report.
  3. How are the transplant identified in the EMR and billing system to facilitate this process.
  4. Are there dedicated and knowledgeable personnel in Finance and Patient Financial Services supporting this activity and ensuring accurate billing.
  5. How is this data reviewed regularly to ascertain accuracy and identify areas of concern.
- *Managed Care Contracting and Negotiations*
  1. Who does this negotiation; who reviews contract content.
  2. How are insurance company site visits managed, who does presentations.
  3. Who collects and submits RFI data, who reviews to ensure accuracy.
  4. Who signs off on final contract terms, are these contracts reviewed at regular intervals.
- *Finance- transplant specific profit and loss statements*; transplant event as well as "halo" effect revenue generated.
  1. What is programmatic contribution margin?
  2. Is the program profitable after fully loaded expenses or does it have a positive contribution margin.
  3. How is the program judged by the organization (by profit or contribution margin?)
  4. Are there regular fiscal reports available to look at not only reimbursement per transplant events but costs incurred and resources utilized.
- *Marketing/Outreach*- promote growth in highly competitive environment
  1. How is this done; is it done? Are there dedicated Marketing personnel assigned to the Program.
  2. What social media is being utilized to promote the program.
  3. Is there regular updates of website information, is website access by the public tracked.

4. Are there outreach clinics, how are they managed and staffed? This may overlap with strategies that overlap with strategies for other work units within the Heart/Cardiovascular/Heart and Vascular Center.

- *Organ Procurement organizations (OPO) Relationships/Organ Allocation*
  1. Being familiar with rule changes and cost impact on the program and organization.
  2. Allocation changes may have impact on elements such as utilization of ICU beds, ECMO program, MCS/VAD implants and more.
- *HLA/Tissue Typing*- costs and how utilized
  1. Knowing the costs involved for this service.
  2. What is pre transplant testing versus post-transplant donor specific antibody (DSA) monitoring.
  3. Is billing for these services being routed correctly.
  4. Is the lab agreement reviewed annually.
- Scientific Registry of Transplant Recipients (SRTR)Reporting-
  1. How is data collected, who performs this function, how is data integrity achieved.
  2. Impact on reported program outcomes, who reviews SRTR data reports.
  3. Are these reports reviewed to ensure accuracy and corrections made before final reports issued.
- *General Administrative Issues*:
  1. Managing personnel and identifying resource needs, staffing.
  2. Staffing survey in UNeT, identifying benchmarks for patient to staff ratios.
  3. Staff development to attract and retain top quality staff in all levels; RN coordinators; APP's, Social workers, Financial counselors, IT personnel, pharmacists, etc.
  4. Leveraging the EMR and its tools to facilitate both data collection on this complex population and overall population management tool development within the EMR along with some form of a database for this population. Ideally this should reside within the EMR system or else be integrated into it.

These elements are all important to being able to successfully manage the heart transplant program and support the faculty and staff in their desire for the program to develop and flourish. To be able to provide services to the patients in a manner that supports them, allows for good follow up and ongoing education of the patient and their family in how to maintain their health to promote long term survival and wellbeing. Many of these factors are also critical to maintain program compliance with CMS and UNOS regulations and reporting requirements that also impact what is reported as program outcomes.

Many of the issues that create difficulties for any transplant program are similar to other healthcare settings; staff turnover, staff retention issues, workplace satisfaction, professional development opportunities, adequate staffing numbers, increased workload; physician work relationships and collaboration, and opportunity for advancement for staff.

In some ways these issues are magnified in transplant because of the specialized knowledge and skills needed within the program. Often transplant programs are not large departments or divisions and therefore there may be limited opportunities for advancement for nurses or other personnel within the program. Opportunities to advance to positions such as a "senior coordinator" or "senior/lead social worker" may be limited and those that want to advance certain aspects of their careers may be essentially forced to go outside the program to meet those career goals. Such turnover of experienced and trained staff is very costly to any department but with the unique rules and regulations that are part of that training in transplant it's even more costly. While in other areas one may be able to hire a "float nurse" or a "float social worker"; unless those staff are oriented adequately to transplant regulations, they may inadvertently not document adequately for CMS regulatory purposes or be able to demonstrate adequate "transplant specific" education and training. Such factors then place program certification in potential jeopardy.

As such, being able to retain staff in one's transplant program becomes even more critical beyond the obvious inconvenience of staff turnover. The difficulty in recruiting appropriate candidates to such roles, especially in more rural areas of the country, makes the issue of staff retention strategies more challenging. A related feature is the need to maintain and justify adequate staffing ratios when there are limited tools available such as

benchmarking in Action O-I or other comparative tools in Vizient (previously known as United Hospital Consortium). Lack of such commonly used tools that are familiar to the C-suite makes it more challenging to justify additional resources. Being familiar with the Transplant Administrator Staffing Survey is a tool that can be utilized as a benchmarking tool for transplant programs. Many of the challenges experienced in transplant revolve around data collection and who performs this data Collection and the integrity of that data.

Underlying all of these issues and regardless of whichever particular organizational structure the heart transplant program resides within; the leadership of the transplant program needs to maintain an active relationship with senior organizational leaders and keep them apprised of the programs status and needs. Transplant programs are important entities to medical centers. The denote a certain level of clinical and academic expertise, they help attract faculty to the organization, they can help promote positive, high profile stories in the press and can promote fund raising. They can equally be high risk programs if there are outcomes problems placing managed care contracts and referrals at risk which can equally be advertised in the press but obviously be negative stories. All the more reasons for senior leadership to be kept regularly apprised about program status and issues so that appropriate interventions can be implemented quickly to prevent major problems, obtain support for resources that may be needed and coordinate strategic planning that may overlap with multiple divisions and departments of the organization. It is important for senior leadership to be aware of not only the positive aspects and achievements of the program but any possible risks and threats to the program's success which would also reflect on the overall organization.

Conclusion

In conclusion, transplant is a complex business. Heart transplant programs live in a variety of organizational settings that may present some additional challenges in providing appropriate administrative support for their functioning and compliance needs. This is a specialty that is not readily learned and requires committed time, effort and development of expertise to address the numerous issues that have been listed above and greatly impact program faculty and staff as well as program outcomes and overall success and survival of the program.

Transplant is the ultimate team sport, each component is highly dependent on other team members in order to get their job done. Transplant has been a leader in many models that are now the norm in healthcare, items such as "Centers" as work units crossing departmental and divisional lines. Dealing with bundled payment for services and learning to be efficient and creative in service delivery; looking at care delivery as a continuum from inpatient to outpatient and back again as the team's take care of patients for multi years pre and post-transplant. The patient being the core or the center of that service delivery hub.

Managing these different components is a complex effort and one that is critical to the success of the overall operation of the program and needs to be managed by an appropriately prepared and educated individual familiar with the myriad of unique rules and processes.

Cross-References

▶ Quality Assurance and Process Improvements
▶ Regulatory Agencies

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Part XI

Special Topics

Retransplantation

23

Monique S. Tanna, Allison Padegimas, and Joyce W. Wald

Contents

Abstract

Cardiac retransplantation accounts for a small percentage of heart transplants every year. For many patients, cardiac retransplantation is the only option for survival. As survival after heart transplantation continues to improve, this population will likely increase. However, given the paucity of available organs, there is considerable ethical debate over cardiac retransplantation. Waitlist mortality remains high for patients awaiting initial transplant, and survival after retransplantation has varied among retrospective studies. However, recent studies have shown that in carefully selected patients, survival after cardiac retransplantation approaches that of initial heart transplant. Paramount to optimizing the efficacy of cardiac retransplantation and making this lifesaving therapy a viable option in a resource-limited reality is the ability to accurately assess risk factors affecting retransplantation outcomes in order to guide patient selection. In this chapter, the indications, outcomes, risk factors, patient selection, and specific management principles of cardiac retransplantation are discussed.

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Retransplant · Cardiac retransplantation · Heart transplant · Cardiac allograft failure · Cardiac allograft vasculopathy

Introduction

The cardiac allograft can fail due to a variety of reasons, and these patients may be candidates for cardiac retransplantation, first described in 1977 (Copeland et al. 1977). As survival after heart transplant continues to improve, there will likely be more patients in need of retransplantation. Though the overall survival rate after cardiac retransplantation is historically lower than that after primary cardiac transplantation, it varies with specific recipient and donor characteristics. Moreover, given the scarcity of donor organs, there has been much debate regarding the ethical considerations surrounding retransplantation. Patient selection and management is therefore imperative to ensure that this scarce resource is being used in the appropriate patients to allow for the best achievable outcomes.

Indications

Currently, approximately 3% of adult and 5% of pediatric heart transplant recipients are retransplants (Conway et al. 2014; Lund et al. 2017). As primary cardiac transplant recipients enjoy improved post-transplant survival, the number of patients meeting indication for retransplantation will likely increase. The most common indication for cardiac retransplantation is cardiac allograft vasculopathy (CAV), which remains the most common cause of graft dysfunction. This is followed by primary graft failure, acute rejection, and chronic rejection (Tsao et al. 2009). Accordingly, the largest percentage of retransplant recipients had undergone initial heart transplant more than 10 years prior (Lund et al. 2014). Among those retransplanted in the first month after initial transplant, the dominant indication is primary graft failure, although this practice is becoming less common due to worse outcomes in those retransplanted for this indication.

Outcomes

According to ISHLT data from 1982 to 2012, survival after cardiac retransplantation was 70% at 1 year and 38% at 10 years, which is significantly worse compared to the 81% 1-year survival and 11-year median survival of all adult and pediatric heart transplant recipients during that time (Lund et al. 2014). Reported survival estimates after retransplantation have varied in the literature. Some of this variability is due to improvement in medical and surgical protocols, including candidate selection and immunosuppressive medications, which has affected survival in both primary and retransplant patients. Similar to primary transplant, survival after retransplant improved until 2002 but has not changed significantly since that time. Retrospective studies have also elucidated different survival curves for retransplantation patients based on indication, with CAV having the best outcomes, while primary graft failure and ongoing acute rejection have worse outcomes. Accordingly, shorter time from primary transplant to retransplant has also been associated with worse outcomes.

Outcomes of retransplant patients are affected by recipient comorbidities and clinical status, as well as their indication for retransplantation. A retrospective analysis of the International Society for Heart and Lung Transplantation (ISHLT) registry found that those undergoing retransplantation, although younger, were more acutely ill than primary transplant recipients. Retransplant recipients were more highly sensitized, had higher creatinine, and were more frequently hospitalized and treated with dialysis, inotropes, ventilator, and ECMO support (Lund et al. 2014). Regarding indication for retransplantation, several retrospective analyses have shown that retransplantation for certain indications has significantly better mortality curves than others. Specifically, those with CAV have the best post-transplant survival, while those undergoing retransplant for primary graft failure have the

worst, with a mortality of 46% in the first year (Lund et al. 2014).

Earlier retrospective data which reported lower survival rates for retransplantation had a higher prevalence of transplantation for acute rejection and primary graft failure. This coincided with higher numbers of retransplantations performed within 6 months or 1 year after initial cardiac transplant. Retrospective data published in 1995 from Stanford showed that in 65 patients undergoing retransplantation, 1-year and 3-year actuarial survival rates were 55% and 33%, respectively. However, 1-year survival rates varied greatly based on the indication for retransplant: 69% survival at 1 year for patients retransplanted for CAV compared to 33% for those retransplanted for acute rejection (Smith et al. 1995). The specific survival rates observed in this study are less relevant in the current era of improved immunosuppression, however were an early signal of differential survivals by indication.

Similarly, a small retrospective series from Germany published in 2014 showed 30-day and 1-year survival after primary and retransplant were 91.3% and 78.2% compared to 68% and 43%, respectively. In this series of 28 retransplantations in 25 patients, 54% had an indication of primary graft failure or intractable acute cardiac rejection compared to 46% with CAV. The patients who underwent retransplant for intractable acute cardiac rejection had a short mean time between transplants of 60.8 ± 43.5 days, as did those whose indication was primary graft failure (2 ± 1.5 days), compared to a much longer interval for those with CAV (3154.7 ± 1579.5 days). Thirty-day and one-year survival for intractable acute cardiac rejection, primary graft failure, and CAV were 50%/0%, 64%/46%, and 85%/68%, respectively (Yoda et al. 2008). Based on these observations and a growing body of evidence, practice evolved to favor performing retransplantation for CAV instead of acute rejection or primary graft failure and also to prioritize retransplantation as a safer option at least 1 year after primary transplant.

Following this change, a larger retrospective study from Columbia University Medical Center reported improved outcomes in retransplantation, although still inferior to primary transplant outcomes. This retrospective analysis of 780 cardiac transplant recipients between 1996 and 2007, of whom 45 underwent retransplant, reported 1-year survival among retransplanted patients compared to primary transplant recipients of 75% vs. 87% ($p < 0.003$) (Tsao et al. 2009). This transplant program stopped retransplantation for the indication of primary graft failure in 1993. Baseline characteristics were similar between the two groups with the exception of a higher rate of coronary artery disease, shorter ischemic time, and higher serum creatinine (1.9 ± 0.7 vs 1.5 ± 0.5, $p < 0.001$) in the retransplantation group. Retransplantation was performed primarily for severe transplant vasculopathy (93%) and occurred at 8.2 ± 5.3 years after the first transplant (Tsao et al. 2009).

These improving survival rates with better patient selection have been confirmed in multiple studies. A French retrospective analysis of 820 heart transplants from 2000 to 2012 including 21 retransplantations (2.5%) noted survival at 1 and 5 years of 70% and 53.3%, respectively (Pozzi et al. 2014). Similarly, a large 2014 retrospective analysis of UNOS data showed that of 28,464 transplantations performed from 1995 to 2012, 987 were retransplantations (3.5%). Among all retransplantations, overall 1-, 5-, and 10-year survival rates were 80%, 64%, and 47%, respectively. Overall patients receiving retransplant more than 1 year after initial transplant had a relative risk of death of 1.27 compared to primary transplant patients. Although this survival is significantly lower than primary transplantation, median survival was overall acceptable at 9 years (Belli et al. 2014).

Expectedly, with reduced prevalence of retransplantation for acute rejection and primary graft failure, the survival of retransplant patients has improved in more recent cohorts. This difference of course is multifactorial with changes in medical and surgical techniques also contributing largely during this time period. For example, in 2008 the University of Pennsylvania published a retrospective series of 709 orthotopic heart transplants from 1987 to 2007. Although only 66.7%

of the 15 retransplants were performed for the indication of CAV, survival approached that of primary transplant given improved surgical and medical techniques as well as rigorous patient selection criteria. Exclusion criteria for repeat transplant included pulmonary hypertension, HIV, major systemic illness, active or recent malignancy, end-organ damage due to diabetes, symptomatic peripheral vascular or carotid disease, active mental illness or psychosocial instability, history of immunosuppression intolerance, and history of noncompliance. This series included three patients with acute rejection and one patient with hyperacute rejection. In this study, 1- and 5-year survival post-retransplantation was 86.6% and 71.4%, respectively, compared with primary transplant survival of 90.9% and 70.1%, respectively, at the same institution. Though this was a small cohort with only four patients retransplanted for acute or hyperacute rejection, the survival differences among the various retransplant indications were not significant (Atluri et al. 2008).

The causes of death of retransplant recipients are the same as those of primary transplant recipients: graft failure, infection and multisystem organ failure in the early years after transplant, and malignancy, CAV, and renal failure in subsequent years. An analysis of the UNOS Thoracic Registry database of 20,787 primary cardiac transplants compared to 594 cardiac retransplants found similar predictors of survival among both groups (Shuhaiber et al. 2007). Multisystem organ failure and graft failure are more common among retransplant recipients than primary transplant recipients (Lund et al. 2014). Similarly, the retrospective study from Columbia University Medical Center showed that the most common causes of death were malignancy, perioperative multisystem failure, and infection (Tsao et al. 2009).

Patient Selection

In order to achieve the best outcomes after cardiac retransplantation, it is imperative that patients are carefully selected after considering several risk factors. As discussed above, evidence supports that optimal outcomes for survival after cardiac retransplantation are found in patients who are retransplanted for indication of CAV at least 1 year after primary transplant, at a younger age, and without preoperative LVAD or ECMO use. Those being retransplanted for acute rejection and primary graft failure have the poorest survival. Related to this finding, intertransplant time has also been independently correlated with outcomes with shorter times (defined as 6 or 12 months) being associated with worse outcomes (John et al. 1999).

Ross and colleagues performed an analysis of 4595 heart transplant recipients with CAV who were either retransplanted within 2 years of diagnosis or medically managed and still alive at 2 years. The 65 patients who were retransplanted were younger, more likely to be CMV seropositive, and more frequently on immunosuppression with proliferation signal inhibitors (PSI). Overall survival at 9 years was not different between the two groups, including death from heart failure and graft dysfunction. When compared to the subgroup of medically managed patients who also experienced systolic graft dysfunction 1 year after diagnosis of CAV, however, retransplanted patients had a significantly improved survival ($p = 0.002$) (Goldraich et al. 2016).

Several additional patient and donor characteristics have been identified to impact outcomes and should be used to guide patient selection. As is true for primary transplant recipients, increasing recipient age has been associated with decreased survival after retransplantation in multiple studies including the referenced ISHLT and UNOS registries (Belli et al. 2014; Lund et al. 2014). The UNOS database also identified ischemic time and number of days between first and second transplants as predictors of increased mortality. Additionally, in this study, univariate analysis demonstrated that the total serum albumin, need for mechanical ventilation, and presence of IABP had shown significant association with mortality, but these variables did not meet statistical significance in the multivariate analysis (Belli et al. 2014). A multivariate analysis of the retrospective

study of cardiac retransplants at Columbia University identified the following independent risk factors for decreased long-term survival: high-grade rejection of the first heart transplant, recipient age > 58 years at retransplant, and development of de novo malignancy after retransplant (Tsao et al. 2009).

There is inconsistent evidence regarding the success of using advanced circulatory support as a bridge to retransplantation. Mechanical circulatory support seems to be an acceptable means to increase survival to transplant but has also been associated with worse post-transplant mortality. A retrospective study from Columbia University found that in 48 patients who underwent retransplantation from 2000 to 2014, 11 were bridged with biventricular mechanical circulatory support (Thoratec IVAD, Heartware BiVAD, Total Artificial Heart, Centrimag BiVAD). There was no difference in waitlist mortality between patients with and without mechanical circulatory support (81.3%), though death from cardiac arrest or multiorgan failure with infection were more frequent in the medically managed group (Clerkin et al. 2015). ISHLT data review from 2006 to 2013 found that retransplant recipients were less likely than primary heart transplant recipients to be dependent on LVAD support. However, whereas preoperative LVAD support in the current device era among patients undergoing initial heart transplant did not confer worse outcomes, there was significantly worse postoperative survival among retransplant recipients requiring LVAD support (Lund et al. 2014). This suggests that although mechanical circulatory support with biventricular VADs is a stable platform while awaiting retransplant, it selects a clinically sicker population and may predict worse survival after retransplant. In the retrospective UNOS database analysis of 987 patients undergoing cardiac retransplantation between 1995 and 2012, 3% of patients required pre-transplant ECMO, and those patients had an increased relative risk of death (RR, 3.91; $p < 0.001$) (Belli et al. 2014). There is discordant evidence regarding whether the use of preoperative mechanical ventilation or inotropes is associated with poorer outcomes.

Studies have also found higher rates of malignancy in retransplanted patients which is thought to be due to the intense immunosuppression used at the time of retransplant in patients who have already been on long-term chronic immunosuppression (Tsao et al. 2009). Potential candidates for cardiac retransplantation should be carefully screened for any occult malignancies.

Individual center experience has also been shown to affect outcomes. One early study using ISHLT data from 1987 to 1998 showed that centers performing at least nine heart transplants per year had improved outcomes in cardiac retransplantation (Srivastava et al. 2000).

Management

There is no universally accepted protocol for induction or maintenance immunosuppression after cardiac retransplantation. Induction immunosuppression is used in approximately 55% of cardiac retransplant patients in North America based on data collected in the ISHLT registry (Lund et al. 2014). Retransplant patients more commonly received polyclonal anti-lymphocyte globulin/anti-thymocyte globulin, while primary transplants were more commonly treated with interleukin-2 receptor antagonists (Lund et al. 2014). From previous literature, it is known that although induction with cytolytic anti-lymphocyte antibodies has been associated with decreased rates of allograft rejection, it is also associated with nine times higher rates of lymphoproliferative disorders, viral and bacterial infections, meningitis, and respiratory distress (Atluri et al. 2008).

Preferred agents for maintenance immunosuppression are the same in primary and retransplant patients. Some centers will use everolimus instead of mycophenolate mofetil in patients who were retransplanted for CAV (Pozzi et al. 2014). Sirolimus is often used either post-retransplantation or prior to retransplantation in a patient with ongoing concerns for rejection, specifically CAV. Given the concern regarding increased risk of surgical site healing complications with PSI, its

use is often delayed until after wounds are healed. Likewise, PSI should be stopped prior to listing patients for retransplantation.

Further surgical concerns regarding retransplantation anatomy remain understudied. The renal transplant literature suggests that the presence of multiple grafts from different donors increases rates of rejection. For patients whose initial heart transplant was performed using biatrial anastomosis, removing all initial donor graft tissue would necessitate removal of the donor aorta, pulmonary artery, and atrial tissue (Atluri et al. 2008). It remains unclear whether specific surgical techniques may reduce rates of postoperative rejection in cardiac retransplantation.

Ethical Considerations

There has been much ethical debate regarding retransplantation given that many patients die on the transplant list awaiting their first transplant, while other patients receive a second and some even a third or fourth cardiac allograft. Though there were 5074 heart transplants performed in 2015, the number of available organs continues to fall short of those waiting on the transplant list. The number of organs available has not changed significantly over the years, and the disparity in supply and demand of organs continues to exist. In 2015, there were approximately 3000 people still waiting on the list, an increase of 51% over the last 10 years. Waitlist mortality is a staggering 10.6 per 100 waitlist years (Colvin et al. 2017).

Perhaps most relevant to the ethical dilemma surrounding resource allocation as it pertains to retransplantation is the ability to select patients with acceptable outcomes. Most centers currently do not support retransplantation for the indication of acute rejection or primary graft failure within 1 year of initial transplant given the proven worse survival outcomes in these patients. Given the scarcity of donor organs, allocating a heart to a patient who will have significantly worse survival is considered a poor use of a limited resource and overall unadvisable. Unfortunately, these patients also have no other options for curative treatment. On the contrary, those with CAV and intertransplant time of greater than 1 year have similar or slightly reduced survival compared to primary transplant recipients as discussed above. Using rigorous patient selection criteria in selecting appropriate candidates for retransplantation is therefore imperative to ensure comparable survival post-transplant and more equal organ utility. Furthermore, as discussed above, there is some evidence that patients with both CAV and graft dysfunction may have better outcomes with cardiac retransplantation compared to medical management alone. Whether it is fair to consider two candidates who are largely equivalent in terms of predicted post-transplant survival equally on the transplant list when one is awaiting a second heart transplant and the other is awaiting a first remains an ethical debate.

Conclusions

In conclusion, cardiac retransplantation, similar to initial cardiac transplant, represents the only lifesaving intervention for the approximately 3% of transplant recipients who receive a second heart. As our field becomes more experienced in this application, survival rates after retransplantation are improving and for certain populations approach those after initial transplant. Rigorous patient selection, improved medical and surgical techniques, and better immunosuppressive regimens have all contributed to improved survival. The persistent inequality between supply and demand for this lifesaving organ continues to mandate our vigilance to strict criteria and consideration of difficult ethical dilemmas. Additional research is needed to determine optimal immunosuppressive regimens, risk of mechanical support prior to transplant, and further delineation of patient and donor factors affecting outcomes. Overall, improving survival rates after retransplantation make it an acceptable option for ideal candidates.

Cross-References

- ▶ Cardiac Allograft Rejection
- ▶ Chronic Rejection
- ▶ Contemporary Survival in Heart Transplantation

- ▶ Contraindications to Heart Transplantation
- ▶ Current Listing System
- ▶ Induction and Maintenance Agents
- ▶ Recent Changes and Future Challenges in the Heart Allocation System

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Combined Heart Transplantation with Other Organ Transplantation

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Abstract

Patients with end-stage heart failure often have comorbid failure of another organ as a sequelae of advanced heart disease or an underlying systemic disease affecting multiple organs. In select patients, combined heart-lung, heart-liver, or heart-kidney transplantation is the only definitive therapy to extend survival and improve quality of life. One challenge in combined transplant is the absence of standardized guidelines to identify appropriate candidates, with variable practices among transplant centers. Once listed for transplant, combined transplant patients have universally higher wait list mortality than isolated heart transplant patients. Combined transplantation remains relatively rare, comprising only a small amount of the total organ transplantation performed annually. These patients typically have good outcomes, with survival after heart-lung transplant on par with isolated lung transplant and survival after heart-liver and heart-kidney transplant similar to isolated heart transplant. Patients who undergo dual solid organ transplantation enjoy lower rates of rejection than isolated heart transplantation with similar rates of other posttransplant complications including infection and malignancy.

Keywords

Heart-lung transplant · Heart-liver transplant · Heart-kidney transplant · Dual organ transplantation · Combined transplantation of the heart · Cardiorenal syndrome · Cardiac cirrhosis

Introduction

Heart transplant candidacy requires adequate function of other end organs. Some patients, however, have involvement of a second organ as sequelae of long-standing heart failure or systemic diseases that lead to multi-organ dysfunction such that heart transplantation alone is not possible. Heart-lung, heart-liver, and heart-kidney transplant are all done in relatively small numbers; however understanding the indications for and benefits of these procedures remains of vital importance to a group of patients with no other viable therapeutic options.

In any patient being evaluated for dual organ transplantation, the remainder of the recipient's organs should have normal function. Common contraindications to combined organ transplantation are abnormalities in a third organ or advanced age, with age cutoffs being center specific (often age 60).

Combined Heart-Lung Transplant

Introduction

The first heart-lung transplants in humans were uniformly unsuccessful in the pre-immunosuppression era – the first child to undergo heart-lung transplant HLTx in 1967 survived only 14 h and the first adult to undergo HLTx in 1970 died on postoperative day 8. Both expired from respiratory collapse. Following the introduction of cyclosporine, the first adult heart-lung transplants were successfully performed at Stanford University in 1981. The Stanford group's 1984 publication described the first series of patients to successfully undergo HLTx. Of the 13 patients who were transplanted for primary pulmonary hypertension or pulmonary hypertension secondary to Eisenmenger syndrome, 10 were alive at the time of publication, with 2 surviving for more than 2 years. This publication hailed the beginning of HLTx as a viable option for patients with end-stage cardiac and pulmonary disease.

According to the International Society for Heart and Lung Transplantation (ISHLT) Registry, as of June 30, 2015, a total of 3,879 HLTx have been performed worldwide. Use of HLTx peaked in 1989, with 284 transplants performed that year. HLTx frequency has decreased and plateaued over the course of the last two decades, with 49 to 92 HLTx per year worldwide for the last 10 years. In 2014, 40 centers reported a total of 58 adult HLTx. The number of patients worldwide to undergo a single thoracic organ transplant is over 2 orders of magnitude higher, with over 3700 single or bilateral lung transplant over 4000 heart transplants in 2014. While the low number of HLTx reflects advances in non-transplant therapies as well as lower thresholds to perform single-organ transplant in patients who may have previously been referred for dual organ transplant, there remains a group of patients with end-stage cardiac and pulmonary disease for whom heart-lung transplant remains their only viable therapeutic option.

Indications

Approximately two thirds of patients undergoing HLTx are referred to transplantation for definitive management of congenital heart disease (35%) or idiopathic pulmonary arterial hypertension (IPAH) (27%). Acquired conditions such as cardiomyopathy in the setting of significant pulmonary disease have become an increasing proportion of patients undergoing HLTx, with this group representing the third most common indication for HLTx from 2004 to 2015 (11%). While cystic fibrosis has historically been a more common indication for HLTx, cystic fibrosis and bronchiectasis patients typically undergo bilateral lung transplant and for the last decade have only represented 7% of patients who underwent HLTx. Other less common indications include interstitial lung disease (6%), sarcoidosis (4%), and COPD (3%). Retransplantation makes up a very small number of the HLTx performed – only 92 patients have undergone a heart-lung retransplantation since 1982, comprising less than 1% of the total number of HLTx.

Congenital heart disease remains the most common indication for HLTx. Despite advancement in surgical techniques to palliate congenital lesions, long-term survival is limited by the durability of surgical repairs and the development of Eisenmenger syndrome. In congenital heart diseases with left to right shunt, blood flow through the pulmonary vasculature is chronically elevated. Over time, increased blood flow in the pulmonary circulation results in irreversible changes to the vasculature of the lungs. As the vasculature of the lungs becomes more diseased, the resistance of these blood vessels rises. When the resistance across the lungs is high enough, blood flow across the shunt reverses, resulting in a right to left shunt, cyanosis, and marked functional decline. This phenomenon, known as Eisenmenger syndrome, is the most common indicator for HLTx in patients with congenital heart disease. While there is a survival benefit in patients with Eisenmenger syndrome who undergo HLTx compared to lung transplant alone, development of dysfunction of other organs (cirrhosis from chronic hepatic congestion, renal insufficiency from advanced heart failure) limits the transplant candidacy of many of these patients.

In patients with IPAH, HLTx was the main transplant strategy for patients with pulmonary hypertension and right ventricular dysfunction in the 1980s. Subsequent studies in patients with IPAH and chronic thromboembolic disease, however, found that right ventricular dysfunction rapidly resolves following bilateral lung transplant. As there is similar morbidity and mortality between bilateral lung transplant and HLTx, bilateral lung transplant became the operation of choice for many primary pulmonary diseases with secondary right ventricular failure, including IPAH. Despite these findings, studies suggest that in patients with IPAH who require ICU level of care prior to undergoing transplant, there is a mortality benefit to undergoing HLTx over bilateral lung transplant. This survival benefit is mostly seen in a reduction in early mortality, suggesting that patients who are sicker may be more susceptible to primary graft dysfunction or other organ failure after undergoing bilateral lung transplant.

Among patients with end-stage pulmonary disease and cardiac disease without cardiomyopathy (i.e., coronary artery disease, valvular disease, septal defects), lung transplant with repair of the cardiac defect at the time of lung transplant is preferable to HLTx. Patients with end-stage cardiomyopathy who have significant pulmonary vascular disease despite advanced heart failure therapies including mechanical circulatory support and pulmonary vasodilators should be considered for HLTx. Generally, pulmonary vascular resistance greater than 5 Wood units, a pulmonary vascular resistance index greater than 6, or a transpulmonary gradient greater than 16–20 mm Hg despite maximal medical therapy should be considered contraindications for heart transplant alone and should prompt evaluation for HLTx.

Recipient Selection

The timing of HLTx takes into account both cardiac and pulmonary status. Given high perioperative mortality with HLTx, the ideal transplant candidate is one whose underlying disease has a higher mortality than the expected transplant mortality but who is not too sick to withstand the surgical procedure and introduction of high-dose immunosuppression. Generally, patients who are listed for HLTx have NYHA class IV symptoms despite optimal management of their underlying cardiopulmonary disease. Other disease-specific prognostic indicators such as cardiopulmonary testing (VO2), 6-min walk test, and indices of cardiac function (filling pressures, cardiac output) are used to determine prognosis and HLTx candidacy.

There is limited data looking at outcomes of patients who are sicker going into HLTx – those on mechanical ventilation and extracorporeal membrane oxygenation (ECMO) prior to transplant. One retrospective analysis found that risk-adjusted 30-day morality for patients who required ECMO prior to HLTx was 83.5% compared 20% in patients who did not require mechanical support prior to HLTx. Similarly, patients who required mechanical ventilation had significantly worse outcomes at 30 days than those who did not (77.5% survival versus 83.5% survival). While retrospective and limited in power, these findings suggest that patients who require ECMO or mechanical ventilation may be poor candidates for HLTx.

Immunosuppression Considerations

Given the limited number of HLTx done in the era of modern immunosuppression, there is no universally accepted immunosuppression strategy for combined HLTx. As a result, immunosuppression is center specific and generally follows lung transplant protocols with minor modifications.

Induction immunosuppression in HLTx is controversial. While induction immunosuppression has been shown to confer a survival benefit to patients undergoing lung transplant, the benefits of induction immunosuppression in isolated heart transplant have not been as clearly demonstrated. Given limited data, there is no standard induction strategy for patients undergoing HLTx. Between 2010 and 2013, 49% of patients who underwent HLTx had induction immunosuppression with basiliximab, ALT/ATG/thymoglobulin, or alemtuzumab. 56% of patients received high-dose corticosteroids in the perioperative period. Retrospective analysis showed no benefit for posttransplant survival in those who underwent induction versus those who did not.

The most common maintenance immunosuppression regimen in HLTx is a combination of tacrolimus, mycophenolate acid, and corticosteroids (46%). Cyclosporine, azathioprine, and corticosteroids (12%) or cyclosporine, mycophenolate acid, and corticosteroids (12%) are accepted, though less commonly used, regimens.

Rates of acute and chronic lung allograft rejection in patients undergoing HLTx are similar to those undergoing bilateral lung transplant. The rate of acute rejection is in the range of 50% over the course of 5 years. Bronchiolitis obliterans syndrome (BOS), chronic immune-mediated damage to the lung allograft, increases over time and occurs at a rate of 15%, 41%, and 48% at 1, 3, and 5 years after transplant. Risk factors for the

development of BOS in patients undergoing HLTx are male donor, younger recipient age, a diagnosis other than cystic fibrosis, and the use of OKT3 induction therapy.

A unique feature in HLTx is that the lung allograft plays a significant role in protecting the heart from rejection. Lung allografts are more antigenic than hearts due to the presence of bronchial-associated lymphoid tissue. The lung functions as an immunologic "sponge," protecting the heart allograft from the recipient's immune system. Clinically, this manifests as chronic rejection of the lung allograft (bronchiolitis obliteration syndrome, or BOS) occurring at three times the rate of coronary artery vasculopathy, the chronic immune-mediated vascular damage to the cardiac allograft. Monitoring for subclinical rejection in patients with HLTx is also very different than isolated heart transplant patients – after the first year, the majority of transplant centers perform relatively few surveillance endomyocardial biopsies and instead monitor for rejection of the lung allograft with regular transbronchial biopsies and pulmonary function tests.

Outcomes

Morbidity and mortality following HLTx have improved as surgical technique, perioperative management, and immunosuppression have improved. Of nearly 4000 HLTx performed between 1982 and June 2014, survival rates are 71% at 3 months, 63% at 1 year, 45% at 5 years, and 32% at 10 years. The median survival of patients transplanted between 2004 and June 2014 was 5.8 years. Of patients who survived the first year after transplant, the median survival in the modern era is over 10 years.

Operative mortality for HLTx in the 1980s was 25%. While this as improved to 16.8% operative morality between 2002 and 2012, the upfront mortality of HLTx is considerably higher than lung or heart transplant alone. The most common causes of death in the first 30 days after transplant are early heart or lung graft failure, technical complications of the surgery, and non-CMV infections. The incidence of early graft failure ranges from 3% to 12% and uniformly results in death or, much less commonly, retransplantation.

Long-term outcomes and complications after HLTx are similar to lung transplantation, though significantly worse than after heart transplant alone. After the first year, bronchiolitis obliterans syndrome (BOS), chronic lung allograft dysfunction, and non-CMV infections were the most common causes of death.

Morbidity associated with the long-term use of immunosuppressant therapy is also seen in patients undergoing HLTx. At 5 years post-transplant, hypertension (88.1%), hyperlipidemia (70%), and renal dysfunction (45.5%) were extremely common.

Complications

HLTx patients are at higher risk of mechanical complications as a result of the surgery, notably phrenic nerve dysfunction and gastroparesis. In a 10-year retrospective analysis, phrenic nerve dysfunction was much more common in patients undergoing HLTx than lung transplant alone (42.8% versus 9.3%). Phrenic nerve dysfunction in HLTx patients was associated with significantly more ventilator days and a prolonged intensive care unit length of stay. Additionally, injury to the vagus nerve can result in gastroparesis, a delay in emptying of solids and liquids from the stomach. One retrospective chart review found 83% of HLTx patients had symptoms of nausea, vomiting, and abdominal distention after eating. All of these patients had abnormal gastric emptying studies, consistent with a diagnosis of gastroparesis. In addition to a marked reduction in quality of life, over half of the patients in this study required placement of a feeding tube to receive adequate nutrition and immunosuppression medications. Abnormal stomach emptying also predisposes patients to gastroesophageal reflux and microaspiration which has been shown to have a very detrimental effect on the transplanted lungs.

Infectious complications of HLTx are a significant cause of morbidity and mortality in both

the early and late posttransplant period. Most infections (61%) are located in the tracheobronchial tree or lower respiratory tract. In the first 30 days after transplant, approximately 50% of deaths are due to bacterial and fungal infection. The most common pathogens during this period are *Pseudomonas aeruginosa*, *Staphylococcus* species, *Aspergillus* species, and *Candida* species.

Cytomegalovirus is the most common viral pathogen after HLTx, occurring 30% of patients. The highest incidence of CMV infection is in the second month after transplantation. Patients have a range of clinical presentations, from fever and cough to pneumonitis and pulmonary collapse. Other viral infections, such as herpes simplex, herpes zoster, and respiratory viruses, are relatively uncommon.

Infections in the late posttransplant course are commonly associated with bronchiolitis obliterans syndrome. *Pseudomonas aeruginosa* and *Acinetobacter* species, two gram-negative pathogens, colonize diseased lung tissue. Eradication of these infections is very difficult, requiring several weeks of IV antibiotics. The infection also accelerates and worsens BOS. Long-term prophylaxis with trimethoprim-sulfamethoxazole (Bactrim) has reduced rates of *Nocardia* and *Pneumocystis carinii*.

Another important long-term complication of HLTx is posttransplant lymphoproliferative disease (PTLD). PTLD is a heterogeneous group of disorders that occurs in patients who have undergone solid organ transplant as a result of immunosuppression reducing the immune system's antitumor and antiviral surveillance. While relatively rare, PTLD is a very serious complication, with mortality ranging between 50 and 70%. Among all solid organ transplants, HLTx have the highest rate of PTLD (7.6%), most commonly from diffuse large B cell lymphoma. PTLD also presents earlier in HLTx patients (median 0.7 years) than patients undergoing other thoracic organ transplants (median 3.3 years). HLTx patients most commonly present with enlarged lung and mediastinal lymph nodes. Extranodal involvement is also quite common at the time of presentation (82%). Awareness of the timing and typical sites of involvement in HLTx patients is key in the early recognition and treatment of PTLD.

Conclusion

While the use of HLTx has decreased from the 1990s to present, it remains an important therapeutic option for select groups of patients. Combined heart-lung transplantation is most frequently considered in patients with congenital heart disease and Eisenmenger syndrome as well as patients with end-stage idiopathic pulmonary arterial hypertension and irreversible right ventricle failure. Despite a relatively high early mortality, patients undergoing HLTx in the modern era who survive at least 1 year after transplant have a life expectancy of over 10 years. The chronic management of these patients focuses on monitoring for common complications of chronic immunosuppression, including opportunistic infections, malignancy, and rejection. The majority of rejection in this patient population is from BOS, with relatively low rates of acute and chronic cardiac allograft rejection. Several areas of uncertainty in managing patient undergoing HLTx remain, particularly in recipient selection and immunosuppression strategies. These remain areas of ongoing research.

Combined Heart-Liver Transplant

Introduction

The first combined orthotopic heart transplant/orthotopic liver transplant (OHT/OLT) was performed in 1984 by Starzl et al. on a six-year-old girl with end-stage ischemic cardiomyopathy due to familial hypercholesterolemia, a disease caused by mutations involving the low-density lipoprotein (LDL) receptor. In this disease, while the liver function is intact, absence or dysfunction of the LDL receptors on hepatocytes results in very high levels of atherogenic lipids. Chronic exposure to massively elevated lipid levels causes accelerated atherosclerosis and coronary artery disease which, in this case, resulted in multiple

myocardial infarctions and ischemic heart failure in a six-year-old child. While the liver is otherwise normal in familial hyperlipidemia, transplant of the liver in addition to transplant of the failing heart cures the underlying metabolic cause for the heart disease and protects the cardiac allograft from recurrent disease (e.g., coronary atherosclerosis and recurrent myocardial infarctions). After undergoing OHT/OLT, the patient went on to live for 8 years before succumbing to complications of her transplant.

Despite early successes, OHT/OLT has remained a very rare procedure, with only 192 cases reported to the United Network for Organ Sharing (UNOS) in the United States between 1988 and 2015. OHT/OLT represents less than 0.1% of heart and liver transplants done in the United States, and as a result, the majority of published data on OHT/OLT reflects single center experiences.

Therapeutic options in patients with advanced liver disease and end-stage heart failure are limited. These patients are less likely to benefit from durable mechanical circulatory support than patients with isolated cardiac disease given the high surgical mortality associated with open heart surgery in patients with cirrhosis. In this group, OHT/OLT is increasingly being recognized as the only option for definitive management.

While heart-lung transplant has become less frequent in recent years, the rate of OHT/OLT has risen over the course of the last decade. Between one and six OHT/OLT were performed annually before 2004, and more than ten OHT/OLT have been performed annually since 2007. In 2015, 28 OHT/OLT were performed in the United States, the highest number in a single year to date. As outcome data emerges, it is unclear if the rate of OHT/OLT will continue to rise in the coming years or will remain at this level in the future.

Indications

There are three groups of indications OHT/OLT: (1) end-stage cardiac and liver disease because of related causes (e.g., congenital heart disease resulting in cardiac cirrhosis), (2) end-stage cardiac and liver disease from unrelated causes (e.g., dilated ischemic cardiomyopathy and hepatitis C cirrhosis), and (3) end-stage heart disease with liver transplant to correct an underlying metabolic disorder (e.g., familial amyloidosis or hemochromatosis).

The most common indication for OHT/OLT in the United States is familial amyloidosis (26.8%) followed by congenital heart disease (17.5%) with cardiac cirrhosis. End-stage dilated cardiomyopathies (idiopathic, ischemic, alcoholic, and others) make up the majority of other cardiac indications for OHT/OLT (16.3%), with cirrhosis from a variety of etiologies (chronic hepatitis C, alcohol, cryptogenic, etc.) making up the remaining hepatic indications for OHT/OLT.

Historically, an area of controversy was the appropriateness of OHT/OLT for patients with end-stage liver disease and severe but surgically correctable cardiac disease (e.g., coronary artery disease requiring bypass, valvular lesions requiring repair or replacement). Given the scarcity of heart allografts, these patients have generally not been deemed acceptable heart transplant candidates. Surgical management of their cardiac disease however is severely limited by cirrhosis. Historical studies have shown that patients with decompensated cirrhosis have a very high periprocedural mortality from cardiac surgery and cardiopulmonary bypass. In patients with Child-Pugh class B and C cirrhosis, complication rates after cardiac surgery approach 100%, and in-hospital mortality rates are in excess of 80%. The accepted strategy in these patients with decompensated cirrhosis and surgically correctable cardiac disease is cardiac surgery at the time of liver transplant rather than OHT/OLT.

Familial Amyloidosis

Familial amyloidosis accounts for the largest group of patients in the United States who undergo OHT/OLT. Amyloidosis is a disease caused by the extracellular deposition of misfolded protein in tissues leading to end-organ dysfunction. There are several different types of amyloidosis, each characterized by a different

mutant protein that leads to amyloid deposition. The age of onset and the symptoms of amyloidosis are variable, depending on the type of amyloidosis. Amyloidosis can be inherited or acquired, and the precursor proteins can be the result of chronic inflammation or come from the liver or bone marrow.

The most common type of inherited amyloidosis is familial amyloidosis, a subtype of amyloidosis in which a mutant transthyretin (TTR) protein is produced largely by the liver. Familial amyloidosis is an autosomal dominant disease with 100% penetrance. There are over 75 known mutations in the TTR protein that cause familial amyloidosis. Forty-four TTR mutations are known to cause cardiac amyloidosis.

The most common mutations in familial amyloidosis are Val30Met and Val122Ile, which are present in 4% of African-American descendants in the United States. These mutations commonly manifest in the fourth to fifth decade of life with neuropathy and cardiomyopathy. TTR amyloid can also accumulate in the kidneys, gastrointestinal tract, lungs, and other soft tissues. TTR cardiac amyloidosis is characterized as a rapidly progressive restrictive cardiomyopathy. Some patients also develop systolic dysfunction and arrhythmias.

In patients with end-stage cardiomyopathy secondary to amyloidosis, the definitive management is orthotopic heart transplantation. If a patient with familial amyloidosis only undergoes heart transplant, however, the patient is at risk of recurrent amyloid deposition in the cardiac allograft and recurrent heart failure. For that reason, one strategy for patients with TTR amyloidosis with severe cardiac involvement is OHT/OLT.

Despite producing the mutant amyloid protein, livers from patients with TTR amyloidosis have normal synthetic function. One interesting clinical practice, particularly given concerns of giving multiple organs to one recipient, is the practice of "domino" organ transplantation. In "domino" OHT/OLT, the patient with cardiac amyloidosis receives a liver and heart allograft from the same donor. The explanted liver from the patient with amyloidosis, which despite producing a mutant TTR protein has normal synthetic function, is given to another patient listed for liver transplant. In choosing older patients (generally greater than 60 years old) to receive the explanted liver that produces TTR amyloid, the expectation is that the recipient will not live long enough to develop symptoms from production and deposition of amyloid protein. Using this strategy for combined organ transplant, two patients benefit from the organs involved in the OHT/OLT. One institution that transplants the highest volume of patients with familial amyloidosis reported that 57% of explanted livers in patients undergoing OHT/OLT were acceptable for transplant to an isolated liver recipient.

Congenital Heart Disease

Adult congenital heart disease represents only 2% of isolated heart transplants in the United States. While the absolute number remains small with between 15 and 20 OHT/OLT annually for ACHD patients with concomitant liver failure, this group represents nearly 20% all patients undergoing OHT/OLT. Given the highly specialized nature of caring for patients with complex congenital heart disease and the coordination of expertise required to perform and manage OHT/OLT throughout the perioperative period, combined transplantation is not widely available – the majority of OHT/OLT for ACHD occurs in UNOS regions two and five.

Hepatic fibrosis and cirrhosis are very common in ACHD patients with end-stage heart disease. Particularly in patients with Fontan repairs of single ventricle hearts, nearly all patients have at least some extent of hepatic fibrosis, and many have frank cirrhosis and even hepatocellular cancer. Failing Fontan circulation clinically manifests as the signs and symptoms associated with low cardiac output, elevated right atrial pressures, ascites, edema, and protein-losing enteropathy. The pathophysiology of protein-losing enteropathy is unknown; however transplant is curative. While there is emerging data regarding the use of sildenafil to improve hemodynamics as well as exercise tolerance in patients with failing Fontan, this remains controversial.

Risk factors for more advanced liver disease in patients with ACHD include elevated systemic

venous pressures, decreased cardiac output, and Fontan repair. As the liver is exposed to chronically elevated venous pressures, sinusoidal dilation leads to fibrosis which over time progresses to cirrhosis. Liver disease is often not recognized until it is advanced. For that reason, liver biopsy is a recommended part of the heart transplant evaluation for any patient with ACHD, particularly for those with Fontan repairs. In the event that advanced bridging fibrosis or cirrhosis is found, these patients should be considered for OHT/OLT.

Recipient Selection

Pretransplant evaluation typically consists of independent evaluation heart and liver transplant committees. There are no standardized guidelines regarding evaluation for OHT/OLT. In addition to the standard heart transplant evaluation, liver transplant evaluation typically consists of liver biopsy (transjugular or percutaneous), comprehensive metabolic panel and international normalized ratio (INR) to calculate a model for end-stage liver disease (MELD) score, platelet count to evaluate for thrombocytopenia, serologic workup including hepatitis B and C, and abdominal imaging to assess for spleen size, liver nodularity, presence of ascites, or liver masses.

Once the decision has been made by both the heart and liver transplant teams that the patient is an appropriate OHT/OLT recipient, the patient is then listed for a primary and secondary organ. The primary organ is allocated based on the recipient's wait list priority, and the secondary organ is automatically sequestered from the same donor regardless of the recipient's place on the wait list for the second organ. In OHT/OLT, patients are generally listed for heart transplant as their primary organ, and as a result, their liver disease is usually less severe by traditional markers than those undergoing isolated liver transplant. In one series, the average MELD score was 16.8 prior to OHT/OLT. More severe liver disease prior to OHT/OLT is generally associated with worse outcomes. Most centers consider patients with Child-Pugh class C cirrhosis to be too sick to undergo OHT/OLT. One study found that patients listed for liver transplant as the primary organ with secondary heart allocation did not have improved outcomes compared to isolated liver transplant, suggesting that more advanced liver disease is associated with worse outcomes.

Given multiple risk factors for pulmonary hypertension associated with end-stage heart failure and advanced liver disease, assessment of pulmonary hypertension is an important part of the pretransplant evaluation for OHT/OLT. Irreversible pulmonary hypertension due to intrinsic pulmonary vascular disease from either portopulmonary hypertension or as a result of chronic heart failure is generally a contraindication to OHT/OLT. Not all pulmonary hypertension is a contraindication to transplant – hepatopulmonary syndrome is expected to resolve early after OHT/OLT and thus is acceptable to transplant with careful perioperative management. Given the blood product and fluid resuscitation during liver transplant, the newly transplanted right ventricle is vulnerable to volume overload, worsened tricuspid regurgitation, and ultimately right ventricular failure, particularly in the setting of any pulmonary vascular disease. Currently, a pulmonary vascular resistance less than three Wood units is used as a cutoff for OHT/OLT, and perioperative management focuses on minimizing blood product and volume given during the liver transplant.

There are also specific concerns regarding transplant eligibility related to the etiology of heart and liver disease. In patients with ACHD, one common concern is the perioperative risk of patients with prior sternotomies given scar tissue and adhesions making redo sternotomy more technically challenging. Historically, approximately 40% of patients undergoing OHT/OLT have had at least one prior sternotomy. Retrospective analysis has shown that prior sternotomy in patients with ACHD does not confer increased risk for OHT/OLT, though each patient must be evaluated on a case-by-case bases. Prior episodes of mediastinitis, extensive aortopulmonary collaterals, and lack of arterial access for

cardiopulmonary bypass are generally contraindications to repeat sternotomy and listing for OHT/OLT.

In patients with amyloidosis, it is important to evaluate the extent of extracardiac involvement. Patients with significant disease prior to transplant, particularly those with severe neuropathy or gastrointestinal involvement, have worse outcomes after transplantation.

One area that remains poorly defined is how sick is too sick for patients to undergo OHT/OLT. In addition to Child-Pugh class C cirrhosis, patients requiring mechanical ventilation are less fit candidates for OHT/OLT. In terms of temporary mechanical support, only one patient in the literature has been reported to survive ECMO to OHT/OLT. Given the paucity of data and the concern for worse outcomes in this group, requiring temporary mechanical circulatory support remains a relative contraindication to OHT/OLT.

Once listed for OHT/OLT, organ allocation remains a challenge for these patients according to the current UNOS organ allocation system. The need for exception points/status is commonly required to elevate the priority of these patients on the transplant list, particularly given that traditional therapies that provide higher listing status – use of mechanical support, particularly in patients with ACHD – are often of limited or no use. Retrospective analysis has shown higher wait list mortality among patients listed for OHT/OLT than those listed for isolated heart transplant (26% versus 12% at 1 year) and those listed for isolated liver transplant (26% versus 14% at 1 year). Particularly in patients listed for OHT/OLT with a MELD score greater than 20, the mortality at 1 year is over 40% which is nearly double the death rate in patients with a MELD score greater than 20 awaiting an isolated liver transplant. The discrepant mortality rates underline the problem with current organ allocation in patients undergoing OHT/OLT.

At some institutions, the final barrier to OHT/OLT is a minilaparotomy at the time of OHT/OLT to verify cirrhosis by visual inspection prior to liver transplant. Given heterogeneity of liver disease, transjugular or percutaneous liver biopsies can be misleading as to the true extent of liver disease. In a minority of cases, liver biopsy has been reported to overestimate the severity of fibrosis or presence of cirrhosis in patients with cardiac cirrhosis. Given this sampling error, the patient is taken to the operating room for OHT/OLT; however before the liver is implanted, visual inspection, and in the case of ambiguity, pathologic examination of a large core biopsy, is done to confirm cirrhosis. If the patient's liver disease is less severe than previously thought, the liver allograft is given to a different recipient and the patient undergoes isolated heart transplant.

Technical Considerations

Several operative techniques for OHT/OLT have been described: (1) a staged transplant with a heart transplant first and then liver transplant from a different donor during the same hospital admission, (2) heart and then liver transplant from a single donor during the same operation after separation from cardiopulmonary bypass, and (3) heart and liver transplant done in sequence on cardiopulmonary bypass. The most common surgery is heart transplant and then liver transplant from the same donor done sequentially during the same surgery. This technique minimizes cold ischemic time for the heart allograft, which is more sensitive to ischemic time and primary graft dysfunction than the liver.

There have been few reports of liver transplant on venovenous bypass followed by heart transplant on cardiopulmonary bypass ("liver first" transplant technique). This technique has been used in selected patients with high panel reactive antibody levels with the hope that the liver would protect the heart from any circulating antibodies prior to the heart allograft being transplanted into the recipient. Given paucity of data, use of this strategy remains controversial.

Immunosuppression Considerations

Given the low total number of procedures performed, there is no universally accepted immunosuppression regimen for OHT/OLT. Immunosuppression regimens generally follow protocols for isolated heart transplant. Induction therapy is institution and recipient specific, with induction ranging from high-dose corticosteroids and thymoglobulin or basiliximab to no induction therapy. Patients are generally maintained on corticosteroids, mycophenolate mofetil, and either tacrolimus or cyclosporine, with discontinuation of corticosteroids 1 year after transplant. Surveillance biopsies follow the post heart transplant protocol but are sometimes modified per institutional protocols.

Rates of rejection are quite low following OHT/OLT – there is lower incidence of acute cellular rejection, antibody-mediated rejection, and coronary transplant vasculopathy, all of which is attributed to the immunoprotective effect of the transplanted liver. Several mechanisms have been proposed to explain this phenomenon: the liver's ability to "absorb" and "neutralize" lymphocytotoxic antibodies, the release of soluble class I human leukocyte antigens from the liver allograft to "block" the host immune response, the expansion of regulatory cells and deletion of cytotoxic cells, and the higher antigen load (independent of the type of transplanted organ). All of these pathways are thought to result in "activation-induced cell death" of the host's immune response and result in decreased rejection in OHT/OLT.

In patients who survive 1 year or more, the incidence of acute liver rejection is significantly lower in OHT/OLT than isolated liver transplant (5.2% versus 12.2%). Acute cardiac rejection is also much lower in patients undergoing OHT/OLT than in patients who undergo isolated heart transplant (8.9% versus 23.9%). Overall, nearly 90% of patients had no evidence of rejection on follow-up.

While clinical practice is to use similar immunosuppression regimens for OHT/OLT as isolated heart and liver transplants, an area of ongoing investigation is whether patients undergoing combined heart-liver transplants do not require such high levels of immunosuppression.

Outcomes

Mortality in patients undergoing OHT/OLT is between that of isolated liver and isolated heart transplantation. A retrospective analysis looking at all OHT/OLT between 1987 and 2010 found that survival at 1, 3, and 5 years after OHT/OLT is 84%, 74%, and 72%, with mortality for OHT/OLT worse than the liver alone but superior to the heart alone. Graft survival with OHT/OLT is similar to graft survival in isolated heart and liver transplants.

For ACHD patients undergoing OHT/OLT, the short-term outcomes are similar to non-ACHD patients, with approximately 75% survival in the first year after transplant. Multivariate analysis has shown elevated bilirubin to confer elevated early mortality risk, which was true in ACHD and non-ACHD patients.

Complications

The most common postoperative complication from OHT/OLT is acute kidney injury requiring hemodialysis, with over half of patients undergoing OHT/OLT having at least some degree of acute kidney injury and nearly one third requiring temporary hemodialysis. Re-exploration for bleeding or pneumoperitoneum is variable in the postoperative setting – with between 4 and 30% of patients taken back to the operating room for re-exploration in different case series. Other short-term complications in the perioperative period were vocal cord dysfunction, atrial arrhythmias, and volume overload requiring diuretic infusions.

For long-term survivors, morbidity is related to chronic exposure to immunosuppressants. Higher rates of malignancy have been described in these patients. In the relatively small case series

data available, opportunistic infections including cytomegalovirus seem to be relatively rare.

Conclusion

Despite a significant increase in use over the 2000s and 2010s, combined heart and liver transplantation remains a relatively rare procedure available at few high-volume transplant centers. While familial amyloidosis and adult congenital heart disease with cardiac cirrhosis remain the most common indications for combined OHT/OLT, transplants for end-stage heart and liver disease of different etiologies have increased in frequency over the last decade. Given limited retrospective data suggesting worse outcomes in patients with more severe liver dysfunction prior to OHT/OLT, recipient selection in this group will continue to be an active area of controversy and ongoing research. Despite excellent outcomes, particularly with low rates of cardiac rejection in OHT/OLT, high sensitization and organ allocation policies confer additional wait list mortality among this group compared to isolated heart and liver transplant. Exception points and early identification and listing are vital to getting this complicated and sick group of patients safely through transplant. This may be due to lack of mechanical circulatory support should the patient's circulatory status deteriorate.

Combined Heart-Kidney Transplant

Introduction

Chronic heart and kidney disease are closely related conditions – both share many etiologies (hypertension, diabetes mellitus, etc.), and both can cause dysfunction of the other resulting in a negative feedback loop (e.g., cardiorenal syndrome). Among patients hospitalized for acute decompensated heart failure, up to 40% have an elevation in serum creatinine during the hospitalization. As outpatients, nearly one third of patients with heart failure meet criteria for moderate to severe chronic kidney disease. Among patients awaiting heart transplant, studies have estimated between 15% and 30% of listed patients have chronic kidney disease.

Following heart transplant, kidney disease is nearly universal, with less than 10% of isolated heart transplant patients having normal kidney function 10 years after transplant. Patients with worse renal function prior to transplant have greater risk of developing end-stage renal disease (ESRD) after heart transplant. Studies have found between 2% and 18% of heart transplant patients go on to develop ESRD, which confers a significantly increased risk of death as well as a decrease in exercise tolerance and in quality of life.

As a result, combined heart-kidney transplant (HKTx) has become the definitive management of patients with advanced renal disease and end-stage heart failure despite optimal medical therapy. The first HKTx was performed in 1978 – while the patient succumbed to gram-negative sepsis 15 days after transplant, neither allograft was found to have signs of rejection. Despite improvements in surgical technique over time, HKTx remains a relatively rare procedure. HKTx represents 2% of the total heart transplants done annually, with only 593 HKTx performed between 2000 and 2010 according to UNOS. In recent years, there are approximately 50 HKTx carried out annually in the United States. While the total number of heart transplants has remained static, the frequency HKTx has risen over the last decade, with a 147% increase in transplants between 2000 and 2010.

Cardiorenal Syndrome

Cardiorenal syndrome (CRS) refers to the conditions in which heart and renal dysfunction overlap. Hemodynamic causes include decreased cardiac output and increased venous congestion leading to decreased renal perfusion pressure and a decreased glomerular filtration rate (GFR). Increased renal venous pressure also leads to renovascular hypertension which causes tubular hypertrophy, fibrosis, and injury. Other mechanisms have been implicated, including glomerular damage, increased neuroendocrine activity, and

inflammatory and endothelial activation. The chronic use of renin-angiotensin-aldosterone inhibitors also decreases the autoregulatory response of the kidney to reduce perfusion pressure and renal blood flow. While these medications are beneficial for long-term heart failure survival, their effects on the kidney can lead to decreased glomerular filtration and chronic CRS.

Cardiorenal syndrome is divided into five types: Types one and two refer to acute and chronic renal insufficiency caused by heart disease, types three and four refer to acute and chronic heart failure caused by kidney dysfunction, and type five refers to a systemic disease causing both heart and kidney dysfunction.

Type one CRS, or heart failure leading to acute kidney injury, occurs in approximately 25% of patients hospitalized with acute decompensated heart failure. Hemodynamic mechanisms are thought to play an important role in the development of acute kidney injury in type one CRS, with patients in this group having worsened renal function due to decreased renal arterial flow from reduced cardiac output and increased renovascular congestion from elevated filling pressures. Non-hemodynamic mechanisms implicated in type one CRS include high adrenergic tone, renin-angiotensin-aldosterone system activation, chronic inflammation, and impairment of nitrogen oxide production. Medical management of type one CRS parallels the principles of heart failure management: decongestion, improved forward flow, and neurohormonal blockade.

Type two CRS is the chronic renal dysfunction caused by chronic abnormalities in cardiac function. In addition to elevated serum creatinine, patients with type two CRS often have reduced renal cortical thickness and increased parenchymal echogenicity, findings typically seen in medical renal disease. Causes of type two CRS include diuretic-associated hypovolemia leading to prerenal azotemia, chronic renin-angiotensin-aldosterone system blockade, and medication-induced hypotension. In these patients, management is focused at preventing further episodes of acute-on-chronic kidney injury. At present, it remains difficult to predict how much renal function will recover in type two CRS following heart transplant.

Indications

The most frequent indications for HKTx are similar to the indications for isolated heart transplant: coronary artery disease (54%), dilated cardiomyopathy (23%), and chronic rejection of a previous heart graft (18%). The most common causes of renal dysfunction are nephroangiosclerosis (23%) and drug-related toxicity (14%). No specific cause of renal dysfunction was reported in 50% of patients.

Recipient Selection

The overarching principle in HKTx recipient selection is balancing not impairing heart transplant outcomes in patients who would do better with HKTx while not giving the kidneys to heart transplant recipients who do not need them.

Despite over 20 years of HKTx being a common clinical practice, no standardized criteria for recipient selection have been established. As a result, combined recipient criteria for HKTx is variable and center specific. In the majority of transplant centers, patients with ESRD on hemodialysis are generally not considered to be acceptable candidates for isolated heart transplant. These patients have markedly increased mortality in the posttransplant period, with up to 31% mortality in the 3 months following transplant. For this group of patients, consideration of HKTx is recommended.

For patients with chronic kidney disease not requiring hemodialysis, there remains significant controversy regarding which patients should be considered for HKTx and whether HKTx should be offered at all to patients in this group. The decision to list a patient for combined HKTx rather than isolated heart transplant is based on the severity of renal dysfunction and the degree to which the kidney dysfunction is thought to be reversible. No model has been able to reliably

predict which patients will regain renal function following heart transplant versus which patients will have continued and worsened renal function in the posttransplant period. Several tests are used during transplant evaluation to identify intrinsic renal disease versus potentially reversible renal dysfunction related to the hemodynamic and hormonal milieu of end-stage heart failure. Proteinuria and hematuria are more likely to be related to intrinsic kidney disease. Renal ultrasound can be helpful in identifying small, echogenic kidneys which suggest irreversible renal damage. Normal-sized kidneys on ultrasound, however, do not necessarily exclude intrinsic renal disease. Renal biopsy can also be considered to determine the underlying mechanism of kidney disease and help to determine which patients have reversible kidney dysfunction and would thus be appropriate candidates for isolated heart transplant versus those with irreversible disease and would be better suited to HKTx.

In patients with an eGFR less than 50 mL/min, there is a twofold increase in mortality after heart transplant alone (19.7% versus 9.5% mortality at 30 days). Several retrospective studies have identified GFRs below 33 mL/min to 50 mL/min as the cut point at which patients have worse isolated heart transplant outcomes. In light of these findings, the 2006 ISHLT guidelines consider irreversible renal dysfunction with an eGFR less than 40 mL/min to be a relative contraindication to isolated heart transplant. These patients should also be considered for HKTx.

An important consideration in listing patients with acceptable renal function for isolated heart transplant is that, in general, renal function worsens among patients awaiting heart transplant. One study found that over half of patients had significant worsening in their renal function between initial listing and transplant. As a result, ongoing monitoring of renal function while patients are listed for isolated heart transplant is important to evaluate the appropriateness of their listing for a single organ versus consideration of dual organ listing.

Among patients with advanced heart failure, a group that receives special consideration is those with renal failure after LVAD implant. In LVAD patients requiring hemodialysis, the prognosis is grim in the absence of HKTx. Among those who develop dialysis-dependent renal failure after LVAD implant, there is over 60% mortality in the first 30 days after surgery. The largest study to date found no dialysis-dependent LVAD patients survived to 1 year after LVAD implant. The same study found a 100% 30-day survival among dialysis-dependent LVAD patients who underwent HKTx, with an 83% survival at 1 and 2 years.

Retrospective studies have identified several risk factors for poor outcomes after HKTx, including recipient age greater than 65 years, peripheral vascular disease, nonischemic cardiomyopathy, mechanical circulatory support (e.g., left ventricular assist devices), body mass index greater than 35 kg/m^2, and elevated serum bilirubin. These factors should be taken into account when decided a patient's candidacy for HKTx.

Technical Considerations

There are two main techniques for combined HKTx. Historically, patients have undergone staged transplant with cardiac transplant performed first followed by stabilization in the intensive care unit and reversal of coagulopathy. The patient returns to the operating room 24 to 48 h later for implantation of the renal allograft. The benefit of this strategy is the ability to stabilize the patient after heart transplant, making the hemodynamic and vascular milieu more favorable for the renal allograft. Additionally, in patients with primary cardiac graft dysfunction, the kidney can be allocated to another donor, thus not giving two organs to one patient who will likely have a poor outcome. With prolonged cold ischemic time, however, the kidney allograft is at increased risk of ischemic injury, which makes the kidney allograft more immunogenic. This is thought to possibly lead to increased risk of rejection and worse long-term survival.

Given improvements in surgical technique, anesthesia, and critical care, the majority of HKTx are now done during the same operation, with delayed operation reserved for patients

who are hemodynamically unstable after heart transplant. The combined surgery allows urine output to occur earlier and avoids the patient having to undergo a second anesthetic.

While no head-to-head comparison has been done of the two techniques at the same institution, case series suggest that immediate kidney transplant after heart transplantation does not negatively affect the renal allograft, with no differences in the need for hemodialysis after HKTx or the length of ICU or hospital stay.

Immunosuppression Considerations

Prior to isolated renal transplant, the donor and recipient undergo crossmatch to determine if there are any preformed anti-donor antibodies in the serum of the potential recipient. Crossmatch prior to HKTx is variably done due to time considerations – prolonging cold ischemic time of the cardiac allograft beyond 4 h significantly increases the risk of primary graft dysfunction. In institutions where crossmatch is done before HKTx, the acceptable geographic area for a donor is very limited due to travel and surgical time considerations. Institutions that do not crossmatch kidneys prior to transplant have interestingly not noticed an increase in rates of kidney allograft rejection in patients with a positive crossmatch.

While the use of induction immunosuppression is controversial in isolated heart transplants, it is used in the majority of kidney transplant recipients. The majority of HKTx patients undergo induction of immunosuppression with high-dose corticosteroids and OKT3, thymoglobulin, or basiliximab depending on institutional practices. In the year following transplant, patients are generally on triple immunosuppression with corticosteroids, cyclosporine or tacrolimus, and mycophenolate mofetil. After 1 year, steroids are often weaned off. In patients with calcineurin-induced nephrotoxicity, sirolimus replaces cyclosporine in the immunosuppression regimen, though there is concern for higher rates of rejection with sirolimus.

Monitoring for rejection follows heart transplant protocols, with regular endomyocardial biopsies in the posttransplant period. Renal allograft function is followed by serum creatinine levels, and renal biopsies are generally only performed in the case of clinical suspicion of rejection (e.g., elevation in serum creatinine, abnormal urinalysis, and allograft pain).

Similar to patients undergoing heart-liver transplant and heart-lung transplant, HKTx confers a protective effect on the cardiac and renal allografts. Rejection-free survival is significantly longer in HKTx compared to isolated heart transplant and deceased donor kidney transplant. The proposed mechanisms for this phenomenon are similar to OHT/OLT and HLTx, namely, higher degrees of microchimerism (the presence and persistent of passenger donor leukocytes in the peripheral blood of the host leading to induction of tolerance), enhanced induction of regulatory T cells, high antigen loads leading to immune paralysis, and immune diversion (one organ diverts the immune attack from the second organ). There is little evidence to support any of these theories above the others. Practically, the decreased episodes of rejection results in a low incidence of coronary arterial vasculopathy, with minimal burden of smooth muscle hyperplasia leading to increased intimal thickness as measured by intravascular ultrasound.

Outcomes

Patients awaiting HKTx have a higher cumulative incidence of death than patients awaiting isolated heart transplant (22% versus 12% at 1 year) and a lower cumulative incidence of transplant (47% versus 58% at 1 year). Despite wait list mortality similar to status 1A heart transplant patients, more than half of dialysis-dependent patients are listed status as 2 or 1B for the heart portion of the HKTx. Patients with non-dialysis-dependent renal dysfunction have mortality similar to patients listed as a status 1B heart transplant patient, though nearly half are listed as status 2. These findings suggest that the current criteria for heart transplant listing do not adequately capture the influence of renal disease on wait list mortality, necessitating exception points in prioritizing wait list position

in patients with end-stage heart disease and advanced renal dysfunction.

Following transplant, multiple studies have shown no difference in overall survival between HKTx and isolated heart transplant (7.7 years versus 8.4 years after risk adjustment). This suggests that the increased risk of morbidity and mortality due to renal dysfunction in heart transplant is completely mitigated by renal transplant at the time of heart transplant. Patients with ESRD on hemodialysis have significantly better post-transplant survival than propensity-matched patients who underwent isolated heart transplant (84% versus 69% at 1 year and 73% versus 51% at 5 years), suggesting that these patients benefit most from HKTx. Patients with non-dialysis-dependent renal dysfunction have improved outcomes with HKTx, though the magnitude of the improvement in mortality is considerably less than those with ESRD.

Complications

Following isolated heart transplant, acute renal failure requiring hemodialysis occurs in 5% to 15% of patients. Following HKTx, up to 33% of patients develop delayed kidney allograft function necessitating temporary dialysis. The relatively high rate of delayed allograft function compared to isolated kidney transplant is thought to be multifactorial, with causes including ischemia due to hypotension and pressor requirement, prerenal azotemia from right ventricular dysfunction and elevated central venous pressures, and temporary vasopressin deficiency due to cardiopulmonary bypass, sepsis, and some induction therapies. Patients requiring hemodialysis following HKTx have increased early mortality, particularly from infections.

The complication causing the most mortality in the peri-transplant period is bacterial infections. Early studies identified intra-abdominal sepsis as an important complication in the postoperative period, though with improvements in surgical technique, this complication is less common.

In the first year after transplant, HKTx patients are have similar rates of hospitalization for infectious complications as isolated heart transplant patients (40% versus 36%). The second leading cause of death following HKTx is cardiovascular causes. Malignancy is also common in the years following HKTx, with 14.7% of HKTx patients being diagnosed with malignancy compared to 17.4% of isolated heart transplant recipients and 5.6% of isolated kidney transplant recipients. HKTx patients also go on to have a significant burden of comorbidities as sequelae of chronic immunosuppression, including hypertension (73%), diabetes mellitus (27%), hyperlipidemia (25%), malignancy (15%), and chronic liver disease (2%).

Conclusions

Patients with advanced, irreversible renal dysfunction have worse outcomes after isolated heart transplant. As a result, patients with dialysis-dependent renal failure are generally not considered isolated heart transplant candidates and should be referred for consideration of HKTx. The management of patients with significant renal dysfunction not requiring hemodialysis and end-stage heart disease remains controversial. Identifying patients who will have progressive renal dysfunction and failure after isolated heart transplant versus those who will have recovery of renal function remains a significant clinical challenge for heart transplant centers. The current criteria for combined HKTx are creatinine clearance less than 30 to 40 mL/min, not thought to be reversible with aggressive medical management. Among patients listed for combined HKTx, outcomes following transplant are similar to isolated heart transplant, suggesting that kidney transplant ameliorates the additional risk of transplanting patients with more advanced kidney disease. These patients enjoy lower rates of heart and kidney allograft rejection, though in the long term, they have similar rates of infectious complications and possibly higher rates of malignancy.

Conclusion

Despite the extent of comorbidities and severity of end-organ dysfunction in patients listed for combined organ transplantation, the outcomes are encouraging. Survival after HLTx is similar to lung transplant, and survival after OHT/OLT and HKTx is similar to heart transplant. All patients undergoing combined transplant enjoy lower rates of rejection through mechanisms that are not fully understood. As the rates of OHT/OLT and HKTx have risen and may continue to rise, many questions remain: Who are the best candidates for combined heart-solid organ transplantation? What perioperative strategies are most helpful in reducing short-term mortality? What is the optimal immunosuppressive regimen that takes advantage of the lower rates of rejection following dual organ transplant to hopefully expose patients to less of the long-term complications of immunosuppression? Further study and refinement of research questions are key to the ongoing growth of this burgeoning field.

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Part XII

Outcomes Data

Contemporary Survival in Heart Transplantation

25

Hampton A. Crimm, Nicholas R. Fiacco, and M. Casey Flanagan

Contents

Abstract

The growing prevalence of heart failure in the worldwide population coupled with its high socioeconomic burden has escalated interest in any treatment modality that can dramatically affect the estimated 50% 5-year mortality commonly associated with heart failure. Cardiac transplantation remains the definitive therapy for most patients with advanced heart failure and confers improvements in both survival and quality of life. Since the first cardiac transplant in 1967, the transplant community has been on a relentless pursuit to perfect this highly individualized and resource-heavy treatment modality. As a result of major advances in nearly every component of the heart transplant process, survival has incrementally improved in every decade, and most patients are surviving decades, and not months to years, after their transplant. This chapter examines the multitude of factors, from pre-transplant comorbidities, to surgical variables, to post-transplant management and comorbidities that have been proven to affect short-, intermediate-, and long-term survival in heart transplant recipients.

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Heart transplantation · Survival · Conditional survival · Rejection · Primary graft failure · Coronary artery vasculopathy · Malignancy

Introduction

The first human-to-human orthotopic heart transplant (OHT) was performed by Dr. Christiaan Barnard in 1967 inspiring rapid worldwide adoption with over 100 cases performed in 1968 (Gass et al. 2015). Hampered by primitive surgical techniques, limited understanding of rejection and immunology, and rampant infection, early transplants produced a 10% 2-year survival which dampened enthusiasm and prompted a dramatic reduction in international case volume over the subsequent decade (Gass et al. 2015). However, starting with Caves' introduction of the endomyocardial biopsy for the diagnosis of rejection in 1973, including the FDA approval of cyclosporine in 1983, and continuing through today's study of preservation solutions, nearly every aspect of cardiac transplantation has produced a multitude of scientific advances which have collectively and progressively improved survival (Hunt and Haddad 2008).

The most robust data set on cardiac transplantation is the International Society for Heart and Lung Transplant's (ISHLT) registry. Published in 2018, the 35rd annual ISHLT report estimates a 1-year survival above 80% and a 5-year survival exceeding 70% (Fig. 1) (Khush et al. 2018). The median survival remains stable at 12.4 years, and conditional survival, defined as the median survival of all recipients who survive the first post-transplant year, now stands at 13.2 years (Khush et al. 2018). Since the registry's inception in 1982, patients in each subsequent decade have experienced improved survival across all pre-transplant diagnoses, age groups, sexes, and survival intervals (1 year, 5 years, and 10 years) (Khush et al. 2018).

These gains in treatment efficacy and survival occurred in the face of a professional willingness to transplant higher-risk patients as evidenced by increased rates of recipients with congenital heart disease, utilization of combined organ transplants, inclusion of highly sensitized recipients, the increasing prevalence of mechanical support, and the presence of recipients with significant comorbidities (Khush et al. 2018). Moreover, the average age of donors and recipients continues to increase further adding complexity to the field cardiac transplantation. As research begins to advance organ preservation and immune monitoring, scientists attempt to replicate the doubling of median survival experienced with the development of immunosuppression in the 1980s and 1990s. Despite the significant gains of the past several decades, room for improvement persists in short-term (1 year), intermediate-term (1–5 years), and long-term transplant survival (greater than 10 years).

Pre-transplant Variables

When strictly assessing the effect of recipient age on survival, data shows a linear relationship between age and mortality, attributed in part to longer wait times and the presence of more significant comorbidities in older recipients. Retrospective transplant survival data has repeatedly shown improved survival for those recipients under the age of 60 (Cooper et al. 2016). Interestingly, more recent studies have demonstrated comparable survival in patients between 60 and 70 years of age with those older than 70 (Cooper et al. 2016). The commonly cited age cutoff of 65 makes the data involving septuagenarians particularly germane. This data is intriguing given the lack of well-defined, evidenced-based guidelines for the management of advanced heart failure in patients older than 60. Whether heart transplant provides incremental benefit over mechanical circulatory support in the elderly population remains unclear. Sorabella showed equivalent survival between isolated transplant, left ventricular assist device used as a bridge to transplant (BTT-LVAD) or as destination therapy (DT-LVAD) in patients aged 65–72 (Sorabella et al. 2015). Post-transplant quality of life is as important as length of survival. When controlled for other transplant variables, functional outcome benefits are

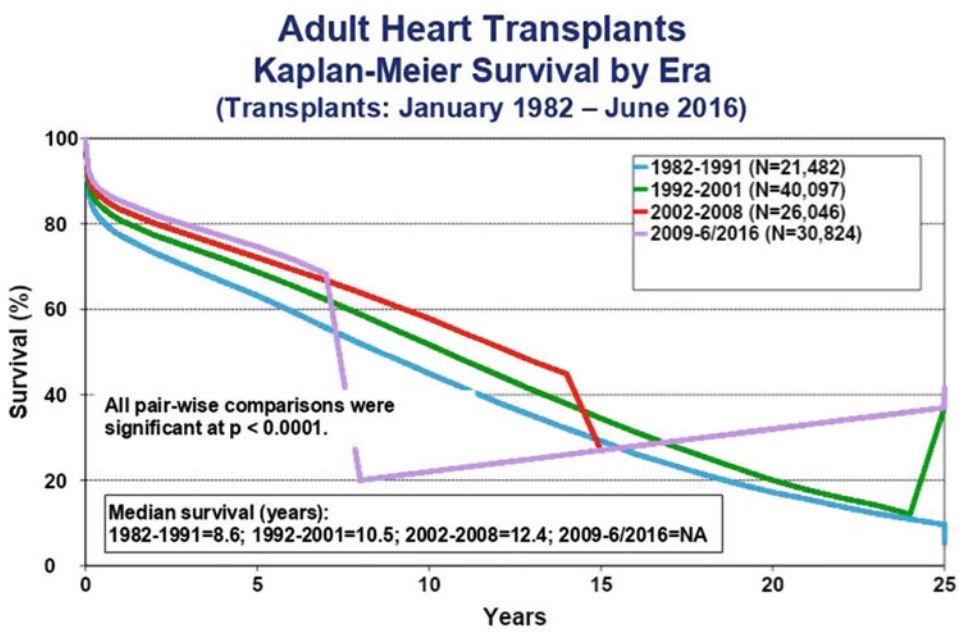

Fig. 1 Heart transplant survival by era (JHLT 2018 Oct; 37(10): 1155–1206)

preserved across the entire age spectrum (Kilic et al. 2014). While advancing age will always present a greater risk compared to younger cohorts, the summation of this data indicates that despite superior survival for recipients under the age of 60, a meaningful benefit of cardiac transplantation exists in older patients.

Much like age, simply comparing survival by recipient sex is an oversimplification. Immunogenicity and sex hormones, though not well understood, likely have a role in determining long-term outcomes in heart transplantation. As such, sex matching donor and recipient impacts rejection frequency and long-term mortality. While male recipients are generally older and have a greater burden of cardiovascular comorbidities, female recipients experience an increased frequency of acute rejection and moderate to severe coronary allograft vasculopathy (CAV) (Khush et al. 2018). Despite this, female recipients have a slightly better survival than men. Retrospective studies of sex mismatch demonstrate that female recipients have equivalent survival regardless of the sex of their donor. In contrast, male recipients experience improved survival when the donor is matched for sex (Khush et al. 2012).

Among the multitude of pre-transplant factors affecting post-transplant survival, the etiology of the recipient's cardiomyopathy may have the most variable impact on short- and long-term mortality (Fig. 2). Nonischemic cardiomyopathies constitute the most common indication for heart transplantation. Unfortunately, due to the heterogeneity of this cohort and the relative rarity of each specific kind of nonischemic cardiomyopathy, most studies examining the underlying cardiomyopathy prior to transplant are small, retrospective case series. Coincident with advances in coronary artery interventions, the percentage of heart transplantations for ischemic cardiomyopathy has decreased slightly over time, comprising 45% of transplants in the 1990s and 33% in the past decade (Khush et al. 2018). It remains the second most common indication for transplantation and a frequent benchmark for comparing transplant outcomes from other cardiomyopathies.

In general, nonischemic cardiomyopathies have the highest 1-year survival followed closely by ischemic and valvular cardiomyopathies (Khush et al. 2018). Congenital heart disease has by far the best conditional survival and the best chance of long-term survival after the 5-year

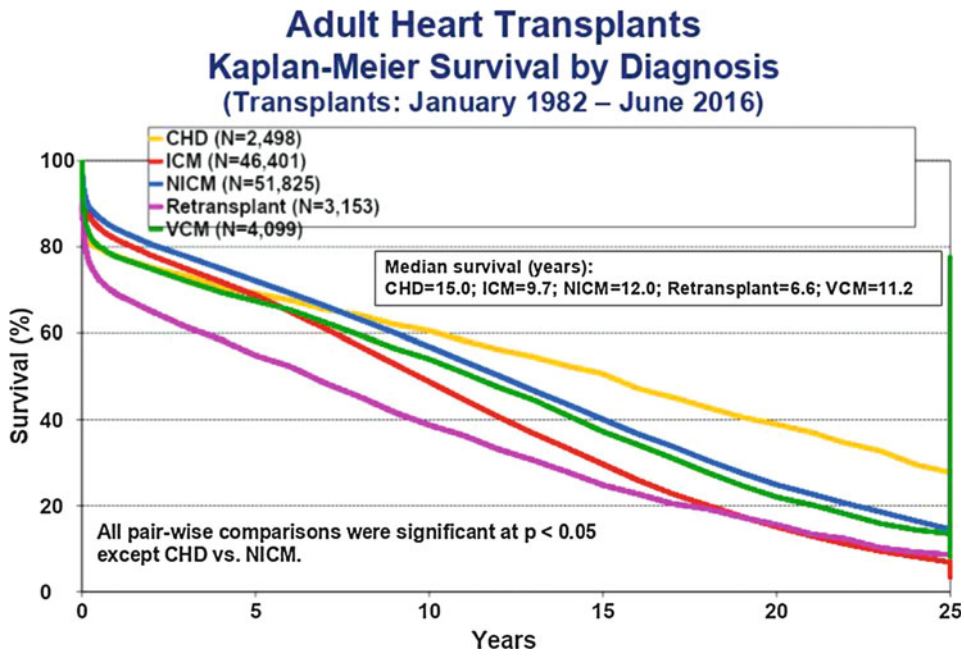

Fig. 2 Heart transplant survival by diagnosis (JHLT 2018 Oct; 37(10): 1155–1206)

post-transplant mark, but its high 30-day mortality rate truncates overall long-term survival. Congenital heart disease (CHD), while comprising only 2–4% of the transplant population, has historically been considered among the highest risk. While the average age of a CHD patient is nearly two decades younger than the average transplant recipient (Bhama et al. 2013), reduced survival in this cohort has long been attributed to challenging surgical techniques associated with prior sternotomies and unusual anatomy, increased bleeding risk from collateralization, and a higher incidence of sensitization (Hunt and Haddad 2008). In the 1990s, post-transplant 1-year mortality in this population was as high as 50% (Pigula et al. 2001), but more contemporary data suggests 1- and 5-year survival averages at 84% and 70%, respectively (Bhama et al. 2013). Consequently, median survival for CHD patients post-transplant has reached 15 years, and conditional survival has eclipsed 20 years (Khush et al. 2018). Despite these advances, 30-day survival remains at 80–89% and continues to lag behind non-CHD transplant recipients (Bhama et al. 2013). The elevated 30-day mortality rate reflects the higher perioperative risk involved in this population.

Myocarditis is an infrequent indication for cardiac transplantation and survival outcomes may be linked with patient's age. In a single-center retrospective study, adults with myocarditis had a median survival of 12 years, significantly better than the adolescent population included in the study (Savla 2014). Historically, the presence of lymphocytic myocarditis was associated with reduced survival. However, a more contemporary review of 32 such patients demonstrated comparable survival to age-matched patients with idiopathic or ischemic cardiomyopathies despite a higher rate of acute cellular rejection during the first year in the lymphocytic myocarditis patients (Yoshizawa 2013a). Similarly in the setting of hypersensitivity myocarditis, post-transplant survival was equal to patients without HSM (Yoshizawa 2013b).

Arrhythmogenic right ventricular cardiomyopathy (ARVD) and left ventricular non-compaction (LVNCC) are rare diseases infrequently requiring transplantation, usually in the context of advanced heart failure or recalcitrant ventricular

tachycardia. Survival data for ARVD is predominately derived from small case series, the largest of which showed a 1-year survival of 94% (Tedford 2012). Utilizing the United Network for Organ Sharing (UNOS) database over a 13-year period, only 78 patients underwent transplant for LVNCC (Al-Kindi 2015). Allograft survival was equivalent to an unmatched idiopathic cardiomyopathy cohort. Similarly, small case series have shown hypertrophic cardiomyopathy patients have comparable short-, intermediate-, and long-term survival to ischemic cardiomyopathy patients (Coutu et al. 2004).

Among cardiomyopathies, re-transplantation carries the worst prognosis with mortality rates as high as 43% at a mean follow-up of 4.3 years (Kilic 2012). Median survival following re-transplantation remains at 6.6 years, far below the median expected survival in primary transplantation (Khush et al. 2018).

Limited data on racial survival disparities suggests inferior outcomes among African American recipients. A retrospective, single-center study evaluating all transplants over a 26-year period found improved survival at 1, 5, and 10 years among non-African Americans when compared to their age-matched African American cohorts (Suryanarayana et al. 2014). African American recipients had an 11.4% absolute decrease in 10-year survival and a 46% increase in cumulative mortality compared to Caucasians in a 10-year review of the UNOS database (Allen et al. 2010). The study notes that biologic factors typically thought to influence survival differences in African American patients did not independently affect survival, suggesting that socioeconomic disparities may play a role in diminished post-transplant survival among African Americans (Allen et al. 2010).

Mechanical circulatory support (MCS) is increasingly utilized as both an alternative therapy and a bridge to heart transplantation among all age groups. Based on ISHLT data, from 2009 to 2015, 44.7% of OHT recipients had an MCS device at the time of transplant, and over 50% of heart transplant recipients in 2015 alone had an MCS device, more than double the incidence from 1992 to 2003 (Lund et al. 2015). While early studies suggested worse outcomes in MCS patients compared to direct OHT, recent data has failed to replicate this discrepancy in short-, intermediate-, or long-term survival (Awad et al. 2016). Statistics from the International Society for Heart and Lung Transplant show equivalent 5-year and 14-year post-transplant survival in patients with MCS compared to those without MCS when excluding extracorporeal membrane oxygenation (ECMO) patients (Fig. 3). LVAD patients experience more perioperative complications, including longer duration on cardiopulmonary bypass and more intraoperative blood product utilization, but those complications do not appear to impact survival (Award 2016). A debate on whether continuous flow LVADs conferred a post-transplant survival benefit compared to pulsatile devices has been rendered moot in the last decade by the overwhelming utilization of continuous flow VADs.

Whether patients enter transplantation with or without mechanical support, they tend to arrive to the operating room with systemic dysfunction and not isolated cardiac disease. The degree of multi-organ dysfunction affects post-transplant survival regardless of whether these comorbidities are the etiology of heart failure or the result of it. Cardiorenal syndrome, the complex interplay of the heart and kidneys in heart failure, coupled with the effect of heart failure and immunosuppressive medications makes renal dysfunction a common ailment both pre- and post-transplant. Patients with heart failure and concurrent chronic kidney disease undergoing cardiac transplantation experience worsening renal function post-transplant. In a retrospective review of over 1700 patients undergoing transplants in the United Kingdom, 50% entered surgery with CKD stage 3, but over 77% had developed stage 3 chronic kidney disease by the completion of the first transplant year. Patients with CKD3 at the time of transplant had a 50% increased mortality compared to age-matched patients with normal renal function. Stage 4 and 5 CKD fared even worse, with six times the mortality rate (Thomas et al. 2012).

The presence of diabetes pre-transplant increases infection risk, leads to greater blood glucose instability in the setting of

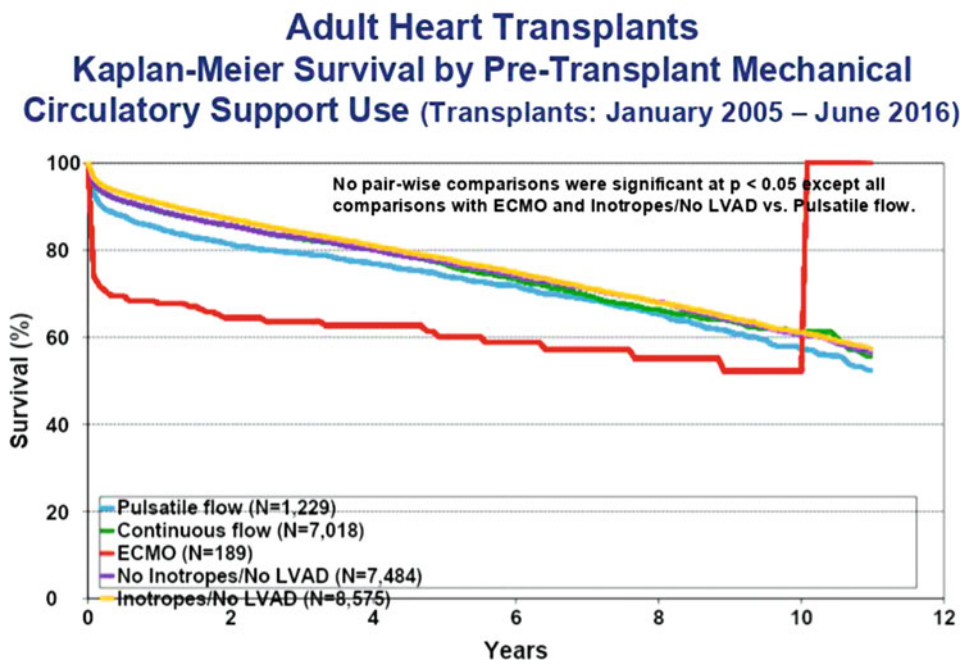

Fig. 3 Heart transplant survival by pre-transplant mechanical circulatory support use (JHLT 2018 Oct; 37(10): 1155–1206)

immunosuppressive therapy, and increases the risk of development of cardiac allograft vasculopathy and renal failure. Retrospective data indicates that diabetic patients tend to be older and possess lower creatinine clearance than their nondiabetic counterparts at the time of transplant. These factors translate into diminished survival at 5 and 10 years post-transplant. The ISHLT database validates this conclusion, with diabetic recipients having increased mortality at 2 years post-transplant. Increased mortality persists throughout a 10-year follow-up period (Khush et al. 2018).

Nonmedical factors like marital status, employment, or insurance coverage appear to have implications on post-transplant survival. The demands of transplantation – complicated medication regimens, significant clinical follow-up requirements, and frequent rehospitalizations – make social and logistical support key components of the transplanted patient. Recipients that are married, have insurance, and are educated appear to have improved survival. Venissa and colleagues showed that being married, regardless of sex, conferred a survival benefit of 15% over unmarried recipients (Venissa Tam 2011). Patients who return to work after transplant have improved survival at 5 and 10 years, though it is difficult to assign causality (Khush et al. 2018). Similarly, in a large retrospective court study utilizing the UNOS database, Allen found that private insurance, compared to Medicare/Medicaid, and a college degree were associated with improved long-term survival (Allen 2012). Privately insured patients in the study experienced a 9% improvement in survival at 10 years, while college educated patients enjoyed a 7% improvement in a 10-year survival. Similar results have been observed among patients undergoing transplantation of other organs.

The ability to accurately predict risk and survival based on laboratory assessment offers an attractive, objective, and reproducible method to stratify patients awaiting heart transplantation. While the presence of an elevated creatinine (>2.0 mg/dL) or bilirubin (>1.5 mg/dL) among cardiac donors is relatively common (10% and 19%, respectively), organ repairment among recipients has been associated with reduced longevity following transplantation (Sorabella 2015).

Recently, the MELD-XI scoring system, which excludes INR and is solely based on creatinine and bilirubin, accurately predicted worse survival (Grimm 2015). The reduction in survival appeared at 30 days and persisted at 1 and 5 years.

The heterogeneous nature of heart failure and the multitude of variables involved in determining adequate donors and appropriately matched recipients coupled with a finite donor pool and the massive amount of resources required for a single transplant have led several centers to develop risk scores in an effort to standardized and improve organ allocation. The IMPACT score sought to develop a simple scoring system to assess recipient risk that correlated with post-transplant survival (Weiss et al. 2011). Utilizing the UNOS database, Weiss and colleagues examined all 461 variables archived on the 21,378 patients who received orthotopic heart transplants from 1997 to 2008. Univariate logistic regression identified 19 recipient variables which increased the risk of 1-year mortality. Twelve met criteria for multivariate analysis, and the final 50-point recipient risk score weighted each variable based on their relative odds ratio. The presence of temporary extracorporeal support, need for mechanical ventilation or hemodialysis, and presence of congenital heart disease conferred the highest risk with recipient age, serum bilirubin, creatinine clearance, and race also contributing significantly when correcting for donor age and ischemic time (Weiss et al. 2011). In the study population, a cumulative score of greater than 15 had a 35% lower 1-year survival compared to scores between 0 and 2 (92.5% vs. 57.6%). Furthermore, a 14% increase risk of 1-year mortality was seen with each 1-point increase in the IMPACT score. These findings were validated through a smaller second cohort of transplant recipients over the same study time.

Transplant Variables

The authors of the aforementioned IMPACT trial employed a similar statistical model to develop a donor risk score. Examining 284 donor specific variables of all primary adult OHT patients in the UNOS database over a 12-year period, Weiss and colleagues isolated 9 variables that increased the risk of 1-year mortality (Weiss et al. 2012). Only four variables (ischemic time $>$ 2 h, donor age $>$ 40, race mismatch, and BUN/Cr ratio $>$ 30) were strongly associated with 1-year mortality after multivariate analysis (Weiss et al. 2012). Ischemic time and donor age were continuous variables with incrementally worse outcomes associated with longer ischemic times and older donors. Using regression coefficients, the authors assigned points to generate a donor risk score (maximum of 15). Each 1-point increase correlated with an 11% increase in 1-year mortality, and scores $>$9 were associated with a 9% lower 5-year cumulative survival compared to scores of 0–2. A separate donor score, designed to predict donor discard rates, was calculated using all heart donors in the Eurotransplant database from 2005 to 2009 (Smits et al. 2012). Using ten variables (age, cause of death, hypertension, cardiac arrest, ejection fraction, valve function, ventricular hypertrophy, coronary angiogram, noradrenaline dose, and dopamine/dobutamine dose), donors were classified into low-risk or high-risk cohorts. A low-risk donor score predicted improved 30-day, 1-year, and 3-year survival. Interestingly, only donor age and left ventricular hypertrophy predicted mortality in multivariate analysis (Smits et al. 2012). While none of these scores have been prospectively validated, they highlight the complex and multivariate decisions encountered in assessing donor organs and allocating them to recipients.

In order to meet the exploding societal impact of advanced heart failure, more centers than ever are offering cardiac transplantation. Unfortunately, studies repeatedly show that survival is proportional to institutional case volume and procedural experience. No consistent definitions for a high-volume or low-volume center exist. However, ISHLT data shows a linear decrease in hazard ratio for postoperative mortality as center volume approaches 20 cases annually (Lund et al. 2015). Grimm and colleagues reviewed UNOS data on nearly 20,000 cardiac transplants over a 10-year period and reported that serious complications associated with heart transplant

(a composite of infection, reoperation, hemodialysis, rejection, and stroke during the index hospitalization) occurred more frequently in low-volume centers (<14.5 cases per year) when compared to intermediate- and high-volume institutions. This translated into lower survival rate at 90 days, 1 year, and 5 years for OHT recipients at low-volume centers (Grimm et al. 2015). These survival advantages occurred despite high-volume centers transplanting a higher rate of recipients requiring ICU level care, on ECMO support, or with prior thoracic transplantation. Grimm's data suggests a complication and 1-year mortality inflection point at 15 cases annually. The increased prevalence of LVADs has contributed to the complexity of OHT and further highlighted the benefits of an experienced transplant team. Most authors suggest that procedural experience, while clearly impactful, is not sufficient to explain the discrepancy in survival among transplant centers. Careful patient selection, well-trained ancillary staff, a practice of heightened suspicion, and aggressive management all contribute to improved outcomes in a manner that is difficult to verify objectively.

Not surprisingly, the development of any perioperative complication during the index hospitalization negatively impacts mortality at all time periods. In one study, patients who developed renal failure and require hemodialysis or experienced a perioperative CVA had the greatest risk mortality in the first postoperative year (Grimm et al. 2015). Intraoperative characteristics also play a role in predicting short- and intermediate-term outcomes. Cardiopulmonary bypass has been associated with increased morbidity and mortality in the cardiothoracic surgery literature, owing to the deleterious effects of a stimulated inflammatory response, activation of the coagulation cascade, generation of microemboli, or presence of foreign bodies commonly seen in CPB. A retrospective study of 67 OHT patients found that the 20 non-survivors at 1 year averaged 40 min longer on cardiopulmonary bypass than survivors after controlling for other variables (Bianco et al. 2014). Whether due to the consequences of CPB or the fact that prolonged CPB time often reflects enhanced surgical complexity or early allograft dysfunction, it is clear that longer CPB times are predictive of worse outcomes and diminished survival. Likewise, requiring two or more inotropes intraoperatively also negatively impacted survival (Bianco et al. 2014).

Cold ischemic time, defined as the duration of time the procured organ spends without blood flow and cooled, has deleterious effects on the allograft. Cold ischemia produces oxidative stress, in the form of free radical generation, and generalized inflammation through cytokine production. The transplant community has long attempted to minimize ischemic time, with 1-year survival precipitously falling with cold ischemic times longer than 4 h. However, data collected in the contemporary era of improved immunosuppression, infection prophylaxis, and rejection monitoring suggests that the cold ischemic time may be safely extended to 5 h without impacting 1-year mortality (Yeen et al. 2013). Warm ischemia, when the allograft is not receiving blood but remains at body temperature, also impacts allograft function, and survival through the extent of its influence on survival remains uncertain.

Worldwide, male patients represent around 68% of the donor population but roughly 75% of the recipient pool (Khush et al. 2018), making donor-recipient sex mismatching inevitable. While sex mismatch clearly impacts post-transplant survival, the mechanisms for this relationship remain incompletely elucidated. Differences in hormonal influences, organ size, cavity size, and immunogenicity between male and female patients have been causally implicated. A retrospective analysis of 4625 patients from the Spanish Heart Transplantation Registry revealed an increased mortality in male patients who received female allografts compared to sex-matched controls. Primary graft dysfunction in the early postoperative period accounted for the entirety of the mortality difference. Conversely, female recipients receiving male hearts experienced a nonsignificant trend toward improved survival compared to their sex-matched cohorts (Martinez-Selles et al. 2014). ISHLT 2018 survival data show that male recipients of female donor hearts experienced decreased survival at

every post-transplant milestone compared to all other donor-recipient sex combinations. This group has a median survival of 10.1 years, falling 2 years behind a median survival of 12.1 years in sex-matched female transplants. There does not appear to be a survival difference between recipients of male hearts based on recipient sex. These trends continued when controlling for patients who survived the first year post-transplant (Khush et al. 2018). Reed and colleagues largely attributed this survival difference in donor-recipient sex mismatch heart transplants to discrepancies in heart size between donor and recipient. Specifically, a higher risk of acute graft rejection was observed in undersized hearts regardless of sex mismatch, while a lower risk of acute rejection existed in oversized hearts (Reed et al. 2014). Since the 1990s there has been a steady decline in the number of males receiving female allografts as a result of this mortality disadvantage.

The use of induction agents during orthotopic heart transplant remains inconsistent from institution to institution. However, its use is generally on the rise with some form of induction utilized in roughly 50% of all cardiac transplants between 2009 and 2017 (Khush et al. 2018). Through the depletion of graft T lymphocytic activity, induction is a prophylactic therapy that theoretically achieves improved immunosuppression during the early postoperative period limiting acute rejection while reducing or delaying the institution of post-transplant immunosuppression. The delay in initiating calcineurin inhibitors mitigates postoperative nephrotoxicity. IL-2 receptor antagonists (IL-2rA), polyclonal antithymocyte globulin (ATG), and the monoclonal antibody muromonab-CD3 (OKT3) are the most commonly used induction agents with specific selection dependent upon individual institution or surgeon preference. ATG is a polyclonal anti-lymphocyte infusion of either horse- or rabbit-derived antibodies against human T lymphocytes. It is used to deplete the donor tissue of lymphocytes preventing graft versus host disease. OKT3 is a monoclonal antibody that inhibits T-cell activation through antagonistically binding CD3 receptors on graft T lymphocytes. Its use has diminished over the past decade due to its relationship with increased malignancy rates. IL-2 monoclonal antibodies like basiliximab or daclizumab block T lymphocyte activation and proliferation through inhibition of cytokine IL-2, but do not affect resting T lymphocytes.

Most large studies of induction in cardiac transplantation have resulted in equivalent short- and longer-term survival when compared to standard immunosuppression cohorts. ISHLT data comparing survival of patients receiving ATG, IL-2 receptor antagonism, or OKT3 with no induction therapy failed to show a significant difference in any pairwise comparison over a 10-year survival period. This data did not control for maintenance immunosuppressive agents. In a retrospective analysis of over 2000 OHT in the United Kingdom, ATG induction produced a similar 10-year survival (59.5%) as their non-induced counterparts (56.2%) (Emin et al. 2011). Furthermore, a review of UNOS data from 2001 through 2011 found equivalent survival in non-induced and induced OHT recipients regardless of the specific induction agent utilized. While all three major inducing agents were used in the study, the majority (55%) received IL-2R antagonists. Further analysis of the individual induction agents demonstrated a trend toward improved survival in the ATG group, but this failed to maintain statistical significance when controlling for other confounders (Whitson et al. 2015). In another study, ATG induction was compared to IL-2R antagonism in 9324 patients transplanted worldwide from 2000 to 2011 and showed similar 1-year survival, but ATG induction conferred an improved 5- and 10-year post-transplant survival (Ansari et al. 2015). In multivariate analysis, use of basiliximab was associated with increased mortality at a mean follow-up of 3 years and had increased rates of mortality due to infection, cardiovascular events, and graft failure. In addition to a mild survival advantage, use of ATG required less early rejection treatment compared to IL-2 receptor antagonism (Ansari et al. 2015). Patients receiving ATG induction more commonly can delay immunosuppression initiation beyond hospital day 1 and have a lower rate of rejection in the first postoperative year, though at the expense of a

higher infection risk (Emin et al. 2011). Induction therapy may delay time to initiation of maintenance immunosuppression and decrease early rejection though it is associated with an increased risk of infection and has no observed benefit on long-term survival.

Multiple organ transplants remain infrequently performed at only select centers with the utmost experience. Small overall numbers limit meaningful survival analysis, but the increased complexity of multi-organ failure as well as the technical aspects of transplanting two separate organs generally portends worse survival. Heart-lung transplants remain the most common, with over 4600 logged in the ISHLT database since 1981 (Khush et al. 2018). Survival for such cases remains significantly lower than isolated cardiac transplantation. ISHLT worldwide data suggested that heart-lung recipients have survival rates at 1, 5, and 10 years of 63%, 44%, and 31% (Toyoda 2014), well below single-organ transplant survival expectations, though a few high-volume centers have demonstrated slightly better outcomes in large case series. Combined heart-liver transplants are exceedingly rare, with around 200 historical cases worldwide, making meaningful conclusions on survival somewhat limited and fraught with institutional bias. Likewise, the largest series of heart-kidney transplants includes 35 patients. Based on the limited data, it appears that patients receiving either of these combined organ transplants have acceptable 1-year and 5-year survival results, but generally fare worse than single-organ transplants. While the data sets are small, it is clear the double-organ transplant should only be considered in isolated clinical scenarios and performed only at highly experienced and specialized centers.

The relative organ shortage coupled with the increasing prevalence of end-stage heart failure has forced the transplant community to look at high-risk donors to expand the donor pool. Emerging data has suggested that a variety of donor variables, like bacteremia, alcohol use, troponin levels, and CPR status, once considered influential in recipient survival may not have as deleterious an impact as once envisioned. The Centers for Disease Control and Prevention defines high-risk donors as those at elevated risk of having seronegative HIV or hepatitis at the time of organ procurement. This group includes homosexual men, donors with nonmedical intravenous or intramuscular use of drugs in the preceding 5 years, hemophiliacs or patients with related clotting factor disorders, donors who have engaged in sex for money in the preceding 5 years, or inmates at correctional facilities. Multiple studies have shown similar survival in recipients of carefully selected, high-risk donors compared to standard donor risk profile. The presence of infection in the donor intuitively raises the likelihood of postoperative infection in an immunocompromised recipient and thus is often considered high risk. The largest study investigating this risk involved 900 culture positive bacteremic donors. When compared to a non-infected cohort, recipients of hearts from bacteremic donors were more likely to need antibiotics postoperatively, but did not have a higher incidence of rejection (Forest 2015). Most importantly, the presence of preoperative infection in a donor did not alter 1-year or 15-year survival post-transplant (Forest 2015). As with any registry derived study, the loss of granularity in the data set prohibits anything other than broad conclusions as specific organisms were not identified. The presence of cytomegalovirus (CMV) in either the donor or recipient complicates transplantation. CMV has been associated with worse outcomes in most solid organ transplants. More specific to cardiac transplantation, CMV infection has been linked to both increased episodes of graft rejection and coronary artery vasculopathy (CAV) and increased rates of fungal and other opportunistic infections. CAV is one of the most common complications of transplant and a major driver of long-term morbidity and mortality. The use of CMVIG and antivirals in the perioperative time frame may help to stem short- and long-term CMV-related morbidity and mortality.

Troponins are the most commonly used biomarker of myocardial cell injury, and it stands to reason that elevated levels of troponin in the donor heart signify a higher-risk donor. Some theorize that even mild increases of troponin represent subclinical myocyte damage from brain death-

induced adrenergic storm likely to be completely unmasked by the trauma of ischemic reperfusion injury. Early studies identified donor troponin elevations (TnI > 1.6 micro/mL) as a predictor of recipient graft failure (Potapov 2001), while others have demonstrated increased inotrope use and higher rates of rejection. These trials are usually smaller, single-center studies. However, more recent data suggests donor troponin levels do not influence short- or intermediate-term mortality in transplant recipients. In a study of over 10,000 transplants with normal ejection fraction, donor troponin levels did not influence short- or intermediate-term survival. Recipients were further divided into three categories based on troponin I levels. Multivariate analysis showed no significant differences in 30-day, 1-year, 3-year, or 5-year mortality between the lowest troponin cohort (<1 mcg/mL) and the highest cohort (>10 mcg/mL) (Madan 2016). Overall survival rates in this study at 30 days, 1 year, and 5 years were 96%, 90%, and 77%, respectively, commensurate with international averages. However, the combination of elevated troponins and ventricular dysfunction indicates a high-risk allograft that predicts worse survival. Much like elevated troponin, the presence of CPR prior to donation was once believed to be a marker for a damaged allograft. However, in the only study to investigate CPR duration's impact on survival, the presence of CPR (median duration 20 min) did not affect post-transplant survival with 1-year and 5-year survivals of 88% and 73%, respectively (Quader et al. 2013). This data lends support to the continued use of CPR donors for cardiac transplant, a trend that has increased over the past decade.

There are a multitude of other donor characteristics that could potentially impact allograft function and recipient survival. Hypertension, smoking history, alcohol use, diabetes, tricuspid regurgitation, and baseline renal function's impact on survival have all been examined. The difficulty of isolating single variables from a complex equation coupled with the small sample size of most trials has hampered the development of concise conclusions on donor comorbidities' impact on allograft survival. Perhaps the most robust study to examine individual donor profiles investigated 512 consecutive Brazilian donors from 2002 to 2008 (Fiorelli et al. 2012). Multivariate analysis of 30 individual donor variables found that only donor age > 40 had a negative impact on recipient survival.

Despite attempts to standardize the process, donor-recipient matching remains a highly individualized clinical decision. Recent retrospective database analyses have shown that donor traits once considered to be absolute contraindications to transplantation may in fact be safe. These studies have demonstrated that with the exception of age, accepting an allograft with one high-risk feature likely doesn't significantly impact short- or intermediate-term survival. However, the presence of more than one high-risk characteristic exponentially increases allograft risk and post-transplant survival. It is important to consider that while donor variables can impact post-transplant outcomes, they are less influential on survival than pre-transplant recipient comorbidities.

Post-Transplant

Immediately post-transplant, recipients are at risk of graft failure, infection, multiple organ failure, and acute rejection. For patients who survive the first year post-transplant, the leading causes of mortality shift to include coronary artery vasculopathy, immunosuppression-induced malignancy, and medication-induced comorbidities (diabetes, renal failure, and hypertension).

Conveying a grim prognosis, early graft failure (also referred to as primary graft failure) is an ominous development following heart transplantation and the most common cause of early mortality, accounting for 40% of deaths within the first month of surgery. Characterized as severe ventricular dysfunction manifesting as hypotension, diminished cardiac output, and elevated filling pressures in the absence of secondary causes of graft failure, early graft failure's (EGF) mortality is in excess of 50% (Amareli et al. 2012). The broad definition of EGF makes assigning prevalence difficult, but most estimates range from 5% to 10%. Generally an idiopathic process, redo

transplants, baseline valvular cardiomyopathies, female to male donors, donor-weight mismatch, ischemic time, and high inotropic support are all associated with increased rates of early graft failure. Given the multitude of risk factors encompassing donor, recipient, and surgical variables, early graft failure likely represents several distinct pathophysiologic entities held together by a common phenotype: severe ventricular dysfunction early after surgery. The other major early mechanical complication affecting cardiac transplant patients is right ventricular dysfunction. Right ventricular (RV) dysfunction secondary to pulmonary hypertension accounts for 20% of deaths in the first month (Stobierska-Dzierzek et al. 2005). Though similar to EGF in that ventricular dysfunction is the hallmark, RV dysfunction is usually attributable to the allograft's inability to meet the increased pulmonary vascular resistance commonly seen in transplant recipients. As such, patients with a pulmonary vascular resistance of greater than 4 Woods units (WU), pulmonary artery systolic pressures of >60 mmHg, or transpulmonic gradients of greater than 15 are at elevated risk of RV dysfunction post-transplant. However, ISHLT registry data failed to show a difference in 1-, 5-, or 10-year mortality for preoperative PVR <3 WU, between 3 and 5 WU, and > 5 WU (ISHLT slide set 2018).

Outside of the first month, the vast majority of graft failure can generally be divided into antibody-mediated rejection, cellular rejection, or the development of coronary artery vasculopathy. In-hospital mortality rates following idiopathic graft failure during this time frame still exceed 50% in small case series, though mortality was less striking when a specific etiology could be ascribed. Antibody-mediated rejection, allograft vasculopathy, and acute cellular rejection predicted in-hospital mortality rates of 20%, 15%, and 6%, respectively. Fortunately, the incidence of rejection has been steadily declining over the last two decades with less than 15% of all cardiac transplant patients requiring treatment of rejection during the first year (Khush et al. 2018). Patients who require at least one treatment of rejection during the first year have diminished survival at 10 years compared to patients who had no rejection or had rejection that did not require treatment (Khush et al. 2018). Re-transplanted patients who receive treatment for rejection during the first year have the worst 5- and 10-year survival.

Due to an incomplete understanding of rejection and immunosuppression, early cardiac transplant survival was measured in days to months. Primitive immunosuppressive regimens revolved around glucocorticoids, and the antiproliferative agent azathioprine, a purine analog, allowed most patients to survive the first year post-transplant. The addition of cyclosporine, a calcineurin inhibitor, to the AZA and glucocorticoid backbone produced the most dramatic improvement in survival seen in modern cardiac transplantation, nearly doubling 3-year survival from 40% to 70% (Hosenpud et al. 1995). Cyclosporine has largely been replaced by another calcineurin inhibitor, tacrolimus. Although the three small prospectively randomized trials failed to show a mortality benefit of tacrolimus over cyclosporine A, several retrospective analyses have demonstrated improved 1-year survival with the newer calcineurin inhibitor (Castle et al. 2011). Similarly, azathioprine has been replaced by mycophenolate mofetil (MMF), a noncompetitive inhibitor of inosine monophosphate dehydrogenase enzyme essential for de novo synthesis of guanine nucleotides. In a randomized controlled trial, 1-year mortality with MMF was 6.2%, a nearly 50% reduction compared to AZA's 11.6% (Kobashigowa et al. 1998). The survival benefit persisted at the 3-year mark. Thus, most modern immunosuppressive regimens include tacrolimus, MMF, and a glucocorticoid that is tapered off during the first postoperative year (Fig. 4). However, the need for combination therapy has recently been called into question as the TICTAC trial showed similar mortality and allograft failure at 3 years when single-drug therapy tacrolimus was compared to the conventional three-drug regimen. The lack of statistical power of this study has limited widespread use of single-drug therapy.

Non-CMV infection is a major source of transplant mortality during all time periods. It accounts for over 30% of all fatalities in the first year post-

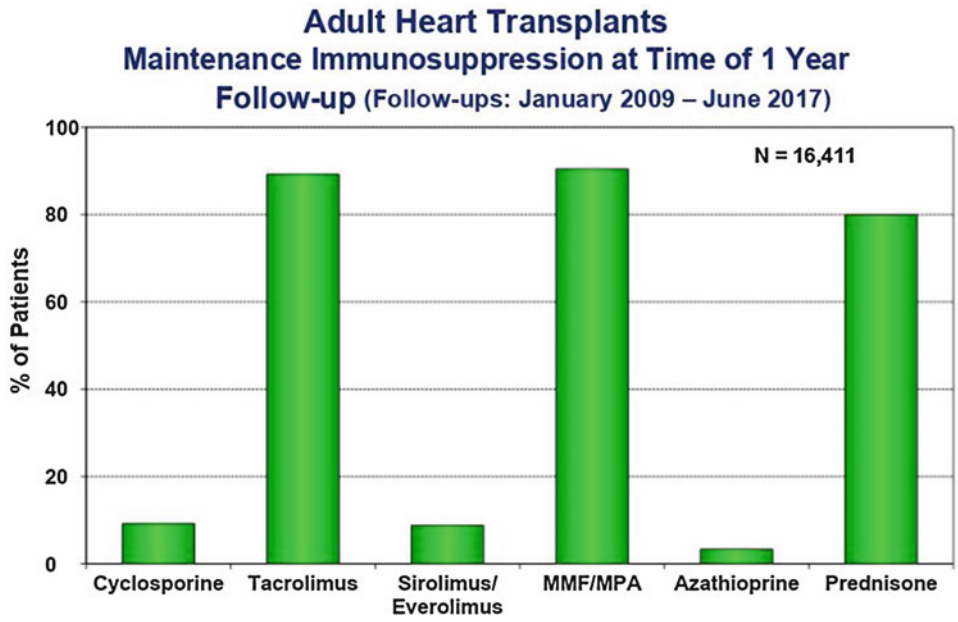

Fig. 4 Heart transplant immunosuppression maintenance at 1 year (JHLT 2018 Oct; 37(10): 1155–1206)

transplant (Khush et al. 2018). After the first year, some form of infection accounts for 10–15% of all post-transplant deaths. There is limited data on what infectious agents are most commonly associated with mortality. Early postoperatively, gram-positive bacterial infections predominate, but fungal infections tend to be most deleterious with mortality rates as high as 23% (Kriklin et al. 2004). Any risk factor that reflects decreased resistance to infection, older recipient age, concurrent pulmonary disease, or ventilator dependence, not only increases infection risk but also increases mortality (Kriklin et al. 2004). Advances in immunosuppression, heightened awareness, and improved chemoprophylaxis for opportunistic infections have led to a decline in the overall infection rate.

Malignancy affects upward to 50% of all cardiac transplant patients, and it remains the leading cause of late-term mortality (Crespo-Leiro 2014). Prolonged immunosuppression inhibits the immune system's ability to detect and destroy cancer cells while simultaneously impeding an immune response to counteract oncogenic viruses and opportunistic infections. Cutaneous neoplasms make up the vast majority of post-transplant cancers with lymphomatous malignancies constituting a significant minority. The incidence of squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) in recipients at 10-year post-cardiac transplant is 11% and 8%, respectively, nearly ten times more common than melanoma (Alam et al. 2011). Melanomas, however, impact survival with greater impunity registering 50% mortality at 3 years post-diagnosis (Alam et al. 2011). Traditional skin cancer risk factors, a fair-skinned complexion, older age, or living in a geographic area associated with increased sun exposure, persist in the transplant population. In addition, a higher degree of immunosuppression, regardless of the agent, is associated with an enhanced skin cancer risk. Interestingly, cutaneous malignancies occur on average 2 years later in the post-transplant period than other neoplasms. Unlike the relatively benign course of SCC or BCC, hematological malignancies convey a grim prognosis with 60% mortality at 2 years post-diagnosis. Post-transplant lymphoproliferative disorder (PTLD), an EBV-mediated neoplasm, is the most common hematological malignancy constituting nearly 10% of all post-cardiac transplant cancers (Alam et al. 2011),

but its incidence is on the decline as OKT-3 induction and high-dose cyclosporine use have fallen out of favor. As more contemporary immunosuppressive regimens have been adopted, the incidence of cancer in the post-cardiac transplant population may be decreasing (Khush et al. 2018). A dramatically lower rate of hematological malignancies (1.4 vs 3.4 occurrences per 1000 patient years) has been appreciated in the post-2000 transplant cohort compared to pre-2000 historical norms which corresponds to a drop in OKT-3 induction utilization (Crespo-Leiro 2014).

Cardiac allograft vasculopathy (CAV) is a major cause of conditional mortality following heart transplantation, affecting 10–20% of transplant recipients. CAV is a diffuse and insidious process characterized by perivascular inflammation and intimal hyperplasia affecting small vessels first and moving proximally to affect epicardial coronaries. Cardiac denervation likely lends to the asymptomatic development of CAV. While the underlying pathophysiology remains incompletely elucidated, both immune and nonimmune-mediated mechanisms have been implicated. Hypertension, CMV infection, ischemic-reperfusion injury, rejection, and smoking history have been implicated to increase CAV risk. CAV incidence at 1, 5, and 10 years is 7.6%, 29.2, and 47.2% (ISHLT slide set 2018), but invasive evaluation with IVUS indicates that the prevalence is significantly higher. Data suggests that women have a higher incidence of CAV free survival when compared to men (Khush et al. 2018). Not surprisingly, diagnosis of CAV within the first 3 years post-transplant confers increased mortality at every time frame compared to those without CAV (Khush et al. 2018). While there is an increased incidence of CAV over time, the incidence of death directly attributed to CAV plateaus between 11 and 14% after the third year post-transplant (Khush et al. 2018).

Given the intense resource utilization and personal risk exposure involved in each cardiac transplant, it is imperative that any intervention which maximizes allograft function and improves post-transplant survival be elucidated and universally employed. Cardiac rehabilitation, a supervised aerobic exercise and strength training program spread over 12 weeks, has long been associated with improved outcomes in post-cardiac surgery and heart failure patients. The lack of inherent risk in the program coupled with the possibility of improved cardiovascular fitness makes it an attractive therapeutic strategy in almost any patient population. Non-randomized studies of cardiac rehab in post-transplant patients have demonstrated improvements in lean body mass, resting heart rate, blood pressure, and peak VO2 (Rosenbaum et al. 2016). Rosenbaum and colleagues retrospectively reviewed 201 OHT patients over a 13-year period and found that early enrollment in cardiac rehab was associated with improved survival (Rosenbaum et al. 2016). Moreover, after controlling for pre-transplant fitness level, there was a linear relationship between the number of cardiac rehab sessions attended and survival. Each CR session produced a 10% reduction in mortality (Rosenbaum et al. 2016). Similarly, patients with higher perceived (self-reported on SF-36 quality of life survey) or objective (VO2 max) exercise capacity were linked with a significantly longer survival time (Yardley et al. 2016). Patients with SF-36 scores above the mean (collected at an average of 5 years post-transplant) were more likely to survive to 16 years than their counterparts with lower SF-36 scores. Moreover, a VO2 peak above the median conferred an average survival of 16 years, 4 years longer than patients with VO2 peaks below the mean (Yardley et al. 2016). In sum, data suggests that improved physical capacity is strongly predictive of longer-term survival, and thus any intervention aimed at increasing physical activity should be employed.

Aside from immunosuppressive medications, statins have the largest impact on survival. In addition to their lipid lowering effect through the enzymatic inhibition of hydroxyl-methyl-glutaryl-coenzyme A reductase (statins), the pleotropic or anti-inflammatory effects of statins reduce allograft dysfunction. While the most common cause of late mortality, CAV, has a different mechanism than traditional coronary artery disease, statins appear to convey a survival benefit. Utilization of statins was associated with improved 5-year survival (85% vs. 74%) in a single-center retrospective analysis (Luo 2014).

Conclusion

Orthotopic heart transplant continues to be the gold standard treatment for advanced heart failure. Significant advances have improved nearly every component of this complicated and individualized therapy. Improved immunosuppression and rejection evaluation over the past two decades has dramatically enhanced survival in every patient population and over every time period. The median and conditional survival is now measured in decades for most patients and centers are routinely accepting older donors and recipients. Donors once considered high-risk have, in many cases, been reclassified as viable allografts augmenting the donor pool. International data shows that the etiology of the underlying heart failure predicts survival, with the greatest benefits seen in the nonischemic cardiomyopathy group. Furthermore, younger donor age, younger recipient age, ischemic times between 1 and 4 h, and institutional experience and volume are all continuous variables predictive of improved intermediate- and long-term survival.

Cross-References

- ▶ Advances in Immunosuppression
- ▶ Malignancy After Transplant
- ▶ Monitoring for Rejection

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Chronic Rejection

26

Laurie Letarte and Arvind Bhimaraj

Contents

Abstract

Chronic rejection is the culmination of many immune and nonimmune mechanisms that alter the structure and function of the allograft, thereby contributing to graft dysfunction in the long term. Chronic rejection remains a major limitation to allograft longevity and patient

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survival. The alterations in the heart include the following: (1) vascular changes (starting at the microvascular level and progressing to epicardial vessels), (2) allograft hypertrophy, and (3) allograft fibrosis. The vascular changes have been investigated extensively and currently represent most of our understanding of chronic rejection. Allograft hypertrophy and fibrosis are becoming more recognized as early markers of evolving changes with evidence reflecting that these changes could be independent of vascular changes. Current therapies may temporize the initiation and progression of chronic rejection, but have not made significant contributions to long-term survival beyond the first year post-transplant. This chapter will discuss the following: mechanisms contributing to chronic rejection, structural changes to the allograft, risk factors for chronic rejection, screening for allograft rejection, as well as preventive, suppressive, and interventional therapies.

Keywords

Chronic rejection · Cardiac allograft vasculopathy · Cell-mediated injury · Antibody-mediated injury · Complement pathway · Endothelium · Intimal hyperplasia · Myocyte hypertrophy · Interstitial fibrosis · Coronary angiography · Coronary artery bypass · Retransplantation

Introduction

Since the advent of cardiac transplantation, advancements in immunosuppressive therapy have improved immediate and short-term outcomes. However, median survival of post-heart transplant patients has remained about the same over the last few decades with chronic rejection posing a significant impediment to long-term survival. Defining, treating, and managing chronic rejection remain challenging. The term *chronic rejection* is often used interchangeably with *cardiac allograft vasculopathy* (CAV). In this chapter, we propose that chronic rejection encompasses more than vasculopathy alone and that the terms are not entirely synonymous. Hypertrophy and fibrosis that occur in the cardiac allograft will be discussed as consequences of chronic rejection. As graft vascular disease, or CAV, has been studied extensively, most of the chapter will elucidate information related to this entity.

Mechanisms of Chronic Rejection and Associated Structural Changes

Chronic rejection is an indolent process mediated by both immune and nonimmune mechanisms. A basic tenet of rejection is immune incompatibility due to antigenic differences between donor and recipient HLA, and many experts believe that immune-mediated injury is the predominant underlying cause of CAV and chronic rejection. This theory is supported by the fact that only donor arteries, not recipient arteries, are affected by CAV (Ramzy et al. 2005). Transplant vasculopathy is marked by diffuse arterial disease distinct from native vessel coronary disease, as will be discussed. Normal organ parenchyma is replaced by fibrotic tissue, graft function is compromised, and the recipient may experience late graft failure. The nonimmune factors that contribute to chronic rejection are typically related to common risk factors like uncontrolled hypertension, diabetes, and dyslipidemia that have established pathways of injury to the myocardium in the non-transplant setting. The mechanisms of these pathways are beyond the scope of this chapter, which will focus on immune mechanisms specific to the transplant setting.

Immune Cell-Mediated Mechanisms

After thymic selection during embryonic development and growth, it is estimated that there are ~10^{12} unique T-cell receptors that could potentially react to non-self-antigens and initiate a cascade of anti-self-responses. It is unclear how many unique antigen reactions can be initiated or how many T-cell

clones are activated, but because of imperfect HLA matching, it is reasonable to postulate that there are many active T-cell clones during the lifetime of a heart transplant recipient. With the advent of current immunosuppression, particularly calcineurin inhibitors, the acute effector response of direct cell injury on the allograft has been significantly reduced. However, the consequences of cell-cell interactions of various uninhibited participants of the immune response likely contribute to chronic immune activation and the accompanying long-term organ changes seen in chronic graft failure. Evidence points toward the role of the indirect and semi-direct pathways contributing to graft vascular disease and chronic rejection (Mitchell 2009). These pathways are discussed in detail in ▶ Chap. 16, "Cardiac Allograft Rejection." Macrophages, the predominant effector cells of the CD4+ T-cell-mediated response, cause the release of eicosanoids and cytokines and dysregulation of nitric oxide synthase expression, which negatively influences endothelial cells, smooth muscle cells, and vascular function. Though T-cell interactions with major histocompatibility (MHC) molecules are central to the immune response against the donor antigens, co-stimulatory signals seem to play important roles in allograft vascular disease. For example, blockade of CD40-CD40 ligand interaction facilitates allograft tolerance but does not prevent allograft vasculopathy, while blockade of the B7-CD-28 interaction (co-stimulatory pathway) does protect against vascular thickening. In addition, T-cell interaction with smooth muscle cells (SMC) via inducible co-stimulator and its ligand on SMC's induces proliferation of the latter, thereby contributing to the vascular changes (Mitchell 2009). Though older, retrospective studies failed to show an association of acute rejection episodes and future CAV (Gao et al. 1988; Stovin et al. 1993), more recent studies have confirmed this relationship (Raichlin et al. 2009a). Acute rejection episodes are associated with long-term adverse clinical outcomes. Hence, it may hold true that such episodes mediate activation of the immune system that is not mitigated by current immunosuppressive medications, thereby perpetuating chronic injury.

Antibody-Mediated Mechanisms

Recent studies support the role of antibody-mediated injury as an important contributor to CAV (Loupy et al. 2016). The allograft goes through multiple stressors starting with injuries sustained while in the donor environment, ischemia-reperfusion injury during harvest and implant, episodes of rejection, infections, and physiological stress. Cell injury and destruction during such stressors make the allograft more immunogenic by exposing the recipient's immune system to immunologically non-compatible proteins. The antigens that have been studied and that are most often considered responsible for triggering the recipient immune system are the human MHC I and MHC II antigens. However, studies have also documented an autoimmune-mediated mechanism directed against various non-HLA antigens, including cardiac proteins like cardiac myosin that could contribute to chronic rejection. Such an autoimmune response can lead to subsequent loss of tolerance to self-antigens. In addition, immune injury to endothelial cells can cause them to express aberrant class I proteins, thereby further promoting autoimmunity (Weiss et al. 2008).

With criteria for antibody-mediated rejection (AMR) being standardized recently (Berry et al. 2013), more centers are screening for donor-specific antibodies and performing specific histologic and immunologic assays for AMR providing opportunities to understand its contribution to chronic injury. Asymptomatic AMR and mixed rejection are being recognized as clinically important for future adverse events (Loupy et al. 2016; Wu et al. 2009; Kfoury et al. 2009), while the paradigm of antibody-mediated impact on the graft as being only an acute phenomenon is fast changing. In a study from France, explanted hearts and historical, preserved endomyocardial biopsy samples from 40 patients receiving a repeat transplant were evaluated. AMR was observed in 47% (19/40) of failing grafts, while 40% (16/40) had unrecognized subclinical AMR in their biopsy samples approximately 4 years prior to graft loss (Loupy et al. 2016). In a recent

retrospective study of 221 patients followed for an average of 5.5 years, 3,790 DSA samples and endomyocardial biopsies were examined with a focus on AMR and outcomes. Development of de novo posttransplant DSA, particularly MHC class II, was associated with an increased risk of graft loss even when controlling for cellular rejection and recurrent AMR. Allograft loss was not influenced by individual history of AMR, but augmentation of immunosuppression in patients with AMR was not accounted for in this study and could have confounded the impact of AMR on future graft changes. Moreover, there was no significant difference in freedom from CAV in the various subgroups except for a trend toward increased CAV in patients with AMR and DSA positivity compared with patients without AMR or DSA positivity (Clerkin et al. 2017). The role of antibodies in chronic rejection, especially those against MHC II antigens and non-HLA antigens, may be mediated by a cascade of events triggered early after transplant since current pharmacotherapies primarily focus on T-cell pathways. The fact that DSAs do not reliably correlate with pathological AMR but have an adverse prognostication could mean that non-complement-mediated effects of antibodies could be contributing to chronic antibody-mediated injury. The existence of chronic antibody-mediated rejection is an entity that has not been firmly established but has been discussed in consensus proceedings (Kobashigawa et al. 2011). Current definitions of antibody-mediated injury rely heavily on evidence of overt graft injury in the form of dysfunction or complement activation and focus on immediate impact of antibodies. Subtle pathological changes in the microvasculature, even in the absence of overt organ damage, could represent early markers of future adverse events. A classification capturing changes representative of microvasculopathy was found to predict adverse survival and fatal cardiac events independently and is detailed in the section on histopathology (Hiemann et al. 2007). Studies to evaluate the clinical utility of such pathological changes might be limited due to unavailability of any therapeutic strategies to modulate microvasculopathy. Consensus efforts to learn more about the role of reporting these changes in biopsies are needed.

Complement-Mediated Mechanisms

The complement pathway is a harbinger of effector systems of the antibody-antigen complex. Due to a very short half-life of many complement proteins, it was not until recently that C4d, an inactive breakdown product of the complement cascade, was identified as a marker of complement activation. Apart from the immediate cell lysis by the membrane attack complex (MAC), other complement products like C5a and C3a act as chemoattractants recruiting cells such as macrophages, neutrophils, and monocytes that perpetuate injury (Monsinjon et al. 2003). Sub-lytic quantities of MAC can activate endothelial cells leading to upregulation of surface molecules, platelet activation, and increased porosity of the endothelial layers causing recruitment of inflammatory mediators into the vessel wall and into the organ (Saadi et al. 1995; Saadi and Platt 1995). It has been shown that patients with increased C4d deposition have a greater incidence of CAV, mortality, and a trend toward increased graft failure in the future (Luk et al. 2015). C3d has been suggested (along with C4d) as a marker to evaluate for AMR (Rodriguez et al. 2005), and cross-linked C3d stimulates B-cell proliferation (Dempsey et al. 1996), while C3 and C5 modulate T-cell responses to antigen presentation (Peng et al. 2006). These mechanisms could contribute to ongoing chronic graft injury.

Hypertrophy and Fibrosis

Organ-level cardiac hypertrophy is obvious in many failing allografts and encompasses histological components of myocyte hypertrophy, interstitial fibrosis, and healing fibrosis secondary to ischemia. Though there has been extensive research into understanding the pathophysiology of cardiac hypertrophy in the non-transplant setting, it has not been established if the same mechanisms play a role in allograft hypertrophy.

TNF-α, which contributes to cardiac hypertrophy in a non-transplant setting in animal models, is persistently elevated in biopsy samples of heart transplant patients with associated increases in myocyte size and production of collagen I and III. It was previously thought that the cardiac allograft undergoes hypertrophy due to prevalent nonimmune risk factors like hypertension, diabetes, and the use of calcineurin inhibitors. However, comparison of changes in left ventricular (LV) mass between lung transplant patients and heart transplant patients, two groups with similar exposure to the aforementioned risk factors, shows a significantly greater increase in mass in patients receiving a heart transplant (73% vs. 7%, $P < 0.0001$) (Stetson et al. 2001). This suggests immune mechanisms may be responsible for the hypertrophy in transplanted hearts.

While presence of collagen is an integral histological finding in fibrotic areas, the origin of collagen-producing fibroblasts in the cardiac allograft is controversial. Current theories include those that fibroblasts originate or transform from resident (donor) fibroblasts, resident (donor) endothelial cells, or (recipient) bone marrow. A mouse model of chronic rejection showed a substantial portion of fibroblasts in the allograft to be derived from the recipient (Wu et al. 2003). On the other hand, a human study using myocardial biopsy samples from sex-mismatched heart transplant recipients (female donor heart transplanted to a male recipient) found Y-chromosome-negative putative fibroblasts in areas of fibrosis, suggesting they were derived from an intracardiac (i.e., the female donor) source (Pichler et al. 2012). Epithelial/endothelial to mesenchymal transition (E/End MT) is a condition where under appropriate stimuli, the epithelial and/or endothelial cells transform into mesenchymal cells. This process is well described in organogenesis in the embryo, cancer metastasis, and is gaining recognition in fibrotic disorders including heart failure. In a mouse heart failure model (aortic banding), Zeisberg et al. showed that 30% of the cardiac fibroblasts were of endothelial cell origin using lineage-tracing mice. The investigators also performed an experiment with a mouse model of chronic rejection where the mice underwent heterotopic heart transplantation with an organ with MHC II mismatch. Fibrosis in the failed grafts was evident with abundant dual-staining cells that expressed markers of both endothelial and mesenchymal origin (the presence of double-stained cells is a hallmark of EndMT), supporting the notion that EndMT contributes to fibrosis in chronic rejection (Zeisberg et al. 2007). There have been no studies confirming the role of EndMT in human heart transplants. Considering that the endothelium is the first boundary between the donor heart and the host, it has the potential to play a central role in changes that occur in chronic rejection by being the mediator in the response to injury. Though the endothelial layer is donor-derived, there is evidence of injury followed by partial re-endothelialization from recipient-derived cells (Kapessidou et al. 2006). It is not clear if the replacement of the donor endothelium is a consequence of cell apoptosis secondary to injury or due to replacement of endothelial cells lost in the process of EndMT. Fibroblasts are recognized as perpetuators of remodeling with collagen deposition, irrespective of their origin. The origin of these cells might be important in the context of future therapeutic options to limit cell transitions at the source and to decrease the number of fibroblasts. It is also important to recognize that none of the current posttransplant therapies target anti-fibrotic mechanisms that can prevent onset and progression of collagen production.

Histopathology of Chronic Rejection

CAV is marked by pan-arterial disease with diffuse intimal hyperplasia, narrowing and progressive obliteration of the vessel lumen, and involvement of large and small intramyocardial arteries. Intimal thickening is caused by increased extracellular matrix and smooth muscle cell proliferation and migration with relatively intact elastic lamina (Fig. 1). Early on, there is subendothelial inflammation associated with markers of endothelial activation causing an "endotheliitis." Various inflammatory cells including T and B lymphocytes, macrophages, natural killer cells, neutrophils, eosinophils, and platelets can

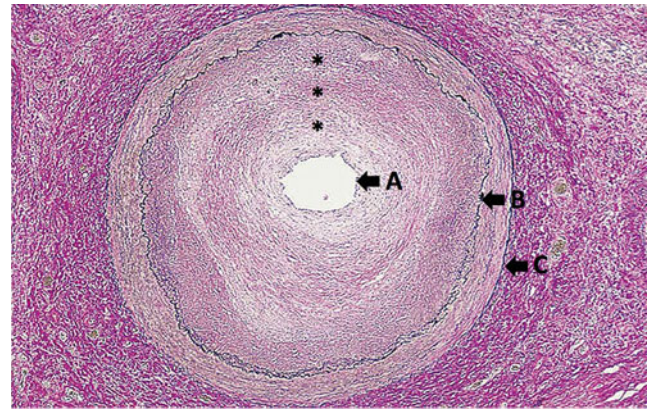

Fig. 1 Cross-section of an epicardial coronary artery demonstrating intimal hyperplasia seen in allograft vasculopathy. (A) Endothelial cell layer, (B) internal elastic lamina, (C) external elastic lamina, and **asterisks** spanning the media reflecting the abnormal thickness

be found in the evolving lesion. Calcification and atheroma formation are less likely, particularly in the early stages of vasculopathy. After the first year, the large- and medium-sized epicardial arteries commonly develop atheromatous plaques, and beyond 6 years posttransplant, lesions are more likely to be eccentric with significant extracellular lipid. The internal elastic lamina often remains intact but may be disrupted in more advanced stages of the disease when the disease process looks similar to native vessel atherosclerotic disease. The media of epicardial vessels may be relatively unaffected or widely replaced by fibrous tissue (Ramzy et al. 2005). Individual variations have been noted in studies due to differences in duration from transplant, area of sampling, uneven degrees of injury, and pre-transplant vessel pathology.

Involvement of the microvasculature is characteristic of transplant vasculopathy and occurs early after transplant. Hiemann et al. proposed a pathological classification with prognostic implications (Fig. 2). More than 9,000 biopsies from 873 patients within the first year posttransplant were studied. Of the 379 patients who had stenotic microvasculopathy, 91% had concentric medial disease rather than endothelial disease. This medial disease noted in the small vessels has a distinctly different phenotype compared to the intimal disease found in the epicardial arteries of patients with CAV and could represent an early response to endothelial activation/injury. The medial stenotic microvasculopathy predicted long-term adverse outcomes and onset of future epicardial disease, while endothelial thickening by itself did not predict any future adverse events. However, the endothelial thickening did predict future onset of stenotic microvasculopathy, indirectly suggesting a temporal sequence of endothelial changes that translate to medial disease in the small vessels and, finally, to intimal disease in larger epicardial vessels (Hiemann et al. 2007).

As detailed in the mechanism section previously, myocyte hypertrophy and interstitial fibrosis can contribute to pathology in the allograft. Myocyte size progressively increases in the allograft over 6 years posttransplant such that the average myocyte size is larger than normal controls at 1 year but does not reach a diameter greater than that in patients with dilated cardiomyopathy. Interstitial fibrosis, on the other hand, is greater in cardiac allografts than in controls at 2 months posttransplant with no significant change in mean values of percent fibrosis in the allograft over time during 6 years of follow-up (Fig. 3). Unlike myocyte size, fibrosis of the cardiac allograft does exceed that found in dilated cardiomyopathy samples (Armstrong et al. 1998). The clinical relevance of these changes is detailed in later sections.

Clinical Perspectives of Cardiac Allograft Vasculopathy

CAV remains a significant impediment to long-term survival and a primary contributor to late graft failure and death in heart transplantation (Lund et al. 2016). The process predominantly

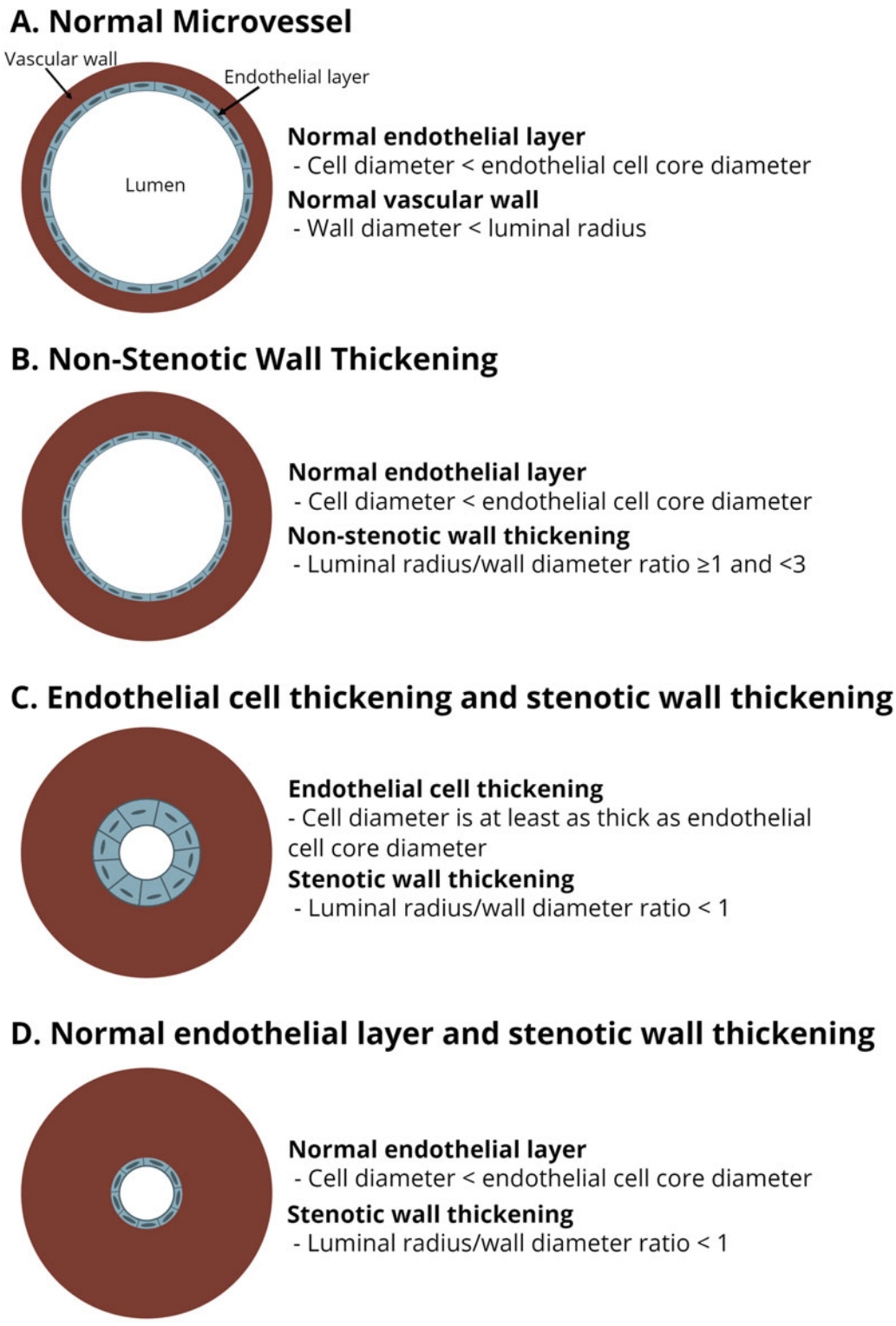

Fig. 2 (continued)

involves arteries of the donor organ, including epicardial arteries as well as the lower-level arterial branches and intramyocardial arteries. CAV is a distinct process that evolves over time after transplantation. Whereas common atherosclerosis is marked by focal, eccentric disease with lipid-rich plaques, the hallmark of CAV is thickening of arterial walls due to intimal hyperplasia with lipid-poor lesions. The rate of CAV progression is much faster than that of common atherosclerosis, leading to clinical significance in a matter of years as opposed to decades in non-transplant atherosclerosis. As the process involves the entire cardiac arterial tree, the geometrically smaller branches may be occluded before the larger caliber epicardial arteries are significantly affected. This results in widespread myocardial pathology and clinical outcomes like graft dysfunction, diastolic heart failure, and sudden cardiac death despite patent epicardial coronary arteries (Billingham 1987).

Clinically significant CAV typically has its greatest impact several years after transplant, but the disease process starts much earlier. It affects 8% of heart transplant recipients by 1 year, 30% by 5 years, and 50% by 10 years (Lund et al. 2013). Notably, recent registry data suggest a small but significant decrease in the cumulative incidence of CAV at 7 years posttransplant. 37% of patients transplanted between 2003 and 2010 developed CAV compared with 42% of patients transplanted between April 1994 and 2002. In addition, there was improved survival among patients transplanted during the later era compared to those transplanted between 1994 and 2002 (Stehlik et al. 2012). This improvement could be due to advancements in immunosuppression leading to fewer acute rejection episodes and, with that, less graft injury, CAV-specific therapies like mTOR inhibitors, statins, or advancements in interventions targeted to epicardial disease. Despite this positive trend, CAV remains a significant barrier to organ longevity.

Risk Factors for CAV

Risk factors for development of CAV are both immune and nonimmune in nature and are related to both the donor and the recipient (Fig. 4). While the details of the mechanisms relating to these risk factors and their associations with CAV are not well understood, it is evident that some seemingly nonimmune factors exert their influence on CAV progression via activation of an immune response (Stehlik et al. 2012; Mehra et al. 2004). Some risk factors for CAV are detailed in this section.

Donor-Related Factors

Multiple donor variables are associated with CAV. Older donor age, diabetes, and hypertension increase the risk of CAV, while female donor-recipient gender match appears protective compared to other donor-recipient gender combinations (Stehlik et al. 2012). Mechanisms of donor brain death influence immune pathways that contribute to vasculopathy and impact long-term survival. Explosive brain death, defined as that caused by gunshot wounds to the head, head trauma, or intracranial bleed with rapid progression to brain death, is associated with inflammatory cytokine activation, upregulation of immunoregulatory and cell adhesion molecules, and endothelial dysfunction and inflammation. The stimulation of these inflammatory mediators contributes to increased immunogenicity of the allograft. In a study by Mehra et al., recipients of donors who experienced explosive brain death had greater intimal thickening, more cardiac events, and decreased long-term survival compared to recipients whose donor mode of demise was nonexplosive brain death. Cardiac events observed included percutaneous coronary intervention, myocardial infarction, sudden cardiac death, and death due to allograft failure (Mehra et al. 2004).

Fig. 2 Schematic representation of the gradations of microvasculopathy adapted from Hiemann et al. Blue inner layer represents monocellular endothelial layer. Red outer layer represents vessel wall, including intima, adventitia, internal and external laminae. (Schematic based on classification of microvasculopathy from Hiemann et al. (2007))

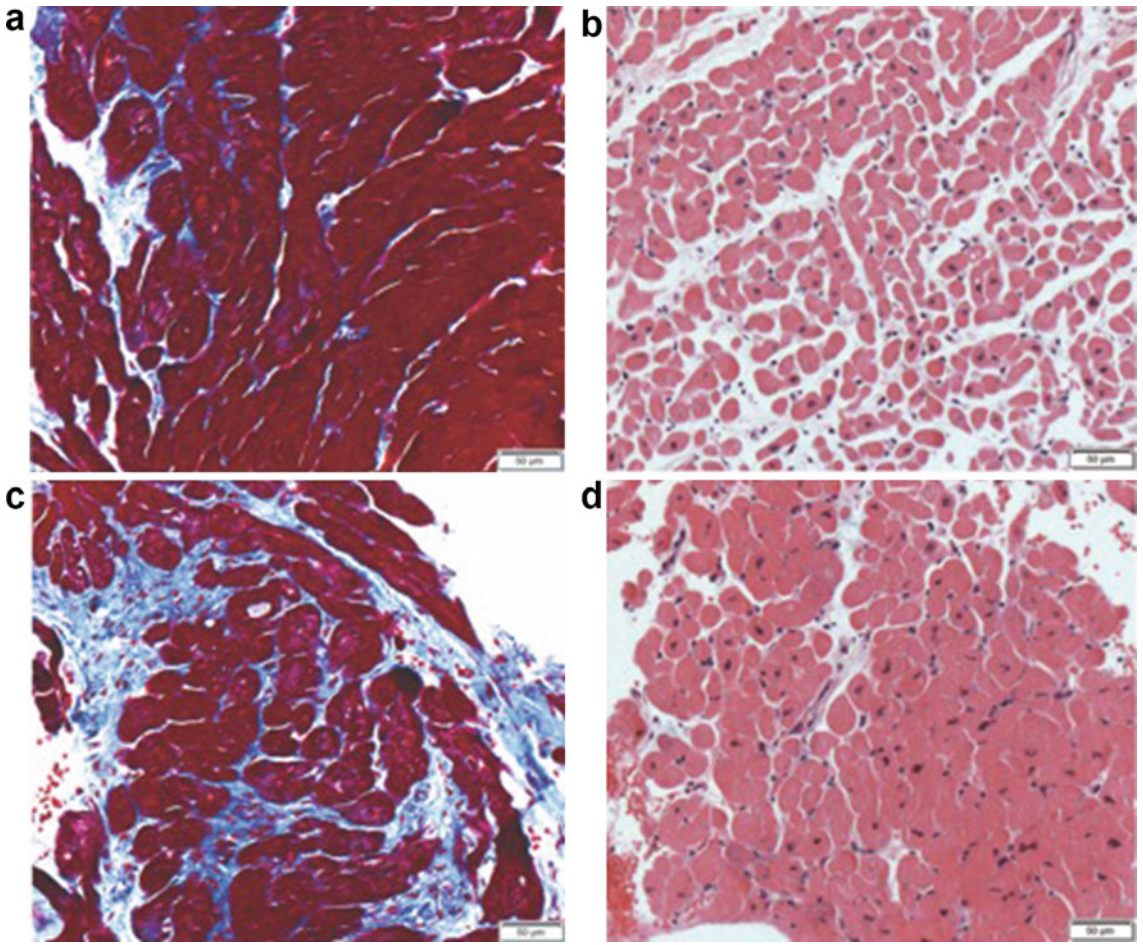

Fig. 3 Endomyocardial biopsies within a month after transplant showing (**a**) normal myocardium with minimal fibrosis (stained blue) and (**b**) normal myocyte diameter. Also shown are (**c**) significant interstitial fibrosis and (**d**) myocyte hypertrophy, which can be seen as early as 6 months after transplant in some patients. (Images courtesy of AS Cruz-Solbes, MD, Houston Methodist Research Institute, Houston, TX)

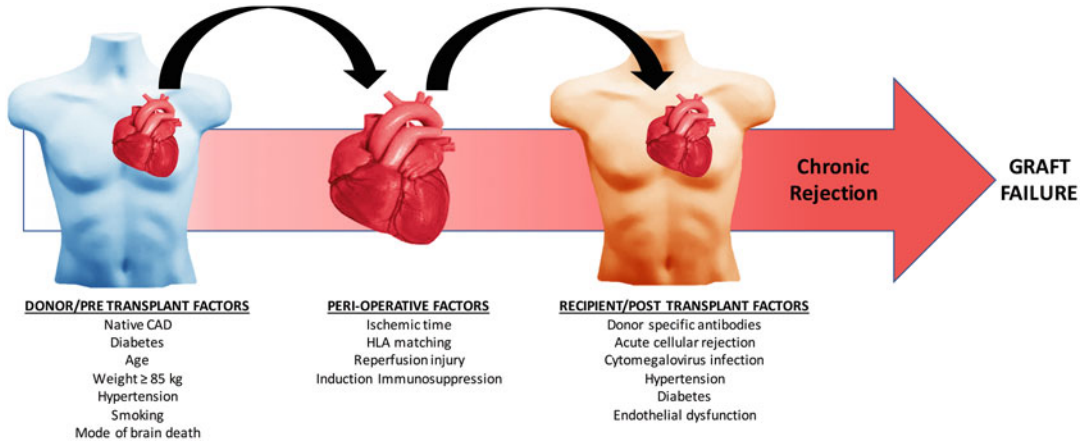

Fig. 4 Schematic representing the various contributors to the mechanisms of chronic rejection, including early donor-related factors, perioperative events, and ongoing influences throughout the life of the recipient. (Image courtesy of AS Cruz-Solbes, MD, Houston Methodist Research Institute, Houston, TX)

Atherosclerosis carried from the donor can inherently cause progression of the fibrofatty plaque posttransplant, particularly in the presence of accelerating risk factors like hyperglycemia, hypertension, and dyslipidemia. Intravascular ultrasound (IVUS) studies have identified post-transplant vascular disease as early as a few weeks postoperatively, which is highly suggestive of donor-derived routine atherosclerosis. Studies utilizing two-dimensional IVUS suggested that the early presence of donor-derived atherosclerosis did not negatively impact onset or severity of CAV (Wong et al. 2001). However, more recent studies with three-dimensional IVUS suggest that donor-derived atherosclerosis is predictive of CAV presence at 3 years (Watanabe et al. 2017). It is not standard practice for angiography or IVUS to be performed early (less than 1 year posttransplant), so donor-derived vascular disease might remain undefined in routine clinical practice. It may be prudent to implement more aggressive risk factor control in those with known nonobstructive CAD identified in donor angiograms.

Ischemia-Reperfusion Injury

Suboptimal organ preservation and ischemia-reperfusion injury contribute to CAV development via activation of the inflammatory response. The allograft is subjected to ischemic insults related to brain death, hemodynamic changes, and preservation during procurement and transplantation. Increased ischemic time is directly related to intensity of the inflammatory response. The injury provokes shedding of intact HLA, triggering an alloimmune response that can lead to acute and chronic rejection (Weiss et al. 2008). Restoration of blood flow in the previously ischemic graft may potentiate production of reactive oxygen species, activate the complement pathway, and induce production of inflammatory mediators (Khalifian et al. 2013). Shortly after reperfusion, graft endothelial and parenchymal cells also produce pro-inflammatory cytokines including TNF-α and IL-1. These cytokines promote the production of neutrophil- and macrophage-attractant chemokines and stimulate adhesion molecule and MHC molecule expression on vascular endothelium, further promoting an inflammatory cascade (el-Sawy et al. 2002). Though earlier data suggested increasing 1-year and 5-year mortality with progressively increased ischemic time (Hosenpud et al. 2001), the same has not been corroborated in more recent registry data (Lund et al. 2016).

Rejection and Immune Modulation

Induction with IL-2 antagonists or OKT3 at the time of transplant is associated with CAV. Maintenance immunosuppression with

azathioprine versus mycophenolate and cyclosporine versus tacrolimus has a higher predisposition for vasculopathy (Stehlik et al. 2012). An increased number of HLA-DR mismatches and higher rejection burden also contribute to CAV (Weiss et al. 2008). During an episode of acute rejection, inflammatory pathways are activated, potentially leading to vascular and organ injury. Using virtual histology intravascular ultrasound (VH-IVUS), Raichlin et al. showed that cellular rejection burden in the first 6 months correlated with significantly higher incidence of inflammatory burden. Individuals with an inflammatory pattern in their vessels at 6 months progressed more at 12 months compared to those who did not have any initial inflammatory burden, supporting the notion that rejection history is associated with future CAV development (Raichlin et al. 2009a). Together, these studies reflect the complex interactions of factors that either directly impact pathways leading to CAV or that indirectly influence CAV progression by impacting the burden of acute rejection.

Infections

Systemic inflammation has been suggested as a contributor to graft vascular disease and chronic rejection. Infections could promote CAV by this mechanism. *C. pneumoniae* and cytomegalovirus (CMV) are the most commonly studied infections related to chronic rejection and CAV. Seropositivity for *C. pneumoniae* antibody and CMV infection are associated with greater incidence and increased severity and progression of CAV (Stehlik et al. 2012; Weiss et al. 2008). CMV can invade the endothelium and is associated with perivascular inflammation and chronic vascular rejection (Weiss et al. 2008). In addition, a region from the CMV immediate-early protein codes for an amino acid with sequence homology with the HLA-DR β chain. This can account for immune cross-reactivity and the association between viral infection and allograft rejection. Furthermore, a gene product of CMV binds to p53 and inhibits its role in apoptosis. This enhances cellular and smooth muscle proliferation and accumulation, further contributing to vasculopathy (Tanaka et al. 1999). Fortunately, widespread adoption of anti-CMV prophylaxis has reduced the impact of significant CMV infections on CAV development.

Diagnostic Testing for Detection of Cardiac Allograft Vasculopathy

Though it is well known that graft vascular disease involves the entire vascular tree, most of the clinically utilized diagnostic testing evaluates only the epicardial arteries. The International Society for Heart and Lung Transplantation (ISHLT) guidelines for the care of heart transplant patients give coronary angiography a class Ia recommendation, while most other testing modalities have a class IIa indication for CAV screening (Costanzo et al. 2010). Diagnostic testing is used for early surveillance, detection, and follow-up after diagnosis. Serial assessment allows for close monitoring of progression, as rapid progression has particularly adverse clinical implications.

Coronary Angiography

Coronary angiography remains the most common and accepted way to identify graft vascular disease. Contrast injection in the coronaries clearly defines eccentric obstructive lesions in the epicardial vessels and identifies distal, small vessel pruning that is characteristic of CAV (Fig. 5). Despite its acceptance, it is widely acknowledged that the early disease process in the arterial wall often goes unrecognized by this method. A detailed anatomical classification of the type, location, and complexity of lesions was proposed but did not facilitate clinical prognostication (Gao et al. 1988). A simplified classification of the severity of disease using angiographic luminal stenosis severity along with the location based on data from the Cardiac Transplant Research Database showed better prognostic utility (Costanzo et al. 1998), which led to its incorporation into the current ISHLT classification along with the assessment of allograft function (Mehra et al. 2010) (Table 1). In addition to assessment of epicardial vessel patency, angiography can reveal advanced microvascular disease by slow contrast

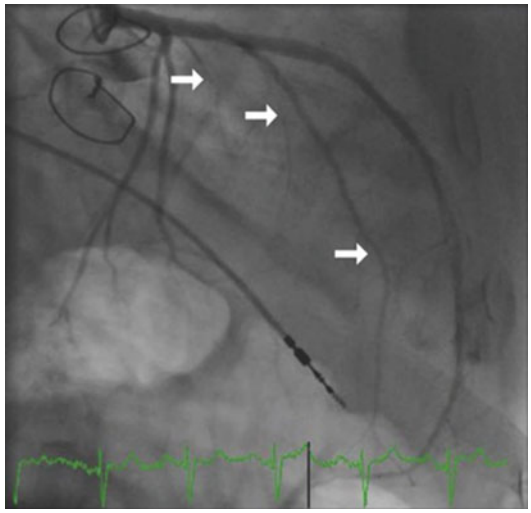

Fig. 5 Angiogram of the left coronary system showing pruning of the septal perforators and a diagonal branch (arrows)

filling as a result of increased resistance in the microvasculature.

Due to graft denervation, CAV does not usually present with classical symptoms of angina. Patients may present with dyspnea on exertion, arrhythmia, Q waves on EKG, decreased ejection fraction on echocardiographic exam, or sudden cardiac death. By the time CAV is symptomatic, the disease process is usually advanced, and damage to the myocardium may be irreversible. Therefore, it is recommended that screening angiography for CAV be performed as a matter of protocol to assess for occult lesions. The 2010 ISHLT guidelines recommend that angiography be performed annually or biannually. Patients free of CAV at 3–5 years, particularly those with renal insufficiency, may undergo less frequent screening (Costanzo et al. 2010).

Table 1 Classification of CAV as recommended by consensus statement from ISHLT (Mehra et al. 2010)

ISHLT CAV Nomenclature	
ISHLT CAV0 (not significant)	No detectable angiographic lesion
ISHLT CAV1 (mild)	Angiographic narrowing of left main <50%, primary vessel with <70% maximal lesion, or any branch stenosis <70% (including diffuse narrowing) without allograft dysfunction
ISHLT CAV2 (moderate)	Angiographic left main lesion ≥50%, a single primary vessel ≥70%, or isolated branch stenosis ≥70% in branches of two systems, without allograft dysfunction
ISHLT CAV3 (severe)	Angiographic left main lesion ≥50%, two or more primary vessels ≥70%, or isolated branch stenosis ≥70% in all three systems; or ISHLT CAV1 or CAV2 with allograft dysfunction (defined as LVEF ≤45%) or evidence of significant restrictive physiology (*significant restrictive physiology is defined as the following: symptomatic heart failure with (a) echocardiography demonstrating E to A ratio >2, shortened deceleration time (<150 msec), shortened isovolumic relaxation time (<60 msec), or (b) restrictive hemodynamic values with right atrial pressure >12 mmHg, pulmonary capillary wedge pressure >25 mmHg, cardiac index <2 l/min/m^2*)

Invasive Physiological Testing and Imaging

Coronary Flow Reserve

Assessment of the microvasculature relies on physiological testing as an indirect measurement of function. During angiography, flow assessment techniques can be performed to assess microvasculature health. Coronary flow reserve (CFR) is defined as the ratio of peak hyperemic to resting flow. A reduction of flow reserve in the absence of epicardial obstruction is used as an index of microvascular dysfunction. An impairment in CFR, especially in the setting of a >50% epicardial obstruction, predicts adverse events (death and heart failure) in this population (Rodrigues et al. 2005). Abnormal response to intracoronary infusion of acetylcholine, but not to adenosine or nitroglycerin, can also predict onset of epicardial CAV (Hollenberg et al. 2001). Early abnormal microvascular dysfunction has been shown to predict epicardial coronary changes in the first year, suggesting that early

endothelial microvascular injury precedes long-term vascular remodeling (Fearon et al. 2006). Despite these small studies evaluating the utility of invasive physiological testing to evaluate coronary microvascular flow, there is no sufficient and consistent evidence to justify routine clinical use.

Right Heart Catheterization

While invasive intracardiac hemodynamics do not provide direct insight into vascular function and are not considered a screening tool for vasculopathy, the current consensus classification of CAV does include hemodynamic variables suggestive of a restrictive hemodynamic pattern as one of the criteria (right atrial pressure >12 mmHg, pulmonary capillary wedge pressure >25 mmHg, cardiac index <2 L/min/m^2) for allograft dysfunction (Mehra et al. 2010). Hemodynamic assessment during annual surveillance coronary angiogram is not standard practice but could be beneficial to identify organ-level impact of chronic rejection.

Intravascular Ultrasound

IVUS is a more sensitive technique for detecting CAV than angiography alone, as it provides accurate definition of the magnitude of intimal thickening with high-resolution imaging of the layers of the vessel wall (Fig. 6). With early baseline examination, it has the ability to distinguish donor-derived atherosclerotic disease from CAV, and serial assessments permit more detailed monitoring of disease progression. An increase of ≥0.5 mm in the maximal intimal thickness (MIT) at a specific site in the first year post-transplant predicts an onset of more overt angiographic CAV, myocardial infarction, and mortality at 5 years (Kobashigawa et al. 2005). IVUS studies have also highlighted that, although CAV is often considered a late clinical problem, its onset can be quite early. Sato et al. showed that 42% of the patients develop CAV within 3 years (Sato et al. 2016). Various types of plaques have been described in transplant patients, similar to routine atherosclerotic disease, but the predominant morphologies identified by IVUS are those of fibrous and fibrofatty plaques. Some of the phenotypes are due to CAV, others are due to traditional atherosclerosis, and both processes can coexist.

Even though IVUS is a more sensitive test than angiography, it is not used as a matter of standard practice for reasons like lack of universal availability, limited therapeutic options for CAV, added procedural risk, and extra procedural time. The current guidelines do not recommend routine use

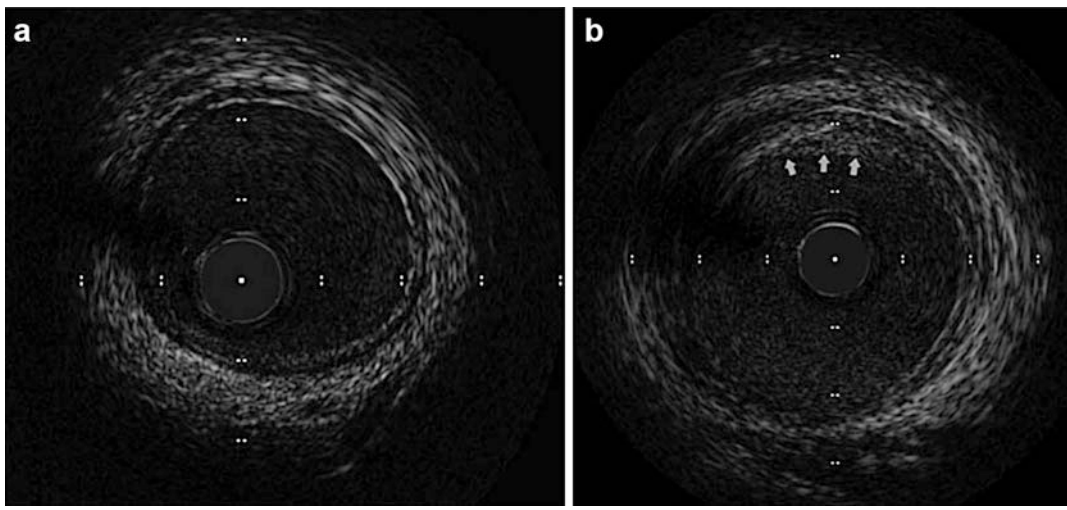

Fig. 6 Intravascular ultrasound (IVUS) images of (**a**) a normal coronary artery and (**b**) a coronary artery demonstrating allograft vasculopathy with intimal thickening (arrows) and medial intimal thickness measuring 0.6 mm. (Image used with permission from Wolters Kluwer Health, Inc. © 2017)

in post-heart transplant patients (Costanzo et al. 2010). Moreover, although intimal proliferation assessed by IVUS has long-term prognostic value, it does not correlate with presence or severity of small vessel disease, where onset of changes is an early marker of chronic rejection (Clausell et al. 1995). This limits its utility in early disease detection.

Optical Coherence Tomography

Optical coherence tomography (OCT) has a resolution ten times greater than IVUS, allowing detailed evaluation of the vessel wall (Cassar et al. 2013; Clemmensen et al. 2017). Intimal hyperplasia can be clearly identified, as can the internal and external elastic laminae (Fig. 7). Qualitative analysis by OCT allows characterization of CAV morphology (eccentric lesion, lipid pool, calcification) and plaque morphology (fibrofatty, fibroatheroma, calcific). It also permits identification of features of high-risk plaque such as thin-cap fibroatheroma and macrophages, signifying inflammation (Garrido et al. 2012; Tomai et al. 2016).

Detection of CAV by OCT is superior to angiography, as it identifies early changes of CAV before angiographic disease is present (Cassar et al. 2013; Tomai et al. 2016). In a study by Tomai

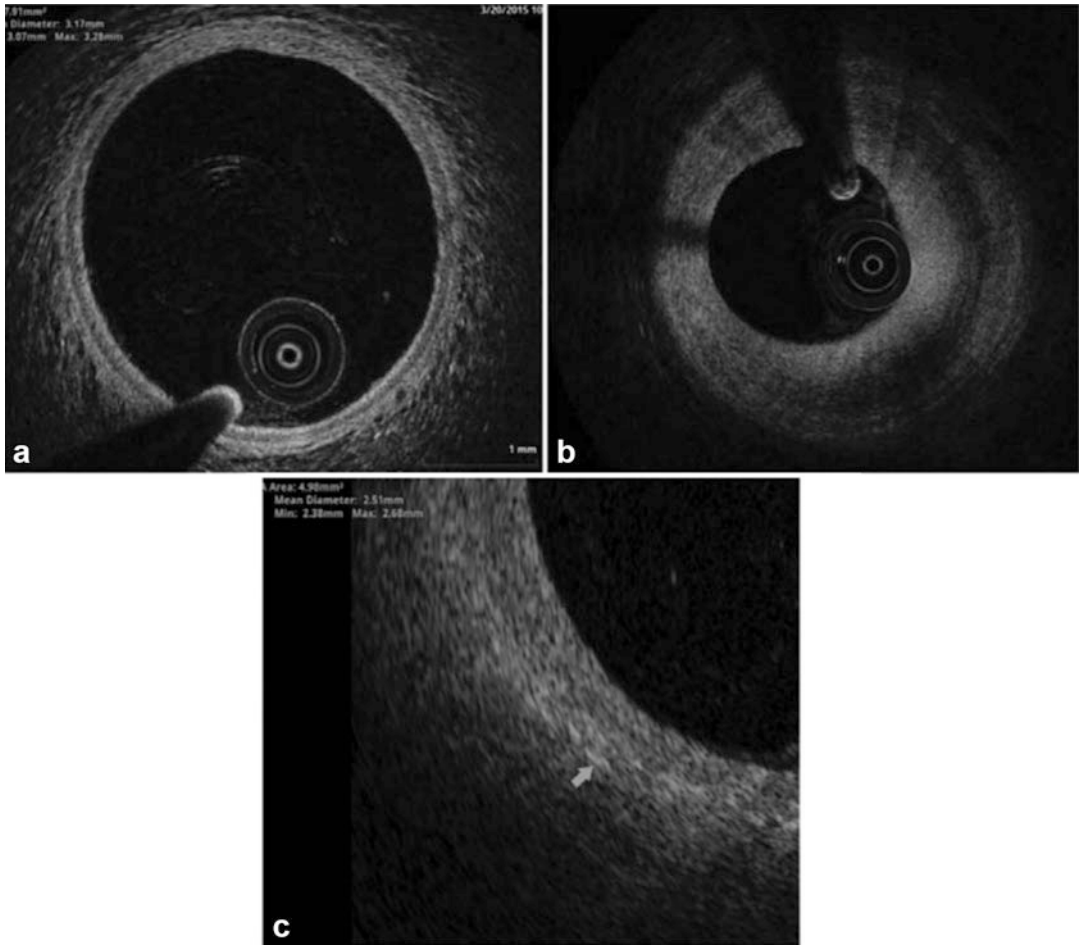

Fig. 7 Optical coherence tomography (OCT) images of (**a**) a normal coronary artery, (**b**) CAV with marked intimal thickening, and (**c**) CAV with macrophage accumulation (arrow) in a region of intimal thickening. (Image used with permission from Wolters Kluwer Health, Inc. © 2017)

et al., angiography detected CAV in 8 of 21 patients. However, CAV was detected in all patients by both OCT and VH-IVUS (Tomai et al. 2016). In contrast, OCT and IVUS perform equally well for the detection of CAV (Garrido et al. 2012; Clemmensen et al. 2017). Studies also demonstrate good correlation between these two modalities for measurement of MIT and measurement of luminal area (Garrido et al. 2012; Tomai et al. 2016). In addition, the intra- and inter-observer variations with OCT are very favorable, with superior inter-observer variability compared to IVUS (Tomai et al. 2016; Clemmensen et al. 2017).

With its high resolution, OCT may facilitate better understanding and identification of CAV. However, studies demonstrating the impact of this information on clinical outcomes in transplant patients with CAV are currently lacking.

Noninvasive Imaging

Exercise Echocardiography

Exercise stress echocardiography (ESE) has been an insensitive method for detection of CAV in the past (Collings et al. 1994). This is at least partly due to the chronotropic incompetence of the denervated heart, which was problematic prior to the era of bicaval anastomosis during the heart transplant procedure (Cohn et al. 1996; Collings et al. 1994). In a more recent study, ESE was used to evaluate the ability of LV longitudinal myocardial deformation to identify patients with CAV. This study suggested that lower LV global longitudinal strain at rest and during exercise and a lower echocardiographic CFR are associated with more severe CAV on angiography (Clemmensen et al. 2016). Nonetheless, ESE is not routinely used for CAV screening in the heart transplant population.

Dobutamine Stress Echocardiography

Dobutamine stress echocardiography (DSE) is a noninvasive alternative to angiography used to screen for CAV either alternating with angiography or as a substitute in certain scenarios. Studies have documented DSE to have a strong negative predictive value (NPV) in detecting angiographic CAV (Spes et al. 1996). However, the NPV of DSE is decreased when IVUS is used as a gold standard diagnostic test, likely due to the higher sensitivity of IVUS (Spes et al. 1996, 1999). More recently published studies have called the historical data about DSE into question. Comparing dobutamine stress testing to coronary angiography and using the current ISHLT classification of CAV, two separate studies have shown a very low sensitivity of DSE for CAV detection in patients both within and beyond 5 years of transplantation (Clerkin et al. 2016; Chirakarnjanakorn et al. 2015). Though both studies show safety of the test, approximately 20% of the time dobutamine stress test was nondiagnostic, while 2.3–4% of them were aborted due to complications during testing. The sensitivity, specificity, positive predictive value (PPV), and NPV of detecting any CAV were 7%, 98%, 82%, and 41%, respectively, for the dobutamine stress testing beyond 5 years (Chirakarnjanakorn et al. 2015) and 0%, 99%, 0%, and 82%, respectively, for dobutamine stress testing within 5 years (Clerkin et al. 2016). With the availability and advancements of other imaging techniques, the authors of both studies suggest the current widespread practice of using DSE as a screening test lacks efficacy.

Contrast-enhanced transthoracic echocardiogram has been used as a noninvasive test to study coronary blood flow reserve and has been proposed as an alternative to angiography in the transplant population. By measuring LAD flow before and after adenosine infusion with the help of an ultrasound system connected to a broadband transducer with a second harmonic capability, the coronary flow velocity reserve (CFVR) can be calculated. Sade et al. showed that by adding CFVR assessment to DSE, the specificity of DSE is improved from 64% to 87%, while sensitivity remained the same at 78% (Sade et al. 2014). Echo-derived CFVR has not gained acceptance as a routine test.

Though a standard Doppler echocardiogram is a not a part of routine surveillance for CAV, it is worth mentioning that in the current recommended classification of CAV, allograft

function is integral and can be based on echocardiographic parameters of ejection fraction and hemodynamic assessment for restrictive physiology. Specifically, restrictive physiology is defined as echocardiographic E/A ratio >2, shortened isovolumic relaxation time (<60 msec), and shortened deceleration time (<150 msec) (Mehra et al. 2010).

Coronary Computed Tomography Angiography

Coronary computed tomography angiography (CCTA) has been investigated as a potential non-invasive alternative for angiography due to its ability to provide information about the vessel lumen, the vessel wall, as well as calcified and non-calcified plaques. Using invasive angiography as the gold standard, studies of CCTA with multi-detector computed tomography (16- and 64-slice) and dual-source computed tomography demonstrate high sensitivity, specificity, and NPV. In a meta-analysis of 13 studies including 615 patients, the combined weighted sensitivity, specificity, PPV, and NPV for CCTA were 97%, 81%, 78%, and 97%, respectively, for patient-based analysis when angiography was used as the reference standard. Fewer studies in this meta-analysis used IVUS as the reference standard, but where it was used, the combined weighted sensitivity, specificity, PPV, and NPV were 81%, 75%, 93%, and 50% for the ability of CCTA to detect significant disease (intimal thickness >0.5 mm) (Wever-Pinzon et al. 2014).

There are important limitations to the clinical use of CCTA. It is largely limited to evaluation of vessels at least 1.0–1.5 mm in diameter. As a result, small vessel disease and vessel pruning may be underappreciated (Gregory et al. 2006). A technical challenge revolves around reduction of the heart rate to minimize motion artifact, ideally to <65 beats per minute. This is often achieved with the administration of β-blockers in non-transplant patients, but higher resting heart rates in transplant recipients as a result of denervation, decreased vagal tone, and variable response to β-blockers may negatively impact image quality. In addition, patients with renal dysfunction were excluded from studies because of the requirement for a large bolus of contrast (60–100 cc) (Mittal et al. 2013; Gregory et al. 2006; von Ziegler et al. 2009). This is an important consideration in the heart transplant population, as 51% of patients have renal dysfunction within 5 years of transplant (Lund et al. 2016). Furthermore, radiation with CCTA is higher than with invasive coronary angiography, and cumulative exposure with repeated screening tests could be harmful. Current guidelines suggest CCTA with only a IIb recommendation as a screening test for CAV (Costanzo et al. 2010).

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMR) is another imaging modality of potential utility in CAV surveillance. CMR does not require radiation, making it appealing for patients requiring serial evaluation (Miller et al. 2014). Advantages of CMR over other screening techniques include its ability to detect asymptomatic infarcts in patients without detectable CAV by angiography, the ability to measure infarct size (Braggion-Santos et al. 2014), and the potential to help with diagnosis and understanding of microvascular disease (Chih et al. 2016). Tissue characterization by CMR may also facilitate better understanding of CAV and its effect on the myocardium. Myocardial perfusion reserve (MPR, measured by dividing mean hyperemic myocardial blood flow by mean resting myocardial blood flow) is measured on CMR and provides functional assessment of both the epicardial and microvascular systems (Miller et al. 2014). Some studies have compared CMR to angiography alone (Braggion-Santos et al. 2014), while others used IVUS as the reference standard and demonstrated that MPR may outperform angiography alone in detecting coronary vascular disease (Miller et al. 2014; Chih et al. 2016). Qualitative analysis with late gadolinium enhancement (LGE) identifies infarct-typical and infarct-atypical patterns (Braggion-Santos et al. 2014) with associations found between areas with infarct patterns and reduced MPR (Miller et al. 2014). In the absence of epicardial disease, microvascular disease can cause a decreased MPR, though the two entities often coexist. MPR < 2.0 is generally considered

abnormal, but the technique and references need to be vetted in the transplant population since these patients have an increased resting myocardial blood flow (due to their increased resting heart rate) that can impact the MPR. Several of these concepts were nicely demonstrated in a study of 29 patients by Chih et al., in which CMR was compared to angiography and IVUS. Most patients (69%) had mild CAV, and only two patients had coronary stenosis ≥50% by angiography. IVUS revealed 70% of patients to have increased MIT (≥0.5 mm). Patients with increased MIT were identified on CMR by significantly lower MPR (1.35 ± 0.23 for MIT ≥ 0.5 mm vs. 1.71 ± 0.45 for MIT < 0.5 mm, $p = 0.013$). Of interest, few patients had perfusion defects on qualitative analysis, which the authors note is likely due to the diffuse nature of CAV and possible balanced ischemia. A cutoff MPR of ≤1.68 predicted CAV with a sensitivity of 100%, specificity of 63%, NPV of 100%, and PPV of 86% in this study (Chih et al. 2016).

With the advantages of being noninvasive and likely more sensitive than angiography alone, CMR has the potential to be a very useful tool for CAV screening. It is not currently one of the mainstream surveillance tests, probably due to a number of factors. It needs to be better validated in the heart transplant population. CMR is time-consuming and requires a trained reader, and facilities may not have the capacity to accommodate a significantly increased study demand. From a safety perspective, gadolinium is necessary for tissue characterization. This poses a limitation for a number of posttransplant patients given the prevalence of renal insufficiency in these patients (Lund et al. 2016) and the risk of nephrogenic systemic fibrosis with gadolinium use in patients with significantly impaired renal function. Lastly, data demonstrating clinical benefit of CMR are lacking at present.

Myocardial Perfusion Imaging

Studies have compared single-photon emission computed tomography (SPECT) and positron emission tomography (PET) imaging to coronary angiography to examine the role of these noninvasive modalities as alternatives for the assessment of CAV. Both PET and SPECT expose the patient to radiation. For SPECT, this is about 10–20 mSv per patient per test. For PET, it is <2 mSv. This is an important consideration when managing a population requiring serial evaluation (Mc Ardle et al. 2014).

SPECT Imaging

Results of studies using vasodilators with SPECT MPI to detect coronary stenosis of at least 50% are variable. Using primarily dipyridamole with 99mTc-sestamibi or 99mTc-tetrofosmin SPECT imaging, Carlsen et al. demonstrated a sensitivity of 80% and specificity of 92%. NPV of a normal SPECT was 98% for CAV suitable for revascularization (Carlsen et al. 2000). Ciliberto et al. integrated data from resting echocardiogram and high-dose dipyridamole 99mTc-sestamibi perfusion imaging. A normal echocardiogram and SPECT were associated with a NPV of 100% for significant CAV and 82% for any CAV detected by angiography. If both the echocardiogram and the SPECT were abnormal, sensitivity for severe CAV was 100%, and, for any CAV, it was 60%. When the results of the echocardiogram and the SPECT were concordant, accuracy of the test combination was 100% for significant CAV and 83% for any CAV (Ciliberto et al. 2001). Results were less favorable in another study. Manrique et al. reported a sensitivity and NPV of 63% and 75%, respectively, for the detection of any CAV. For the detection of severe CAV, sensitivity and NPV were and 84% and 96% (Manrique et al. 2010).

Using dobutamine 99mTc-tetrofosmin imaging, one study reported a sensitivity of 85%, 90%, and 100% in one-, two-, and three-vessel disease, respectively. Specificity was 55% and the negative predictive value was 79% (Elhendy et al. 2000). In another study, the presence of large, reversible perfusion defects with dobutamine ^{201}TI SPECT imaging was highly predictive for significant CAV with sensitivity, specificity, positive predictive value, and negative predictive value of 89%, 71%, 42%, and 96%, respectively. Large perfusion defects always predicted significant CAV. Lung-heart ratio (LHR) during stress, but not rest, was significantly higher in patients

with CAV. Furthermore, LHR $\geq$ 0.37 was an independent predictor of angiographic CAV in patients with normal LV function (Wu et al. 2005b).

Taken in aggregate, the data suggest that a normal SPECT is reassuring if trying to exclude severe CAV. However, SPECT may not detect early CAV that would prompt modification of the therapeutic regimen, such as the introduction of mTOR inhibitors.

PET Imaging

In addition to providing information about myocardial perfusion, PET has the ability to provide data about myocardial blood flow (MBF) and allows for the detection of microvascular disease and balanced ischemia. In non-transplant patients, PET has been shown to have prognostic value (Mc Ardle et al. 2014).

McArdle and colleagues showed that PET has predictive value for adverse events and mortality in heart transplant patients. More abnormal perfusion at rest and stress, lower myocardial flow reserve (MFR), and lower estimated glomerular filtration rate were associated with a higher rate of adverse events. Those patients also had a higher prevalence of CAV documented on a previous coronary angiogram (Mc Ardle et al. 2014).

A study published in 2018 confirmed the notion that PET may have prognostic value in the transplant population. Integration of data from PET, MBF, and echocardiography was used to formulate diagnostic algorithm for CAV. This algorithm was superior for the diagnosis of ISHLT CAV 2/3 compared to MPI or MBF alone. Furthermore, there was a direct correlation between PET CAV severity and adverse outcomes (Bravo et al. 2018).

Preventive Therapies and Treatment for Cardiac Allograft Vasculopathy

Directed treatment for CAV remains elusive. The complex mechanisms and interactions of immune and nonimmune factors make this multifactorial process more complicated than atherosclerosis, though classic atherosclerosis can contribute to CAV. Hence, goal-directed treatments relevant to atherosclerosis also apply to CAV risk modification. Medications and treatments shown to be of benefit in allograft vasculopathy are discussed here.

Statins

Statins have shown a great deal of benefit in atherosclerosis in the non-transplant population with both a direct effect on modulation of cholesterol and indirect, pleiotropic effects on inflammation and vascular remodeling (Balk et al. 2004). Dyslipidemia is common after cardiac transplantation and can cause atherosclerotic coronary disease in the transplanted heart, but its impact and contribution to the onset and progression of CAV are less clear. While some studies have shown no association between hyperlipidemia and CAV, others have shown that dyslipidemia is an independent risk factor for CAV (Escobar et al. 1994; Sanchez Lazaro et al. 2008). Due to the benefits of their pleiotropic effects, statins are considered standard of care in all patients post-heart transplant regardless of lipid levels. The ISHLT guidelines recommend the use of statins 1–2 weeks after heart transplant irrespective of lipid levels (Costanzo et al. 2010).

Kobashigawa et al. examined the effect of pravastatin on outcomes after cardiac transplantation and demonstrated improved 1-year survival in the pravastatin group compared to controls. The statin group had decreased development of CAV marked by less progression of MIT. Although the frequency of rejection was not decreased, the group receiving therapy had significantly fewer rejections with hemodynamic compromise (Kobashigawa et al. 1995). These findings were replicated in a more contemporary study showing long-term benefit of statin therapy in the cardiac transplant population with significantly improved 8-year survival when simvastatin therapy was started early after transplantation. This held true even when the control group began receiving statin therapy later in the posttransplant course

(Wenke et al. 2003). In these studies, it was postulated that the decrease in rejection with associated hemodynamic compromise or graft failure was the result of immunomodulatory effects of statins independent of cholesterol lowering (Wenke et al. 2003; Kobashigawa et al. 1995). Similar findings of decreased mortality and fatal rejections were reported in a multivariate analysis of 1,186 patients in the Heart Transplant Lipid Registry (Wu et al. 2005a). In vitro studies of statins have reported a variety of immunomodulatory effects. These include inhibition of lymphocytes, macrophages, and endothelial cells by disrupting co-stimulatory molecules, reducing the effect of IFN-γ on MHC class II expression, blocking interaction between leukocyte function antigen-1 and ICAM-1 to prevent leukocyte migration and T-cell co-stimulation, suppression of natural killer cells and regulation of natural killer cell cytotoxicity, inhibition of chemotaxis, and inhibition of antibody-dependent cellular cytotoxicity (Kwak et al. 2000; Weitz-Schmidt et al. 2001; Cutts and Bankhurst 1990).

Multiple studies in transplant patients have established the safety profiles of pravastatin, simvastatin, atorvastatin, fluvastatin, lovastatin, and rosuvastatin with recommendations for adjusted highest tolerable dosing. Pravastatin is considered the safest because it interacts the least with the metabolism of immunosuppressant drugs by the liver. Inhibition of drug metabolism by the CYP3A4 system in the liver or inhibition of drug transport by the *P*-glycoprotein transporter and organic anion transporting polypeptide in patients taking cyclosporine can lead to increased levels of statin in the blood. Tacrolimus does not have similar interactions, and the combination of statins and tacrolimus seems to be safe (Lemahieu et al. 2004).

Proliferation Signal Inhibitors

Rapamycin, also called sirolimus, was the first proliferation signal inhibitor (PSI). It is produced by the bacteria *Streptomyces hygroscopicus* and was discovered from the soil on Easter Island (called Rapa Nui in Polynesian). Everolimus is a derivative of sirolimus with an extra hydroxyethyl group. These agents bind to the FK506 binding protein 12 (FK506BP), and the combined product inhibits a serine/threonine kinase leading to cell cycle arrest in the mid- to late-G1 phase. (Detailed pharmacology is reviewed in ▶ Chap. 14, "Induction and Maintenance Agents.") PSIs inhibit proliferation of immune cells and also inhibit the proliferation and migration of fibroblasts and smooth muscle cells, thereby slowing the progression of vasculopathy, allograft hypertrophy, and graft failure. Additional mechanisms of PSIs that mediate these effects include induction of apoptosis, prevention of p27KIP (cyclin-dependent kinase inhibitor) degradation, and activation of autophagy (Eisen et al. 2003; Mancini et al. 2003).

Eisen et al. showed that everolimus started within 72 h of heart transplantation (in combination with cyclosporine and steroids) was more effective than azathioprine in preventing the development of CAV with all IVUS parameters significantly reduced at 1 year in the everolimus group compared to the azathioprine group. These results were validated in a 2-year follow-up study. Furthermore, there was less rejection associated with hemodynamic compromise in the everolimus group, particularly in those treated with 3.0 mg/day versus 1.5 mg/day compared to the azathioprine group. Tolerability was similar in all groups. There was a significant increase in serum creatinine in the everolimus groups possibly related to potentiation of the renal effects of cyclosporine unrelated to serum levels of the CNI (Eisen et al. 2003). Similar findings were published regarding sirolimus. Manicini et al. demonstrated that sirolimus slowed the progression of graft vasculopathy and reduced the incidence of significant cardiac events in patients with severe CAV compared to standard of care with azathioprine or mycophenolate mofetil (MMF) (Mancini et al. 2003). In a randomized, open-label study, patients started on sirolimus at the time of heart transplantation had significantly less development of CAV at 6 months compared to patients on azathioprine. This difference was

sustained to the 2-year observation point in the study (Keogh et al. 2004). More recently, everolimus (1.5 mg/day or 3.0 mg/day) + low-dose CNI was compared with MMF + standard-dose CNI. Everolimus 3.0 mg/day was stopped prematurely because of increased mortality. The primary efficacy endpoint was non-inferior for everolimus 1.5 mg/day, but concerns regarding increased adverse outcomes with everolimus were raised due to increased mortality in the low-dose everolimus group at 3 months. Further analysis attributed this to increased infection in patients who received rabbit antithymocyte globulin induction. 24-month mortality was similar between the everolimus and MMF groups. The everolimus group showed less intimal proliferation and a lower incidence of CAV compared to the group receiving MMF (Eisen et al. 2013). While early use of sirolimus in the context of renal sparing has been shown to be safe and effective, a randomized trial of early (within 12 weeks) replacement of CNI with sirolimus showed increased incidence of significant rejection and was terminated (Hunt et al. 2007). Similarly, the SCHEDULE trial, in which everolimus was studied as an early substitute to CNI around 11 weeks posttransplant, showed an increase in 2R rejections. The increased rejection burden did not persist beyond the first 12 months. At the conclusion of the 3-year follow-up, the increased early rejection did not translate into long-term adverse outcomes. The everolimus group had significantly less progression of CAV and MIT on IVUS compared to the CNI group (0.10 mm vs. 0.15 mm, respectively). With no meaningful difference in clinical outcomes in this study, the authors concluded that despite early rejection, intermediate outcomes at 3 years showed benefit with a strategy of early CNI withdrawal and substitution with PSIs (Andreassen et al. 2016). Despite this particular conclusion, with studies suggesting higher rejection burden and possibly increased adverse outcomes, there has been a gradual decrease in the utilization of PSIs early after transplant. Less than 10% of patients are on these medications at the end of 1 year, and approximately 20% are taking these medications at the end of 5 years posttransplant (Lund et al. 2016).

Revascularization

Due to the diffuse nature of the disease and involvement of small vessels, revascularization is not always a viable option in patients with CAV. Moreover, even when significant epicardial lesions can be revascularized, the long-term benefit of such interventions is controversial because the disease process in the rest of the vasculature is not easily modified.

Percutaneous Coronary Intervention

Lesions resulting from diffuse, circumferential disease in CAV are not typically amenable to intervention with percutaneous coronary intervention (PCI) or bypass surgery. Interventions are reserved for discrete, epicardial lesions (Benza et al. 2004). Data from the National Cardiovascular Data Registry shows that over a period of 4 years, 0.03% of percutaneous interventions performed in the United States were in heart transplant patients. In this study, transplant patients undergoing PCI were less likely to present as STEMI (0.9%) and NSTEMI (5.4%), have an abnormal noninvasive test (13.5%), or have angina (35%) compared to non-transplant individuals. Transplant patients were more likely to experience heart failure in the prior 2 weeks (20%). Half of the heart transplant recipients in this study received a prior PCI, consistent with the unrelenting nature of the disease (Dasari et al. 2015). The low prevalence of symptoms is not unexpected with the structured surveillance for CAV in this population.

In-hospital outcomes of heart transplant patients are similar to non-transplant individuals undergoing PCI (Dasari et al. 2015). Historically, however, restenosis in the transplant population was considerably higher with percutaneous revascularization being considered only a temporizing measure. Similar to native vessel disease, the use of stents has resulted in greater freedom from restenosis than balloon angioplasty. With the utilization of stents along with higher-dose antiproliferative agents, including mycophenolate and azathioprine, the restenosis rate at 8 months was found to be only 10%, compared to 33% without these agents

(Benza et al. 2004). While the use of drug-eluting stents (DES) has become a routine practice in all percutaneous interventions, review of the literature specific to allograft vasculopathy does not show a clinical advantage of DES compared to bare-metal stents. The restenosis rate for CAV is still higher than in native coronary artery disease with a suggestion that there might be a late catchup of the in-segment restenosis rates by 3–5 years for both sirolimus and everolimus stents due to the nature of CAV progression (Cheng et al. 2017). Inevitably, due to the lack of effective disease-modulating therapeutics, patients undergoing interventions for allograft vasculopathy have unfavorable long-term clinical outcomes. In one of the larger series, at 5 years post-PCI, freedom from death or graft loss was 0%, 42%, and 64% in patients with three-, two-, and one-vessel disease, respectively (Benza et al. 2004). A more recent study showed 80% survival and 52% survival at 2 years and 5 years post-PCI, respectively. Moreover, this study found that when vasculature is amenable to PCI, survival is improved compared to those with severe CAV that cannot be treated with PCI (Agarwal et al. 2014).

Coronary Artery Bypass Surgery

Few patients are candidates for coronary artery bypass grafting (CABG) due to the diffuse nature of transplant vasculopathy and the challenge of identifying appropriate targets for revascularization. Perioperative mortality is a concern and, historically, was significantly worse compared to the non-transplant population. Studies from the mid-1990s reported significant CABG-associated perioperative mortality in heart transplant patients (Halle et al. 1995). Contributors to mortality included significant distal vasculopathy, perioperative bleeding, and inability to come off bypass. More recent analysis has shown better outcomes with Bhama et al. reporting a 77% survival at 39 $\pm$ 36 months (Bhama et al. 2009). While CABG may be technically possible in some patients, the risk-benefit analysis and long-term benefit need to be weighed meticulously.

Retransplantation

Retransplantation is the only definitive therapy for severe CAV. Although it remains small, the share of heart transplant patients that are retransplants has slowly increased in recent decades and now comprises about 2–3% of transplants (Johnson et al. 2007; Lund et al. 2016). Nonetheless, registry data reveals that repeat heart transplantation is associated with higher morbidity and mortality than primary heart transplantation (Lund et al. 2016), and analyses have demonstrated that patients retransplanted within 2 years of primary transplant have less than 60% 1-year survival (Johnson et al. 2007). Srivastava et al. published data from 1987 to 1998 demonstrating 1-, 2-, and 3-year survival of 65%, 59%, and 55%, respectively, after retransplantation (Srivastava et al. 2000). Similarly, 1-, 3-, and 5-year survival was lower among retransplant patients compared to first-time heart recipients according to data from the Scientific Registry of Transplant Recipients from 2000 to 2005 (82% vs. 86%, 70% vs. 80%, 58% vs. 73%, respectively) (Johnson et al. 2007). Radovancevic and colleagues found that survival after retransplantation improved over a 10-year period such that during the later era, survival after retransplantation for CAV was identical to that for primary transplantation (Radovancevic et al. 2003). More recent data from the International Society of Heart and Lung Transplantation reports 70% 1-year survival for all heart retransplantation. While improved from earlier eras, this remains lower compared to first-time transplants (Lund et al. 2014). The role of retransplantation remains controversial because of inferior outcomes relative to first heart transplant as well as the debated ethics of utilizing limited donor organs for repeat transplant when many individuals remain waiting for a first transplant. In 2006, a working group was convened as part of a Consensus Conference on Retransplantation sponsored by the American Society of Transplantation, the American Society of Transplant Surgeons, and the National Institute of Allergy and Infectious Diseases. Based on data available and expert

opinion, the working group developed recommendations for indications for heart retransplantation, which are as follows:

1. Chronic severe cardiac allograft vasculopathy not amenable to medical or surgical therapy with:
   (a) Symptoms of ischemia or heart failure (should be considered)
   (b) Asymptomatic moderate to severe LV dysfunction (may be considered)
2. Chronic graft dysfunction with progressive heart failure in the absence of active rejection (Johnson et al. 2007)

Additional considerations for retransplantation recommended by the consensus group are as follows:

1. Patients with graft failure due to ongoing acute rejection with hemodynamic compromise, especially less than 6 months posttransplant, are inappropriate retransplant candidates.
2. Patients requiring short-term mechanical cardiorespiratory support may not be good retransplant candidates and deserve careful consideration on an individual basis.
3. The efficacy of retransplantation in older candidates (60–65 years) is not well established.
4. The efficacy of retransplantation in the presence of posttransplant lymphoproliferative disorder (disease-free less than 2 years) is not established.
5. Guidelines established for primary transplant candidates should be strictly followed in selecting candidates for retransplantation (Johnson et al. 2007).

Clinical Implications of Cardiac Allograft Hypertrophy

The development of organ allograft hypertrophy after heart transplant is common, occurring in over 80% of patients in one study (Goodroe et al. 2007). As detailed in previous sections, the etiology of the hypertrophy is still not entirely understood but seems to have a significant immune component. In non-transplant patients, LV hypertrophy is a known predictor of increased cardiovascular morbidity and mortality. Similarly, allograft hypertrophy was shown to be an independent predictor of increased morbidity and mortality posttransplant (Goodroe et al. 2007; Raichlin et al. 2009b). Patients whose echocardiographic calculated LV mass was >250 g had increased mortality from graft failure, myocardial infarction, or sudden death (Goodroe et al. 2007). In addition, ventricular hypertrophy at 1-year posttransplant has been shown to predict onset of significant CAV at 5 years (Raichlin et al. 2009b). The macroscopic hypertrophy of the allograft is secondary to cardiomyocyte hypertrophy and myocardial fibrosis (Armstrong et al. 1998). Though not as well studied as CAV, evidence suggests that these histopathological changes are the result of chronic rejection. These pathological changes lead to the physiology of a restricted heart with diastolic dysfunction and the clinical presentation of heart failure. As these structural changes are irreversible, slowing of progression with the aforementioned therapies and management of any symptoms is essential.

Conclusion

Chronic rejection remains a rate-limiting factor in promoting longevity in heart transplant patients. Current understanding of the mechanisms that initiate and promote chronic rejection is still limited. While animal models of allograft vasculopathy have provided some insight, they have major limitations. Current practice guidelines are focused on early detection but have no strong evidence for disease-modulating therapies. It is imperative for the transplant community to come together to overcome the challenge of chronic rejection. Defining various facets of chronic changes in the graft, especially those related to immune injury, will be important to characterize mechanisms and help future investigations of therapeutic interventions that alter such pathways.

Cross-References

- Cardiac Allograft Rejection
- Chronic Immunosuppression Medications
- Donor Operation and Organ Preservation
- Induction and Maintenance Agents
- Infection Prophylaxis
- Matching Donor to Recipient
- Monitoring for Rejection
- Retransplantation

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Malignancy After Transplant

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Abstract

An underappreciated but important complication of heart transplantation is the development of post-transplant malignancy. With continued improvements of heart transplant recipient survival, the prominence of these malignancies has been increasingly recognized, leading to more investigation regarding their pathophysiology and impacts on treatment and prognosis. As a result, there is a better understanding of the unique malignancy risks associated with transplant recipients and the effects on clinical outcomes. Although there are a variety of risk factors for malignancy that overlap with non-transplant recipients, immunosuppression plays a unique and significant role in malignancy pathogenesis. Malignancy type varies widely, from virus-associated malignancies such as post-transplant lymphoproliferative disorder to dermatologic malignancies such as non-melanomatous skin cancer. Strategies for

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prevention, screening, and treatment of these malignancies are continually evolving. This chapter reviews the epidemiology and types of malignancies post-transplant and the role immunosuppression regimens may play toward the development and in treatment of these malignancies.

Keywords

Malignancy · Immunosuppression · Heart transplantation · Post-transplant lymphoproliferative disorder · Kaposi sarcoma · Solid organ tumor · Skin cancer

Introduction

Malignancy is a major complication of all solid organ transplantation – including heart transplantation. In comparison to the general population, solid organ transplant recipients are at an increased risk of developing malignancy. Data from the US Scientific Registry of Transplant Recipients from 1987 to 2008, encompassing over 175,000 solid organ transplants, showed a sobering incidence rate of 1374.7 per 100,000 patient years (Engels et al. 2011), nearly twice that seen in the general population. Furthermore, this risk covers a spectrum of malignancy types from non-Hodgkin's lymphoma and lung cancer to Kaposi sarcoma and renal carcinoma.

In comparison to other types of solid organ transplant, heart transplant recipients are at especially high risk. Results from a Norwegian cohort of 2397 renal transplant recipients and 164 heart transplant recipients suggested that heart transplant recipients had approximately three times the risk of developing a malignancy when compared to their renal counterparts (Relative Risk 2.9, 95% Confidence Interval: 1.3–6.2) (Jensen et al. 1999). Moreover, this risk increases the longer a patient has had his/her transplant. Specifically, data collected from 1990 to 2000 suggests that malignancy accounted for 3% of the deaths of cardiac transplant recipients within the first year post-transplant, 16% from 1 to 4 years post-transplant, and 29% 5 to 10 years post-transplant. In light of this, a significant focus of research in patient's post-transplantation has been understanding the biological underpinnings to their heightened malignancy risk. Indeed, there are a variety of risk factors for developing a malignancy post-transplantation. What cannot be ignored, however, is the overarching contribution of immunosuppression exposure toward the development of malignancy and unique malignancy pathogenesis. This chapter aims to discuss the unique post-transplant malignancy risk attributed to various immunosuppression strategies, commonly occurring malignancies, and provide an overview of transplant-specific malignancy.

Role of Immunosuppression and Malignancy

Preventing organ rejection with immunosuppression is the medically essential theme of post-transplant care. Despite the lifesaving role immunosuppressants play to preserve organ function through inhibition of the immune system, these same pharmacological properties also impair the immune system's ability to fight infection and prevent malignancy. Thus, not surprisingly, immunosuppression increases the risk for malignancy. Studies in the transplant population have suggested that the intensity and type of immunosuppression may be directly related to the risk of malignancy post-cardiac transplant (Rinaldi et al. 2001; Crespo-Leiro et al. 2007; Jensen et al. 1999).

Calcineurin Inhibitors: Cyclosporine and Tacrolimus. Since the introduction of cyclosporin A (Griffith et al. 1982), calcineurin inhibitors (CNI) have been the cornerstone of immunosuppressive therapy post heart transplant. The two major CNIs used clinically are cyclosporine and tacrolimus. While they have slightly different mechanisms of action, the end result is the inhibition of the calcineurin molecule, a phosphatase critical to the proliferation of T lymphocytes. Cyclosporine binds to cyclophilins to create a drug-receptor complex that inhibits calcineurin; tacrolimus binds to FK-binding proteins to create a drug-receptor complex that also inhibits calcineurin. Between the two drugs, tacrolimus

is generally considered to be the more potent calcineurin inhibitor. Their effect on malignancy post-transplant remains somewhat controversial, however, as there is conflicting data in the literature.

Much of what is known about cyclosporine and its relation to malignancy in post-transplant patients comes from renal transplant data. Some studies looking at this population have associated cyclosporine with increased rates of malignancy. For example, the addition of cyclosporine to an azathioprine and prednisolone immunosuppression regimen increased the relative risk of developing malignancy by a factor of 2.8 (95% CI: 1.4–5.3) compared to the cyclosporine-free regimen (Jensen et al. 1999). In contrast, other data suggest that cyclosporine does not confer an increased overall malignancy risk. A study of 722 renal transplant patients receiving either cyclosporine as part of combination immunosuppression regimens or cyclosporine-free regimens showed that there was no statistically significant difference in the overall rate of malignancy (4.7% vs. 10.6%, $p = 0.41$) (Gruber et al. 1994). However, this same study did demonstrate that the time to diagnosis of a malignancy was significantly shorter in the group treated with cyclosporine compared to the group treated without cyclosporine (37 months vs. 90 months, $p < 0.001$).

Similar to cyclosporine, tacrolimus' role in malignancy development or prevention in the post-transplant patient is uncertain. In a Chinese study of 66 heart transplant patients, a significantly higher percentage of patients on tacrolimus developed malignancies when compared to patients receiving cyclosporine (22% vs. 0%, $p = 0.006$) (Chen et al. 2009). However, data from non-cardiac transplant cohorts seems to suggest that tacrolimus and cyclosporine may not be very different in their contribution to malignancy development. In a study of over 500 liver transplant patients, cyclosporine- and tacrolimus-treated patients had similar rates of malignancy (9.6% vs. 8.8%, respectively) (Wiesner 1998). Similar data is present in renal transplant patients; a study of 76 paired cadaveric renal transplant recipients showed no significant difference in malignancy rate (10.5% vs. 10.5%, $p > 0.99$) (Cheung et al. 2009). In addition, a univariate analysis of different immunosuppression regimens and their association with malignancy development in a Spanish post heart transplant registry suggests that tacrolimus confers a lower relative risk for development of skin cancer (RR 0.3, 95% CI: 0.1–0.8, $p = 0.0105$), though the risk for the development of lymphoma (RR 0.8, 95% CI: 0.2–3.2, $p = 0.7298$) or all other types of cancer (RR 1.0, CI: 0.5–1.9; $p = 0.9601$) was unchanged when compared to that in the general population (Crespo-Leiro et al. 2008). Given the conflicting data, it remains unclear as to whether these medications are significant contributors to development of malignancy post-transplant and whether one agent has more significant effect than the other.

Antiproliferative Agents: Azathioprine and Mycophenolic Acid. Azathioprine (AZA) is a purine analogue antiproliferative agent commonly used in combination immunosuppressive regimens for post-transplant therapy, in addition to a variety of other diseases such as rheumatoid arthritis and ulcerative colitis. Its role in the development of post-transplant malignancy is believed to be due to its effects on DNA synthesis. AZA leads to the accumulation of 6-thioguanine (6-TG) in the DNA, especially at higher doses (O'Donovan et al. 2005). This accumulation leads to mistakes in the replication of DNA by causing errors in the mismatch repair mechanism (Swann et al. 1996). This is compounded by the fact that 6-TG accumulation also induces photosensitivity to UVA light, an independent risk factor for the development of skin cancer.

Thus, perhaps not surprisingly, much of the literature as it relates to AZA and its role in the development of malignancy has focused on the risk of dermatologic malignancies. A Spanish registry of heart transplant patients taking AZA found a hazard ratio of 1.56 (95% CI: 1.2–2.7, $p < 0.0032$) for the development of non-melanoma skin cancers (NMSCs) when compared to patients with AZA-free immunosuppression regimens (Molina et al. 2010). However, there is conflicting data on whether AZA increases malignancy risk in heart transplant patients.

A meta-analysis of 27 studies including multiple different types of organ transplant recipients also showed a significantly increased risk of squamous cell carcinoma of the skin (HR 1.56, 95% CI: 1.11–2.18), but the heart transplant-specific sub-analysis was nonsignificant (Jiyad et al. 2016). Other studies have similarly failed to show an association (Geusau et al. 2008).

Based on the mechanism of action described above, it was believed that the increased risk of NMSC associated with AZA may be limited to those patients taking higher doses of the drug. However, a cohort of 388 patient's post-OHT revealed an association between average doses of AZA and development of any malignancy (Rinaldi et al. 2001). Furthermore, AZA treatment may lead to more aggressive squamous cell carcinomas of the skin as well (Ducroux et al. 2017).

Mycophenolic acid (MPA) is thought to be less carcinogenic than azathioprine and, interestingly, may have some protective effects. MPA inhibits inosine 5′-monophosphate dehydrogenase (IMPDH), a key enzyme in nucleotide synthesis. While suppressing IMPDH inhibits the proliferation of T- and B-lymphocytes, thereby providing the immunosuppressive effects of MPA, this same mechanism may also be associated with the drug's possible anti-malignancy properties. Specifically, IMPDH is upregulated in cancer cells and is thus considered a target for anticancer therapies (Chen and Pankiewicz 2007; Hedstrom 2009). In heart transplant patients, MPA was found to have a lower risk for malignancy than AZA, even possibly be protective in regard to squamous cell carcinoma (HR 0.3, 95% CI: 0.2–0.6, $p < 0.0005$) (Molina et al. 2010). Other studies have found the same effect. In a retrospective review of over 3000 patients, MPA treatment as part of the immunosuppressive regimen was found to be associated with lower risk of development of malignancy compared to immunosuppressive regimens without MPA (RR 0.73, 95% CI: 0.56–0.95) even after adjustment for other factors (O'Neill et al. 2006).

Induction Agents. Induction therapy is a common but controversial method of achieving rapid, highly potent immunosuppression in the immediate postoperative period after transplant. This strategy is designed to minimize the risk of early graft failure while delaying patient exposure to nephrotoxic immunosuppression medications such as CNIs (Rosenberg et al. 2005; Cantarovich et al. 2004). It is estimated that approximately 50% of all heart transplant patients receive induction therapy (Lund et al. 2015).

Induction therapy is commonly performed using one of three different agents: a monoclonal anti-CD3 antibody (OKT3); anti-thymocyte globulin (ATG), a polyclonal horse- or rabbit-derived antibody against human T-cells; or basiliximab, a monoclonal antibody against the CD25 moiety on the T-cell interleukin-2 receptor (IL-2R). Each of these drugs is thought to increase the risk of malignancy via a different pathway. A candidate mechanism of malignancy mediation by OKT3 might be an increased release of IL-6 and IL-10 (Swinnen and Fisher 1993). These cytokines are significant contributors to B-cell neoplasia which might evolve into post-transplant lymphoproliferative disorder (PTLD). In addition, OKT3 causes significant T-cell depletion which contributes to poor lymphoid tumor suppression. In comparison, ATG leads to significant T-cell depletion and induction of B-cell apoptosis which lead to poor tumor suppression (Zand et al. 2005). Basiliximab is thought to inhibit natural killer (NK) cell function, thereby leading to decreased tumor suppression (Morteau et al. 2010).

Due to its impact on immune-mediated malignancy surveillance, induction immunotherapy is not surprisingly associated with an increased risk of malignancy, particularly PTLD. A retrospective series of patients who underwent cardiac transplant found that induction therapy with OKT3 was associated with a ninefold increased risk of PTLD (HR 9.5, 95% CI: 1.6–54.7) (Swinnen et al. 1990). Although retrospective studies are inherently limited by the nature of their design, it is worth noting that following a multivariable analysis induction immunosuppression with OKT3 was the only variable in this study that was found to be associated with an increased risk of PTLD ($p = 0.001$).

Further, a retrospective cohort study in renal transplant patients compared the malignancy-related outcomes in individuals who received

one of the three different types of induction therapies, OKT3, ATG, or basiliximab; this latter study found that ATG was associated with the highest risk (HR 1.72, 95% CI: 1.04–2.83), followed by OKT3 (HR 1.29, 95% CI: 0.82–2.03), with the lowest risk being with basiliximab (HR 1.14, 95% CI: 0.77–1.70) (Cherikh et al. 2003).

Additional data from at least one registry of heart transplant patients appear to support the notion that at least some forms of induction immunotherapy may be associated with higher rates of malignancy. Specifically, this registry revealed a significantly increased relative risk relative to no induction therapy for skin cancer and non-lymphoma tumors in patients who received OKT3 [(HR 2.5, 95% CI: 1.9–3.3) and (HR 2.1, 95% CI: 1.5–2.9)] and skin, lymphoma, and other tumors in those treated with ATG [(HR 1.6, 95% CI: 1.1–2.2), (HR 2.4, 95% CI: 1.3–4.5), and (HR 2.5, 95% CI: 1.8–3.6), respectively] (Crespo-Leiro et al. 2008).

In contrast, a prospective trial comparing heart transplant patients who did or did not receive ATG induction therapy found no significant increase in the incidence of malignancy in the group receiving ATG (ATG+ 17%, ATG− 27%, $p = 0.16$) (El-Hamamsy et al. 2005). Similarly, investigators found no evidence of association between OKT3 induction and development of PTLD after adjustment of various other factors such as recipient age, donor age, and other immunosuppressive medications ($p = 0.20$) or with a lower dose of OKT3 (Gao et al. 2003; Peraira et al. 2003).

The data presented in this section is admittedly inconsistent and originate from studies fraught with bias. However, through this uncertainty, concerning trends have emerged that suggest the possibility of an association between induction immunotherapy and a higher incidence of malignancy which warrant further investigation.

mTOR: Sirolimus and Everolimus. The mammalian target of rapamycin (mTOR) plays a significant role in protein translation via enhancement of mRNA translation (via activation of ribosomal S6K1 and suppression of 4E-BPs) (Bjornsti and Houghton 2004). Inhibition of the serine/threonine kinase mTOR can blunt the response of cells to IL-2, thereby preventing activation of both T-cells and B-cells. This has led to their use in immunosuppression post solid organ transplant (Ventura-Aguiar et al. 2016). In oncology, mTOR inhibitors have been shown to have anticancer effects in many different types of malignancies such as mantle cell lymphoma, malignant melanoma, hepatocellular carcinoma, and lung cancer, among others (Zhou and Huang 2012; Faivre et al. 2006). These anticancer effects have led to studies looking at whether mTOR inhibitors may decrease the incidence of malignancy post-transplant.

There are primarily two mTOR inhibitors used clinically: sirolimus and everolimus. Both agents are thought to be less carcinogenic than other immunosuppressants and perhaps even onco-protective. In one study of patients with squamous cell carcinoma, conversion from CNI therapy to sirolimus was associated with thinner lesions with less peritumoral vascularization, suggesting possible regression of the tumor (Rival-Tringali et al. 2009). Similarly, additional studies have shown that switching immunosuppression from a CNI-based regimen to a sirolimus-based program has resulted in a decrease in the size of Kaposi sarcoma and other types of tumors (Stallone et al. 2005, 2008; Wasywich et al. 2006; Krishnan et al. 2008).

Similar results have been observed with everolimus with regard to malignancy post-transplant. In liver transplant patients, everolimus has been used to treat patients with neoplasms, including hepatocellular carcinoma (Ferreiro et al. 2014; Gomez-Martin et al. 2012). Akin to sirolimus, switching to everolimus-based immunosuppression regimens has been shown to lead to regression of Kaposi sarcoma post-transplant (Campistol and Schena 2007).

While available data suggests that the use of mTOR inhibitors is consistently associated with regression of existing dermatologic malignancies, data looking at the ability of mTOR inhibitors to prevent malignancy are more variable. A trial of 300 kidney transplant patients randomized to continue cyclosporine treatment or transition to everolimus showed no difference in the rate of neoplasms between the groups

(Budde et al. 2015). However, a Taiwanese retrospective analysis of heart transplant patients suggested that patients treated with everolimus had a significantly lower incidence of malignancy compared to those treated with mycophenolate (9.9% vs. 1.8%, $p = 0.001$) (Wang et al. 2016).

Virus-Associated Malignancies

Given that immunosuppression is a large contributor to malignancy risk post-transplant, malignancies related to infectious agents are frequently seen. This section will focus on two specific virus-associated malignancies, post-transplant lymphoproliferative disorder (PTLD) and Kaposi sarcoma (KS).

Post-transplant Lymphoproliferative Disorder. PTLD warrants special attention among post-transplant malignancies. It is currently the second most common post-transplant malignancy in the heart transplant recipient behind skin cancer and accounts for nearly a third of all non-dermatologic malignancies in this population (Roithmaier et al. 2007). While the incidence is highest in the pediatric cardiac transplant population, the rate in adults is still significant at 1–6% (LaCasce 2006). By comparison, incidence of up to 9.4% has been reported in those patients who have undergone a combined heart-lung transplant (Randhawa et al. 1989; Armitage et al. 1991).

PTLD can either occur early (<1 year) and late (>1 year) after transplant. Incidence peaks in the first year post solid organ transplant and then decreases as the patient gets further out from their date of transplant (Opelz and Dohler 2004). While both forms of PTLD carry a significant mortality risk, early PTLD carries a better prognosis than those with late onset and may be treated with reduction in immunosuppression alone. Late-onset cases are morphologically different, more likely to be histologically heterogeneous, and more likely to be disseminated or resemble non-Hodgkin's lymphoma (Leblond et al. 1998; Nalesnik 2001). Further, late cases were less likely to respond to reduction in immunosuppression alone.

A variety of risk factors appear to be associated with the development of PTLD. However, the specific risk factors are different for each form of the disease. PTLD risk in the early post-transplant period is related to the type of organ transplanted (with heart transplant being at higher risk than their kidney or liver counterparts) and is likely a function of the degree of T-cell inhibition leading to unchecked B-cell proliferation, younger age at the time of transplant, primary EBV infection, and CMV mismatch (Cockfield 2001). As stated above, currently available data is inconclusive regarding the risk of PTLD following induction immunosuppression. In contrast, late development of the disease is associated with older age at transplant and duration of immunosuppression, along with type of organ transplanted (Cockfield 2001).

The role of Epstein-Barr virus (EBV) is well described in the development of PTLD. EBV, present in over 90% of the general population, is associated with nearly all cases of PTLD (Cohen 2000). EBV seronegativity at the time of transplant confers a significantly increased risk for development of PTLD compared to latent infection. Data in renal transplant patients shows that the risk in patient's post renal transplant is over six times higher in those patients who are seronegative at time of transplant compared to those who are latently infected (Sampaio et al. 2012b). However, there are cases of PTLD not associated with EBV. Late onset PTLD is more often not associated with EBV (Dotti et al. 2000). The median time to diagnosis of EBV-negative PTLD is approximately 50 months post-transplant, with sobering median survival times of only 1–7 months (Leblond et al. 1998; Nelson et al. 2000).

Cytomegalovirus (CMV) is also thought to play a role in the development of PTLD, and its associated risk is synergistic with that of EBV status and immunosuppression. CMV mismatch (donor IgG positive/recipient IgG negative) in non-renal transplant patients has been found to confer a sixfold increased risk in seropositive EBV transplant recipients and an even higher 24-fold increase in seronegative EBV recipients (Walker et al. 1995). Further, the combination of

EBV seronegativity, OKT3 treatment, and CMV mismatch increased the risk of PTLD by 500-fold when compared to patients without any of these risk factors (Walker et al. 1995). Similarly, hepatitis C infection appears to increase the development of PTLD. In 1 retrospective series of over 400 OHT patients, the patients with HCV positivity were about 4 times more likely to develop PTLD (8% vs. 2%, $p = 0.017$) (Buda et al. 2000).

As mentioned above, there remains significant uncertainty as to whether induction immunotherapy with OKT3 or ATG is associated with an increase in the risk of developing PTLD (Swinnen et al. 1990; Swinnen and Fisher 1993). The data regarding the risk for developing PTLD when using other immunosuppressive agents is similarly inconclusive. Much of the work in this area to date has been performed in the renal transplant population, and there does not appear to be any difference in the rate of PTLD between those patients treated with cyclosporine and those treated with tacrolimus (Pirsch 1999). Similarly, a large review of renal transplant patients failed to show that any one particular immunosuppressive agent led to higher PTLD risk than the others (Birkeland and Hamilton-Dutoit 2003). Cumulative immunosuppression (likely mediated by more intense and chronic T-cell suppression) is thought to be a major risk factor, rather than any specific immunosuppressive agent (Nijland et al. 2016; Cockfield 2001; Birkeland and Hamilton-Dutoit 2003).

Given the relationship of immunosuppression to the development of PTLD, it follows that the mainstay of treatment for PTLD in the post-transplant patient is to reduce immunosuppression. Remission rates of up to 89% have been reported in patients with lymphoma or early-onset PTLD (Armitage et al. 1991). However, the same data set also showed that few patients who presented with disseminated or late-onset disease responded to immunosuppression reduction alone. In cases not responsive to immunosuppression reduction alone, they may require cytotoxic therapies. For example, rituximab, an anti-CD20 antibody, can improve outcomes in solid organ transplant recipients with PTLD (Evens et al. 2010; Trappe et al. 2012). One of the more commonly used chemotherapy regimens in solid organ transplant recipients with PTLD is "CHOP" (cyclophosphamide, doxorubicin, Oncovin, prednisone) (Choquet et al. 2007; Trappe et al. 2012; Mamzer-Bruneel et al. 2000).

Further, as the etiology of PTLD is frequently associated with viral infection, antiviral therapy is thought to play a significant role in reducing this risk. Data from the Spanish Post-Heart Transplant Tumour Registry confirmed that the addition of antiviral prophylaxis significantly reduces the risk for development of PTLD. Use of acyclovir or ganciclovir in patients who received induction therapy with either OKT3 or ATG was associated with a decrease in relative risk from 3.2 (95% CI: 1.6–6.6) to 0.7 (95% CI: 0.2–1.9) (Crespo-Leiro et al. 2007).

Kaposi Sarcoma. Kaposi sarcoma (KS) is a malignancy associated with infection by *Human herpesvirus 8* (HHV-8). Classically contracted via contact with infected bodily fluids (i.e., sexual contact, blood transfusions, saliva), HHV-8 can also be transmitted via organ transplantation (Operskalski 2012; Ariza-Heredia and Razonable 2011). Thought to traditionally be an AIDS-defining malignancy, Kaposi sarcoma is now also recognized as a complication of post-transplant immunosuppression. In a cohort of approximately 100 solid organ transplant recipients, the rates of HHV-8 seropositivity were significantly higher than in general population (20.9% vs. 9.9%, $p < 0.05$) (Jenkins et al. 2002). The prevalence of Kaposi sarcoma in the solid organ transplant population depends greatly on the region, coinciding with the varying rates of endemic HHV-8 infection, and can range from <1% in non-endemic areas such as the United States, France, and Spain to 3–4% in areas with higher HHV-8 infection rates such as Italy and South Africa (Garcia-Astudillo and Leyva-Cobian 2006; Bergallo et al. 2007; Moosa 2005; Jenkins et al. 2002). Risk factors associated with development of KS, aside from geographic location, appear to be age at time of transplant and male sex (Mbulaiteye and Engels 2006). The risks associated with the specific type and the intensity of immunosuppressive agents are less clear (Tessari et al. 2006).

The mainstay treatment of KS in the post-transplant patient is targeting lower immunosuppression levels. There is also evidence that switching immunosuppressive strategies may have some benefit. For instance, switching cyclosporine to sirolimus has been shown to have some effectiveness in treatment of dermal KS in renal transplant patients (Stallone et al. 2005). In advanced cases that do not respond to immunosuppression reduction or medication change, combination chemotherapy, with either CHOP or paclitaxel, might be efficacious (Shepherd et al. 1997; Brambilla et al. 2008).

Skin Cancer

Akin to the general US population, skin cancers are the most common types of malignancy found in the post-transplant population. However, the different subtypes of skin cancer occur with different frequency within the transplant population.

Whereas basal cell carcinoma (BCC) is the most common form of skin cancer in the general population, squamous cell carcinoma (SCC) is most commonly seen in the transplant population. In a study of nearly 300 heart transplant patients from 1985 to 1996, 41 of them developed SCC or BCC; 90% of these lesions were SCC (Lampros et al. 1998). Other studies have demonstrated ratios of SCC:BCC ranged from 1.43:1 to 3:1 (Caforio et al. 2000; Ong et al. 1999). Incidence rates of both these cancers are significantly elevated compared to the general population, with SCC having a rate of 8.5 cases per 1000 person years and BCC having a rate of 5.2 per 1000 years (Molina et al. 2010).

The incidence of melanoma also increases in the post-transplant population. A meta-analysis of 12 studies examining all types of solid organ transplant found a 2.4-fold increase in the incidence of melanoma (Dahlke et al. 2014). In those with heart transplants, the rate of melanoma is over two times higher than that in the general population (Collett et al. 2010; Jiang et al. 2010; Engels et al. 2011). It is important to note that the rates of all three types of skin cancer are magnified in patients with independent risk factors for skin cancer, such as those patients with light skin, blue hair, blonde eyes, and sun exposure (Berg and Otley 2002).

As discussed earlier in this chapter, immunosuppressive medications appear to play a significant role in the development of hematologic malignancy post-transplant. The majority of studies show that immunosuppression appears to be a risk factor for development of skin malignancies as well. The relative risk of developing either BCC or SCC with the use of azathioprine was 1.8 (95% CI: 1.2–2.7] (Molina et al. 2010). In contrast, this same cohort suggested that mycophenolate mofetil may be somewhat protective, with a relative risk of 0.3 (95% CI: 0.2–0.6), whereas CNI use was not associated with a significant change in overall risk. Cumulative immunosuppressive drug dose, however, seems to be an independent risk factor, with patients receiving higher cumulative doses of a combination of azathioprine, cyclosporine, and corticosteroids being at an increased risk for SCC (HR 4.0, 95% CI: 1.4–11.4; $p = 0.008$), though not for BCC (Fortina et al. 2004). Other cohorts have shown that patients receiving higher immunosuppression doses had a relative risk of 5.7 ($p = 0.003$) for developing skin cancer when compared to those with lower goals (Caforio et al. 2000). While not an immunosuppressive agent, voriconazole, another medication sometimes used post-transplant, may lead to an increased risk of SCC [HR 2.1, $p = 0.04$] (Vadnerkar et al. 2010). This is thought to be due to voriconazole causing photosensitivity, leading to increased DNA damage by UV light (Epaulard et al. 2011; Ona and Oh 2015).

Nearly all studies examining risk factors for skin cancer development post-transplant find that age at time of transplant and cumulative sun exposure are major contributing factors. On multivariable analysis of 230 heart transplant recipients, 21% of whom developed non-melanoma skin cancer (NMSC); age at time of transplant was the most significant risk factor. Patients older than 59 years of age at time of transplant had a relative risk of 36.2 (95% CI: 4.1–314.9; $p < 0.001$) for developing SCC compared to those younger than 43 years old (Fortina

et al. 2004). Cumulative sun exposure (HR 7.6, 95% CI: 2.5–22.8) and residing in an areas with high sun exposure have also been associated with an increased risk of SCC in patients with solid organ transplants (HR 3.8, $p = 0.0004$) (Vadnerkar et al. 2010; Caforio et al. 2000).

There is also a higher risk for developing skin malignancies on the sun-exposed areas of the body. A study of 172 post solid organ transplant patients with 325 NMSCs and 6 malignant melanomas showed that, when broken down by location, the highest risk portions of the body were the upper extremities (Lindelof et al. 2000). A patient's skin tone and type is also a risk factor, as it is the general population. Transplant recipients with sun-sensitive skin (burn easily, tan minimally) have a significantly increased risk of developing BCC compared to those with less sun-sensitive skin types (RR 5.7, 95% CI: 2.0–16.6; $p = 0.001$) (Fortina et al. 2004). These studies suggest that despite the unique risks faced by transplant patients, sun protection remains an important strategy to prevent skin cancer development.

Despite the above data, it remains inconclusive as to whether the occurrence of NMSC post-transplant affects overall survival. Fortunately, the majority of skin cancers found post-transplant are either BCC or SCC, both of which are easily detected and treated. As such, they have had minimal impact on mortality irrespective of their increased incidence (Sánchez-Lázaro et al. 2010). However, melanoma is an important exception. Unlike the more benign NMSC, melanoma portends a poorer prognosis. Transplant patients with melanoma have been shown to have worse 5-year survival rates compared to the general population (Dinh and Chong 2007). While there does not appear to be a significant difference in the histopathology of post-transplant melanomas as compared to those in the general population, organ transplant recipients do worse with the more invasive, thicker lesions than non-transplant patients (Matin et al. 2008; Brewer et al. 2011). This emphasizes the importance of regular skin checks and aggressive management of suspicious lesions in the post heart transplant patient.

Solid Organ Tumors

In addition to the hematologic and dermatologic malignancies described above, solid organ tumors are also encountered with increased frequency in the post-transplant population. While the exact risk of developing a solid organ tumor post-transplant remains unclear, currently available data suggests it is lower than the risk of developing skin cancer(s) and/or lymphomas.

Data from the United Kingdom Transplant Registry shows that rate of de novo malignancies of all types is about two times that of the general population, while a Swedish nationwide cohort demonstrated a four times higher than normal risk (Collett et al. 2010; Adami et al. 2003). This increased risk held true for both sexes and all age groups. When the patients in the UK cohort were stratified by which organ was transplanted, heart transplant patients (SIR 2.5, 95% CI: 2.2–2.7) were observed to have a risk comparable to those of their renal (SIR 2.4, 95% CI: 2.3–2.5) and hepatic (SIR 2.2, 95% CI: 2.0–2.4) counterparts; pulmonary transplant patients, on the other hand, had an increased risk compared to the other subgroups (SIR 3.6, 95% CI: 3.0–4.4) (Collett et al. 2010).

A Canadian series of heart transplant patients also demonstrated an increase in incidence of solid organ malignancy post-transplant (Jiang et al. 2010). Significantly increased incidence rates were seen in oral cancer (HR 4.3, 95% CI: 2.1–8.0) and lung cancer (HR 2.0, 95% CI: 1.2–3.0) specifically. Breast, prostate, colorectal, and kidney malignancies were not significantly increased compared to the general population. In heart transplant patients, UK registry data show significantly elevated risk for oral cavity cancers (SIR 5.0, 95% CI: 2.2–9.8), anal cancers (SIR 7.5, 95% CI: 1.6–21.9), kidney cancer (SIR 4.4, 95% CI: 2.5–7.0), and lung/bronchial cancers (SIR 2.1, 95% CI: 1.6–2.8); in contrast, the rates of breast, colorectal, and liver malignancies remained comparable to the general population (Collett et al. 2010). Specific demographic or comorbid factors such as older age at time of transplant, male gender, and a personal history of malignancy have

been identified as independent risk factors for development of solid organ tumors after transplant (Tenderich et al. 2001).

Pulmonary Malignancies. Transplant recipients consistently appear to be at an increased risk of lung cancer. Most commonly, there appears to be an excess risk of bronchogenic carcinoma, with squamous cell carcinoma being more common than adenocarcinoma in most series (Anyanwu et al. 2002; Dorent et al. 2000). From the UNOS database, the incidence of lung cancer post-transplant across all types of solid organ transplant was 173.4 per 1000 person years, compared to 88.1 for the general population ($p < 0.0001$) (Engels et al. 2011). Heart transplant patients specifically were found to have a SIR of 2.67 (95% CI: 2.40–2.95). In fact, the highest individual incidence of solid organ malignancy in the post heart transplant patient is lung cancer (3.24 cases per 1000 patient years) (Sampaio et al. 2012a).

Gastrointestinal Malignancies. Multiple types of malignancies can plaque the alimentary canal, and the risk of developing a GI malignancy post-transplant appears to vary depending on the type of malignancy. For instance, a study including all types of solid organ transplants showed that the risk of developing esophageal (SIR 1.56, 95% CI: 1.26–1.95), small intestine (2.43, 1.80–3.20), pancreatic (1.46, 1.24–1.71), colorectal (1.24, 1.15–1.34), and biliary (2.00, 1.25–3.02) cancers was increased in post-transplant patients as compared to the general population (Engels et al. 2011). Another analysis, from the UNOS database, suggests that the incidence of GI malignancies post heart transplant is 2.5–3.0 times that of the general population (Sampaio et al. 2012a; Engels et al. 2011).

A rare but important GI malignancy to note is the *Helicobacter pylori*-associated lymphoid malignancy known as mucosa-associated lymphoid tissue lymphoma (MALTOMA). MALTOMAs are rare in the general population but may be increased in the transplant population (Aull et al. 2003; Shehab et al. 2001). However, these tend to be low-grade and treatable with decreased immunosuppression and antibiotic therapy for *H. pylori*.

Oral Malignancies. Oral cancers are rare in the general population; however post-transplant patients appear to be particularly susceptible to these malignancies. In the US transplant population, oropharyngeal (SIR 2.01, 95% CI: 1.64–2.43) and lip cancer (SIR 1.97, 95% CI: 1.86–2.08) are diagnosed twice as frequently as in the general population (Engels et al. 2011). This increased risk may be even higher in heart transplant recipients. The United Kingdom Transplant Registry showed that oral cancer was five times more likely to occur in heart transplant patients than non-transplant patients (Collett et al. 2010). In general, oral cancers in the transplant population are disproportionately squamous cell carcinoma and are managed by local resection of the tumor.

Genitourinary Malignancies. The GU system also appears to have a higher risk for development of malignancy post-transplant. In the US transplant population, bladder (SIR 1.52, 95% CI: 1.33–1.73), penile (SIR 4.13, 95% CI: 2.59–6.26), vulvar (SIR 7.60, 95% CI: 5.77–9.83), and testicular (SIR 1.96, 95% CI: 1.40–2.67) cancer all occur at increased rates compared to the general population (Engels et al. 2011). In heart transplant patients specifically, the incidence of GU malignancies as a whole is approximately 4.8 per 1000 patient years, higher than that of the general population (Sampaio et al. 2012a). Renal cancer also occurs at a higher rate in the OHT population, with an incidence about 1.8 times that of the general population (Engels et al. 2011).

Transmission from Donor to Recipient

During the early days of transplant, transplant from donors with cancer was more common than the modern era. Donor transmission of cancer to a recipient has been described in the heart transplant patient, with particularly high risk seen in organs coming from donor-derived malignancies with high metastatic potential such as melanoma (Buell et al. 2001). It should be emphasized, however, that the absolute risk of malignancy transmission is likely low. In a study of renal transplant

patients, the donor-related tumor rates were less than 1%, and the death rate due to transmitted malignancy was minimal compared to the waiting list mortality (Myron Kauffman et al. 2002). Similarly, a series in the United Kingdom showed a donor-related cancer rate of less than 1%, though those that did develop donor-related malignancies had poor outcomes (Desai et al. 2012).

Review of the data in the UNOS database has led to guidelines for the use of organs from patients with known malignancy, based on their risk (Nalesnik et al. 2011). Benign tumors such as angiomyolipomas of the kidney or adenomas of the GI tract are considered to carry no significant risk of transmission, while tumors such as SCC of the skin without metastases or vocal cord carcinomas are considered minimal risk (<0.1% risk of transmission). However, any malignancy with a greater than 1% risk of transmission to the recipient, such as colon carcinomas, CNS malignancies, or malignant melanomas, are considered to have an intermediate to high risk of transmission; organs from these donors generally should not be considered for use.

While this is the current standard, given the need to increase the donor pool, there has been some study of the outcomes of patients receiving organs from high-risk donors. In the United Kingdom, a study of over 100 transplant recipients who received organs from donors with malignancies considered high risk for transmission showed that there was no significantly increased hazard for death compared to those who received organs from standard-risk donors (Desai et al. 2014). Specifically in heart transplant recipients, the hazard ratio was 0.73 (95% CI: 0.17–3.18). In general, potential donors with malignancies carrying good prognosis (5- or 10-year disease-free survival of greater than 90%) are likely reasonable candidates for organ donation (Nalesnik et al. 2011).

Screening for Malignancy

Data on the effectiveness of screening for malignancies in the post-transplant population are lacking. In renal transplant patients, there are recommendations for increased screening for cervical, breast, colorectal, and renal cancers (Chapman et al. 2013). However, there is little evidence guiding the relative utility and the frequency of malignancy screening (O'Neill et al. 2006). As such, the current recommendations for screening for malignancy in the post heart transplant patient remain similar to those for the general population, with the important caveat of yearly skin exams and aggressive education on skin cancer prevention methods. As further longitudinal data becomes available, there will hopefully be more definitive answers on screening for and management of malignancy post-transplant to help patients achieve the better outcomes.

Conclusion

The risk of developing malignancy in heart transplant recipients is higher than the general population. This is likely due to a wide variety of factors, but the evidence suggests that immunosuppression uniquely places transplant recipients at a heightened malignancy risk. This translates into an increased incidence of a spectrum of malignancies, including both virus-associated malignancies and solid organ tumors. Although current screening for and treatment of malignancy in transplant recipients are similar to the general population, continued efforts for better targeted strategies to mitigate this risk are needed.

Cross-References

- ▶ Advances in Immunosuppression
- ▶ Contemporary Survival in Heart Transplantation
- ▶ Chronic Immunosuppression Medications
- ▶ Induction and Maintenance Agents
- ▶ Infection Prophylaxis

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Part XIII

Future of Heart Transplantation

Advances in Immunosuppression

28

Edward Horn and Moses Demehin

Contents

Abstract

Immunosuppression in heart transplantation has been managed with a roughly unchanged milieu of therapy over the last decade. In order to continue the advancement of long-term patient outcomes, new therapeutic options should be explored that have enhanced efficacy or reduced toxicity over current agents as well as better ways to monitor current

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therapeutic options. Additionally, there has been an increased interest in modulating antibody production as a result of increased insight and experience in treating antibody-mediated rejection (AMR). This has also afforded the opportunity to explore novel therapy in patients with either AMR or elevated panel reactive antibodies prior to transplant. In this chapter, advances in maintenance therapy will be discussed including delayed-release tacrolimus, elevating the role of mammalian target of rapamycin (mTOR) inhibitors, and novel targets. Discussion of a wide variety of agents in development is also included, with a focus on effects on antibody production.

Keywords

Desensitization · mTOR inhibitors · Proteasome · JAK inhibitor · Complement

Introduction

Although calcineurin inhibitors (CNI), antimetabolites, and mammalian target of rapamycin (mTOR) inhibitors significantly improved allograft and patient survival, several unmet needs still exist in the field of immunosuppression. While current therapy is efficacious at promoting excellent short-term outcomes, further research is needed to evaluate new strategies to promote enhanced long-term survival. Additionally, the current armamentarium of immunosuppressive agents carries well-known adverse effects that can further impede long-term survival, including metabolic effects (hypertension, hyperlipidemia, etc.), malignancy, and end-organ damage. According to ISHLT registry data, long-term cardiac allograft survival has a median of roughly 12 years (Lund et al. 2017). In patients with >10 years of survival, the overall frequency of malignancy is almost doubled for patients with 5 years of survival (27.7% vs. 15.9%, respectively). The frequency of cardiac allograft vasculopathy (CAV) also remains a troublesome long-term complication. Newer therapies are needed that decrease these risks and mitigate antibody-mediated allograft injury (Stegall et al. 2016). One of the major barriers to development of new therapies is the lack of novel biomarkers for use as surrogate endpoints. Most studies focus on short-term allograft and patient survival, incidence of biopsy-proven acute rejection, and safety endpoints. Although these endpoints have proven useful, they do not provide a complete picture especially since short-term outcomes have improved significantly. Moving forward, well-designed, large clinical studies would be helpful in determining optimum regimens with good long-term follow-up.

This chapter will focus on updates to current therapies, novel agents under development, potential targets for improved monitoring and decision-making, and the overall direction of transplant pharmacotherapy. It is important to note that majority of the data reviewed will be in non-cardiac allograft recipients and application to cardiac transplantation is, at best, extrapolated.

Current Maintenance Therapy

Since the introduction of cyclosporine in the 1980s and subsequently tacrolimus in the early 1990s, calcineurin inhibitors ushered in an era of significant improvements in allograft and patient survival. Calcineurin inhibitors in combination with antiproliferatives (mycophenolate mofetil, azathioprine), low-dose corticosteroids, or mTOR inhibitors (sirolimus, everolimus) have since become standard of care. This success, however, has been at the expense of associated adverse effects particularly nephrotoxicity, neurotoxicity, and metabolic side effects that predispose recipients to cardiovascular and cerebrovascular disease. Novel maintenance therapy aimed at improved long-term outcomes with better adverse effect profile is needed. This section will focus on the updates to current agents used as maintenance therapy (Table 1).

Tacrolimus

One of the more notable developments in maintenance immunosuppression is the introduction of

Table 1 Summary of current therapies

Drug	Class	Mechanism of action	Therapeutic drug monitoring	Comments
Cyclosporine	Calcineurin inhibitors (CNIs)	Binds to cyclophilin; complex inhibits calcineurin, IL-2-driven T-cell activation	C2 levels or C0 levels	**Toxicities**: nephrotoxicity, hypertension, gingival hyperplasia, hirsutism, lower incidence of neurotoxicity **Role**: second-line CNI, intolerance to tacrolimus
Tacrolimus (FK506)		Binds to FKBP12; complex inhibits calcineurin, IL-2-mediated T-cell activation	C0 levels, trough goal varies depending on risk of rejection, organ, time from transplant, and adjunctive therapy utilized (i.e., antimetabolites vs. PSIs)	**Toxicities**: similar to cyclosporine except more neurotoxicity, new-onset diabetes mellitus, alopecia, less hypertension **Updates**: two novel once-daily, extended-release formulations; LCP-tacrolimus and tacrolimus ER. LCP-tacrolimus utilizes MeltDose® technology that improves bioavailability and peak-to-trough ratio **Role**: first-line maintenance agent in combination with antimetabolites or proliferation signal inhibitors; potential role for LCP-tacrolimus in neurotoxicity
Sirolimus (rapamycin)	Proliferation signal inhibitor	Binds to FKBP12; complex inhibits mammalian target of rapamycin and IL-2-mediated T-cell activation	C0 levels, goal varies depending on monotherapy, combination with antimetabolites, or combination with CNIs	**Toxicities**: hyperlipidemia, thrombocytopenia, hepatic artery thrombosis, delayed wound healing, mouth ulcers, pneumonitis **Role**: cardiac allograft vasculopathy, malignancy, and CMV viremia
Everolimus	Proliferation signal inhibitor	Derivative of sirolimus with similar mechanism of action		
Belatacept	Costimulation inhibitor	Binds to B7 (CD80 and CD86) receptors on antigen-presenting cells and prevents binding to CD28 on T cell which inhibits costimulation	None	**Toxicities**: high rate of rejection, PTLD (in EBV-seronegative patients), peripheral edema, hypertension, hyperkalemia, hypokalemia **Updates**: renal function remained stable at 7 years and similar graft loss in comparison to cyclosporine **Role**: used as backbone in patients intolerant to CNI, combination with low-dose CNI for renal sparing

CNI calcineurin inhibitors, *CMV* cytomegalovirus, *PTLD* posttransplant lymphoproliferative disease

extended-release once-daily tacrolimus formulations. Currently, two extended-release formations exist – tacrolimus ER (Astagraf XL, Advagraf XL, Astellas) and LCP-tacrolimus (Envarsus XR, Veloxis). Although both formulations are dosed once daily, important differences in their formulations impact their pharmacokinetic profiles. Tacrolimus ER was developed by the addition of ethyl cellulose which slows down the diffusion rate of tacrolimus, thereby providing the prolonged release and half-life (Astragraf 2015). In contrast, LCP-tacrolimus uses a MeltDose® technology which reduces tacrolimus particle size and decreases surface area of the drug particles, thereby translating to improved solubility and bioavailability. This improvement is notable as the recommended conversion to LCP-tacrolimus is 80% of total daily dose of the immediate-release formulation (Envarsus 2017). Additionally, LCP-tacrolimus is associated with less fluctuation between peak exposure and trough concentrations, and both formulations have demonstrated noninferiority when compared with immediate-release tacrolimus. Applications for extended-release formation theoretically range from improved compliance to potential reduction in neurotoxicity. In a recent phase IIIb trial, the effect of switching stable renal transplant recipients from immediate-release to LCP-tacrolimus on tremor was studied. Thirty-eight patients were converted to LCP-tacrolimus and improvement in tremor was studied using the Fahn-Tolosa-Marin (FTM) scale, an accelerometry device, and the quality of life in essential tremor (QUEST). 78% of patients reported improvement following the switch and statistically significant reduction in FTM score as well as the accelerometer were noted (Langone 2015).

Proliferation Signal Inhibitors (mTOR Inhibitors)

The two mammalian targets of rapamycin inhibitors, sirolimus and everolimus, were introduced in 1999 and 2009, respectively. Following the advent, it was thought that these agents would replace calcineurin inhibitors and mitigate the metabolic adverse events as well as the nephrotoxicity. Unfortunately, studies have shown inferior outcomes with sirolimus as evidenced by overall higher acute rejection rates in CNI withdrawal and sparing regimens substituted with sirolimus in comparison with CNI standard of therapy (ORION, ELITE-SYMPHONY). The renal-sparing effect of sirolimus was evaluated in a randomized controlled trial in cardiac allograft recipients. Patients 1–8 years posttransplantation with mild to moderate renal impairment were either maintained on CNI-containing regimens or converted to sirolimus-based regimens. Although the mean change in creatinine clearance was significantly higher in the sirolimus arm, acute rejection associated with hemodynamic compromise and higher discontinuation rate attributable to adverse effects were also common in the sirolimus arm (Zuckermann et al. 2012). Post hoc analysis of the same cohort was conducted to determine predictors of renal function response and risk factors for acute rejection. The findings showed mycophenolate doses less than 1000 mg daily and preexisting diabetes were predictors for acute rejection and decreased renal function. It was therefore concluded that sirolimus-based therapy is an option for improving renal function in patients without preexisting diabetes and on optimal mycophenolate doses (Zuckermann et al. 2014). Additionally, delayed wound healing, proteinuria, and hyperlipidemia were more frequent in the sirolimus group. Interestingly, mTOR inhibitors are associated with lower CMV infection rates, but the utility of this property warrants further investigation (Andrassy et al. 2012). Antiproliferatives have also been shown to reduce the incidence of cardiac allograft vasculopathy (Kaczmarek et al. 2013; Mancini et al. 2003). In an open-label, prospective, randomized study of patients with documented cardiac allograft vasculopathy (CAV), a subset of patients was allotted to receive sirolimus in comparison to standard of care. It was concluded that the use of sirolimus slowed the progression of CAV and the mechanism was unlikely to be related to B-cell suppression due to lack of differences in antibody production between both groups (Mancini et al. 2003).

Another large randomized, double-blind trial ($n = 634$) compared everolimus in combination with cyclosporine to azathioprine. Everolimus was more efficacious than azathioprine in reducing incidence of CAV (Eisen et al. 2003). Furthermore, given that increased incidence of posttransplant malignancy particularly skin cancers and the fact that the mTOR pathway has been implicated in progression of malignancies, proliferation signal inhibitors may play a role in risk reduction (Karia et al. 2016).

Belatacept

Belatacept, which was also designed with hopes of providing similar efficacy to calcineurin inhibitors without the associated nephrotoxicity, is a selective costimulation blocker exerts its effects by inhibiting signal 2 of T-cell activation. Since its approval in 2011, belatacept has been received with mixed reservations and is yet to find its niche due to the high risk of rejection and post-transplant lymphoproliferative disease (PTLD).

As hypothesized, the BENEFIT study, which compared belatacept to cyclosporine in renal transplant recipients, demonstrated superior renal function in the belatacept group but higher early rejection rates. Patient and graft survival at 12 months were however similar between both groups. Interestingly, belatacept groups demonstrated lower donor-specific antibody (DSA) formation rate (Vincenti et al. 2010). The BENEFIT-EXT study was restricted to recipients from extended criteria donor or cold ischemia times over 24 h (Durrbach et al. 2010). This study found 36-month rate of acute rejection, graft loss, and treatment failure was similar across all groups. Furthermore, 7-year results and post hoc analysis of the BENEFIT-EXT study showed similar time to death or graft loss between the belatacept and cyclosporine group. Estimated mean GFR increased for the belatacept group but declined in the cyclosporine group (Florman et al. 2017).

The role for belatacept in the future will be determined by identifying subpopulations that may benefit from utilizing this medication. To this end, several case studies and case series utilizing modified dosing regimens presented findings worth mentioning. A recent retrospective study reported the outcomes of conversion from tacrolimus to belatacept in high immunologic renal allograft recipient. In contrast to the BENEFIT studies, the authors included six high-risk patients defined as cPRA >80%, retransplantation, positive crossmatch at time of transplantation, and history of antibody-mediated rejection less than 3 months before the switch. Renal function improved with peak eGFR pre and post switch reported as 23.8 ± 12.9 ml/min/1.73 m^2 and 42 ± 12.5 ml/min/1.73 m^2, respectively. Additionally, two recipients on HD due to prolonged delayed graft function had renal recovery. Finally, overall biopsy findings improved post conversion to belatacept (Gupta et al. 2015). In the largest single-center, retrospective data to date, Adams and colleagues compared a modified belatacept regimen with a matched control group on standard tacrolimus-based maintenance regimen in kidney allograft recipients. Given the increased risk of early rejection seen in the BENEFIT studies, the group developed a modified belatacept-based regimen in combination with transient calcineurin inhibitor. Three tacrolimus groups with different trough goals and weaning duration were utilized: bela/tac short with trough goal of 8–12 ng/ml weaned off after 3 months; bela/tac extended A with trough goals 8–12 ng/ml in 3 months, 5–8 ng/ml until 6-month post-op, and 3–5 ng/ml until 9-month mark at which point tacrolimus weaning began; and lastly bela/tac extended B with trough goals 8–12 ng/ml in the first month, 5–8 ng/ml until the 6-month mark, and 3–5 ng/ml until the 9-month mark where tacrolimus weaning began. In addition to belatacept, all patients received mycophenolate mofetil 1000 mg BID and maintenance prednisone. Results showed comparable overall short-term patient and graft survival as well as improved renal function with belatacept similar to previous studies. Higher rejection rates were seen in the group modeled after the BENEFIT regimen in comparison to the historical tacrolimus cohort at 12 months (50.5% vs. 20.5%). Bela/tac short group experienced higher

rejection rates versus historical tacrolimus cohort at 12 months (33/3% vs. 20.5%) but better in comparison to the low-intensity group modeled after the BENEFIT regimen. Finally, rates of acute rejection in the extended tacrolimus-belatacept regimen were similar to those seen in the historical belatacept regimen (16% vs. 20.5%). It was thereby concluded that the addition of a transient tacrolimus course to belatacept produces comparable rates of rejects and confers renal protection benefits (Adams et al. 2017).

Reported use of belatacept in cardiac transplantation is limited to one case study thus far. Briefly, a 26-year-old female heart transplant recipient secondary to postpartum cardiomyopathy was found to have erratic tacrolimus levels with raised concerns for noncompliance. The patient was noted to have several episodes of mild to moderate rejection and eventually severe grade 3R rejection with decreased ejection fraction. Following several treatments for rejection including photopheresis, high-dose methylprednisolone, addition of sirolimus, plasmapheresis, and alemtuzumab, belatacept was initiated in addition to her maintenance regimen of tacrolimus, sirolimus, mycophenolate mofetil, and prednisone. While on belatacept, both tacrolimus and sirolimus levels fluctuated and were often undetectable, biopsies remained grade 0, and echocardiography revealed normal ejection fraction. The patient expired 7 months after belatacept was initiated, but an autopsy was not performed (Enderby et al. 2014). Further evaluation of its effect is warranted before discussing broader use in heart transplant recipients.

Monitoring Advancements with Current Pharmacologic Options

Pharmacogenetics

Years ago, pharmacogenetics was predicted to revolutionize pharmacotherapy. Individualized medicine based on genetic profiling and anticipated effect of single nuclear polymorphisms (SNPs) on drug metabolism however has yet to become mainstay for most therapies. The initial limiting factors were cost and time required to genotype, but these tests are now affordable and readily available. Given that calcineurin inhibitors and mTOR inhibitors are metabolized by CYP enzymes, the most relevant polymorphism in the field of transplantation is in the CYP3A subfamily. Cyclosporine and tacrolimus are both substrates of CYP3A4, CYP3A5, and P-glycoprotein (ABCB1) efflux pump. Interpatient variability occurs due to difference in expression as well as mutations in the genes encoding these enzymes (Staatz et al. 2010).

Interestingly, it has been reported that race plays a role in these polymorphisms which results in varied dose requirements between white and black allograft recipients. The loss-of-function allele CYP3A5∗3, which is the major allele in whites, has been identified as a major determinant of variation in tacrolimus metabolism due to reduction in activity which results in higher drug concentrations. The loss of activity results from alternate splicing of the third intron of the CYP3A5 gene which leads to an out-of-frame mRNA variant that codes for a nonfunctional protein. Conversely, persons with CYP3A5∗1 allele metabolize tacrolimus rapidly resulting in overall lower whole blood concentrations and higher dose requirements. Additionally, a recent genomewide association study of tacrolimus trough in black kidney allograft recipients identified two novel CYP3A5 variants that were associated with tacrolimus troughs. The two loss-of-function alleles CYP3A5∗6 and CYP3A5∗7 were found to play significant roles in tacrolimus metabolism (Oetting et al. 2016).

The role of CYP3A5 genotype on dose requirement of tacrolimus and everolimus was evaluated in white cardiac allograft recipients by Kniepeiss and colleagues. In this study, 15 patients received tacrolimus-based regimens, whereas 30 patients received everolimus-based regimens. Thirteen subjects in the tacrolimus group were CYP3A5 non-expressers, i.e., homozygous for ∗3 allele, whereas two were heterozygous expressers. When compared, average tacrolimus dose requirement was significantly higher in the expressers. In the everolimus group, 27 patients were homozygous for ∗3 allele, and 3 were

heterozygous. Interestingly, there was no significant difference in dose or levels between expressers and non-expressers. It was thereby concluded that CYP3A5 polymorphism affects tacrolimus dose requirement but the same influence is not seen with everolimus (Kniepeiss et al. 2011). Most recently, the impact of CYP3A5 genotype on extended-release formulation of tacrolimus (LCP) was studied in 50 black renal allograft recipients. Eighty percent were CYP3A5 expressers, and there were no significant differences in AUC between expressers with immediate-release and LCP-tacrolimus. Interestingly, Cmax was 33% higher with the immediate-release formulation in CYP3A5 expressers in comparison to 11% higher with LCP-tacrolimus. It was concluded that this difference in peak could theoretically reduce peak-related toxicities (Trofe-Clark et al. 2017).

In conclusion, determination of CYP3A5 polymorphism in combination with therapeutic drug monitoring potentially reduces time to therapeutic levels (MacPhee et al. 2004). The clinical benefit in terms of allograft function and rejection of this strategy however is yet to be established.

Immune Cell Function Monitoring

Immune cell function monitoring, FDA approved in 2002, takes a unique approach to monitoring patients on immunosuppressive regimens. This assay, commercially known as ImmuKnow, utilizes lymphocyte activation to ascertain a net state of immune function. Lymphocytes are stimulated with phytohemagglutinin (PHA), thus resulting in an increase in cellular energy supply and utilization. This assay then determines the amount of intracellular adenosine triphosphate (ATP) in lymphocytes upon activation. Given that CD4 cells are the target for major immunosuppressive drugs like cyclosporine and tacrolimus, this cell line was chosen by investigators to undergo ATP measurements (Kowalski et al. 2003).

Kowalski and colleagues evaluated this monitoring modality in 127 transplant patients (compared with healthy individuals) to attempt to determine if breakpoints exist where patients may be over- or under immunosuppressed. Patients were determined to have a "low immune response" if ATP levels were $\leq$225 ng/ml, whereas "strong immune response" was defined as ATP levels $\geq$525 ng/ml; 94% of healthy volunteers had values $\geq$225 ng/ml versus 92% of transplant patients had values $\leq$525 ng/ml. When patients were analyzed depending on the immunosuppressant used, there was no difference in ATP levels between patients treated with cyclosporine versus tacrolimus. The authors did note that drug levels did not correlate with ATP levels, citing the importance of assessing overall immune function not just readily available therapeutic drug monitoring (Kowalski et al. 2003).

Kobashigawa and colleagues evaluated the clinical utility of this assay in heart transplantation in a single-center study (Kobashigawa et al. 2010). Patients had ATP assays ranging from 1 month to 10 years after transplant and were treated with tacrolimus, mycophenolate, and corticosteroid without induction therapy. The authors' goal was to determine if breakpoints existed to identify patients at risk for either infection or rejection based upon their ATP results. Patients that developed infections had a statically lower ATP level than patients at steady state without infections (187 ± 126 ng ATP/ml vs. 280 ± 126 ng ATP/ml, $p < 0.001$). There was no difference in mean ATP levels in steady-state patients versus those with rejection, but this could have been due to the low frequency of rejection overall in this study population. These results with respect to infection were consistent with what has been reported in other trials (Kowalski 2006; Thai et al. 2006).

Immune function monitoring has had more recent data published examining its utility in the management of transplant patients. Ben Gal and colleagues evaluated immune monitoring (IM) in 34 heart transplant recipients managed with everolimus-based immunosuppression (Ben Gal et al. 2014). Patients had a wide variance in follow-up periods, with samples being drawn at 1 week after transplant. ATP levels obtained during infection episodes were significantly lower when compared to patients who were not infected

(188 ± 122 ng/ml vs. 338 ± 137 ng/ml; $p < 0.05$). Again, there was no difference in values between patients with and without rejection.

Ravaioli and colleagues evaluated immune function monitoring in a novel way by using it to aid in adjusting tacrolimus levels in liver transplant recipients (Ravaioli et al. 2015). Liver transplant recipients from July 2008 to March 2013 were randomized to standard care ($n = 102$) described as tacrolimus-based immunosuppression with oral steroids. Goal tacrolimus levels for standard care were 8–12 ng/ml for the first 4 months and 6–10 ng/ml thereafter. Patients who had therapy guided by immune function monitoring had goal tacrolimus levels reduced by 25% when ATP levels <130 ng/ml and increased by 25% when ATP levels were >450 ng/ml ($n = 100$). Patient survival was higher at 12 months in the intervention group (89% vs. 80%, $p < 0.05$). Additionally, patients managed with immune function monitoring had less infection episodes (42% vs. 56%, $p < 0.05$). Rejection episodes were not different between groups. The authors concluded that goal-level adjustments with the immune function assay were beneficial in this patient population by providing additional data on the net state of immunosuppression.

Immune function monitoring can be of assistance in patients at risk for infectious complications, especially in a low-rejection risk patient population. Results from clinical trials have not shown the same benefit with respect to rejection reduction. This is mostly due to low rejection numbers in these reports. Immune function monitoring does provide additional information with respect to the net state of immunosuppression that cannot be ascertained by drug-level monitoring alone. Use of these advanced monitoring techniques, as well as pharmacogenomics analysis, can help transplant centers manage patients in a more precise fashion. Pharmacogenomics can assist in determining upfront dosing strategies by identifying metabolic differences among patients. When immune function monitoring is utilized to guide traditional therapeutic drug monitoring strategies, it appears that we can reduce infectious complications of transplantation which is a major obstacle to avoid in providing successful outcomes in this patient population.

Investigational Agents for Maintenance Immunosuppression

ASKP1240

Blocking the CD40–CD40 ligand (CD154) interaction has been of particular interest for immunosuppression. Early clinical trials with several humanized monoclonal antibodies targeting CD150 were halted due to thromboembolic events caused by platelet aggregation, either directly related to the monoclonal antibody itself or the potential instability of thrombi regulated by soluble CD154. Consequently, inhibition of the CD40 receptor was postulated to be an alternative that would avoid the thromboembolic events. This has led to the development of the costimulation inhibitor ASKP1240, which blocks CD40 receptor, with hopes of bridging the current gaps in immunosuppression (Okimura et al. 2014) (Table 2).

In a phase Ib study, the efficacy and safety of ASKP1240 were evaluated in 138 renal transplant recipients stratified to either a calcineurin-free regimen containing solely of the study drug and MMF ($n = 46$) versus study drug in combination with reduced-intensity tacrolimus ($n = 44$) versus standard of care which comprised of tacrolimus and MMF ($n = 48$). With respect to safety, none of the subjects experienced thromboembolic events or PTLD; however, three patients developed malignancies, and higher rates of viral infections were reported in the study group. It was concluded that ASKP1240 in combination with reduced-intensity tacrolimus attained similar efficacy at 6 months, while similar efficacy was not achieved in the ASKP1240 + MMF group (Harland et al. 2015). Given the limited efficacy as backbone immunosuppression and increased incidence of viral infections, the utility, as well as the future, of ASKP1240 remains unclear. CFZ533 is another antiCD40 fully human monoclonal antibody that is currently being evaluated for safety and efficacy (NCT02217410).

Table 2 Emerging immunosuppressants currently in development phase

Drug	Class	Mechanism of action	Place in therapy	Comments
ASKP1240	Costimulation (CD40–CD154) inhibitor	Inhibits humoral and cellular immune responses by blocking the CD40/CD154 interaction between antigen-presenting cells and T cells	Maintenance	Similar efficacy outcomes at 6 months when combined with low-dose tacrolimus but inferior when combined with MMF
Tofacitinib	Janus kinase inhibitor	Inhibits JAK/signal and transducers and activators of transcription which prevents T-cell proliferation	Maintenance	Similar BPAR at 6 months in comparison to cyclosporine but higher incidence of anemia, PTLD, and viral infections associated with excessive immunosuppression in the tofacitinib group
Bortezomib	Proteasome inhibitor	Reversible inhibition of the 26S proteasome resulting in plasma cell death	Desensitization, AMR	Peripheral neuropathy (dose dependent), thrombocytopenia, neutropenia, neuralgia, gastrointestinal toxicity, CYP3A4-mediated drug interactions
Carfilzomib	Proteasome inhibitor	Irreversible inhibition of the 26S proteasome resulting in plasma cell death		Acute renal insufficiency, venous thrombosis, hypertension, thrombocytopenia, no CYP-mediated drug interactions
Eculizumab	Anti-C5	Binds C5 protein of the complement cascade, thereby preventing formation of the membrane attack complex		FDA approved for atypical hemolytic uremic syndrome and paroxysmal nocturnal hemoglobinuria. Due to life-threatening meningococcal infections, meningococcal vaccines required at least 2 weeks prior to the first dose of eculizumab Toxicities include hypertension, tachycardia, rash, headache, diarrhea, nausea and vomiting, and upper respiratory infection
C1 inhibitor	C1 esterase inhibitor	Inhibits complement proteins C1r and C1s through which the classical complement pathway is interrupted		Toxicities include headache, abdominal pain, and oropharyngeal pain
Belimumab	B-lymphocyte stimulator (BLyS) protein inhibitor	Prevents BLyS from binding to receptors on B cells which reduces B-cell-mediated immunity		FDA approved for systemic lupus erythematous. Toxicities include nausea, diarrhea, infusion-related reaction, and hypersensitivity

(continued)

Table 2 (continued)

Drug	Class	Mechanism of action	Place in therapy	Comments
Tocilizumab (TCZ)	Anti-interleukin-6	IL-6 inhibition inhibits B-cell progression to plasma cell		FDA-approved rheumatoid arthritis and idiopathic juvenile arthritis In a phase II trial, TCZ used in combination with IVIg and rituximab allowed the transplantation of 5 highly sensitized patients
IgG endopeptidase (IdeS)	Bacterial IgG proteinase	Bacterial IgG isolated from *Streptococcus pyogenes* proteinase that cleaves all 4 human IgG subtypes	Desensitization	In a phase II trial, 24 of 25 highly sensitized patients successfully underwent renal transplantation from HLA-incompatible donors

MMF mycophenolate mofetil, *BPAR* biopsy-proven acute rejection, *PTLD* posttransplant lymphoproliferative disease

JAK Inhibition with Tofacitinib

As an overview, JAKs are tyrosine kinases that facilitate signal transduction and activators of transcription (STAT) phosphorylation, dimerization, and nuclear transport which results in transcription and gene expression. There are four mammalian JAK subtypes, namely, JAK1, JAK2, JAK3, and tyrosine kinase 2 (Wojciechowski 2013). Unlike other subtypes, JAK3 is found primarily on hematopoietic cells, and the importance in immunosuppression has been demonstrated through murine models. Mice that lacked common gamma chain (cy) of cytokines or JAK3 were found to develop severe combined immunodeficiency syndrome (Wojciechowski 2013). Additionally, tofacitinib is 20- to 100-fold less potent for JAK2 and JAK1 which could translate to less hematologic adverse effects such as anemia, thrombocytopenia, and leukopenia (Wojciechowski 2013).

Tofacitinib, formerly known as CP-690,550, is an orally active Janus kinase (JAK) inhibitor that is FDA-indicated for treatment of moderate to severe rheumatoid arthritis (Xeljanz 2015). In the tri-signal model of T-cell activation, induction of signals 1 and 2 lead to expression of cytokines such as IL-2 and IL-15. These cytokines subsequently activate the mammalian target of rapamycin via phosphatidylinositol 3-kinase and the JAK/STAT signal transduction pathway. Activation of the final signal transduction, in combination with de novo nucleotide synthesis, results in lymphocyte proliferation constituted by signal 3. By inhibiting the JAK/signal transducers and activators of transcription (STAT) pathway, signal 3 of T-cell activation is terminated. Thus, it has been theorized that tofacitinib offers an alternative to CNI-based protocols.

To date, two clinical trials have examined the safety and efficacy of tofacitinib when used for rejection prophylaxis. The first trial which was a phase IIa pilot study compared two doses of tofacitinib 15 mg ($n = 20$) and 30 mg twice daily ($n = 20$) versus tacrolimus ($n = 21$) in renal transplant recipients (Busque et al. 2009). In brief, patients received IL-2 receptor antagonist induction, mycophenolate mofetil, and corticosteroids. Biopsy-proven acute rejection (BPAR) after 6 months was 5 [−8.4, 9.4], 21 [2.9, 29.7], and 4.8% for 15 mg twice daily, 30 mg twice daily, and tacrolimus groups, respectively. Furthermore, the risk of BK virus nephropathy and cytomegalovirus was higher in patients treated with tofacitinib when compared to patients treated with tacrolimus. This study concluded that 15 mg twice daily was the preferred dose as 30 mg twice daily resulted in excessive immunosuppression without benefit in allograft or patient survival. In a phase IIb study, the second trial compared the efficacy and safety of tofacitinib at two different dosing strategies to cyclosporine in renal transplant recipients (Vincenti et al. 2012). Similar to the previous trial, all patients received

basiliximab induction, mycophenolic acid, and corticosteroids. Similar BPAR at 6 months was observed for all groups, but anemia, neutropenia, and posttransplant lymphoproliferative disorder (PTLD) occurred more frequently in the tofacitinib groups. This study concluded that when combined with mycophenolic acid, tofacitinib is effective in preventing allograft rejection, demonstrated a beneficial effect on renal function, but exposes patients to higher risk of excessive immunosuppression as evidenced by incidences of serious infections, opportunistic infection, and PTLD (Vincenti et al. 2012). Finally, a post hoc analysis of the second study aimed to determine if a patient subgroup with an acceptable risk-benefit profile could be identified based on median exposure. Higher 2-hour post-dose levels (C2) correlated with the incidence of serious infection, but leukopenia and neutropenia remained significant in both the above-median exposure group and the below-median group. The findings from this study raise the potential role of therapeutic drug monitoring in minimizing toxicities while retaining efficacy (Vincenti et al. 2015; Moore et al. 2017).

Desensitization and Antibody-Mediated Rejection

Allosensitization can occur due to pregnancy, blood transfusion, and mechanical circulatory support devices. Rates of transplantation for sensitized patients remain low due to known increased risk for antibody-mediated rejection (AMR) and poor graft and patient outcomes. Approximately 20% of patients that receive heart transplants have an elevated panel reactive antibody (PRA >10%) at the time of transplant (Lund et al. 2017). Traditional efforts to reduce sensitization to HLA antigens, also known as desensitization, include plasmapheresis, IVIg, and rituximab. Although often successful, these therapies remove circulating antibodies but have negligible effect on plasma cells. Due to this, a significant percentage of the sensitized patients are refractory to standard of therapy; hence, novel therapies aimed at alternate mechanisms are crucial. Furthermore, antibody-mediated rejection is often difficult to treat and is treated using similar agents. Finally, it is important to note that there is a paucity of well-designed studies to guide therapy in AMR in heart transplant recipients. While consensus definitions exist for AMR diagnosis, there remains a clinical conundrum with respect to patients with circulating DSA without overt signs of graft damage or graft dysfunction. Currently, there are no FDA-approved agents for desensitization or treatment of AMR. This section will focus on emerging therapies and the future of desensitization as well as antibody-mediated rejection.

Proteasome Inhibitors

Proteasome inhibitors are FDA approved for the treatment of myeloma. There are three proteasome inhibitors currently available – bortezomib and carfilzomib which are available as intravenous formations and, most recently, ixazomib which is available as an oral formulation. To appreciate the utility of proteasome inhibitors, understanding the role of the proteasome is crucial. The 26S proteasome is a multi-catalytic enzyme expressed in the cytoplasm of eukaryotic cells. Its primary function is targeted degradation of ubiquitin-labeled misfolded proteins, cell cycle regulatory proteins, transcription factors, and inhibitory molecules (Walsh et al. 2012). Plasma cells produce antibodies, a proportion of which will be misfolded and ultimately require degradation by proteasome complex. Proteasome inhibition therefore disrupts homeostasis ultimately resulting in apoptosis. Other mechanisms through which proteasome inhibitors exert immunomodulatory effects include inhibition of class I MHC expression through reduction of endogenous peptide production, as well as inhibition of nuclear factor kappa B (NF-kB) activity which leads to subsequent reduction in cytokine production including IL-6 (Sadaka et al. 2012). Bortezomib is a first-in-class proteasome inhibitor that binds the 26S proteasome reversibly, whereas carfilzomib is a second-generation proteasome inhibitor that binds irreversibly. When compared, bortezomib has potential for neurotoxicity and drug-drug interactions through CYP3A4 and

2C19, whereas carfilzomib has lower incidence of neurotoxicity and no CYP-mediated drug interactions (Velcade PI, Kyprolis PI). Although they are not FDA approved for AMR or desensitization, these agents are being used in refractory cases in combination with standard of care. Ixazomib gained FDA approval in 2015 and like bortezomib is a reversible proteasome inhibitor (Ninlaro PI 2017), but it has yet to be used in transplantation. Like other modalities, proteasome inhibitors have been studied mainly in renal allograft with a few case series emerging in cardiac allograft recipients. In a pilot study, bortezomib was utilized in six allosensitized patients awaiting cardiac transplantation with persistently elevated anti-HLA antibodies despite conventional therapy with IVIg and rituximab. Mean calculated panel reactive antibody (cPRA) reduced from 62% to 35%, but infection was common after treatment (Patel et al. 2011). A recent case series described the use of carfilzomib in 14 lung allograft recipients with AMR. The regimen included plasma exchange and IVIg in combination with carfilzomib. Patients were deemed responders if complement-1q (C1q) was suppressed after treatment. Seventy-one percent responded to carfilzomib and had less chronic lung allograft dysfunction or progression when compared to nonresponders (Ensor et al. 2017). Moving forward, the role of proteasome inhibitors may not be limited to AMR and desensitization. Several ongoing studies are evaluating the utility in induction strategies as well as chronic rejection. Given the current body of evidence and clinical experience, proteasome inhibitors have been added to centers' regimens as agents for desensitization and antibody-mediated rejection. Their place in therapeutic algorithms remains to be determined due to the lack of large-scale clinical trial data.

Belimumab

B-lymphocyte stimulation (BLyS) family of cytokines can regulate clonal selection and the B-cell lifespan (Parsons et al. 2010). Belimumab exerts its effect by preventing BlyS protein from stimulating B-cell activation and differentiation (Sethi et al. 2017). It is FDA approved for systemic lupus erythematous. Currently, induction and maintenance therapy are T lymphocyte directed with negligible effects on B lymphocyte. B lymphocytes have been implicated in chronic antibody-mediated rejection; thus, exploring depletion at the time of transplant could be beneficial in both allosensitized and non-sensitized patients (Parsons et al. 2010). A recent case report demonstrated the potential efficacy of belimumab for AMR in a kidney-pancreas recipient. Briefly, the patient developed AMR associated with high levels of HLA-DR53 antibodies which was resistant to treatment with plasmapheresis, IVIg, and rituximab. Following treatment with belimumab, HLA-DR53 mean fluorescence intensity (MFI) decreased by 30%, and serum creatinine decreased from 4.5 to 2.8 mg/dl. It was thereby concluded that belimumab could be an effective therapy for AMR (Leca and Muczynski 2013). A clinical trial aimed at examining the effect of belimumab as a desensitizing agent in kidney transplantation was terminated due to lack of efficacy (NCT01025193). Another phase 2 trial examining belimumab for rejection prophylaxis in combination with standard of therapy is currently ongoing (NCT01536379).

Eculizumab (C5 Inhibitor)

Complement activation is another interesting target in the field of transplantation, with the ultimate formation of the membrane attack complex resulting in devastating cellular injury. Eculizumab is a humanized monoclonal antibody that exerts its effect by binding to C5 protein of the complement cascade, thereby preventing formation of the membrane attack complex. It carries the FDA indication for atypical hemolytic uremic syndrome (aHUS) and paroxysmal nocturnal hemoglobinuria (PNH). Most studies in transplantation have been in renal allografts for treatment and prevention of AMR. In an open-label trial, the effect of eculizumab in addition to plasmapheresis and thymoglobulin on AMR 3 months posttransplant in 26 highly sensitized renal allograft recipients

(defined as positive crossmatch against their donors) was evaluated. The study group was compared to a historical highly sensitized group ($n = 51$) who received similar plasmapheresis-based protocol. Incidence of AMR was significantly lower in the study group (7.7% vs. 41.2%, $p = 0.0031$). It was thereby concluded that eculizumab decreases the incidence of early AMR in sensitized renal allograft recipients (Stegall et al. 2011). A nonrandomized, open-label study investigating the use of eculizumab in combination with conventional therapy in highly sensitized cardiac transplant patients is currently ongoing. This study aims to determine if this strategy will prevent antibody-mediated rejection and prolong long-term cardiac allograft survival (NCT02013037). Interestingly, eculizumab may not be effective in c4d-negative AMR as evidenced by two case reports in renal transplant recipients (Burbach 2014; Tran 2016). Since c4d is a sign of complement activation, the lack of efficacy of eculizumab in c4d AMR cases suggests other mechanisms may be involved in AMR. Finally eculizumab is an expensive treatment and is not without risk. Specifically, due to increase in incidence of life-threatening and fatal meningococcal infections with eculizumab use, patients must be immunized with meningococcal vaccines at least 2 weeks prior to administering the first dose (Soliris PI). Given the economic consideration as well as the risk for infection, most centers employ eculizumab strictly on a case-by-case basis for both desensitization and treatment of antibody-mediated rejection.

C1 Esterase Inhibitor

C1 esterase inhibitor (C1-INH) is an investigation agent that inhibits complement proteins C1r and C1s. Through this inhibition, activation of the classical complement pathway is interrupted. Additionally, C1-INH inhibits mannose-binding lectin pathway through inhibition of the serine protease. In a recent phase I/II study completed with the aim of preventing antibody-mediated rejection in highly sensitized kidney transplant recipients, no antibody-mediated rejection was seen in the C1-INH group during the study duration in comparison to one AMR in the control group during the study and two afterward. It was concluded that C1-INH may be useful in preventing AMR following transplantation in highly sensitized patients (Vo et al. 2015a).

Tocilizumab (TCZ)

Tocilizumab (TCZ) is an IL-6 and binds both soluble and membrane-bound IL-6 receptors antagonist that carries the FDA approval for treatment of moderate to severe rheumatoid arthritis (RA) and idiopathic juvenile arthritis. IL-6 is a major cytokine involved in B-cell progression to plasma cells. Targeting this pathway leads to reduction of plasma cells and ultimately antibody production which has potential for both desensitization and antibody-mediated rejection (Jordan et al. 2015). A recent phase I/II single-center, open-label, exploratory study examined the safety and limited efficacy of the addition of TCZ to IVIg for desensitization in highly sensitized patients unresponsive to IVIg and rituximab. Ten patients were enrolled, five were transplanted, and 6-month protocol biopsies showed no antibody-mediated rejection. It was concluded that the addition of TCZ to IVIg for desensitization appears to be safe and a possible alternative in highly sensitized patients refractory to standard therapy (Vo et al. 2015b). Large, randomized controlled studies are required to confirm these findings before the utility of TCZ in transplantation can be confirmed.

IgG Endopeptidase (IdeS)

IdeS (IgG endopeptidase) is a bacterial IgG proteinase isolated from *Streptococcus pyogenes*. IgG endopeptidase cleaves all four subtypes of human IgG with high specificity (Björck 2016). This presents a novel avenue for desensitization as proteolytic cleavage of IgG molecules should prevent IgG-mediated antibody-dependent cytotoxicity as well as complement-mediated

cytotoxicity. In 2 recent phase II trials evaluating the safety and efficacy of IdeS for desensitization, 25 highly sensitized patients received study drug prior to renal transplantation from HLA-incompatible donors. Reduction or elimination of DSAs permitted successful transplantation in 24 of 25 patients. Antibody-mediated rejection occurred in ten patients who were all responsive to treatment, and one graft loss mediated by non-HLA IgM and IgA antibodies occurred. It was concluded that IdeS reduced or eliminated DSAs at time of transplantation but it did not prevent reconstitution of the DSAs (Jordan et al. 2017).

Conclusion

Over the last 50 years, the field of cardiac transplantation has continually evolved from fringe medical science to an incredibly viable option for thousands of patients with advanced heart failure. For outcomes to continue on the current trajectory, development and research must exist to both optimize the way currently available agents are utilized as well as discovering improved therapeutic targets. While the majority of recent advances in transplant therapy have been for desensitization and antibody-mediated rejection, these advances borrow from other immunologic focused fields such as oncology and rheumatology. Agents such as bortezomib and carfilzomib, although still investigational, are gaining more ground as standard of therapy. Conversely, other therapies such as belimumab, c1 esterase inhibitors, IgG endopeptidase, and eculizumab are still finding their niche. Expanded understanding of mTOR inhibition, especially combined with other conventional therapies, will aid in fully harnessing the benefits of this novel class of agents. Lastly, continuing to develop improved formulations to enhance patient compliance is an important, if not overlooked, aspect to advancing cardiac transplant care. Continued focused efforts should aim to both better define the roles of our current agents and expand the number of agents available to clinicians and ultimately our patients.

Cross-References

▶ Cardiac Allograft Rejection
▶ Chronic Immunosuppression Medications

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Stem Cells and the Future of Heart Transplantation

29

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Contents

Abstract

Allogenic heart transplantation remains the only curative therapy for heart failure. Several strategies have been proposed including cell replacement therapy, engineered cardiac tissues, and novel transplant grafts derived from decellularized organs or xenotransplantation. Cell replacement therapy is the most mature of these technologies, but despite decades of clinical investigation, cardiac cell therapy has yet to enter cardiovascular practice. The major obstacle to replacing lost or injured myocardium remains a reproducible source of electro-, mechano-, and immunocompatible cardiomyocytes. Noncontractile cells like bone marrow or adult heart derivatives neither engraft long-term nor induce new muscle formation. Correspondingly, these cells offer little functional benefit to infarct patients. In contrast, transplantation of bona fide cardiomyocytes derived from pluripotent stem cells produces direct remuscularization. This new myocardium beats synchronously with the host heart and induces substantial contractile benefits. This chapter reviews the recent progress made

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toward novel cardiac transplantation strategies with attention to the underlying mechanisms of benefit to appreciate the barriers to cardiac repair and establish a rational path for optimizing therapeutic benefit.

Keywords

Stem cell · Cell therapy · Cardiac remuscularization · Transplantation

Introduction

Pioneered over half a century ago, allogenic heart transplantation remains the only curative therapy for heart failure. Substantial advances in patient selection, operative technique, and optimization of medical therapy and immunosuppression have improved outcomes and quality of life for patients eligible and fortunate to receive a compatible heart. However, supply of donor organs remains relatively unchanged despite rapidly increasing incidence of heart failure. As such, demand for organs continues to far outpace supply worldwide (Khush et al. 2018). The search for alternative sources of cells, tissues, and organs to restore and replace failing hearts is an active and increasingly diverse field of research.

Seminal advances in developmental biology now make novel methods for the transplantation of cell-, tissue-, and organ-based grafts clinically plausible although none are ready yet for clinical use. While evolution of this field will require a spectrum of tailored technologies to replace dysfunctional or deficient myocardium from diffuse disease processes, present efforts focus almost entirely on treatment of ischemic cardiomyopathy. Myocardial infarction (MI) is the most prevalent driver of heart failure and represents a demarcated loss of contractile myocardium supplanted by stabilizing scar. Use of stem cell-derived cardiomyocytes to remuscularize an infarcted territory is intuitive and supported by preclinical studies in small and large animal models. For other cardiomyopathies where disease affects the entire heart, large tissue grafting or organ transplantation may be required. The sources for such transplants as well as general considerations and challenges of each strategy will be reviewed in this chapter.

Cardiac Cell Therapies

Skeletal Myocytes: The first cell type transplanted to directly remuscularize infarcted myocardium was adult skeletal myoblasts over two decades ago (Murry et al. 1996; Taylor et al. 1997). While initially hypothesized to transdifferentiate into cardiomyocytes, this has been conclusively shown not to be the case (Reinecke et al. 2002), and the cells themselves do not electromechanically couple with the host myocardium (Dib et al. 2005; Reinecke et al. 2000). Early clinical trials showed promising benefit, but effects proved transient and appear mediated through noncontractile, paracrine mechanisms (Menasche et al. 2008; Povsic et al. 2011; Taylor et al. 1998). Pivotal clinical trials of autologous skeletal myoblast transplantation in patients with heart failure did not durably improve regional or global left ventricular (LV) function and caused persistent ventricular arrhythmias (Fouts et al. 2006), prompting abandonment of this cell type for therapy (Menasche et al. 2008).

Non-myocyte Stem Cells: More recent efforts have shifted to other adult sources of cells purporting regenerative benefit through cell-cell and paracrine mechanisms, activating and stimulating endogenous regeneration, and modulating repair processes. Numerous autologous and -allogeneic adult cell types have been investigated clinically including adult-derived cells of cardiac origin such as cardiosphere-derived cells (CDCs) and non-cardiac origin such as various bone marrow (BM)-derived cells [e.g., BM-derived mononuclear stem cells (BM-MNCs) and mesenchymal stromal cells (BM-MSCs)] (Cambria et al. 2017; Menasche 2018). These so-called "first-generation" cell types have been further refined as "second-generation" cells composed of purified or cytokine-stimulated subpopulations to potentiate their regenerative capacity. In all, 15 types of adult-derived cells have shown benefit in small animal models of myocardial infarction (Cambria et al. 2017).

Investigators have hypothesized multiple effects of these cells in addition to regeneration including paracrine secretion of cardioactive cytokines and growth factors, leading to expanded indications for cell therapy from acute myocardial infarction, where preclinical evidence was already lacking, to ischemic and nonischemic cardiomyopathy to refractory angina (Perin et al. 2012), peripheral artery disease (Losordo et al. 2012), and stroke (Misra et al. 2012). Notably, the field of adult cell transplantation is marred by the recent retraction of multiple papers from a single lab on the regenerative capacity of BM-derived adult "stem" cells and, secondly, the existence of an endogenous cardiac stem cell phenotype as c-kit^{+} (Chien et al. 2019). Nevertheless, in preclinical models, diverse cell therapies may have modest benefit through noncontractile mechanisms. These effects do not appear restricted to adult-derived cells, and their derivatives give the remarkable heterogeneity of cells that appear efficacious. For example, pluripotent-derived cardiomyocytes ectopically transplanted in engineered scaffolds have shown similar benefit as adult-derived cells in infarcted pigs, despite such grafts failing to couple electromechanically or vascularize with the host myocardium (Gao et al. 2017; Gerbin et al. 2015; Jackman et al. 2018; Shadrin et al. 2017; Weinberger et al. 2016). In one of the most rigorous mechanistic studies specifically of adult cell therapy, a preliminary report from Vagnozzi, Molkentin et al. describe a novel innate immune response that explains the benefit through induction of a specific subset of macrophages to modulate wound healing in the infarct area (Vagnozzi et al. 2018). Taken collectively, the poorly understood yet reproducible benefit of noncontractile cell transplantation in various disease states appears remarkably conserved across various cardiac and non-cardiac cells suggesting a non-specific effect of cell therapy of modest clinical benefit without concomitant restoration of contractile myocardium.

Therapeutic development of these adult cell types has been accelerated to numerous phase 2/3 clinical trials within the past decade prior to clear mechanistic understanding of their function (Broughton and Sussman 2016; Madonna et al. 2016). Trials to date have generally employed heterogeneous populations of adult cell types and have, for the most part, shown safety regardless of the specific investigational cell product, delivery approach, dosing protocol, or patient characteristics. Individual trials initially suggested efficacy, but these early trials were small without randomization, standardized enrollment criteria, endpoints, or adjudication. More recent trials with larger cohorts and superior study design have generally failed to convincingly show benefit over guideline-directed medical therapy (Fernández-Avilés et al. 2017; Fisher et al. 2015; Gyongyosi et al. 2016; Madonna et al. 2016) (Table 1). A recent Cochrane meta-analysis of 38 randomized controlled trials capturing 1,907 post-MI patients concluded the that the current body of evidence for cell therapy to be low quality and lacking evidence for benefit by composite endpoint of mortality, nonfatal myocardial infarction, and/or heart failure readmission (Fisher et al. 2016). Long-term mortality >12 months and incidence of nonfatal myocardial infarction were individually reduced with cell therapy, but confounded by relatively low event rates, small study cohorts, and non-standardized trial designs and adjudication.

Pluripotent Stem Cells: Human pluripotent stem cells, a renewable source of all somatic cell types including cardiomyocytes, have received the most study for application in regenerative therapies. The availability of well-characterized cardiomyocytes in substantial and reproducible quantities enables novel cell-, tissue-, and organ-based therapies. Both human embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) have been used as a renewable source of differentiated cardiomyocytes.

First isolated in 1998 (Thomson et al. 1998), human ESCs have been characterized for decades and specific lines with favorable attributes for clinical development such as karyotypic stability, facile differentiation into the cell of interest, and ethical sourcing. ESCs are isolated from the inner cell mass of the blastocyst in the early stages of embryogenesis and retain the potential to

Table 1 Select randomized controlled trials of adult cell transplantation for myocardial infarction and ischemic cardiomyopathy

Study	Design	Number of subjects		Cell type	Route	Cell number ($\times 10^6$)	Timing (post-AMI)	Follow-up (mo)	Primary outcome	Result
		T	C							
Acute myocardial infarction										
BOOST (Wollert et al. 2004)	SC, OL	30	30	Allo BM-MNC	IC	2460	5–7 days	6	Global LVEF	Positive
REPAIR–AMI (Schachinger et al. 2006)	MC, DB	95	92	Auto BM-MNC	IC	236 ± 174	3–6 days	4	Global LVEF	Positive
Leuven-AMI (Janssens et al. 2006)	SC, DB	33	34	Auto BM-MNC	IC	172 ± 72	24 h	4	Global LVEF	Negative
FINCELL (Huikuri et al. 2008)	MC, DB	39	38	Auto BM-MNC	IC	402 ± 196	3 days	6	Global LVEF	Positive
REGENT (Tendera et al. 2009)	SC, OL	97	20	Auto BM-MNC or $CD34^+CXCR4^+$ BM-MNC	IC	178 (BM-MNC) 1.90 ($CD34^+CXCR4^+$ BMCs)	3–12 days	6	Global LVEF	Negative
BONAMI (Roncalli et al. 2011)	MC, OL	52	49	Auto BM-MNC	IC	98.3 ± 8.7	9 days	3	Myocardial viability	Negative
HEBE (Hirsch et al. 2011)	MC, OL	69	65	BM-MNC/PB-MNC	IC	296 ± 164 (BM) 287 ± 137 (PB)	5–7 days	4	Global or regional LVEF	Negative
LateTIME Trial (Traverse et al. 2011)	MC, DB	58	29	Auto BM-MNC	IC	150	2–3 weeks	6	Global LVEF	Negative
REGENERATE-AMI (Choudry et al. 2016)	MC, DB	55	45	Auto BM-MNC	IC	60	<24 h	12	Global LVEF	Negative
SWISS-AMI (Sürder et al. 2016)	MC, DB	95	55	Auto BM-MNC	IC	152	5–7 days or 3–4 weeks	12	Global LVEF	Negative
PreSERVE-AMI (Quyyumi et al. 2017)	MC, DB	78	83	Auto CD34+ cells	IC	10 ± 2	9 days	6	Resting myocardial perfusion	Negative

BOOST-2 (Wollert et al. 2017)	SC, OL	151	37	Allo BM-MNC	IC	700–2080	8.1 ± 2.6 days	6	Global LVEF	Negative
TIME (Traverse et al. 2012, 2018)	MC, DB	79	41	Auto BM-MNC	IC	147 ± 17	3 or 7 days	6 and 24	Global or regional LVEF	Negative
CAREMI (Fernández-Avilés et al. 2018)	MC, DB	33	16	Allo BM-c-kit$^+$ CSC	IC	35	5–7 days	1	Safety, all-cause mortality, reinfarction, HF hospitalization, VT/VF, stroke)	Negative
BAMI, NCT01569178 (Mathur et al. 2017)	MC, DB	~175	~175	Auto BM-MNC	IC	n/a	2–8 days	24	All-cause mortality	Recruiting, est. completion 2019
Ischemic cardiomyopathy										
MAGIC (Menasche et al. 2008)	MC, DB	67	30	Skeletal myoblasts	TEP	400 or 800	>1 mo		Global or regional LVEF	Negative
FOCUS-HF (Perin et al. 2011)	SC, OL	20	10	Auto BM-MNC	TEN	178	>3 mos	12	QOL, MLHFQ	Positive
FOCUS-CCTRN (Perin et al. 2012)	MC, DB	61	31	Auto BM-MNC	TEN	100	>1 mo	6	LVESV, VO_2 max, SPECT reversibility	Negative
POSEIDON (Hare et al. 2012)	SC	31	0	Allo or auto BM-MSC	TEN	20, 100, or 200	n/a	1	Treatment-emergent serious adverse events	n/a
CELLWAVE (Assmus et al. 2013)	SC, DB	82	40	Auto BM-MNC	IC	205 ± 110	>3 mos	4	Global LVEF	Positive
TAC-HF (Heldman et al. 2014)	SC, DB, sham control	38	21	Auto BM-MNC or auto BM-MSC	TEN	100 or 200	n/a	12	Treatment-emergent serious adverse events	Neutral
MSC-HF (Mathiasen et al. 2015)	SC, DB	40	20	Auto BM-MSC	TEN	77.5 ± 67.9	>6 weeks	6	LVESV	Positive
ixCell-DCM (Patel et al. 2016)	MC, DB, sham control	58	51	Proprietary auto BM-MSC and M2 macrophages	TEN	n/a	>3 mos	12	Composite (all-cause death, cardiovascular hospitalizations, worsening HF, etc.)	Positive

(continued)

Table 1 (continued)

Study	Design	Number of subjects		Cell type	Route	Cell number ($\times 10^6$)	Timing (post-AMI)	Follow-up (mo)	Primary outcome	Result
		T	C							
CHART-1 (Bartunek et al. 2017)	MC, DB, sham control	120	151	Auto BM-MSC (CpSC)	TEN	24	>3 mos	40	Composite (all-cause death, worsening HF, MLHFQ, 6MWT, LVESV, and LVEF)	Negative
REGENERATE-IHD (Choudhury et al. 2017)	SC, DB	70	35	G-CSF/auto BM-MNC	IC or TEN	115.1	>3 mos	12	Global LVEF	Positive for TEN
POSEIDON-DCM (Hare et al. 2017)	SC	37	0	Allo or auto BM-MSC	TEN	100	n/a	12	Treatment-emergent serious adverse events	Neutral
CONCERT-HF (NCT02501811) (Bolli et al. 2018)	MC, DB	~72	~72	Auto BM-MSC + c-kit$^+$ CSC	TEN	n/a	n/a	12	Global LVEF, VO_2 max, 6MWT, etc.	Paused
DREAM HF-1 (NCT02032004)	MC, DB	~300	~300	Auto BM-MSC (MPCs)	TEN	n/a	n/a	12	Time to HF exacerbation	Paused
CHART-2 (NCT02317458)	MC, DB, sham control	~200	~200	Auto BM-MSC (CpSC)	TEN	n/a	n/a	52	Composite (CV death, worsening HF, MLHFQ)	Canceled
CardiAMP (NCT02438306) (Raval et al. 2018)	MC, DB, sham control	167	83	Potency-screened auto BM-MNC	TEN	200	n/a	12	6MWT	Recruiting, est. completion 2021
REPEAT (NCT01693042) (Assmus et al. 2016)	MC, OL	~334	~334	Auto BM-MNC	Repeated IC	n/a	n/a	24	All-cause mortality	Recruiting, est. completion 2025

differentiate into any somatic cell type given the appropriate stimulation. Initially, there was hope that the heart milieu itself could provide either critical cell-cell cues or growth factors to guide ESCs to a cardiac phenotype and integrate into host myocardium. This notion was quickly dispelled as injected ESCs into mouse myocardium formed teratomas rather than mature cardiomyocytes (Nussbaum et al. 2007) in addition to eliciting immunogenicity and graft rejection (Swijnenburg et al. 2005). Cardiomyocytes derived from human ESCs, however, can be transplanted and survive in normal rodent hearts (Laflamme et al. 2005) and electrically couple with existing cardiomyocytes in porcine models (Kehat et al. 2004). When transplanted into recipient rodent models after MI, there was a reproducible and durable improvement in LV function and electrical coupling with the host myocardium (Caspi et al. 2007; Laflamme et al. 2007; Mummery et al. 2003; Qiao et al. 2011; Shiba et al. 2012).

The discovery of an alternative pluripotent stem cell, induced pluripotent stem cells (iPSCs), by Takahashi and Yamanaka et al. in 2007 has markedly accelerated pluripotent stem cell research and translation into potential therapies (Takahashi et al. 2007). Overexpression of four genes (c-Myc, Oct3/4, SOX2, and Klf4) known to maintain pluripotency in stem cells reprogrammed somatic cells back to a state of pluripotency. The process has been validated using a full spectrum of somatic cells including cells isolated from a single hair follicle or a sample of blood. iPSCs offer benefits over ESCs such as autologous source, allowing patient-specific HLA compatibility, potentially obviating the need for immunosuppression, and avoiding the societal issues surrounding blastocyst and embryo research. However, the reprograming process has been reported to result in genomic abnormalities and incomplete reprogramming, leaving residual epigenetic marks that are of uncertain clinical significance (Kim et al. 2010). Cardiomyocytes generated from iPSCs, however, appear functionally indistinguishable from cardiomyocytes derived from ESCs and native cardiomyocytes, albeit with similar immaturity as all pluripotent-derived myocytes (Schenke-Layland et al. 2008; Zhang et al. 2009).

Preclinical proof-of-concept studies of pluripotent stem cell-derived cardiomyocytes are increasingly promising as the field transitions from in vitro and small animal models to more relevant large animal studies (Milani-Nejad and Janssen 2014; van der Spoel et al. 2011). Efficient methods for high-purity, clinical-grade cardiomyocyte production from ESCs now allow extension of transplant cell strategies into preclinical large animal studies (Thies and Murry 2015). Murry and colleagues have transplanted one billion human ESC-derived human cardiomyocytes (hESC-CMs), approximating the cell loss during human myocardial infarction, to successfully create a large tissue graft in subacutely infarcted nonhuman primates (Chong et al. 2014). In this study, hESC-CMs were surgically injected into the hearts of immunosuppressed primates 2 weeks after infarction, resulting in significant remuscularization of the infarcted myocardium. The human graft became vascularized and electromechanically coupled with the host myocardium within 2 weeks posttransplant, and such grafts have remained durable up to 3 months (Fig. 1).

More recent examples demonstrate the effectiveness and durability of human pluripotent stem cell (hPSC)-CM transplantation up 3 months. Shiba et al. transplanted 400 million nonhuman primate (NHP)-induced pluripotent stem cell (iPSC)-derived cardiomyocytes into MHC-matched NHPs with follow-up to 3 months (Shiba et al. 2016). Following transplantation, global contractility improved at 1 month and was sustained at 3 months compared to cell-free vehicle treatment. Importantly, this allogenic transplantation study expands our understanding of the immunology of hPSC-CM grafts. With MHC homozygosity, grafts were supported without rejection up to 3 months using a moderate immunosuppression regimen commonly used clinically. The minimum immunosuppression required for MHC-matched, PSC-CM allografts was not tested, but this study suggests that immunotolerance of these grafts is possible

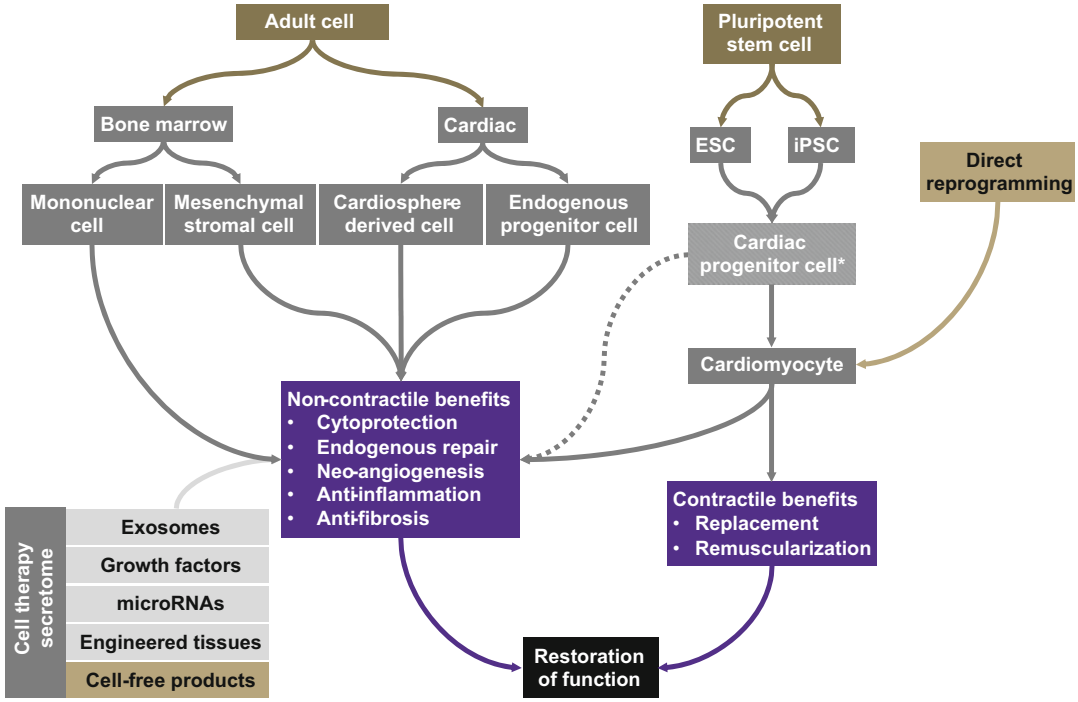

Fig. 1 Function follows form: proposed cell types for therapeutic cardiac regeneration. (*Cardiac progenitor cell is theoretical given populations such as c-kit^{+} cell have been proven not to be cardiopoietic)

without the prohibitive immunosuppression required for xenotransplantation.

Murry et al. recently reported the long-term functional benefit of 750 million hESC-CM in nonhuman primates (Liu et al. 2018). Improved contractile function was again seen at 1 month, and at 3 months, function continued to improve to fully normalize left ventricular function with hESC-CM therapy (Fig. 2). Control subjects negatively remodeled during the study with a continual decline in LV function over time as expected without background medical therapy. The persistent and cumulative benefit of engrafted hESC-CM both subacutely and chronically may reflect the importance of cellular engraftment to exert continuous benefit through both contractile and noncontractile mechanisms. Dissecting the relative contribution of each in this setting is challenging. Whereas prior attempts at cardiac regeneration did not result in meaningful retainment of cell product, and thus any benefit can be safely attributed to noncontractile benefit, hPSC-CM transplantation clearly results in durable engraftment. While observation of large-scale remuscularization with contractile and electromechanically coupled grafts suggests a direct functional benefit, conclusive evidence requires careful genetic and pharmacologic studies to isolate contractile from noncontractile effects. Mechanistic studies to investigate the relative contribution of contractile and noncontractile effects will be important to understand the core mechanisms of benefit to maximize efficacy of this promising technology while minimizing complications such as malignant tachyarrhythmias.

A speculative model may be that the hPSC-CM transplantation uniquely matches the natural history of an evolving MI with both noncontractile and contractile effects. Early post-injury, hPSC-CM may impart immediate and critical benefit to the subacute infarct by stimulating paracrine-mediated repair and moderation of injury. Indeed, pilot small animal studies have failed to show benefit of remuscularization in chronic ischemic cardiomyopathy (Fernandes et al. 2010; Shiba

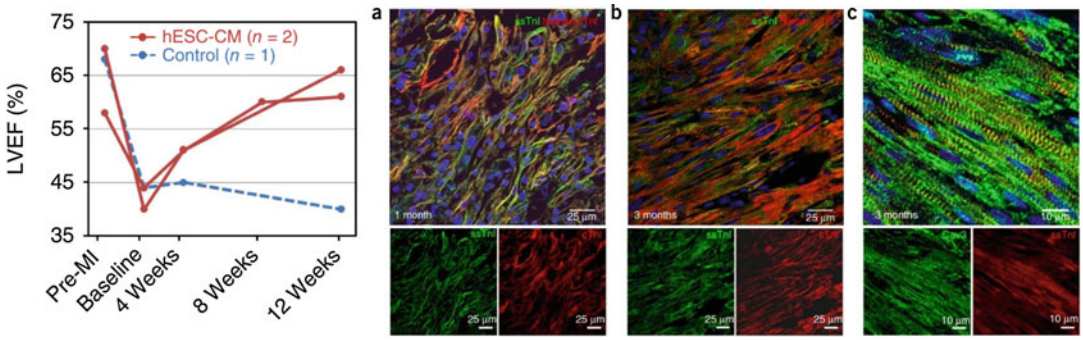

Fig. 2 Long-term benefit maturation of hESC-CM therapy following subacute myocardial infarction in nonhuman primate. Left panel: Benefit of hESC-CM therapy continues up to 3 months (red) compared continued functional decline in control-treated subject (blue). Right panel: hESC-CM grafts stained for slow skeletal troponin I (ssTnI, green) and human cardiac troponin I (cTnI, red). Merged image on top, individual channels below. Scale bar, 25 μm. (**a**) At 1 month the hESC-CMs are relatively small, have peripheral myofibrils, and exhibit low cellular alignment. Low-level expression of cTnI is evident. This experiment was repeated in two biologically independent hESC-CM-treated hearts with similar results. (**b**) At 3 months the cells have hypertrophied, have myofibrils throughout the cytoplasm, and are better aligned. Increased expression of cTnI is evident. This experiment was repeated in two biologically independent hESC-CM-treated hearts with similar results. (**c**) At 3 months, graft T-tubule networks are present, shown by caveolin-3 staining (Cav3, green). ssTnI, red. This experiment was repeated in two biologically independent hESC-CM-treated hearts with similar results. Scale bar, 10 μm. Abbreviations: cTnI, cardiac troponin, isotype I; hESCM-CM, human ESC-derived human cardiomyocytes; LVEF, left ventricular ejection fraction; MI, myocardial infarction; ssTni, slow skeletal troponin, isotype I. (Reproduced from Liu et al. 2018)

et al. 2014), suggesting a finite window of intervention for hPSC-CM remuscularization therapy to alter long-term disease trajectory. As cardiomyocytes are replaced with scar and the LV negatively remodels, the nascent cardiomyocyte graft is maturing and increasingly exerts contractile benefits including force generation and structural support. This transition parallels structural and electrical changes that occur in implanted hPSC-CM over the next 3 months resulting in higher sarcomeric organization and electrical quiescence. Indeed, hPSC-CM cells are fetal-like at the time of delivery which is a requisite phenotype to survive the hostile post-infarct myocardium and effectively engraft (Gerbin and Murry 2015; Zhang et al. 2009). The cells rapidly mature in vivo and ultimately contribute directly to contractile function and positive remodeling.

Despite the promise of hPSC-CM transplantation, significant challenges to clinical translation remain, including scaling cell manufacturing to clinical levels, graft tolerance and immunosuppression, tumorigenicity, delivery, and, most acutely, arrhythmogenesis (Stevens and Murry 2018; Thies and Murry 2015). In earlier work with mice, rats, and guinea pigs, no arrhythmias were observed after hESC-CM transplantation. When studies transitioned to macaques, however, a significant burden of ventricular arrhythmias is observed. Electrophysiological studies indicate that these arrhythmias result from ectopic pacemaking activity by the graft cells, rather than reentry due to heterogeneous tissue. These arrhythmias typically last for 2–3 weeks following implantation, after which the hearts return to normal sinus rhythm. The lack of arrhythmias in smaller animals likely relates to host heart rate. Heart rates in model species range from 600 (mouse) to 400 (rat) to 250 (guinea pig) beats per minute. Not until therapy was tested in nonhuman primate with a resting heart rate of 120–150 bpm were ventricular arrhythmias reproducibly observed. One current hypothesis is that arrhythmias stop when there is enough electrical maturation to drop pacemaker rates by the graft below that of the sinus node. Although the ventricular arrhythmias are tolerated by

macaques, it is likely that they will pose an increasing challenge in larger hearts like those in pigs and humans.

Other barriers to hESC-CM therapy include efficient and reproducible cell production and processing, graft survival without prohibitive immunosuppression, and, at present, surgical epicardial delivery, all of which must be addressed prior to clinical feasibility. To circumvent many of these issues, an alternative strategy employing a surgically placed epicardial patch seeded with ESC-derived cardiac progenitor cells is already enrolling a first-in-human trial (Menasche et al. 2015) despite recent evidence suggesting that cardiac progenitors do not durably engraft and any benefit is mediated through transient paracrine mechanisms (Zhu et al. 2018).

Engineered Cardiac Tissues

For over two decades, cardiomyocytes have been cultured in functional three-dimensional matrices to mimic the structure of cardiac tissue. Transplantation of engineered cardiac tissues, rather than an inoculum of cells, offers several potential advantages: (1) more efficient graft retention, (2) better structural support, (3) less arrhythmogenicity, and (4) immunoreactivity more similar to conventional organ transplants. The first functional engineered cardiac tissue was reported by Eschenhagen et al. in 1997 with chick embryonic cardiomyocytes seeded onto a collagen hydrogel matrix that was successfully paced and maintained force generation for 11 days (Eschenhagen et al. 1997). Use of mammalian cells into increasing complex matrices with structures resembling or derived from actual native human myocardium has permitted the use of engineered cardiac tissues in myriad in vitro and in vivo applications. Intuitively, cardiomyocyte maturity, a significant limitation to current cardiomyocyte differentiation protocols, is enhanced when cultured in three-dimensional matrices compared to traditional two-dimensional monolayer cultures (Nunes et al. 2013; Ronaldson-Bouchard et al. 2018; Zhang et al. 2013).

A logical strategy is to use human pluripotent stem cells as an abundant source of cardiomyocytes added to an engineered matrix to create phenotypically acceptable cardiac tissue (Oikonomopoulos et al. 2018). Further advances have scaled these tissue constructs to physiologically relevant dimensions of 10–20 cm^2. These constructs have adequate force generation for therapeutic use and engraft and vascularize with host myocardium (Shadrin et al. 2017). Combined with advanced nano- and micro-fabrication techniques, cardiomyocytes of uniform alignment can be seeded to improve tissue anisotropy. Engineered cardiac tissue transplantation has reported encouraging improvements in function follow myocardial infarction models in rodent (Jackman et al. 2018; Riegler et al. 2015; Shadrin et al. 2017; Weinberger et al. 2016; Wendel et al. 2015) and pig (Gao et al. 2018; Kawamura et al. 2017). Challenges to clinical translation include diffusion limitations to graft thickness, long-term survival of cardiomyocytes, and most significantly lack of electromechanical integration with the host (due to formation of a non-cardiac barrier layer, intervening epicardial fat or dense infarct scar) (Gao et al. 2017; Gerbin et al. 2015; Jackman et al. 2018; Shadrin et al. 2017; Weinberger et al. 2016). The limitation of this technology to directly improve function was demonstrated by hESC-CMs seeded onto an engineered cardiac tissue transplanted into infarcted athymic rats did not show difference in LV ejection fraction up to 1 month whether viable or lethally irradiated cells were used (Riegler et al. 2015). Another limitation with these studies is the fact that the engineered tissues are transplanted minutes following open chest infarction, a timeframe where noncontractile paracrine effects are expected to be maximally beneficial through modulation of the post-infarct, inflamed, and hostile milieu while augmenting repair mechanisms. Translating such studies clinically, however efficacious, would be challenging given the current medical- and percutaneous-based standard of care for acute myocardial infarction. Recently, Menasche et al. (Menasche et al. 2015, 2018) transplanted a 20 cm^2 fibrin scaffold seeded with hESC-derived cardiac progenitor cells into six

patients with severe ischemic cardiomyopathy at the time of coronary artery bypass surgery. Concomitant revascularization of the treatment territory as well as lack of a control cohort severely limits interpretation of the pilot study. The therapy appeared safe without tumorigenicity or arrhythmogenesis during 6 months of follow-up as would be expected given the limited survival and integration at present with engineered cardiac tissues.

A variation of the technology is scaffold-free cardiac tissues developed by Okano et al. (Kawamura et al. 2017). Using a thermosensitive culturing surface, monolayers of up to 100 million iPSC-derived cardiomyocytes can be detached as intact sheets that can be stacked to create a three-dimensional tissue construct up to 0.1 mm thick and 10–20 cm^2 free of a foreign extracellular matrix. These cell-sheet tissues adhere to host epicardium without the need for anchors or suture thus further limiting immunoreactivity and coverage of the graft with omentum during surgical delivery appears to enhance perfusion and graft survival up to 3 months. The technology has shown benefit in various preclinical animal models of ischemic cardiomyopathy (Kawamura et al. 2017; Shimizu et al. 2009), and a clinical trial has been approved in Japan. Without synchronous contractility with the host and long-term cell survival, these patches are unlikely to contribute directly to host mechanical function and are essentially a vehicle to delivery modest paracrine, noncontractile benefits albeit over potentially long durations.

Single Ventricular Transplantation

Efforts to create entire ventricles for transplantation leverages similar technology as engineered cardiac tissues, endeavoring to instead form an entire chamber. An early attempt a "pouch-like" single ventricle construct, created by culturing neonatal rat cardiomyocytes in a casting mold, that was fitted over infarcted rat hearts (Yildirim et al. 2007). Presented as a biologic ventricular support prosthetic, the transplant does not integrate with the host or impart any contractile benefit. Other groups have reported alternative methods using hPSC-CM with generation of contractile forces as demonstrated in pressure-volume loops (Li et al. 2018) and within bioreactors (MacQueen et al. 2018). This strategy faces the same obstacles as cardiac tissues but further challenged by present-day limitations of cardiomyocyte production and anticipated difficulties of scale and delivery for clinical use.

Whole Heart De-/Recellularization

The complexity of the human heart is built upon the highly specialized architecture of an extracellular matrix (ECM) composed of structural and membrane proteins together with bioactive glycosylated protein groups (Rienks et al. 2014). The ECM orchestrates the development and function of 10 billion cells at every plane of biology. At the molecular and cell levels, paracrine signaling and adhesion mediate cardiac development and homeostasis, and at the tissue and organ, biophysical properties such as rigidity and elasticity and conductance of electrical and mechanical forces provide proper form and function. The critical role for ECM is the premise for whole heart de-/recellularization. Various synthetic ECMs have been proposed and have been reviewed recently (Pomeroy et al. 2019). Readily available and appropriate in size, the pig heart is an ideal source for ECM. Decellularization techniques strip >98% of porcine material (Guyette et al. 2014; Hodgson et al. 2018), and several groups have attempted recellularization of porcine ECM which highlight the challenges of this strategy (Kitahara et al. 2016; Lu et al. 2013; Ott et al. 2008). Preservation of the decellularized ECM's functional bioactivity is critical to cellular repopulation of the tissue; however, removal of immunoreactive signatures is necessary to prevent xenograft rejection. To this end, decellularization of human heart tissues has been reported (Guyette et al. 2016; Sanchez et al. 2015), but with limited function and restricted by availability of human donors. Repopulation of the ECM with human cardiomyocytes is

presently primitive, and techniques are required to recellularize to restore organ biomechanics, electrical stability, and vascularization. Additionally, availability of the sheer number of cells required is presently technically limiting.

Xenotransplantation

Genetically modified pig hearts may be a clinically feasible alternative to resource-limited allografts (Mohiuddin et al. 2015). Strategies for immunotolerance are central to the field of xenotransplantation. However, orthotopic transplantation of pig heart into baboon has largely been unsuccessful despite over two decades of investigation. However, advances in attenuating the immunogenicity of pig hearts have allowed the generation of pig hearts that lack galactose-α1,3-galactose epitopes and express the human membrane marker CD46 and human thrombomodulin. These engineered hearts have survived for upward of two and half years of heterotopic xeno-implantation into the abdomen of a baboon host (Mohiuddin et al. 2016). Recently, orthotopic transplantation of a similar pig heart in combination with clinically viable immunosuppression successfully sustained the host for 195 days (Langin et al. 2018), a dramatic improvement from prior studies and if reproducible may herald clinical investigation.

Conclusion

The severe and endemic shortage of donor hearts continues to compel investigators in search of alternative sources and techniques for cardiac transplantation. There have now been over 100 clinical trials of cell therapy for acute myocardial infarction, over 90 for chronic ischemic cardiomyopathy, and 25 for nonischemic cardiomyopathy (Fernández-Avilés et al. 2017). The evolving technologies range from cell-based to whole organ strategies, each demonstrating early feasibility in preclinical studies or pilot clinical trials but also fraught with challenges often specific to the technology. Adult stem cell therapies have been by far the most extensively studied to date, and the disappointing clinical experience reveals the importance of fundamental mechanistic insight and provides a cautionary lesson for investigators considering first-in-human trials for novel transplant technologies to establish protocols through careful preclinical investigation and validation. Numerous open questions remain for the clinical translation of cardiac cell therapy (Madonna et al. 2016) (Fig. 3). Two decades of investigations in adult cell therapy provides a reassuring framework of clinical trial design and infrastructure for the safe delivery of cells in such trials. Paracrine-based strategies, however, likely will provide only modest benefit of unclear durability. Once better understood, these pathways may be an important adjunctive benefit for therapies based on contractile cell, tissue, or organ transplantation. To complement and eventually supersede orthotopic heart transplantation, therapies will require contractile-based mechanisms of action to functionally replace lost or dysfunctional myocardium. Nascent are technologies that inherently do not integrate electrically or mechanically with host myocardium. And while the lack of arrhythmia and immunogenicity is often cited as evidence of safety for such therapies, they are not unexpected through the lens of fundamental mechanism and may represent significant limitations to efficacy. Thus at present, the most promising preclinical investigations of cardiac remuscularization therapy return to the premise that meaningful and durable recovery of injured myocardium requires genuine and direct regeneration of lost myocardium to restore contractility (Bertero and Murry 2018; Eschenhagen et al. 2017; Thies and Murry 2015). The recognized challenges related to arrhythmogenesis, immunosuppression, and efficient cell production with direct cardiac cell replacement require solutions before clinical viability but may be intrinsic to the fundamental strategy of true cardiac remuscularization.

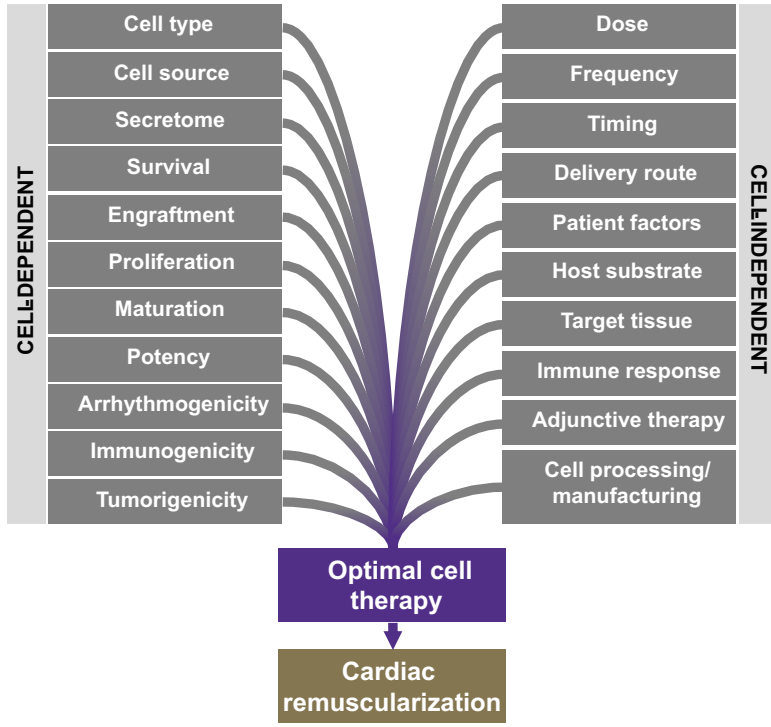

Fig. 3 Open questions in cardiac cell transplantation

Cross-References

- ▶ Pathophysiology of Heart Failure
- ▶ Will We Still Be Doing Heart Transplants in 10 Years?

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Donation After Circulatory Death Donor Use

30

Marijan Koprivanac and Nader Moazami

Contents

Abstract

Strategies for procurement of the heart from brain dead donors (DBD) have been standardized over the past 3 decades and limited by the period of warm and cold ischemic time with acceptable total ischemic time of 4–5 h. This landscape has remained largely unchanged until relatively recent development of pumping systems for continued warm perfusion of

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the heart during transport. Although these technologies for ex-vivo perfusion were initially used for improved organ preservation, recent trials have evaluated the use of this type of technology for resuscitating hearts that would otherwise not be accepted for transplantation to increase the availability of the heart organ. An extension of this methodology has been the quest to reevaluate the potential for recovering hearts from donors who have neurologic function, and therefore are not legally brain dead, but in whom because of an irreversible condition the decision has been made to withdraw life support until circulation ceases; this group of donors are referred to as Donation after Circulatory Death (DCD). Although this strategy has now been widely applied to lungs, livers, and kidneys increasing the availability of these organs by about 10%, applicability to cardiac allograft donation has been limited. This chapter will discuss the process of DCD donation, the pathologic concerns related to the heart, and current existing technologies that have been used for DCD heart transplantation.

Keywords

DCD heart · Donation after circulatory death · Warm ischemia · Reperfusion injury · OCS · Ex-vivo heart perfusion · Organ care system · Normothermic regional perfusion · NRP · Heart postconditioning

Introduction

Strategies for procurement of the heart from brain dead donors (DBD) have been standardized over the past 3 decades. In all instances, with minor variations, the aorta is cross clamped, cardioplegia is administered directly into the aortic root, and the incisions in the inferior vena cava and left atrium are simultaneously performed to minimize ventricular distension and the potential for subendocardial ischemia. Following complete cardiac arrest and delivery of 1–2 L of cardioplegia, the heart is harvested (this time is known as the first phase of warm ischemic time which can take 15–20 min depending on whether the lungs are being procured simultaneously). The heart is then stored in a cold solution of either normal saline, Lactated Ringers, or the cardioplegia solution and immersed on ice with the goal of maintaining a temperature of around 4 degrees centigrade during the transport period. The period of time that the heart is in cold storage is referred to as cold ischemic time. Subsequently, the period during which the heart is actually sewn in but not reperfused is the second period of warm ischemia.

This methodology which has largely remained unchanged over the last 3 decades has proven to be successful and primary graft dysfunction (PGD) requiring temporary mechanical support is less than 5% of transplants in the USA. However, depending on the definition used, PGD may occur in as many as 20% of donated hearts requiring significant inotropic support during the post-transplant phase. The search for better preservation solutions has largely failed in terms of clinical applications and the period of warm and cold ischemic time have largely confined the acceptable total ischemic time for hearts to 4 h as a comfortable period and up to 5 h in selected cases. This landscape has remained largely unchanged despite efforts to develop better methodology for organ procurement with using improved preservation solutions and more recently development of pumping systems for continued warm perfusion of the heart with donor blood during transport. Although these technologies for ex-vivo perfusion were initially used for improved organ preservation, to increase the availability of hearts recent trials have evaluated the use of this type of technology for resuscitating hearts that would otherwise not be accepted for transplantation. An extension of this methodology has been the quest to reevaluate the potential for recovering hearts from donors who have neurologic function, and therefore not legally brain dead, but in whom because of an irreversible condition the decision has been made to withdraw life support until circulation ceases; this group of donors are referred to as donation after circulatory death (DCD). Although this strategy has now been widely applied to lungs, livers, and kidneys and has increased the availability of these organs by

about 10% (Cypel et al. 2015; Jay et al. 2011; Klein et al. 2010; Summers et al. 2010), applicability to cardiac allograft donation has been limited. This chapter will discuss the process of DCD donation, the pathologic concerns related to the heart, and current existing technologies that have been used in the United Kingdom and Australia to use DCD donors for heart transplantation (Boucek et al. 2008; Dhital et al. 2015; Garcia Saez et al. 2016; Garcia Saez et al. 2014; Messer et al. 2016).

Methodology of DCD Organ Donation

DCD organ donation protocol in the USA (UNOS) is very specific given the significant ethical concerns surrounding the donation process. Potential donors are considered suitable candidates if they have nonrecoverable, irreversible neurologic injury resulting in ventilator-dependency, do not fulfill brain death criteria, and have no other contraindications as assessed by the Organ Procurement Organization (OPO) and the primary health care team. Also assessed is the likelihood that the donor will expire within the allotted time frame once withdrawal of support has occurred. This time frame may vary from one OPO to another. Once the candidate is identified, the second step involves consent/approval for every procedure or medication that will be administered for the purposes of organ donation (heparin administration, line placement, ECMO, etc.) and making an alternative plan in case circulatory death does not occur within the allotted time for organ donation (logistics and provisions for continued end-of-life care, including immediate notification of the family). The process of withdrawal of artificial life support to allow for cessation of circulation can be complex as well. During the period of withdrawal, none of the members of the transplant team are allowed to be present, a timeout period is recommended to verify patient identification, the respective roles and responsibilities of the patient care team, OPO staff, and organ recovery team personnel. After proper verification and withdrawal of life support, the declaration of death must comply in all respects with the legal definitions and needs to be done by a member of a patient care team who is not a member of the OPO or the transplant team. Time required from asystole to declaration of death depends on each OPO but usually spans from 2 to 5 min interval.(Bernat et al. 2006) If circulatory death is confirmed within the allotted time period, then organ procurement is commenced. This complex set of rules is in place to ensure that the procedure is done with high medical, ethical, and judiciary standards.

Pathophysiology of Myocardial Acute Ischemic Injury and Reperfusion Injury

In DCD organs, the inherent interval period with reduction in heart rate, blood pressure, and gradual blood deoxygenation compounded by the mandatory wait time to declare death invariably leads to an extended period of warm ischemia which causes more damage to the heart. Energy in myocardial tissue is predominantly generated via oxidative phosphorylation. Oxidative phosphorylation is a highly efficient aerobic metabolic pathway that takes place at the mitochondrial membrane. After normothermic cessation of coronary blood flow and oxygen delivery to myocardial tissue, the oxygen reserves (dissolved in the myocardium and bound to myoglobin) are first utilized which can last for about 8 s or 8 heart contractions (Kubler and Spieckermann 1970). This is followed by a shift from aerobic to anaerobic myocardial metabolism (Pasteur-effect). Anaerobic metabolism (anaerobic glycolysis) is significantly less effective in energy production and is therefore unable to produce the minimal ATP needed to prevent irreversible myocardial damage (Reimer and Jennings 1981). This process is characterized by lactate production, depletion of adenosine stores, and intracellular acidosis (Reimer and Jennings 1981). Acidosis and ischemic metabolites lead to reduction of intracellular potassium and increase in intracellular sodium via membrane transporters (Na^+/H^+, K^+/H^+, Na^+/K^+) (Pridjian et al. 1987). Increase in cytosolic sodium in turn causes increases of cytosolic calcium which activates multiple pathways that lead to apoptosis, microscopically evident in myocytes

as death through hypercontracture (Cooley et al. 1972; Pridjian et al. 1987; Ronchi et al. 2017). The mechanism of increased sodium and calcium in cytosol during acute ischemia is not easily explainable by membrane exchange transports alone but is likely also contributed by a complex redistribution of ions between intracellular compartments specifically mitochondria which is a significant calcium ion reservoir (Ronchi et al. 2017).

Myocardial Damage during Reperfusion Injury

It is believed that up to 50% of the total damage to the DCD heart occurs in the period of initial reperfusion. The main mechanism of reperfusion injury is due to increased electrolyte gradient, primarily hydrogen gradient that causes increased sodium influx by the Na^+/H^+ exchange transporter (Sanada et al. 2011). Subsequent loss of the sodium gradient causes large increase in calcium cytosol concentration and calcium overload, due to Na^+/Ca^{++} exchange transporter working in reversed mode (Sanada et al. 2011). The calcium overload then further worsens damage done to the cell by ischemia.

This chain of events is important as strategies are being researched to minimize the ischemic-reperfusion injury, such as solutions with low calcium concentrations or Na^+/H^+ or Na^+/Ca^{++} exchanger inhibitors that may be added to the initial reperfusion solution (Ferrari et al. 1986; Sanada et al. 2011; Shine and Douglas 1983; Tani and Neely 1990; White et al. 2017).

History of DCD Heart Transplant

The concept of DCD donation actually predates the current accepted policies related to donation after brain death (DBD) given that the laws defining death as neurologic death did not go into effect until 1981 when the Uniform Determination of Death Act (UDDA) was enacted in the USA. In fact, the first heart transplant performed by Christian Barnard in Cape Town, South Africa, in 1967 was a DCD heart transplant from a young woman who sustained a massive head injury from a motor vehicle accident and was diagnosed with a lethal brain injury without a chance for recovery (Barnard 1967). She underwent withdrawal of life support as a prerequisite to officially be pronounced dead. Both donor and recipient were already in the operating room prepped and draped for transplant. The donor chest was opened immediately after she was pronounced dead and extracorporeal reperfusion was initiated with cooling of the heart. The heart was then explanted, subsequently implanted, and reperfused in the recipient. For this initial transplant, care was taken to minimize the ischemic time (warm and cold ischemic time) including measures such as rapid initiation of hypothermia and reperfusion of the donor, rapid transfer from the donor to the recipient by being collocated, and continued perfusion during implantation.

Following the establishment of clear brain death criteria in 1981, the need for withdrawal of life support was eliminated, thus avoiding the extended warm ischemic time. This subsequently led to predominant use of DBD organs as a simpler and a safer option. However, the unbalanced schism between available and needed organs has continued to grow exponentially, forcing increased renewed interest in DCD organs and exploration of new methods for heart preservation. In 2008, Boucek published their experience with transplanting three DCD hearts in pediatric population which in general has a higher wait list mortality (25%), as compared to adults (Boucek et al. 2008). Their protocol was similar to Bernard's in that the donor and recipient were both located at the same hospital, the donor was prepped and draped and ready for surgery with venous and arterial cannulas inserted. If death occurred within 30 min from withdrawal of life support, a patient would be considered a donor candidate. Immediately after withdrawal of donor's life support, and pronunciation of death, complete sternotomy was performed along with instillation of cold preservation fluid through a balloon arterial catheter in the ascending aorta, and topical cooling. All of

these measures were again performed to minimize ischemia time, especially warm ischemia time. New interest in adult DCD heart transplants is evident by the clinical Australian experiences published in 2015, and the UK series in 2016 (Dhital et al. 2015; Messer et al. 2016; Tsui and Oniscu 2017). The Australian experience is based on ex-vivo heart perfusion using the Organ Care System™ (OCS), while the UK group also used the strategy of normothermic regional perfusion (NRP) to assess heart function prior to procurement.

Ex-Vivo Heart Perfusion and Normothermic Regional Perfusion

After initial reperfusion, secondary focus is maintenance perfusion until transplantation of the heart into the recipient. This has not been possible until ex-vivo perfusion devices became available. The first commercially available normothermic ex-vivo perfusion device, the TransMedics Organ Care System (OCS), was used in the UK and Australian DCD protocols (Fig. 1). OCS was developed as a solution to reduce cold ischemia time. Cold ischemia time as well as warm ischemia time are both directly correlated with 30-day mortality after heart transplant (Banner et al. 2008). Cold storage also limits the distance that the recipient heart team can travel between donors and recipients, reducing the ability for optimal matching between the two. This also means discarding viable hearts at locations such as Hawaii where the distance from recipients may be too far. Therefore, the primary goal of OCS is to reduce the cold ischemia time, improve organ preservation, allow longer distance transplants, and possibly allow better matching. In the PROCEED II trial (Randomized Study of Organ Care System Cardiac for Preservation of Donated Hearts for Eventual Transplantation, NCT00855712), OCS showed noninferiority compared to cold storage, but with longer total preservation times (324 mins vs. 195 mins) and at the same time shorter ischemia times (113 mins vs. 195 mins). (Ardehali et al. 2015). In addition, OCS allows procurement and resuscitation of high risk DCD hearts (Garcia Saez et al. 2014). One of the potential advantages of this system is that while on OCS perfusion, the heart's viability and therefore transplant suitability can be evaluated. At present, the main method of evaluation consists of repeated measures of lactate levels in the coronary sinus to determine tends. In addition, coronary flow and visual assessment of the empty contacting heart is possible (Dhital et al. 2015). OCS has been successfully used for high risk and DCD hearts, however, despite reports from Hamed and Deng showing significantly higher lactate levels in the graft failure group or "turned down organ" group as compared to successful transplants, concerns about reliability of using lactate levels for evaluation of the heart viability still exist (Deng et al. 2013; Hamed et al. 2009). One of the added features of this system, which has not yet been thoroughly evaluated, involves the possibility of loading the heart to assess contractile function by echocardiography which may also add to a better assessment of high risk marginal donors.

Normothermic regional perfusion (NRP) , will be described in next sections in more detail, is an extracorporeal membrane oxygenation system that provides circulatory and respiratory support until return of heart function. Once the heart is able to take over the circulation, NRP is weaned. This allows for restoration of the donor's circulatory system and in a way converts a DCD to a DBD donor. Once the NRP is weaned, heart function can be assessed via standard TEE and pulmonary catheter measurements in addition to lactate levels. The benefit of this strategy is the ability to evaluate the heart in vivo (Fig. 2) (Messer et al. 2016; Tsui and Oniscu 2017).

It is worth mentioning that there are also other methods in development for DCD heart preservation, most notably hypothermic ex-vivo heart perfusion. Hypothermic ex-vivo heart perfusion principle is similar to the one of OCS but perfusion is being maintained around 4 °C and usually with lower flows. Caenegem et al. compared heart preservation between hypothermic (4 °C) ex-vivo heart perfusion using HeartPort System (Modified

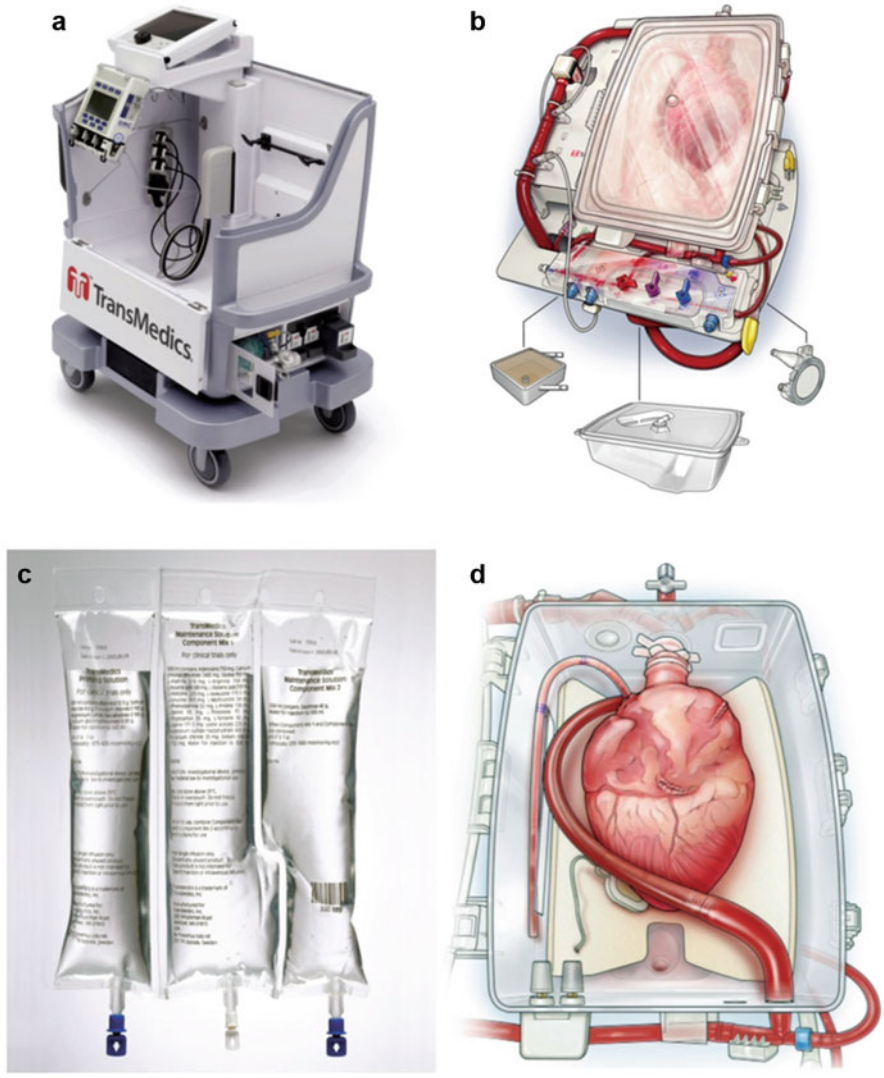

Fig. 1 The Organ Care System is composed of a portable console with heart console (**a**), heart perfusion set (**b**), and heart solution set (**c**). The system is designed for ex-vivo heart perfusion with warm, oxygenated, nutrient-enriched donor blood (**d**). (This figure is reprinted from Ardehali et al. 2015 (PROCEED II trial))

LifePort System, Organ Recovery Systems) and traditional cold storage on 16 pig hearts (Fig. 3) (Van Caenegem et al. 2016). They found that compared to cold storage, cold perfusion has improved preservation and functional recovery of the heart. The cold perfusion group had lower lactate levels, lower adenosine monophosphate/adenosine triphosphate ratio, and higher phosphocreatine/creatine ratio. Using the same cold perfusion system in a canine model ($N = 18$) and measuring several metabolic parameters, Ozeki et al. concluded that cold perfusion reduces tissue injury and improves myocardial recovery when compared with cold storage despite mild transient tissue edema (Fig. 4) (Ozeki et al. 2007). In both studies, coronary flow was 80 mL/min and aortic root pressure was 15 mm Hg, which is about ten times lower than OCS

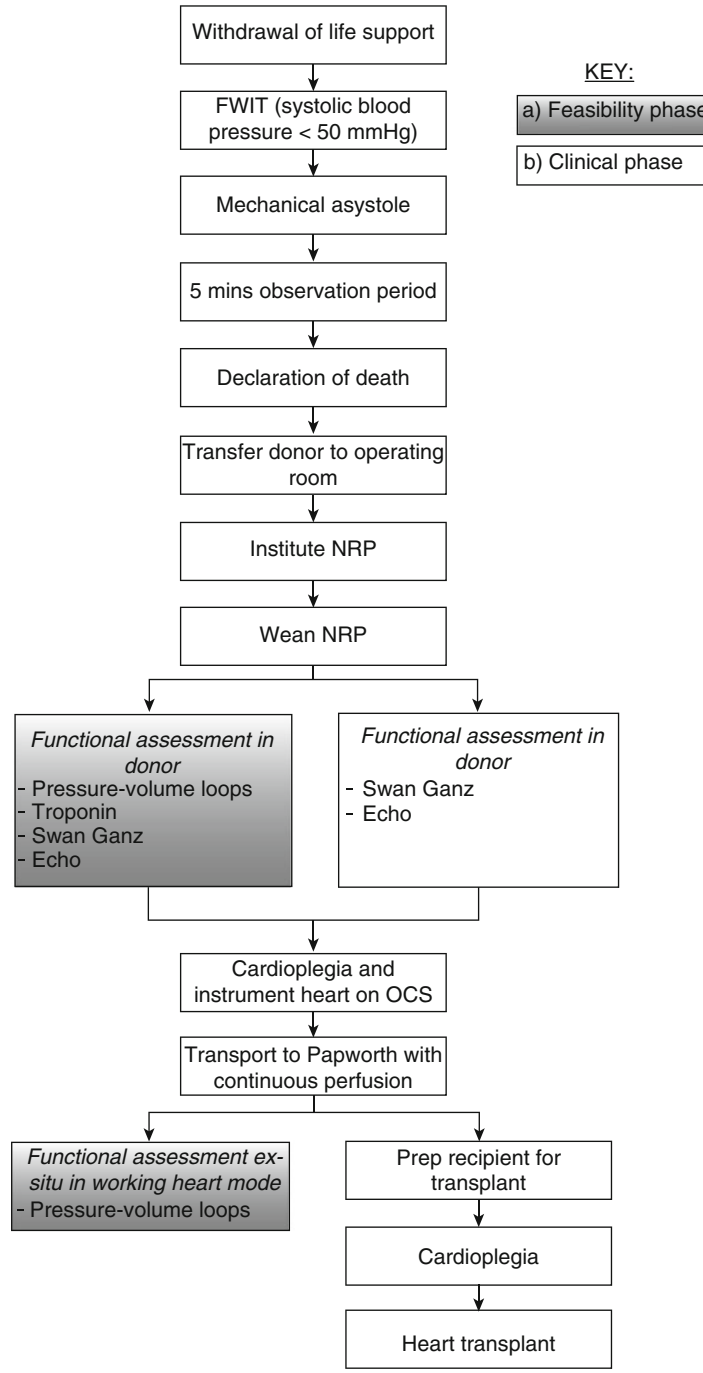

Fig. 2 Flow diagram of DCD heart assessment, protocol, from withdrawal of donor life support to the transplant. (This figure is reprinted from Messer et al. 2016)

normothermic ex-vivo perfusion. Ou et al. and Choong et al. used custom hypothermic low flow perfusion device in canine modes also to compare hypothermic perfusion to cold storage and arrived to the same conclusion. They used 4–12 °C temperature range of perfusion and pressure of 8–10 mm H2O (Choong et al. 2016; Ou et al. 2014).

Fig. 3 Portable perfusion pump. The HeartPort© System is a modified version of the LifePort© System (Organ Recovery Systems©, Itasca, IL, USA), designed for kidney graft perfusion and preservation. The heart grafts were suspended inside a sterile cassette and subjected to retrograde perfusion with 1 L asanguineous preservation solution (KPS-1©, Organ Recovery Systems©, Itasca, Il, USA). The perfusate was cooled to 4 °C by a heater exchanger, oxygenated by oxygenator (Minimax Oxygenation System©, Medtronic, Inc., Minneapolis, MN, USA), and recirculated by means of a pulsatile roller pump. (This figure is reprinted from Caenegem et al. 2016)

Fig. 4 Heart Transporter™, a lithium-powered, ultra-lightweight apparatus equipped with temperature and perfusion pressure controls, as well as a bubble oxygenator (Organ Recovery Systems; Des Plains, IL, USA). (This figure is reprinted from Ozeki et al. 2007)

Comparisons of cold and normothermic ex-vivo perfusion techniques have not been performed yet. While cold ex-vivo perfusion still needs to prove itself clinically, it would be interesting to see whether cold or normothermic perfusion technique would be better for heart preservation and resuscitation.

Experimental and Animal Data on DCD Heart Donation and Resuscitation

Before clinical application, there were a number of experiments exploring the possibility of using DCD hearts. The studies mentioned here and others later in the chapter laid the ground work for the first clinical human transplant of a DCD heart.

Animal Data

Ali et al. compared DCD pig hearts ($N = 8$) resuscitated on CPB and DBD pig hearts ($N = 8$) and found that posttransplant cardiac function was similar between the two, concluding that DCD hearts could be used for transplant and that further research on reperfusion strategies needs to be done (Ali et al. 2011). Repse et al., using a DCD dog model ($N = 15$), determined that pre-reperfusion (acidic, mitochondrial protective cardioplegia) and continuous normothermic perfusion is superior to cold storage and more suitable for transplant (Repse et al. 2010). White et al. looked at cardioprotective strategies on a DCD pig model ($N = 17$) and found improved posttransplant function with initial use of tepid adenosine-lidocaine cardioplegia and continuous myocardial perfusion compared to cold hypokalemic cardioplegia (White et al. 2013). Lyer et al. based on seven DCD pig models found that OCS provides excellent platform for recovery and assessment of DCD hearts and provides viable source of additional organs (Iyer et al. 2013). The same group later compared continuous ex-vivo perfusion and Celsior solution to cold storage preservation (DCD pig model, $N = 8$) and found that the perfusion group was successfully weaned off CPB posttransplant (5/6) while none of cold storage (0/3) hearts were viable (Iyer et al. 2015). Desrois et al. based on pig model ($N = 10$) concluded that cold storage doesn't provide enough protection for DCD hearts (no function was returned at all) and alternative strategies need to be found (Desrois et al. 2014). Saez et al. using pig model ($N = 5$) also found DCD hearts can be successfully resuscitated using OCS (Garcia Saez et al. 2015).

Clinical Procurement Methods of DCD Hearts

Australian Experience

The Australian experience is based on direct organ procurement and use of OCS (Dhital et al. 2015). The process starts with the potential donor located in close proximity to the operating room where transplant teams are ready. Following withdrawal of life support, the patient can legally be pronounced dead 2 or 5 min after cessation of circulation (depending on the Australian States laws). Donor is then urgently transferred to the operating room and prepped for procurement. After sternotomy, 1.5 L of blood is collected for priming of the OCS device with separate administration of heparin. Heparin cannot be given to the DCD donor per Australian regulations prior to declaration of death. The aorta is crossed clamped, and 1 L of crystalloid St. Thomas cardioplegia solution supplemented with erythropoietin and glyceryl trinitrate is administered to aortic root at 150 mmHg of pressure. The heart is vented through the left atrial appendage and IVC incisions and explanted. It is then connected to the OCS device. The OCS circuits are primed with 1.5 L of donor blood and 500 ml of Transmedics priming solution (buffered electrolytes, vitamins, steroids, and mannitol). In addition, Transmedics maintenance solution (isotonic electrolytes, amino acids, dextrose-insulin, and low dose adenosine) is infused at a rate of 0–30 mL/h to maintain coronary perfusion within acceptable range of 650–900 mL/min. After connecting the heart to OCS, oxygenated and supplemented blood flows into the ascending aorta to provide antegrade coronary perfusion. Blood returns to the right side of the heart and is then directed through a cannula into pulmonary artery to the circuit reservoir. The superior and inferior vena cava are closed and a vent is placed into the left atrium for decompression. Additional adenosine and epinephrine infusions, and adjustments in pump flow are used to keep the following parameters within expected range: aortic pressure of 65–90 mmHg, coronary flow of 650–900 mL/min, and heart rate of 65–100 beats per minute.

Once the heart is started on the OCS, its function is determined by aortic pressure, coronary flow, and most of all by lactate concentrations in venous and arterial blood. Total lactate concentration less than 5 mmol/L and evidence of lactate extraction (venous lactate <arterial lactate) is considered criteria for myocardial viability.

UK Experience

The UK group has experience with direct procurement followed by OCS and procurement after establishing normothermic regional perfusion (NRP) followed by OCS (Messer et al. 2016; Tsui and Oniscu 2017). While direct procurement and OCS is similar to the Australian group, use of NRP utilizes a different approach to DCD heart procurement. Procedure setup is similar; after withdrawal of life support, cessation of circulation and 5 min of observation, the donor is taken to the operating room. Following complete sternotomy, 30,000 units of heparin is injected into the heart and aortic arch branches are clamped to prevent circulation to the brain. Extracorporeal oxygenator cannula and pump for NRP are placed into the ascending aorta and right atrium. NRP is started at a flow rate of 5 L/min with concomitant use of vasopressin and dopamine infusions to maintain mean arterial pressure of 50 mmHg and temperature of 35 °C or higher. At the same time, perfusion is restored to other transplantable organs (liver, pancreas, kidneys, lungs), while excluding perfusion to extremities and head. Once the heart function has recovered, NRP is weaned off. During NRP, arterial troponin and lactate are monitored, and following weaning off NRP, the focus is on cardiac index (CI) and pressures (CVP, PCWP) measured via PA catheter, and ventricular and valvular function assessed by TEE. Criteria for accepting the heart after NRP are CI $>$ 2.5 l/min/m2, CVP $<$12, PCWP $<$12, and EF $>$ 50% on TEE. If the heart is functionally and structurally sound, procurement occurs as routinely done and the explanted heart is connected to the OCS.

Clinical Results

What is evident from these DCD protocols is that as compared to simpler method of procuring DBD heart after cardioplegia and cooling, methods of procurement involving DCD hearts are elaborate and complex to allow resuscitation of the heart and final evaluation for transplant viability. Despite this complexity, the clinical data is very promising and both the Australian and UK groups have excellent outcomes. Both 30 day and 1 year survival in the Australian series ($N = 12$) (Dhital et al. 2017) are 100% while in the UK group for direct procurement and perfusion technique ($N = 18$) are 94.4% and for NRP technique ($N = 13$) 100%.

Warm Ischemia and Reperfusion

Even with successful clinical application of some of the methods mentioned herein, search for the composition and properties of the most cardioprotective initial reperfusion solution continues. As discussed previously, the two important factors that are most harmful to the tissue in DCD organs are warm ischemia and reperfusion injury. Harmful effects of warm ischemia are prevented by minimizing its duration while preventing or minimizing reperfusion injury is a subject of ongoing debates. Degree of reperfusion injury is highly influenced by the characteristics of the initial reperfusion solution, and ideal composition of this solution is a subject of ongoing research. Using a principle that intracellular calcium and sodium overload has a central role in the pathogenesis of reperfusion injury, White et al. found that hypocalcemic and moderately acidic (pH = 6.9) initial reperfusion solution minimizes edema and optimizes functional recovery of the heart, thus reducing myocardial stunning in a DCD pig model (White et al. 2017). This is in concordance with multiple studies on the optimal choice of cardioplegia electrolyte composition during cardiac surgery induced ischemia, although the concentrations of calcium differ between the studies, which is likely related to differences in concentration of magnesium. Another study by White et al. found that profoundly hypothermic initial reperfusion had negative effect on myocardial recovery in a pig DCD model (White et al. 2016). Normothermic (35 °C) initial reperfusion solution showed increased coronary flow, less myocardial injury, greater

preservation of endothelial integrity, and myocardial recovery. This is contrary to standard DBD practice where hypothermic cardioplegia is used. While DBD organs are transported in a cold storage after procurement, DCD hearts are placed on normothermic ex-vivo perfusion (OCS) which may be a reason why a few minutes of hypothermia is questionable. On the other side, Farine et al. determined that mild hypothermia (30 °C for 10 min followed by rapid rewarming to 37 °C) mechanical postconditioning (intermittent periods of ischemia, two cycles of reperfusion followed by 30 sec of ischemia), and hypoxia (<10% oxygen for 2 min) during reperfusion improve recovery of hemodynamic function and reduce LDH levels (marker of cell death) in DCD Wister rats models (Farine et al. 2016). The theory of modifying the physical conditions of initial reperfusion lies in slowing down production of free oxygen radicals while restoring electrolyte and acid-base balance. As compared to White et al., Farine found no difference in hemodynamic recovery when using mildly acidic reperfusion (6.8 to 7.4 pH).

Other potential methods for resuscitation of donor hearts include pharmacologic postconditioning to reduce the ischemia reperfusion injury, which is achieved by scavenging free radicals, reducing inflammatory response, activating reperfusion injury salvage kinases associated with reduced apoptosis, and inhibiting cell sodium-hydrogen exchange transporters. For example, Watson et al. showed cardioprotective properties of erythropoietin and reduction of ischemia-reperfusion injury, likely by activating SAFE – kinase cytoprotective signaling pathway on a rat model (Watson et al. 2013). Hing et al. on the other hand showed cytoprotective properties of a combination of cariporide and glyceryl trinitrate by inhibition of sodium–hydrogen exchange transporter and reduction of ischemia-reperfusion injury (Hing et al. 2009). Many other pharmacologic substances (steroids, adenosine, insulin, and others) showed some potential benefit in reduction of ischemia-reperfusion injury via above mentioned mechanisms.

Conclusion

DCD heart transplant is currently in its infancy. The success of initial experiences in Europe and Australia has demonstrated that it can be done, and increasing lack of organs available for transplant implies that it has to be done. Since the DCD heart transplant represents significant distancing in methodology from the DBD transplant, the next step before widespread adoption is to confirm reproducibility of the above mentioned methodologies and results. Continued research on different aspects of DCD procurement and implantation procedure is necessary including determination of optimal physiologic and pharmacologic characteristics of reperfusion and continuous perfusion solutions, superiority between cold low flow ex-vivo perfusion and normothermic higher flow ex-vivo perfusion, improved methods for organ evaluation, and discovery of new biomarkers or other methods for evaluating physical recovery.

Unfortunately, application of these technologies in the USA is far from clinical reality and most efforts have been investigational and concentrated in the laboratories. For true clinical utility, major changes in legislature and policy need to be implemented before this significant and potentially promising process can be developed in the USA. Given the significant organ shortage and the life-saving opportunity that a heart transplant offers, it is imperative that the USA make the necessary changes in this area, which will likely come to fruition in the next 5 years.

Cross-References

- ▶ Donor Operation and Organ Preservation
- ▶ Ex Vivo Perfusion
- ▶ History of Heart Transplant
- ▶ Regulatory Agencies
- ▶ Surgical Complications

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Will We Still Be Doing Heart Transplants in 10 Years?

31

James B. Young

Contents

Abstract

The likelihood that the incidence of advanced heart failure will significantly diminish in the future is not high. Over the past 50 years human heart transplantation has been performed in tens of thousands with end-stage heart failure to forestall misery and premature death. But will that operation still be done in a decade? Tremendous, but still insufficient, insight into heart transplant patient selection and management has accrued. Reasonable short and longer term survival is now seen with the postoperative half-life of recipients in the range of 12 years. However, significant comorbidities occur with substantial frequency, including hypertension, diabetes, hyperlipidemia, renal dysfunction, and allograft vasculopathy. Unfortunately an inadequate number of available donor hearts is a gruesome governor. Over roughly the same period of time, mechanical circulatory assist and replacement devices evolved as a bridge-to-transplant or "destination" therapy (meaning the device would be left in place for a lifetime). A hope has been that these machines would ameliorate the donor organ shortage while improving clinical outcomes compared to heart transplantation by offering an off-the-shelf alternative that had comparable, at the least, outcomes. Will these pumps, or even the much hyped cell transplant procedures, replace the need for heart transplant?

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Keywords

Heart transplantation · Mechanical circulatory support devices · Heart transplant outcomes · Cardiac allograft coronary artery disease · Donor heart supply · Bridge-to-transplant · Destination therapy · Cell transplantation

Introduction

The 50th anniversary of the first "successful" human heart transplant which occurred on December 3, 1967, provided us an opportunity to consider the question "will heart transplantation still be done in a decade?" Reports of Christian Barnard's dramatic, radical, and much-hyped operation stunned the medical community and world at large (Allen et al. 2012; Barnard 1967; Barnard and Pepper 1969). But in reality, a small band of competing professional brethren (few women were in the fray at that time) had been pursuing the holy grail of heart failure therapy for decades (Barnard 1967; Barnard and Pepper 1969; McRae 2006; Winters and Parish 2014, 2016). One must remember that medical therapy for advanced congestive heart failure was rudimentary at that time. For example, furosemide had just been given Food and Drug Administration (FDA) approval that year. A dramatic race had begun to be the first surgeon and team to perform a successful human heart transplant. The concept was buoyed by a platform of improved cardiovascular surgical techniques, better understanding of human immunology, the paucity of therapies available to treat advanced heart failure, and the success, relatively speaking, of other solid organ transplants (particularly kidney and liver) (Starzl 1992; Tilney 2003). And so 50 years later, it is appropriate to consider heart transplantation's role in our present therapeutic armamentarium. Specifically, it is appropriate to reflect on the place of this procedure in our future practices. After all, dozens of surgical adventures have fallen to the wayside as alternative approaches appeared. These alternatives were the result of better insight into disease pathophysiology, newer and better surgical and medical therapies, an understanding of the importance of disease prevention, and better ways to determine the value of any intervention. Will heart transplant join the surgical discards?

Cardiac transplantation haltingly and slowly over the years took its place in the therapeutic tool box. Today the operation plays a profound, but limited, role in select patients with advanced, end-stage heart failure resulting from many different maladies (Lund et al. 2016). For the near-death and dying patient, a successful heart transplant has been demonstrated to often be a miraculous intervention. Of course, heart failure is, as we have learned, an unfortunately common syndrome with many causes and disparate clinical manifestations. Heart transplantation from an epidemiologic perspective is complicated and best looked at as a drop in the massive pool of heart failure patients. It causes only a miniscule ripple. However, for an individual patient, it can lift them out of misery, despite having little impact on the worldwide scourge of the heart failure plague. But because our professional mission is to minister to the ill one by one, as well as from an epidemiologic standpoint, we must press ahead with the procedure. Furthermore, insights into human physiology and pathophysiology generated by the heart transplant experience have great impact on medical care more generally. The operation itself is, relatively speaking, simple when compared to other dramatic and lifesaving cardiovascular interventions. Additionally, we must remember that a heart transplant will not cure any disease. But it can, on balance, diminish mortality and morbidity somewhat, while attenuating symptoms and improving quality of life in many patients. The challenge is great, but not taking the eye off of the horizon, the profession must stay focused on the goal of improving the value of this procedure by improving outcomes, diminishing cost, and looking for alternatives. It would be ideal to find other approaches to heart failure such that in a decade we would not need that surgical option. When considering the question, several pertinent issues must be reviewed. Following basic principles of navigation – knowing where one came from, where one is presently, and where one desires to go – becomes essential. If the destination is to have heart transplantation become

anachronistic, many things must happen. The history of transplantation will be put into perspective by reviewing past and contemporary results while considering future aspirations and alternatives.

Historical Perspectives on Heart Transplantation

Donald McRae has written a captivating history of the development of heart transplantation (McRae 2006). His focus was mostly on the "Race" of the later 1950s and 1960s leading up to Barnard's operation in 1967 (Barnard 1967). Looking back and comparing those days with present times demonstrates improved outcomes, but also the fact that many problems remain. One can argue that the pace of major breakthroughs in heart transplantation have not been seen with the same frequency as in the past. We appear to have stalled with respect to improving donor organ availability and our ability to forestall chronic allograft coronary artery disease, while we have introduced a host of posttransplant comorbidities such as diabetes, hypertension, ischemic cardiomyopathy, renal insufficiency, and malignancies, among others. These complications can be devastating (Lund et al. 2016; Stehlik et al. 2015). This fact emphasizes that a heart transplant simply substitutes a new and different syndrome for the heart failure one being treated. Arguably, heart failure is still present even in an optimally functional allograft. This was not the vision of early heart transplant pioneers, particularly ones in the "Race," who had aspirations of curing end-stage heart disease with the same alacrity that a prosthetic valve might "cure" mitral stenosis (Kirklin et al. 2002, 2010). Of course that doesn't happen; mitral valve replacement simply substitutes a less egregious problem for the pathology being addressed. There is, however, a more permanent benefit and fewer comorbidities seen with mitral valve replacement (and now repair in some situations) than heart transplant. In order to state that heart transplants won't be done in a decade, the pace of discovery and insight into heart failure patient management must accelerate dramatically (Udelson and Stevenson 2016). This is particularly the case if salvation is preventing heart failure from occurring in the first place or having a truly safe, permanent, and durable mechanical support or replacement system. And of course, heart transplantation is not done in isolation from developments in other solid organ transplant settings. Indeed, from a clinical standpoint, heart transplantation was nudged along by discoveries made in the course of kidney and liver transplantation in particular (Starzl 1992; Tilney 2003). Progress made with heart transplantation has not been accomplished in a vacuum.

Although one can find very early references to the concept of heart transplantation in the professional literature, Alexis Carrel, generally working in collaboration with Charles Guthrie, developed techniques for suturing vessels and doing heterotopic heart transplants in dogs (Kirklin et al. 2002; McRae 2006). Carrel was awarded the Nobel Prize in Physiology and Medicine for his work in 1912. Mann and Priestly in 1933 improved the technique of canine heterotopic heart transplant and suggested that "rejection" was the rate limiting factor to success. Demikhov in the 1940s and 1950s experimented with heart-lung transplants in Russia and came to infamy after transplanting the head of a dog onto the neck of another. In the 1950s more generally, canine heterotopic and orthotopic heart transplant technique was improved. In 1951 Marcus, Wong, and Luisada speculated on the therapeutic potential of heart transplantation and then the "Race" gained momentum in the 1960s (McRae 2006). Shumway, later with Lower, further perfected canine orthotopic heart transplant, reported allograft rejection to be the rate limiting factor, but suggested that immunosuppressive therapy similar to that used in kidney transplant recipients might make the procedure a clinical reality. In 1964, James Hardy in Jackson, Mississippi, performed the first xenographic heart transplant using a chimpanzee donor. Hardy left the Race shortly after that, becoming disenchanted with many issues including the brouhaha surrounding donor organ availability and procurement. Barnard traveled to Minnesota, Palo Alto, and Richmond, Virginia, in the 1960s, absorbing all that North American preeminent heart surgeons of the

time had to offer. He returned to South Africa where the first so-called successful human heart transplant was done. The patient was at a very high risk, the donor procurement ethics was tenuous (organ retrieval was done after what we would call today "circulatory" determination of death), and immunosuppression was rudimentary. The donor, Denise Darvall, had been hit by a car while crossing the street, suffering head trauma and irreversible brain damage (Barnard 1967; Barnard and Pepper 1969; McRae 2006). She died a cardiac death and the heart was procured after she was place on cardiopulmonary bypass with hypothermia as an organ resuscitative effort. Louis Washkansky survived the surgery but died on the 12th postoperative day from sepsis. At that time the heart transplant procedure had been perfected from the technical standpoint, the concept of brain death had not quite gelled, bureaucracy and regulation was different (or nonexistent), and immunosuppression was sophomoric. The Race had been won by what some considered an upstart, Barnard, but rapidly, he was followed by Adrien Kantrowitz in New York. Kantrowitz had an opportunity to do the first heart transplant earlier in 1967 but was thwarted by some team members who challenged the use of an anencephalic donor. Norman Shumway in Palo Alto was not far behind to perform his first human heart transplant. By the end of 1968, 102 reported heart transplants had been performed at 50 different institutions in 17 countries with a mean survival of only 29 days. In 1970, the medical community had become disenchanted with heart transplantation and an unofficial moratorium began. The question at that time was not "would heart transplant still be done in a decade," but rather "would heart transplant still be done at all." Only Shumway's team at Stanford cautiously proceeded (Kirklin et al. 2002, 2010; Young et al. 2010). Subsequently, and driven by an intense and aggressive search for new immunosuppressive strategies for renal and liver transplant, cyclosporine emerged clinically and breathed life back into the concept. Heart transplantation began again in earnest in the early 1980s with many new teams and centers never looking back. Important as well was acceptance of the Harvard criteria for brain death (codified in 1968), improved immunosuppression strategies, and the fact that kidney and liver transplant outcomes got better and professional organizations formed and expanded (Kirklin et al. 2010). In 1981 the International Society for Heart (subsequently "and Lung") Transplantation (ISHLT) formed while the United Network of Organ Sharing (UNOS) began in 1977. The ISHLT Registry has become the mainstay data repository giving valuable insight into the successes and failures of heart transplantation. The Registry documents where the field has been, where it is presently, and where it might be going in the future (Stehlik et al. 2015). In the modern era of heart transplantation, the ISHLT Registry has helped identify successes as well as the dark side of the procedure with respect to patient selection, donor availability, problematic postoperative comorbidities, limited length of life of the transplanted heart, and cost. And so, it has been well over a century since Carrell won his Nobel Prize and over a 50-year interval between that and the Washkansky operation. It was another 50 years until the results seen today came to be celebrated.

Present-Day Realities of Heart Transplant

The 33rd ISHLT Adult Heart Transplant Registry report includes data as far back as 1982 with results in 113,472 patients (Lund et al. 2016). There have been 457 heart transplant centers reporting results. It is estimated that this represents approximately two-thirds of all heart transplants done worldwide. During the most active period, and subsequently, more stable years (1990–2014), the annual number of procedures range from almost 5,000 at a peak to just shy of 4,000. More recently, worldwide heart transplant procedures are hovering around 4,500 with about 2,800 done in the United States. This reemphasizes the epidemiologic shortfall of heart transplantation – it is important for an individual patient fortunate enough to get an organ but of limited value when addressing the entire pool of advanced, end-stage heart failure patients. Of course many, if not most, advanced heart

failure patients are not candidates for heart transplantation because of comorbidities, advanced age (a relative contraindication and contentious), social circumstances, or patient desires. Currently there are around 4,000 candidates on the United States heart transplant wait-list with only 2844 procedures done in 2015. Careful scrutiny of the data indicates that over the last decade there has not been a dramatic increase in organ donors for heart transplant. This is unlikely to change significantly over the next decade and is a very important issue to consider while addressing the question about still doing heart transplantation in a decade.

Heart transplant outcomes have improved since 1982. In an epoch-by-epoch analysis, 5 year survival rates for the interval 2002–2008 and 2009–2014 were both about 75% with the latest era significantly better from a statistical point of view. But from the clinical perspective, there does not seem to have been dramatic improvement. Nonetheless, they are dramatically better when compared to the almost certainty of death within months or a year or two that would be anticipated in matched patients not undergoing transplant. Also important is that median survival has risen from 8.5 years in the 1982–1991 cohort to 11.9 years in the 2002–2008 group. This observation is, perhaps, not important for heart transplant patients in their sixth, seventh, or eighth decades but has major ramifications for children, adolescents, and younger adults undergoing the procedure. Posttransplant survival decreased as recipient and donor age increased, but pretransplant mechanical circulatory support did not affect posttransplant survival significantly, with the exception of extracorporeal membrane oxygenation when used. Survival in a decade after transplant was close to 55%. The leading causes of death at the 5 year mark were graft failure (a very nonspecific characterization), acute rejection, multiorgan failure, malignancy, infection, allograft coronary artery disease, and renal failure, in that order. Emphasizing the challenge that still remains are the frequent comorbidities that appear within the 5 and 10 year follow-up points (Table 1). Hypertension is noted at 5 years in 91%, renal dysfunction at 5 years is 51% and at 10 years is 68%, while 6.2% of patients are on dialysis and 3.7% have had renal transplant. Allograft coronary artery disease is reported in 48% of patients at 10 year follow-up. These issues are pestering and likely will not change significantly in the next 10 years unless radical new approaches to immunosuppression are developed, or we have better ways to prevent heart failure or treat it with mechanical circulatory assist devices.

Finally, the cost of heart transplantation needs consideration. Obtaining this data is extremely difficult and cost estimates vary widely. Federal agencies (Medicare primarily) began paying for a limited number of heart transplants in 1987. As the age restriction for transplants eased, more Medicare eligible patients are being transplanted. In 2015, 15.6% were aged greater than 64 years. During the present debate regarding United States

Table 1 Post heart transplant comorbidities at 1, 5, and 10 years after surgery. ISHLT annual report (Lund et al. 2016). Cumulative morbidity rates in survivors within 1, 5, and 10 years after adult heart transplant

Outcome	Within 1 Year %	Within 5 Years %	Within 10 Years %
Hypertension	71	91	N/A
Renal dysfunction	25	51	68
Creatinine, mg/dl			
≤2.5 (abnormal)	17	33	40
>2.5	6.1	14	19
Chronic dialysis	1.7	3.0	6.2
Renal transplant	0.3	1.3	3.7
Hyperlipidemia	60.0	88	N/A
Diabetes	23	37	N/A
CAV	7.8	29	48

CAV cardiac allograft vasculopathy; *N/A* not available

healthcare finances this will become an issue. The Milliman research report on 2014 United States organ and tissue transplant costs suggested that in the period of 30 days before heart transplant to 180 days posttransplant, charges (billings) were $1.2422 million compared to about $334 thousand for kidney and $739 thousand for liver transplant (Bently and Hanson 2014). Heart-lung transplant topped their cost listing at $2.323 million. It is important to understand that this information is based on billings and not what actually was paid. This emphasizes one of the heart transplant dilemmas – cost. One usually argues that cost determined by using the quality life-years extension equation should be competitive with other solid organ transplants and within an acceptable range (perhaps less than $100,000 in quality-adjusted survival years) (Miller et al. 2012). This argument depends greatly on analysis methodology and an arbitrary determination of what an acceptable range might be. Also important when considering this data is the impact of mechanical circulatory support bridging-to-transplant on cost. That issue was not parsed out in the Milliman Research Report. Assuming that around half of the population studied were transplanted after mechanical device support (based on contemporary observations), this procedure is likely to dramatically boost the overall cost of heart transplant (Miller et al. 2012; Moskowitz et al. 2001). This information is critically important as it allows a calculation of the value equation which is clinical outcomes meaningful to patients and caregivers divided by cost. Of course, picking the outcome for the numerator becomes tricky, but survival rates certainly are important and, arguably, top the list. Also, as alluded to above, there are challenges with determining true cost. When mechanical circulatory support options are in play, better financial analyses must be developed. Why financial considerations are so important to the question of doing heart transplants in a decade relates to the choices we make as a society with respect to health care delivery systems. Will our battle with the rising cost of health care in the United States force us into a single payer, more generally government-financed, highly bureaucratic, extensively regulated, system which rations procedures such as heart transplants? A dark consideration when pondering the answer to the "10-year" question is that the financing challenge will be such that the procedure is no longer done. Obviously this argument could be made for many other aggressive and advanced therapies. It is an issue to seriously ponder. Indeed, in many places around the world, heart transplant is simply neither done nor likely to ever be an option and cost is one of the rate limiting factors. This is not likely to change in a decade. We cannot predict what is going to happen with this particular challenge but assume that financial considerations will not be the single limitation to heart transplantation in a decade.

Alternatives to Heart Transplantation

If not heart transplantation in end-stage heart failure patients, what are the alternatives? Of course, the first answer is nothing. The challenge could be abandoned and the focus changes to simply letting them succumb to their disease while palliative care is dispensed. The cost of doing that would surely be less, but suffering would be great. That is not what the profession is trying to do. What then can be done to prevent, cure, or ameliorate the disease and syndrome of heart failure if we take heart transplantation out of the equation? By studying the clinical trajectory of a heart failure patient as proposed in the scientific statement from the American Heart Association about decision making in advanced heart failure we gain insight (Allen et al. 2012).

First and foremost is eliminating the need for heart transplant by preventing development of the difficulty in the first place. Concerted efforts based on best evidence driving creation of guideline directed therapies are pushed hard today. Reimbursement strategies often hinge on health care delivered in a population management setting. Treating hypertension, dyslipidemia, diabetes, obesity, and early stages of heart failure is an obvious tack to sail. Medicare payments for managing heart failure patients in accountable care organizations have been structured to ensure that guidelines for risk reduction of cardiovascular

diseases in general are met. The evidence supporting reduction in heart failure incidence, progression, and morbidity in this environment is, however, paltry and controversial. Nonetheless, there is some suggestion that mortality rates due to heart failure have declined a bit. This is complicated by the fact that our nation is aging rapidly and the syndrome is a result of that to some extent. Thus, it is unlikely that prevention is going to make a major impact over the next decade, and we will continue to be challenged by the heart failure epidemic and patients with advanced illness. It is quite likely that the incidence of advanced heart failure within the heart failure population will rise precipitously. We do not have therapies on the horizon that are likely to attenuate this situation. By no means should we abandon the prevention strategy, but as it relates to the question asked about heart transplantation in a decade, it is unlikely that we will see significant reduction in the challenge. In a decade, we will have prevented little from an epidemiologic standpoint. We will still be faced with decisions regarding advanced therapies which today means heart transplantation and use of mechanical circulatory support systems. Guidelines for heart failure prevention and therapy provides a platform for us to approach the situation (Yancy et al. 2017).

Udelson and Stevenson have provided us with an insightful essay that focuses on the future of heart failure diagnosis, therapy, and management (Udelson and Stevenson 2016). They point out, jumping off from the guidelines, that at Stage A, patients at risk of developing heart failure but without evidence of this syndrome should be treated with prevention measures. Stage B patients, characterized by asymptomatic cardiac dysfunction, require measures to stabilize the situation and reverse or delay disease progression with, in some, measures to prevent premature sudden cardiac death. These maneuvers carry over to Stage C patients, who have symptomatic cardiac dysfunction with the added goal of optimizing functional capacity. The goal in Stage D is to relieve and palliate resting symptoms while considering mechanical assist or replacement devices or cardiac transplantation. Again it is unlikely that in a decade we will have been successful in significantly reducing the epidemiologic challenge such individuals pose. The advanced stages are characterized by, in addition to sudden cardiac death which can be seen at any stage, right ventricular failure, cardiorenal syndrome, repeated hospital admission, home inotrope infusions, hospice care, and heart failure death or death from comorbidities. It is in the later stages of heart failure that that heart transplant and mechanical circulatory support devices will still be considered, even in the distant future. Mechanical assist or replacement devices will continue to have a role in repairing, assisting, modulating, remodeling, and repairing the failing heart in highly select patients. However, the likelihood of generating adequate enough heart failure syndrome improvement to, with substantial frequency, allow device removal and obviate the need for heart transplant is low.

Jakovljevic et al. recently reviewed the progress of left ventricular assist devices as a bridge-to-recovery and noted that in multiple heart transplant and MCSD centers, there had been a few successes (Jakovljevic et al. 2017). In an attempt to determine whether patients undergoing an LVAD bridge-to-recovery operation with subsequent device removal can achieve cardiac and functional capacities similar to patients who were healthy, 58 men who received an LVAD (continuous flow; $n = 18$) were studied. The paucity of continuous flow devices in the study is not what we now see and makes observations less relevant to contemporary practice. They were compared to 24 heart transplant candidates and 97 healthy controls with cardiopulmonary exercise tests and noninvasive hemodynamics. In the explanted group, 38% had peak cardiac power output and 69% peak oxygen consumption within the ranges of healthy controls. Long-term morbidity and mortality in these patients was not the focus of this exercise. Though these findings are encouraging, they need to be juxtaposed to the very few patients logged into the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) database who have had successful device removal for myocardial recovery by 1 year (only 1%) (Kirklin et al. 2015). Longer term follow-up of patients undergoing

MCSD implantation as a bridge-to-recovery, particularly those receiving continuous flow devices, is required to determine the true hope for this approach.

Cell therapies delivered by injection, infusion, or patch delivery systems have been studied with great hype and hope but also seem to consistently fall short in contemporary clinical trials to make the dramatic effect hoped for. Vrtovec et al. summarized prospective randomized trials of stem cell therapy ($n = 8$; 945 patients) in ischemic and nonischemic heart failure subjects (Vrtovec et al. 2013). There were small improvements in ejection fraction, exercise tolerance, and B-natriuretic peptide levels. Arguably encouraging, but much work needs to be done to determine if this strategy will supplant heart transplant in a decade as a bona fide therapeutic alternative. Skeptics remain unconvinced.

Historical Perspectives on Mechanical Circulatory Support Systems

Perhaps coming closest to being more widely successful in supporting or replacing the end-stage failing heart is mechanical circulatory support systems (Kirklin et al. 2012). With the possibility of obviating the need for heart transplant, solving the organ donor availability dilemma (Stevenson et al. 2016), eliminating chronic and acute allograft rejection, and the other problems with transplantation enumerated above, there remains great hope that this will be our salvation in the next decade. But eliminating heart transplantation in a decade will only be seen if outcomes and the value equation is almost equal to, or better than, those detailed for transplant procedures.

It has been just over 50 years since the first total artificial heart (TAH) implant in a canine model was said to be successful (Frazier and Kirklin 2006). The University of Utah Barney Clark experience was in 1982, about 35 years ago. The pace of TAH development has been slow and it is not likely to catch enough wind to play a meaningful role in competing with heart transplant in a decade. The National Institutes of Health Artificial Heart Program began in 1964 and drove development of prototype devices originally designed to replace the heart for life (Winters and Parish 2014, 2016). Luminaries such as Kolf, Jarvik, DeBakey, Cooley, Kantrowitz, Portner, Frazier, Rose, Golding, and many others spent substantial portions of their academic and clinical careers pursuing that elusive goal (Frazier and Kirklin 2006). Setbacks and poor outcomes changed the focus from total artificial hearts to shorter term left ventricular assist devices used to "bridge" patients to heart transplant. Only recently have a few devices been approved for "destination" or more permanent therapy of advanced heart failure (Kirklin et al. 2015). The hope that LVADs might "bridge" patients to heart failure recovery allowing their ultimate removal has been dampened by the limited number of successes reported and discussed above. Device-related comorbidities are still a problem. Nonetheless, outcomes have been reasonable enough to keep up the development pressure for building and implanting newer technology pumps. But concerns remain about their promise to replace heart transplant as a therapeutic option in the next decade (Pinney et al. 2017; Schumer et al. 2016).

INTERMACS is a North American registry established in 2005 for patients who are receiving mechanical circulatory support devices with intent to allow hospital discharge to treat advanced heart failure. It was established as a joint effort of the National Heart, Lung and Blood Institute (NHLBI), the FDA, the Center for Medicare and Medicaid Services (CMS), clinicians, scientists, and industry representatives in conjunction with the University of Alabama at Birmingham (Kirklin et al. 2015). Recently the registry transferred to the purview of the Society of Thoracic Surgeons (STS).

INTERMACS collects and reports on clinical data relevant to MCSDs from index hospitalization through follow-up evaluations. Outcomes after implant including death, explant, rehospitalization, and adverse events are collected and provide the most extensive contemporary data to demonstrate outcomes, as well as insight into risk stratification and patient selection. Death,

transplant, and explant are the major discrete endpoints evaluated. Quality of life and functional limitations are also recorded. By late 2017, there were about 170 actively participating sites and over 21,000 patients with the total implants yearly approaching 2,500. Pediatric MCSD experience is also within INTERMACS (PEDImacs) as is MEDImacs which focuses on advanced end-stage heart failure patients not receiving MCSD therapies. Review of this data helps us answer the question asked regarding heart transplantation in a decade.

As with the ISHLT heart transplant registry which provides the most extensive data on heart transplantation, INTERMACS has emerged as the most extensive MCSD database. However, ISHLT is international with a substantial North American participation, INTERMACS has sites only from the United States and Canada. INTERMACS has, over the last two decades, demonstrated the efficacy of MCSDs as successful bridges to heart transplantation, as a bridge to recovery of myocardial function (rarely seen), and as a permanent or "destination" therapy for intractable heart failure rather than transplant. With the limitations of donor heart availability, the number of MCSDs implants has increased significantly in recent years (Kirklin et al. 2015). The one- and two-year survival for continuous flow pumps is 80% and 70%, respectively. Destination therapy more recently accounts for about half of all implants. Intracorporal pulsatile devices are not presently used with any frequency today, a fascinating paradigm shift. About one-third of adult ventricular assist device patients receive a heart transplant by 1 year. The proportion of patients receiving devices while characterized as "most ill" or INTERMACS level 1 (critical cardiogenic shock sometimes described with jargon as "crashing and burning"), where there is life-threatening hypotension, rapidly escalating inotropic pressor agent support, and critical organ hypoperfusion, was 15%. Biventricular support (BiVAD) was associated with 50% one-year mortality. When pump exchange is required for dysfunction or thrombosis 1-year survival is markedly reduced. Quality of life is significantly improved and functional status increased markedly with a successful VAD insertion.

Despite favorable survival, improved functionality, and better quality of life, MCSDs have severe and sometimes life-threatening complications which include infections, thrombosis, and device failure (Kirklin et al. 2015; Frazier and Kirklin 2006; Paganini et al. 2016, Pinney; Schumer et al. 2016). As we consider the question of replacing heart transplants completely, understanding this issue is important (Table 2). Adverse event rates/100 patient months reported as a rate in the 2012–2014 epoch for continuous flow LVADs and BiVADs were bleeding (7.79), infection (7.28), stroke (1.61), renal dysfunction (1.54), respiratory failure (2.73), and a total burden for all adverse events of 29.20. Cause of death for continuous flow LVADs and BiVADs was neurologic event (18%), multisystem organ failure (16%), withdrawal of MCSD support (10%), major infection (9%), respiratory failure (5%), right heart failure (5%), sudden unexplained death (4%), and device malfunction (5%). The recent publication of the MOMENTUM 3 investigators detailing two-year outcomes with a magnetically levitated LVAD in heart failure demonstrated progress and encouraging results with a significant reduction in morbid events, utilizing a newer continuous flow axial driven circulatory pump (HeartMate 3) (Mehra et al. 2018).

The important issue of heart transplant cost has been addressed and the fact that the rather dramatic recent increase noted might, at least partially, be due to the significant increase in MCSD strategies. There is less information available about this important observation. A dated study of the cost of long-term LVAD implantation suggested a price tag of $222,460 for the first year (Moskowitz et al. 2001). A later report by Miller, Guglin, and Rogers opined that the quality-adjusted life years in cost-effectiveness of destination LVAD therapy was still far greater than the goal of less than $100,000 (Miller et al. 2012). An important consideration when we compare this strategy to accepted standards such as chronic dialysis for end-stage renal failure.

Table 2 Adverse event rates after MCSD surgery. INTERMACS annual report (Kirklin et al. 2015). MCSD adverse event rates (events/100 patient months) in the first 12 months postimplant by Era for CF LVADs/BiVADs ($n = 12{,}030$)

	Era 1 ($n = 4744$): continuous 2008 to 2011		Era 2 ($n = 7286$): continuous 2012 to 2014		Era 1 vs Era 2: 2008 to 2011/2012 to 2014	
Adverse event	Events	Rate	Events	Rate	Ratio	p-value
Bleeding	3932	9.41	4420	7.79	1.21	<0.0001
Cardiac/vascular						
Right heart failure	238	0.57	276	0.49	1.17	0.07
Myocardial infarction	29	0.07	34	0.06	1.16	0.55
Cardiac arrhythmia	2007	4.80	2303	4.06	1.18	<0.0001
Pericardial drainage	271	0.65	305	0.54	1.21	0.02
Hypertension	182	0.44	115	0.20	2.15	<0.0001
Arterial non-CNS thrombosis	70	0.17	94	0.17	1.01	0.93
Venous thrombotic event	304	0.73	286	0.50	1.44	<0.0001
Hemolysis	200	0.48	314	0.55	0.87	0.11
Infection	3435	8.22	4132	7.28	1.13	<0.0001
Stroke	487	1.17	916	1.61	0.72	<0.0001
Renal dysfunction	601	1.44	876	1.54	0.93	0.19
Hepatic dysfunction	246	0.59	326	0.57	1.02	0.76
Respiratory failure	1104	2.64	1551	2.73	0.97	0.39
Wound dehiscence	81	0.19	96	0.17	1.15	0.36
Psychiatric episode	486	1.16	525	0.93	1.26	0.0003
Total burden	13,673	32.72	16,569	29.20	1.12	<0.0001

BiVAD biventricular assist device; *CF* continuous flow; *CNS* central nervous system; *LVAD* left ventricular assist device; *MCSD* mechanical circulatory support device

In the end, though there has been dramatic progress with MCSD for advanced heart failure, we are not quite to the point where we can definitively state that it is equal to heart transplant in most respects. We still have much development and innovation that is required. For MCSD approaches to replace heart transplantation, there will have to be fewer adverse events, increased durability of devices, better multidisciplinary management strategies, improved functional capacity and quality of life for the recipients, and vastly less cost (Pinney et al. 2017; Schumer et al. 2016). The value equation concept is in play.

Conclusion

Yes, heart transplantation will still be done in a decade. The procedure can ameliorate advanced, end-stage heart failure and sometimes has dramatic benefits. The operation has little impact, however, on the overall challenge of heart failure management when considered from the epidemiologic and worldwide scourge. That does not diminish the value of this procedure or that the therapeutic toolbox should be purged of it. An aspirational goal would be to do a better job preventing the heart failure syndrome from developing in the first place, having better options to treat the difficulty if it emerges (perhaps having a cure realizing that antimicrobials for bacterial pneumonia were once aspirational), or achieving the vision of early pioneers in MCSD therapy development which was to have a reliable, effective, and safe mechanical alternative to the native heart that would last an increased lifetime. We see progress in this field. Perhaps, we will have regenerative cell therapies. There is a long road ahead. And so the real question might be "will heart transplantation still be done in two decades?" The answer is yes. Will they be done in "three decades?" The answer is probably. How about

"will heart transplants still be done on the 100th anniversary of Barnard's feat which is fifty years from now?" We should hope not.

Cross-References

- Chronic Rejection
- Contemporary Survival in Heart Transplantation
- History of Heart Transplant
- Malignancy After Transplant

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