Will We Still Be Doing Heart Transplants in 10 Years?

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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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L. Bogar, A. Stempien-Otero (eds.), *Contemporary Heart Transplantation*, Organ and Tissue Transplantation,
https://doi.org/10.1007/978-3-319-58054-8_42

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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