Challenges in Long-Term Mechanical Circulatory Support and Biological Replacement of the Failing Heart

Anuradha Lala, MD; Emer Joyce, MD; John D. Groarke, MD; Mandeep R. Mehra, MD

The burden of advanced heart failure is reaching epidemic proportions. Generally considered for cardiac transplantation, patients often cannot receive this therapy because of their advanced age, comorbidity or the scarcity of donors. Most transplants are concentrated in North America and Europe, with the average center performing fewer than 20 annual transplants. A search for nonbiological means of cardiac support has led to the advent of mechanical circulatory support (MCS), a concept now entrenched as a bridge to transplantation or, for those ineligible for transplantation, as lifetime therapy. In this review we discuss contemporary challenges posed by the changing epidemiology of cardiac transplant and MCS and outline the basis for an understanding of the future of this important therapeutic stance. (Circ J 2014; 78: 288–299)

Key Words: Heart failure; Transplantation; Ventricular assist device

Advanced Heart Failure

The concept of advanced heart failure (also called “end-stage” or “refractory” heart failure) is poorly defined. Commonly, patients have profound structural and functional compromise of the heart that therapy beyond conventional disease-modifying pharmacological therapy is required for prevention or control of systemic end-organ dysfunction, including use of inotropic support, MCS, transplantation or palliative care. In this advanced disease state, patients generally have heart failure because of reduced ejection fraction (HFrEF) but many have heart failure with preserved ejection fraction (HFpEF) as a result of cardiomyopathy with a specific etiology such as infiltrative or restrictive heart disease or complex congenital heart disease (CHD) syndromes. However, these patients are unified by the presence of heart failure symptoms at rest or with limited exertion and an inability to successfully perform activities of daily living. Typical objective measures of such functional limitation include a 6-min walk distance ≤300 m and/or a peak oxygen consumption <12–14 ml·kg⁻¹·min⁻¹ (or ≤50% predicted for age and sex) despite guideline-directed medical therapy. Following rigorous physiological, social, financial, and psychological evaluation, palliative care and hospice may be an appropriate avenue for some patients. For most, durable MCS and/or transplantation remain primary therapeutic options. A discussion of the details involved in patient selection and candidacy for advanced therapies is beyond the scope of this review and the reader is referred to the ISHLT MCS guidelines and Listing criteria guidelines for heart transplantation.

Current Status of Cardiac Transplantation

Epidemiology and Patient Selection

Advances in immunosuppression, diligent patient care and surveillance algorithms have established a 1-year post-transplant survival of 85%, with over 50% surviving beyond a decade. No other therapeutic intervention parallels such success; however, this gold standard is tainted by a limitation of available resources, resulting in a selection bias. According to United...
Network for Organ Sharing (UNOS, USA) data, though over 3,000 patients are listed for transplant, approximately 2,200 are performed annually, causing the waiting list to expand year by year. Thus, allocation algorithms to ethically match the appropriate donors to recipients have been at the forefront of the transplant conversation, with a general struggle between health policy advocates for populations and the clinician confronted by the need to care for an individual—rationing is a necessary evil.

In tandem with more accurate and objective risk scores and more restrictive functional parameters, an epidemiological shift has been noted wherein both donor and recipient characteristics have evolved over time. Table 1 highlights key differences observed from 2006 to 2012. The most common cause of donor death is head trauma. Cardiomyopathy followed by coronary artery disease (CAD) remain the common etiologies of heart failure, representing 54% and 27%, respectively, of all diagnoses. Valvular heart disease, retransplantation, CHD and other causes comprise the remainder. Strikingly, almost 40% of adult recipients are currently bridged with MCS devices (including left ventricular assist devices (LVADs), right ventricular assist devices (RVADs), total artificial hearts) prior to transplantation.

### Contemporary Challenges Surrounding Cardiac Transplantation

#### Ethical Dilemmas

The lack of donor supply to meet demand has fueled debate on the ethics of organ procurement around the world. In China, of the 35,760 solid-organ transplants performed between 2009 and 2013, two-thirds came from deceased donors, a majority derived from executed prisoners. Human rights activists have argued that this provides an incentive to execute. In response to an international expression of concern, the Chinese government is transforming the country’s organ donor system, with a goal of becoming less reliant on the organs of executed prisoners. The new proposed system, the Chinese Organ Transplantation Response System, is proposed to be modeled after the US system in which all organs will be logged into a centralized computer system and matched to patients in need based on urgency and waiting time.

Another controversy is the allocation of adult donor hearts for pediatric recipients. It is known that increasing recipient and donor age is associated with poor survival post transplant. Limited pediatric donor supply has caused many centers to use less strict criteria for pediatric patients listed for transplantation, specifically in the adolescent age group. Though survival is best among pediatric patients who receive hearts from donors aged 13 years or less, in an analysis there was no statistical difference in survival among recipients of grafts from donors aged 14–51 years, offering a median survival exceeding 10 years. Hearts from donors aged greater than 52 years resulted in worse outcomes. Based on individual centers and organ procurement organizations, decisions can be made to accept adult donors for pediatric patients in selected cases.

Finally, it is well established that patient survival following retransplantation (representing 3% of all diagnoses) is diminished (1 year survival of 70% compared with 83% for cardiomyopathy). The most common reason for retransplantation across all age groups is coronary allograft vasculopathy. Some argue that in an era of limited donor supply, retransplantation should be avoided.

#### Extended Donor Organ Criteria

Shortage of donor organs, together with the changing profile of heart transplant candidates (older, more comorbidities), has led to a reconsideration of the criteria for donor heart selection. Several large-volume cardiac transplant programs now offer extended criteria or accept “marginal” donors for borderline candidates, such as for an elderly patient with significant comorbidities or requiring retransplantation. These extended donor criteria include age >55 years, prior drug or long-term alcohol abuse, significant pressor or inotrope requirement, structural heart disease (left ventricular hypertrophy, 1-vessel CAD), long-standing diabetes mellitus, prolonged ischemic time (>4 h), malignant brain tumors and undersized organs. For all transplant candidates, donor age remains a prognostic consideration, and a higher age limit of donors remains contentious. Older donor age increases the risk of early graft failure, and both postoperative and all-cause mortality. However, other studies have shown equivalent short-term and longer-term outcomes with use of carefully selected donor hearts >50 years of age compared with younger donor organs.

The ISHLT guidelines give a Class IIa recommendation for the use of hearts from donors between the ages of 45 and 55 years if projected ischemic time is ≤4 hours, and the recipient is free of significant comorbidities or surgical history in which less than optimal donor heart performance could be fatal. In addition, it recommends the use of organs from donors over 55 years only if the survival benefit of transplantation “unequivocally” exceeds the potential decrease in early survival from transplanting a heart with lower myocardial reserve. Regarding donors with preexisting cardiac disease, donor CAD is associated with early graft failure as well as development of cardiac allograft vasculopathy and diastolic heart failure, with consequent suboptimal long-term survival in the case of donors with left ventricular hypertrophy (LVH). Although reports suggest the risk of early graft failure is strikingly more frequent in those with 2- or 3-vessel disease (42%), with only marginal increased risk in those with 1-vessel disease compared with no CAD (7.5% vs. 6.3%), the lack of significant data has led to the ISHLT guidelines recommending avoidance of donor hearts with obstructive CAD in any major epicardial coronary artery. Recent studies, meanwhile, have shown that mild or moderate LVH does not lead to an increased early or longer-term (median 4 years) mortality compared with donor hearts without LVH; however, early mortality was increased in one study if left ventricular wall thickness exceeded 14 mm. The current guidelines give a Class Ila (level of evidence C) recommendation to the use of donor hearts with LVH provided wall thickness is <14 mm and is not associated with ECG findings of LVH.

#### Extended Candidate Selection Criteria

Aside from iden-
fifying patients without toxic habits capable of adhering to a complex medical regimen, compliance with regular follow-up, and adequate social support, patients must have a suitable biologic substrate to qualify as optimal candidates for cardiac transplantation. Specific populations previously seen as ineligible or “disenfranchised” for transplant listing are discussed below.

Older Age Only 30–40 years ago, transplantation was reserved for patients <55 years of age, but in the current era, though generally reserved for patients <65 years old, no definitive cutoff exists. Improvements in heart failure care and a growing elderly population have distinct implications for MCS and cardiac transplant eligibility. In the past 7 years, the percentage of patients aged 60–69 undergoing transplantation has increased from 14% to 24% and those over the age of 70 have increased from 0.2% of transplants to 1.3%. The larger proportion of older patient recipients is seen in North America as compared with Europe and other parts of the world. Increasing recipient age is associated with worse survival, though causes of death in this population are different, with more patients dying from malignancy, organ failure and infection as opposed to graft failure and acute rejection. It is proposed that the age criteria be clearly outlined and perhaps restricted to account for the thousands of patients who remain on the waiting list without donor hearts.

Restrictive Cardiomyopathies Patients with infiltrating restrictive cardiomyopathies such as amyloidosis were traditionally not considered candidates for cardiac transplantation because of recurrence of the disease and/or systemic involvement. Cardiac amyloidosis has a poor prognosis, with 20% survival at 2 years and a 4–6-month median survival if heart failure is present. The etiology in the majority of cases of cardiac amyloidosis is light-chain type (AL) and transthyretin, both wild-type (ATTRwt) and mutated (ATTRm). Because light-chain amyloidosis (the most common type) is a systemic disease process that can affect any organ, cardiac transplantation must be approached with caution. These patients are often treated with chemotherapeutic agents or by eradication of abnormal plasma cells followed by stem-cell transplantation prior to orthotopic heart transplantation (OHT). Senile amyloidosis, or ATTRwt, is often seen in the elderly population wherein transthyretin slowly forms amyloid deposits in the myocardium with no underlying liver pathology. Mutated transthyretin (in familial amyloidosis) by contrast, is synthesized by the liver and generally prompts consideration of dual heart-liver transplant. The transplanted liver is then able to produce normal non-mutated TTR. Other types of amyloid (secondary amyloidosis and isolated atrial amyloid) rarely affect the myocardium. In a series of 6 patients with cardiac amyloidosis who underwent OHT between 2008 and 2010, 3 had AL amyloid and underwent chemotherapy prior to transplant, 2 had ATTRm and 1 had ATTRwt; 5 of the 6 survived, with follow-up times ranging from 4 to 25 months. A recent review of cardiac amyloid patients undergoing OHT between 1982 and 2010 with long-term follow-up revealed 26 cardiac transplants performed for ATTRm and ATTRwt, 4 for secondary and isolated atrial amyloidosis, and 81 for light-chain amyloidosis. The 5-year survival ranged from 64% to 83%, with outcomes in wild-type, mutant and secondary amyloid patients similar to those of non-amyloid recipients, as compared with the significantly worse outcomes in patients with light-chain amyloidosis. The following generally serve as exclusion criteria for transplantation:

- involvement of more than 2 organs
- autonomic/nervous system involvement with significant orthostatic hypotension
- creatinine >2.0 mg/dL
- alkaline phosphatase >250 IU/L
- large refractory pleural effusions

Select patients have been bridged to transplant with use of MCS, however, including the use of total artificial hearts. Cardiac transplantation for amyloidosis is still considered precarious, with only select centers around the world equipped to diagnose and manage these patients appropriately.

Complex Congenital Heart Disease Today, 85% of children born with CHD survive till adulthood, many because of cardiac transplantation. Approximately 3% of all heart transplants in the adult population are in patients with CHD. Despite a growing number of adults with CHD, the percentage of patients transplanted has remained relatively constant. It has been argued that higher mortality is observed on the waiting list because of decreased relative use of VAD implantation as a BTT. Peri-transplant mortality is also generally higher in the CHD population, attributed to a number of factors: the need for complex cannulation for cardiopulmonary bypass, adhesions from prior operations, unique extracardiac manifestations of disease such as pulmonary vascular disease, protein-losing enteropathy, coagulopathies and hepatic fibrosis, and frequent need for complex reconstruction at the time of surgery. Despite increased 30-day mortality, long-term outcomes for CHD patients post transplant are excellent and comparable to those for other populations.

Blood-Borne Infections (Hepatitis C/Human Immunodeficiency Virus) Since the advent of highly active antiretroviral therapy (HAART), human immunodeficiency virus (HIV) infection has evolved from a rapidly progressive condition to a chronic disease, with cardiovascular causes representing a major non-HIV-related cause of death. Once a contraindication to heart transplantation, there are now reports of favorable outcomes in HIV-positive recipients. Immunosuppression required to prevent graft rejection has not been shown to accelerate HIV disease progression following heart or other solid-organ transplantation. Immunosuppressive drugs, including cyclosporine A and mycophenolate mofetil, appear safe in combination with HAART, and may even have beneficial effects by increasing CD4 T-cell recovery and controlling HIV replication. However, doses of immunosuppressant agents to achieve adequate levels are much lower in patients receiving protease inhibitors, emphasizing the need for careful monitoring of immunosuppressant levels. All possible interactions must be carefully considered before any medication changes in this patient cohort. Evaluation of HIV-positive candidates, and management of recipients, requires an intensive multidisciplinary approach in experienced centers. Most centers still consider this a contraindication by local expertise and choice. One strategy could be to match HIV donors to recipients.

The role of heart transplantation in patients with active hepatitis C (HCV) infection is uncertain because of concerns regarding immunosuppression-related progression of liver disease. The prevalence of HCV among cardiac transplant recipients is reported as 12%, but the breakdown of pretransplant infection compared with infection acquired during or after transplant is uncertain. Outcomes of HCV infection among HCV-seropositive heart transplant recipients are also uncertain. In 224 HCV-seropositive and 10,406 HCV-seronegative recipients of HCV-seronegative donor hearts, adjusted survival rates did not differ significantly between groups. However, in a propensity matched analysis of 443 HCV-seropositive and 20,244 HCV-seronegative heart transplant recipients, followed for 5.6 years, pretransplant HCV seropositivity was associated
### Table 2. Contemporary Immunosuppressive Drugs

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism of action</th>
<th>Typical dosing</th>
<th>Target levels</th>
<th>Major toxicities</th>
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<tr>
<td><strong>Calcineurin inhibitors</strong></td>
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</table>
| Cyclosporine                  | Calcineurin is responsible for transcription of IL-2 and TNF-alpha, granulocyte-macrophage colony stimulating factor and interferon gamma. Inhibition leads to blunting of T-lymphocyte activation and proliferation in response to alloantigens | 4–8 mg·kg⁻¹·day⁻¹ in 2 doses               | 12-h trough levels: 0–6 months: 25–350 ng/ml 6–12 months: 200–250 ng/ml >12 months: 100–200 ng/ml | CV: hypertension, edema  
Neurological: tremors, central/peripheral neuropathy, seizures, hearing loss  
Hematological: anemia, leukopenia, thrombotic microangiopathy, eosinophilia  
Dermatological: gingival hyperplasia, hirsutism, fibrovascular polyps  
GI: nausea, diarrhea, steatohepatitis, choles-tatic, jaundice, eosinophilic colitis, hepatic veno-occlusive disease  
Endocrine: hypophosphatemia, hypomagnesemia, hyperglycemia, hyperkalemia, hyperlipemia  
Renal: insufficiency, nephropathy |
| Tacrolimus                    | Calcineurin inhibitor                                                                 | 0.05–0.1 mg·kg⁻¹·day⁻¹ in 2 doses           | 0–6 months: 10–15 ng/ml 6–12 months: 5–10 ng/ml >12 months: 5–10 ng/ml | CV: hypertension  
Neurological: headache, tremors  
Hematological: anemia, leukopenia  
Dermatological: hirsutism, alopecia  
GI: nausea, diarrhea, abdominal discomfort  
Endocrine: diabetogenic  
Renal: insufficiency, nephropathy |
| **Mammalian target of rapamycin (mTOR) inhibitors** |                                                                                       |                                             |                                                   |                                                                                 |
| Sirolimus (rapamune), everolimus | Calcineurin-independent mechanism of inhibiting T- and B-cell proliferation as mTOR is involved in the transduction signals from IL-2 receptor to the nucleus, causing cell cycle arrest. Sirolimus is a macrolide antibiotic | 1–3 mg/day                                  | 24 hour trough levels: 5–10 ng/ml                | CV: hypertension, edema  
Neurological: headache, progressive multifocal encephalopathy, optic neuropathy  
Hematological: anemia, thrombocytopenia, thrombotic microangiopathy, venous thrombosis  
Respiratory: dyspnea, pulmonary toxicity, interstitial pneumonitis, alveolar hemorrhage, BOOP  
Endocrine: hypertriglyceridemia, hypercholesterolemia  
Dermatological: acneiform dermatitis, hyperglycemia, hyperkalemia, hyperlipemia  
GU: UTI, infertility (oligospermia)  
Musculoskeletal: extremity lymphedema, lingual angioedema |
| **Antiproliferative agents**  |                                                                                       |                                             |                                                   |                                                                                 |
| Mycophenolate mofetil (MMF) (CellCept) | Mycophenolate sodium (Myfortic) = enteric-coated, delayed-release salt of MPA for improved GI tolerability | 1,000–3,000 mg/day in 2 doses               | Mycophenolic acid (MPA): 2–5 μg/ml               | Infection: HSV, CMV  
GI: nausea, constipation, diarrhea, vomiting, dyspepsia, abdominal distension and pain, esophagitis  
Hematological: leukopenia, thrombocytopenia  
Endocrine: hyperglycemia, hypercholesterolemia, gout  
CV: hypertension, edema  
Neurological: headache, tremor  
Respiratory: dyspnea, respiratory tract infections, cough  
Renal: increased BUN and/or Cr  
Dermatological: rash |
| Azathioprine (Imuran)          | Prodrug metabolized into active form, 6-mercaptopurine Antimetabolite is incorporated into DNA and inhibits further nucleotide synthesis, preventing mitosis and proliferation of rapidly dividing cells (T- and B-lymphocytes) | 1.5–3 mg·kg⁻¹·day⁻¹                       | Titrate to keep WBC ≥3,000                          | Hematological: pancytopenia, bone-marrow suppression  
GI: hepatotoxicity, pancreatitis |

(Table 2 continued the next page.)
with increased mortality after heart transplantation (hazard rate 1.32, 95% confidence interval 1.08–1.61), and this association increased with greater time from transplant. Donor HCV seropositivity has been identified as an independent risk factor for development of accelerated post-transplant allograft vasculopathy among HCV-seronegative recipients. The proportion of liver-related deaths in HCV-seropositive patients is reported as 0.9–3.9%, compared with 0.2–0.4% among HCV-seronegative patients. Data on the prognostic influence of antiviral therapy-mediated virologic cure prior to heart transplantation are lacking. Treatment of HCV infection among heart transplant recipients requires caution because of the potential cardiac toxicities of these agents and possible increased incidence of graft rejection. Two small case series (n=3 and n=5, respectively), demonstrated that interferon monotherapy may be effective and well tolerated in treating HCV-seropositive heart transplant patients. Similarly, pegylated interferon and ribavirin were safely used as treatment of 3 HCV-seropositive heart transplant patients. Larger studies are needed to establish the safety and efficacy of contemporary HCV treatments. Furthermore, prospective studies are needed to clarify the influence of HCV seropositivity (present before transplant or acquired with/after transplant) on outcomes, and multicenter, randomized controlled trials are needed to establish optimal pre- and post-transplant approaches to treatment of HCV infection.

**A Contemporary View of Immunosuppression**

The goal of immunosuppressant use post transplant is to strike a favorable balance between preventing and treating rejection of the cardiac allograft while minimizing the toxicities associated with the variety of drugs used. Most patients are on a combination of several agents post transplant, requiring a disciplined adherence, adequate health literacy, and regular follow-up with healthcare practitioners. Maintenance immunosuppression generally consists of a combination of a calcineurin inhibitor (sometimes mammalian target of rapamycin (mTOR) inhibitor in select cases of renal toxicity because of calcineurin inhibitor use), an antiproliferative agent and corticosteroids.
Mechanical Support and Transplantation in HF

Indications and Patient Selection

Rapid advances in technology have enabled durable MCS to emerge as an increasingly viable therapeutic option for advanced heart failure patients. There are 4 major indications for the use of MCS, as illustrated in Figure 2. Classically, MCS may be offered as a BTT for transplant-eligible patients with higher INTERMACS profiles who may be too sick to wait for a donor organ without additional support or who desire improved quality of life while waiting, particularly applicable to those likely to have a long wait time (large size, blood group O, highly sensitized). Over 40% of patients awaiting OHT currently receive MCS prior to transplantation. Durable MCS is also used as a lifetime therapy in patients deemed ineligible for transplantation, an indication designated “destination therapy” (DT). Following the landmark REMATCH trial, which documented 1-year survival rates of 52% with the pulsatile HeartMate XVE device compared with 23% with medical therapy alone in non-transplant candidates, a subsequent randomized trial of the continuous-flow HeartMate II device vs. the HeartMate XVE in the DT population found significantly improved survival (58% vs. 24%) at 2-years. Apart from improved survival, DT patients have shown significant improvements in quality of life, NYHA functional class and 6-min walk test. Overall however, data supporting its routine use are lacking.

Other Post-Transplant Complications

Recipient survival is contingent upon avoiding complications post transplant; namely, infection and rejection, including prevention of cardiac allograft vasculopathy, and treating side effects associated with immunosuppression (Figure 1). Long-term drug side effects include renal failure, hypertension, diabetes and malignancy.

Current Concepts in Mechanical Circulatory Support

Table 2 outlines contemporary immunosuppressive drugs and their mechanisms of action, dosing and major toxicities.

Induction therapy, the use of upstream antibody therapy during the early postoperative period, remains controversial. Despite a lack of consistent evidence of benefit, coupled with increased toxicity including increased incidence of infection and malignancy, over half of all transplant centers continue to use this strategy. Specific populations in whom induction therapy may be advantageous include those at increased risk for earlier severe rejection, such as immunosensitized patients with panel reactive antibody elevations >10%, or those with renal insufficiency requiring delays in calcineurin inhibition. A recent large study looking at the relationship between induction therapy and post-heart transplant outcomes in 6,553 patients between 1990 and 2001 found that the most benefit from this therapy was seen in patients with extensive human leukocyte antigen mismatching alongside those on longer-term VAD support and those of black ethnicity. Overall however, data supporting its routine use are lacking.

Table 2

<table>
<thead>
<tr>
<th>Indication</th>
<th>Contemporary Imunosuppressive Drugs and Their Mechanisms of Action</th>
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</thead>
<tbody>
<tr>
<td>Induction Therapy</td>
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Current Concepts in Mechanical Circulatory Support

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may be used if there is uncertainty regarding reversibility of comorbidities such as hepatic or renal dysfunction or if there are other relative contraindications such as current cigarette smoking or limited psychosocial support that need to be further assessed over time. Indeed, all of the indications as depicted in Figure 2 are fluid, with the possibility of individual patients evolving between categories; for example, a BTT candidate may develop complications of MCS, which may

Table 3. Suggested Patient Selection Criteria for Durable VAD Implantation

<table>
<thead>
<tr>
<th>Indications</th>
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<tbody>
<tr>
<td>NYHA functional class IIb–IV symptoms despite optimal medical therapy</td>
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<td>Frequent hospitalizations for HF</td>
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<td>Intolerance to neurohormonal antagonists</td>
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<td>End-organ dysfunction owing to low cardiac output</td>
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<td>Increasing diuretic requirement</td>
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<td>CRT nonresponder</td>
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<td>Inotrope dependence</td>
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<td>Low peak oxygen consumption (&lt;12–14 mL·kg⁻¹·min⁻¹)</td>
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<td>Recurrent symptomatic sustained VT or VF in the presence of an untreated arrhythmogenic substrate</td>
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<tr>
<td>Requirements specific to DT*</td>
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<tr>
<td>Life expectancy &lt;2 years</td>
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<tr>
<td>Not a candidate for heart transplantation</td>
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<td>LVEF ≤25%</td>
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<td>Failure to respond to optimal medical management for at least 60 of the last 90 days</td>
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<td>Continued need for IV inotropic therapy limited by symptomatic hypotension, decreasing renal function or worsening pulmonary congestion</td>
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<tr>
<td>Contraindications</td>
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<tr>
<td>Absolute</td>
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<td>Irreversible hepatic disease</td>
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<td>Irreversible renal disease</td>
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<td>Irreversible neurological disease</td>
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<td>Recent or evolving stroke</td>
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<td>Coexisting terminal condition (eg, metastatic cancer, cirrhosis)</td>
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<td>Abdominal aortic aneurysm ≥5cm</td>
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<td>Fixed pulmonary or portal hypertension</td>
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<tr>
<td>Severe pulmonary dysfunction (eg, FEV1 &lt;1L)</td>
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<tr>
<td>Multisystem organ failure</td>
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<td>Inability to tolerate anticoagulation</td>
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<td>Heparin-induced thrombocytopenia</td>
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<tr>
<td>Severe psychosocial limitations</td>
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<tr>
<td>Medical nonadherence</td>
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<tr>
<td>Relative**</td>
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<tr>
<td>Age &gt;80 years for DT</td>
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<tr>
<td>Morbid obesity (BMI &gt;40 kg/m²)</td>
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<tr>
<td>Severe chronic malnutrition (BMI &lt;21 kg/m² in males and &lt;19 kg/m² in females)</td>
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<tr>
<td>Musculoskeletal disease that impairs rehabilitation</td>
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<tr>
<td>Active systemic infection</td>
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<tr>
<td>Prolonged intubation</td>
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<tr>
<td>Untreated malignancy</td>
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<tr>
<td>Severe PVD</td>
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<tr>
<td>CKD with serum creatinine level &gt;3.0 mg/dl</td>
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<tr>
<td>Severe mitral stenosis or moderate to severe aortic insufficiency or uncorrectable mitral regurgitation</td>
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<tr>
<td>Active substance abuse</td>
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<tr>
<td>Impaired cognitive function</td>
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<tr>
<td>Unmanaged psychiatric disorder</td>
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<tr>
<td>Lack of social support</td>
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<tr>
<td>Other abbreviations as in Table 1. (Adapted from Peura et al and Wilson et al)</td>
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</tbody>
</table>

* Necessary for destination therapy as stated by Centers for Medicare & Medicaid Services. ** Warrants evaluation by advanced heart failure team. CKD, chronic kidney disease; CRT, cardiac resynchronization therapy; DT, destination therapy; FEV1, forced expiratory volume in 1 s; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association Class; PVD, peripheral vascular disease; VAD, ventricular assist device; VF, ventricular fibrillation VT, ventricular tachycardia. Other abbreviations as in Table 1.
lead to ineligibility for transplantation while conversely a DT patient may have a significant decrease in pulmonary hypertension while on MCS therapy rendering them transplant-eligible in the absence of other contraindications. Of note, 17% of DT patients ultimately undergo transplant. In our opinion, these fractured indications for MCS while serving the regulatory reimbursement arena, tend to partition clinical care into stuttering compartments. It may be better to view MCS as “advanced heart failure therapy”, with subsequent transplant eligibility or lifetime MCS support.

Although there are no absolute consensus guidelines regarding durable MCS implantation, criteria have been developed to optimize patient selection and thereby outcomes. Table 3 outlines specific indications and contraindications prior to consideration of VAD implantation. Several risk scores have also been developed to assess operative risk after MCS implantation and thus aid optimal patient selection.

Although potentially useful for preoperative clinical decision-making, these scoring tools are limited by their development in often small, selected, single-device populations as well as their lack of prospective validation.

### Contemporary Challenges Surrounding Durable MCS

#### Right Heart Failure

Right ventricular (RV) failure after LVAD implantation in the operating room is a serious complication, reported in up to 20–30% of cases. It is commonly defined as a need for right-sided MCS support (RVAD or ECMO), requirement for inotropic support for >14 days, or hospital discharge on an inotrope. Right heart failure after LVAD is associated with up to 6-fold increased risk of death, and independently predicts prolonged intensive care unit and total hospitalization stay, higher incidence of end-organ dysfunction and increased morbidity. The Fifth INTERMACS Annual Report, including 6 years of more than 6,000 durable MCS implants, found that the need for right-sided VAD had a significant detrimental impact on early (1–2 months) mortality, compared with moderate or mild RV dysfunction. Other clinical studies suggest that the higher mortality rate persists even after successful weaning of inotropes, leading to significantly worse survival to transplantation (27% in patients requiring RVAD vs. 83% in those without RVAD) and directly correlates with the duration of inotropic support. Given the clinical consequences of RV failure after LVAD implantation, multiple risk scores have been developed to try to predict its occurrence and thus plan for biventricular support from the outset.

One of these scores (known as the “Right Ventricular Failure Risk Score”) focused on clinical predictors, identifying vasopressor requirement and evidence of hepatic (elevated aspartate aminotransferase and serum bilirubin levels) and renal dysfunction (elevated serum creatinine ≥2.3 mg/dl) as significantly predictive of RV failure and increased mortality. Regarding hemodynamic predictors, low pulmonary arterial pressure and elevated right atrial pressure in the setting of low RV stroke work index and cardiac output have been found to best identify patients with preoperative decreased RV contractility, and thus at increased risk of postoperative RV failure. Pre-implant echocardiographic assessment of the RV is also important; a dilated RV >0.6 that of the LV is of concern. Additionally, severe functional tricuspid regurgitation indicates long-standing volume and pressure overload, and is also a risk factor for early postoperative RV failure. Patients demonstrating these clinical, hemodynamic and echocardiographic profiles associated with high risk of postoperative right heart failure and associated increased morbidity and mortality risk should be considered for either a priori or early use of biventricular support. Survival has been shown to be better with planned RV support compared with salvage right-sided MCS, and also in those with early (within 24 h) salvage RVAD compared with later (70% vs. 57% survival to transplant). Tricuspid valve repair with annuloplasty ring may be considered for patients with moderate-severe tricuspid regurgitation but is controversial. As it turns out, the ability of risk scores or clinical criteria to predict the occurrence of right heart failure is imprecise at best and an area for active investigation.

#### Gastrointestinal Bleeding

The incidence of gastrointestinal (GI) bleeding in patients with continuous-flow devices is estimated at ≥2%, based on in-trial observations and INTERMACS registry data. Because patients with continuous-flow LVADs are maintained on systemic anticoagulation, bleeding anywhere along the GI tract is a common occurrence. Upper GI bleeds are more commonly observed than lower GI bleeds (60% vs. 40%) and one-third of all GI bleeds are caused by angiodysplasia. It is postulated that the high shear stress on the blood as it flows through the device converts globular multimers of von Willebrand factor (vWF) into elongated proteins subject to proteolysis by the metalloprotease ADAMTS 13. This phenomenon was first described in the scenario of severe calcific aortic stenosis and is known as Heyde’s syndrome. In addition to this acquired von Willebrand disease (vWD), an increased propensity for the development of angioectasias is observed, because of the increased intraluminal pressure and muscular contraction, which may result in dilated mucosal veins. Furthermore, the reduced pulse pressure imparted by the VAD may lead to intussusception, regional hypoxia and vascular dilatation. Finally, platelet aggregation is also impaired in many patients and can be measured by a ristocetin cofactor assay. Impaired platelet function and/or hemostasis caused by acquired vWD, the presence of angioectasias and compromised platelet aggregation account for an increased predilection for bleeding. No definitive therapy exists for this commonly encountered complication. Appropriate endoscopic evaluation and holding and potentially reversing anticoagulation are the mainstay of management. Ocreotide has been proposed as a potential therapeutic agent used to decrease the incidence of angiodysplasia-related bleeding, but requires a systematic study to warrant its recommendation. Some data suggest reducing the speed of the VAD to allow for intermittent aortic valve opening and higher pulsatility indices may serve to reduce the frequency of bleeding events. This strategy has also not been proven on a large scale and merits further study.

#### Infection

The most frequent complication post-VAD implantation remains infection, accounting for >16% of all deaths according to the INTERMACS registry and HeartMate II clinical trials. Patients who have undergone MCS implantation are often plagued by a myriad of comorbidities including renal failure, diabetes, malnutrition and chronic lung disease against a backdrop of long-standing chronic low output heart failure and/or cardiogenic shock. This debilitated state serves as an ideal platform for infection. In addition to patient-related factors, pump design (continuous pumps appear less prone than pulsatile pumps), surgical technique and percutaneous lead care appear to be the main determinants of infection risk.

In 2010, the ISHLT working group published standardized criteria for definitions of infections in VAD patients, recognizing the importance of this major limitation to successful MCS therapy. Infections in MCS patients were specifically divided into 3 categories: VAD-specific (if involving the pump, cannula, pocket or percutaneous driveline); VAD-related (in-
In the BTT trial, driveline-exit site infection remained one of the most common postoperative complications, with an incidence of 0.29 events/patient-year. In the HeartWare HVAD for BTT indication has shown similar risk of stroke vs. other VADs.

In the case of AMR and ACR, 10% of patients with hemodynamic instability AMR and ACR can coexist in 25% of cases. Antibody-mediated rejection (AMR) involves immobilization of the driveline to prevent friction and breakdown of the skin barrier, thereby predisposing to infections because of driveline infections. Indeed, the need for a driveline that exits the skin barrier as one of the most important infection allows for an upgrade to urgent transplant priority.

**Table 4. Types, Mechanism, Timing, and Treatment of Graft Rejection (ISHLT Guidelines for the Care of Heart Transplantation Recipients)**

<table>
<thead>
<tr>
<th>Type</th>
<th>Mechanism</th>
<th>Timing after transplant</th>
<th>Frequency</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperacute rejection</td>
<td>Preformed antibodies to donor antigens (generally human leukocyte antigen (HLA) class I on donor vascular endothelium. This causes fixation of complement throughout vasculature and leads to necrosis, thrombosis, graft ischemia</td>
<td>Minutes to hours</td>
<td>Rare</td>
<td>Almost uniformly fatal. Stabilization with mechanical circulatory support as appropriate, possibly retransplantation</td>
</tr>
<tr>
<td>Acute cellular rejection (ACR)</td>
<td>T-cell mediated—donor antigen-presenting cells (APC) migrate from allograft to recipient lymphoid tissue, presenting donor HLA molecules to recipient T cells. T cells, macrophages, B cells and plasma cells infiltrate cardiac allograft</td>
<td>Anytime (but most common in first 6 months)</td>
<td>20–40% of HT recipients will experience in 1st postoperative year</td>
<td>High-dose intravenous corticosteroids first line. If hemodynamic compromise or no clinical improvement, cytolytic therapy (antithymocyte antibodies). Adjustments in maintenance immunosuppression as required to prevent recurrence</td>
</tr>
<tr>
<td>Antibody-mediated rejection (AMR)</td>
<td>Antibodies are directed against donor vascular endothelial antigens leading to B-cell activation, proliferation and maturation. Circulating complement leads to direct cell injury, increased number of inflammatory cells and phagocyte-mediated cell death, which then leads to microvascular coagulation, myocardial ischemia and allograft dysfunction</td>
<td>Usually after 1st year</td>
<td>Less common than ACR; 10% of patients with hemodynamic instability AMR and ACR can coexist in 25% of cases</td>
<td>Plasmapheresis Intravenous immunoglobulin Steroids</td>
</tr>
<tr>
<td>Chronic rejection</td>
<td>Both humoral and cellular mechanisms resulting in diffuse atherosclerosis, myointimal proliferation of coronary vessels</td>
<td>Develops early, within the 1st year post-transplant and is usually progressive</td>
<td>Documented by angiography in 50% of patients at 5–15 years follow-up Leading cause of death up to 5 years post-transplant</td>
<td>Possibly mTOR inhibitors Retransplantation</td>
</tr>
<tr>
<td>Cardiac allograft vasculopathy</td>
<td>Heterogeneous proliferative intimal thickening of the coronary graft vasculature. Initiated and propagated by both immunological and non-immunological insults</td>
<td>Usually after 1st year</td>
<td>Anytime (but most common in first 6 months)</td>
<td>Plasmapheresis Intravenous immunoglobulin Steroids</td>
</tr>
</tbody>
</table>

Concluding infective endocarditis, bloodstream infections with or without an indwelling central venous catheter and mediastinitis and non-VAD-related (including lower respiratory tract infection, cholecystitis and urinary tract infection). The most common of the VAD-specific infections is percutaneous driveline infections. Indeed, the need for a driveline that exits the skin barrier, thereby predisposing to infections because of breakdown of this barrier, remains a fundamental limitation of all currently available durable MCS devices. Percutaneous lead infections occurred at a rate of 0.48 events/patient-year in the HMII DT trial, with associated lead damage the most common cause of VAD replacement. In the HeartWare HVAD BTT trial, driveline-exit site infection remained one of the most common postoperative complications, with an incidence of 0.29 events/patient-year. In order to prevent percutaneous driveline and related device infections, protocols for optimal inpatient and outpatient care have been established and involve immobilization of the driveline to prevent friction and breakdown of the skin barrier as one of the most important components. If infection develops, depending on its severity, increased frequency of dressing changes, hospitalization for intravenous antibiotics, surgical revision, wound vacuum therapy or even pump exchange may be required. Regarding VAD-related infections, pump-related endocarditis (infection involving the blood surface interface of the pump) is a rare but serious complication of VAD implantation, which may be very difficult to eradicate, often requiring chronic antibiotic suppression therapy. For those with a BTT indication, device-related infection allows for an upgrade to urgent transplant priority.

**Stroke** Stroke remains one of the most feared complications of durable MCS. The rate of stroke does not appear to differ between continuous-flow and pulsatile devices whether among BTT or DT populations. In the latter, the rate of disabling stroke also did not differ significantly among device types. Stroke etiology (ischemic or hemorrhagic) was similarly equivalent between groups. Initial data on the HeartWare HVAD for BTT indication has shown similar risk of stroke vs. other VADs. It is worth noting that as the demographic profile of VAD candidates, and in certain DT candidates, continues to evolve, particularly the increased number of implants in those of advancing age, stroke risk may continue to remain significant despite evolving technologies and anticoagulation regimens. To reduce the risk of thrombotic events, both anticoagulation and antiplatelet therapy are recommended as commencing in the postoperative and continuing into the outpatient setting. Optimal levels of both therapies are as yet undefined and in most situations need to be adjusted according to the individual’s unique risk profile. It is important to note that in 331 HeartMate II outpatients followed for 6 months, a total thrombotic event rate of 3.3% was dwarfed by a hemorrhagic event rate of 22%. Following this, for HeartMate II recipients, warfarin doses are typically adjusted to achieve a target international normalized ratio (INR) in most cases of 1.5–2.5 in association with aspirin doses of 81–325 mg. In the case of VAD-associated ischemic stroke or transient ischemic attack, aggressive anticoagulation is not recommended in the acute setting in order to avoid potential transformation to hemorrhagic stroke.
Pump Thrombosis  The incidence of clinically relevant pump thrombosis was infrequent in both the original HeartMate II trial (4% of DT and 1.4% of BTT patients) and in a subsequent real-world retrospective analysis of 331 BTT HeartMate II outpatients published around the same time (n=3, 0.009%). However, since then, a significantly increased incidence of pump thrombosis is being observed in clinical practice, and may be as high as 10% (Table 4). Purported reasons for this increased incidence include the evolving demographics of the VAD population (increasing age and comorbidities likely to be prothrombotic); growing concern over recurrent GI bleeding leading to diminished INR targets and/or discontinuation of antiplatelet therapy, and potentially technical innovations in the HeartMate II device itself (including possible association with the partial bend relief disconnection complication). Thrombus may evolve from smaller deposits within the pump and its components, or may be ingested by the pump following origination in the left atrium and ventricle. Clinically, a patient with pump thrombosis may present with acute or subacute HF symptoms, a new neurological deficit, and/or with the consequences of hemolysis such as dark-colored urine. An LDH >1,000 or 3-fold the previous level, hemoglobinuria and/or significantly elevated plasma free hemoglobin level should also raise suspicion of VAD thrombosis even in the absence of symptoms. Pump thrombosis can affect all 4 HeartMate II parameters; most classically, in the case of a large thrombus in contact with the rotor, leading to power obstruction, normal unloading of the LV with increasing pump pulsatility; in the case of significant flow without an associated increase in arterial blood pressure; this may be apparent as a change in VAD sounds on auscultation with a stethoscope. Definitive treatment is pump replacement/exchange and is recommended in all patients in whom reoperation is appropriate; IV heparin infusion may be initiated initially to prevent progression of thrombus. The use of thrombolysis (directed or systemic) has not been found to be associated with optimal results and should only be used with great caution in highly selected situations.

Conclusions and Future Directions

Today, a patient with advanced heart failure can be offered more options than previously thought possible. Candidates are now more frequently older, sicker, and have a higher prevalence of comorbidities that in the past would have rendered them unsuitable for transplant listing or durable MCS. Many patients who in the past would not be considered as viable candidates for transplantation because of significant pulmonary hypertension or end-organ dysfunction are now becoming candidates following a period of VAD therapy and support.

However, inherent in this evolving older patient population is the likelihood of a greater adverse event burden, which will require increased surveillance and, most likely, challenging decision-making regarding the risk/benefit of subsequent options going forward. As devices become smaller, more durable, and eventually hold promise of being fully entrenched within the body, long-term survival will continue to improve. Interestingly, development of these newer devices with reduced perioperative surgical risk may once again dramatically shift the MCS patient population into those with less severe heart failure. These potential developments in therapy, alongside the expansion of donor criteria, re-examination of previously disenfranchised patient groups and the possibility of more individual-targeted immunosuppression from a transplant perspective add up to an exciting and challenging era ahead for advanced heart failure physicians and their patients alike.

Disclosures

Conflict of Interest: Dr Mehra reports consulting for Thoratec, Boston Scientific, Medtronic, St. Judes, Abbott Vascular, National Institute of Health, American Board of Internal Medicine and International Society for Heart and Lung Transplantation; Drs Lala, Joyce and Groarke report no conflicts.

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