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Current and Future Considerations in the Use of Mechanical Circulatory Support Devices*

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Key Words

heart-assist device, heart failure

Abstract

Heart failure (HF) is a major public health problem in the United States, and its prevalence is likely to increase with the aging U.S. population. Mechanical circulatory support (MCS) utilizing bladder-based blood pumps generating pulsatile flow has been reserved for patients with severe HF failing medical therapy. As MCS technology has advanced to include rotary blood pumps, so has our understanding of the biological and clinical responses to MCS, which in turn has altered the risk/benefit profile of this therapy. This may lead to paradigm shifts in device usage from support of end-stage HF to temporary support for recovery of cardiac function and earlier usage, to, ultimately, prevention of disease progression. This review serves to explore the current state and future opportunities of MCS within our larger understanding of the epidemiology, pathophysiology, and treatment options for HF.

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INTRODUCTION

Heart failure (HF) is one of the largest public health problems in the United States. The mainstay of treatment for HF is lifestyle modification and medications. Medical and surgical treatment of HF has advanced considerably over the past 20 years. Traditionally, mechanical circulatory support (MCS) has been reserved for patients with severe HF failing medical therapy and as bridge to cardiac transplantation. As technology has advanced, so has our understanding of the biological and clinical responses to MCS, resulting in reductions in morbidity and mortality, which in turn has altered the risk/benefit profile of this therapy. Ultimately, this may lead to a paradigm shift in device usage from support of end-stage heart failure to temporary support for recovery of cardiac function and earlier usage to prevent disease progression. This review serves to explore the current state and future opportunities of MCS within our larger understanding of the pathophysiology, epidemiology, and treatment options for HF.

HF: heart failure

MCS: mechanical circulatory support

HEART FAILURE: UNDERSTANDING THE PROBLEM

Definition

HF is the clinical syndrome of fatigue, breathlessness, and/or fluid retention that results from impaired cardiac output. This should be distinguished from ventricular dysfunction, which is a measured impairment in cardiac function and can exist both with and without symptoms of HF. The typical clinical measure of ventricular dysfunction is the left ventricular ejection fraction (LVEF), which is the fraction of blood volume ejected from the ventricle each beat. Cardiogenic shock is the inability of the heart to pump sufficient blood to the body's tissues to maintain organ perfusion. HF and ventricular dysfunction can occur due to impaired ability of the heart to eject blood (systolic HF) or due to impaired filling of the heart (diastolic HF or HF with normal EF).

Additionally, HF can be termed left-sided, right-sided, or biventricular based on the ventricle that is impaired and causing symptoms. HF symptoms result from elevated pressure in the vessels upstream of the failing ventricle. Thus, left-sided failure resulting from left-ventricular dysfunction causes an elevation of left-ventricular end-diastolic pressure (filling pressure) and pulmonary venous pressure. Increased pulmonary venous pressure leads to fluid extravasation in the lungs, causing pulmonary edema and breathlessness. Symptoms of right-sided failure include lower extremity edema, ascites, and hepatic congestion sometimes leading to liver dysfunction. Severity of HF symptoms has been classified by the functional impairment of the patient using a numerical scale from 1 to 4, the New York Heart Association (NYHA) classification (see **Table 1**) (1). This classification has remained useful for more than 30 years owing to its strong association with mortality. An alternative classification system has been put forth by a collaborative effort from the American College of Cardiology and the American Heart Association where HF is stratified based on risk factors, structural abnormalities, and responsiveness to treatment (see **Table 2**) (7). To date, MCS has been reserved for end-stage HF patients at imminent risk of dying from pump failure. However, the scope of the problem and the improving risk-benefit profile of MCS technology offer the opportunity to explore MCS for a broader range of HF patients.

LVEF: left ventricular ejection fraction

NYHA: New York Heart Association

Table 1 New York Heart Association heart failure classification and mortality across clinical trials

Class	Functional limitation	Two-year mortality				
		ACE-I trials	BB trials	ARB trials	ICD and CRT trials	SVR surgical registry
		1987–1999 (18, 20–23)	1996–2003 (25–30)	2001–2003 (31–36)	2002–2005 (68, 69)	2004 (46)
I	No symptoms with ordinary activities	10%–15%	NR	NR	NR	5%
II	Symptoms with ordinary activities	15%–20%	17%	18%–25%	12%–15%	8%
III	Symptoms with less than ordinary activities	30%–40%	25%	20%–25%	18%–25%	11%
IV	Symptoms at rest	40%–60%	20%	NR	NR	30%
IV-inotrope dependent	100% 1 year mortality (42)	NR	NR	NR	NR	NR

ACE-I, angiotensin converting enzyme inhibitor; BB, beta-blocker; ARB, angiotensin receptor blocker; ICD, implantable cardioverter-defibrillator; CRT, cardiac resynchronization therapy; SVR, surgical ventricular remodeling; NR, not reported/not studied.

Table 2 Revised American College of Cardiology/American Heart Association HF classification

Stage	Definition	Examples	Prevalence*	Five-year survival (3)
0	Healthy		32%	
A	Patients at high risk of developing HF	Hypertension, CAD, diabetes, cardiotoxic drug or alcohol use, history of rheumatic fever, relative with cardiomyopathy	22%	99%
B	Patients with structural heart disease but who have never shown signs or symptoms of HF	LV hypertrophy, LV dilatation or hypocontractility, asymptomatic valvular heart disease, previous MI	34%	96%
C	Patients who have current or prior symptoms of HF	Dyspnea or fatigue due to HF, on treatment for previous HF	12%	75%
D	Patients with advanced structural heart disease who require specialized interventions	Frequent HF hospitalization, awaiting cardiac transplant, home inotropes or VAD	0.2%	20%

*Prevalence is in the United States among all people age 45 or over (3).

HF, heart failure; CAD, coronary artery disease; LV, left ventricle; MI, myocardial infarction; VAD, ventricular assist device.

Epidemiology

Cardiovascular disease remains the leading cause of death in the United States, with approximately 5 million having HF and 550,000 new cases diagnosed annually (2). HF is the single most frequent Medicare discharge diagnosis in the United States. Its estimated total cost in the United States for 2006 is \$29.6 billion (2). For 2003, HF resulted in more than 1 million hospitalizations and approximately 250,000 deaths. By comparison, survival rates at one year for HF are below that for breast, prostate, and bladder cancers, above lung and stomach cancers, and similar to colon cancer. Hospitalizations and deaths due to HF have increased linearly over the past 30 years (2). In spite of the advent of many treatments that have improved mortality rates for HF, the rates are still at levels of 20% at 1 year, and 70% to 80% at 8 years in the general population (2).

The risk of developing HF in the overall population is approximately 20%. Of those with HF, 50%–60% have systolic ventricular dysfunction (LVEF <50%), the rest having diastolic dysfunction. Systolic dysfunction is moderate to severe (LVEF <40%) in one third of those who have it. The severity of diastolic dysfunction is associated with increased risk of systolic dysfunction (4). The two largest risk factors for the development of HF are myocardial infarction (MI) and hypertension. Blood pressure >160/100 mm Hg doubles the risk of developing HF (5). After myocardial infarction, 22% of males and 46% of females will develop HF within 6 years (2), occurring in a linear time-dependent manner, with a tenfold increased risk of death (6). Other significant risk factors for developing HF include diabetes, obesity, and impaired renal function. Given the large percent of the population at risk for developing HF, an updated classification system for HF has been developed that recognizes the need to treat high-risk conditions to prevent progression to overt HF (see **Table 2**) (7). As **Table 2** shows, the prevalence of advanced heart disease requiring specialized interventions (Stage D HF) is estimated to be 0.2% of the U.S. population age 45 and over (3). Alternative HF treatments, such as MCS, are necessary to treat this large public health problem, where the gold standard therapy for end-stage disease is cardiac transplantation (see below), which is limited to very few.

MI: myocardial infarction

Pathophysiology of HF

Although HF was once thought to be the result of progressive pump failure, extensive biochemical studies have revealed the complex nature of the disease. HF is usually preceded by an initial insult to ventricular function, such as MI or chronic hypertension. Initial compensatory mechanisms, such as chamber dilation and activation of the sympathetic nervous system, help acutely but over time lead to a vicious cycle of progressive ventricular dysfunction and chamber dilation, a process termed remodeling (see **Figure 1**). MCS reverses many of the adverse physiological changes occurring in HF (see Mechanical Support for Myocardial Recovery), but the link to clinical recovery of cardiac function is still poorly understood.

One of the initial responses to acute injury is chamber dilation. Dilation results in increased wall stress that induces an increase in ventricular wall thickness, termed hypertrophy. This results in several hemodynamic benefits, such as normalization of wall stress and stroke volume. However, the benefits of hypertrophy come at the cost of increased metabolic demand of the myocardium,

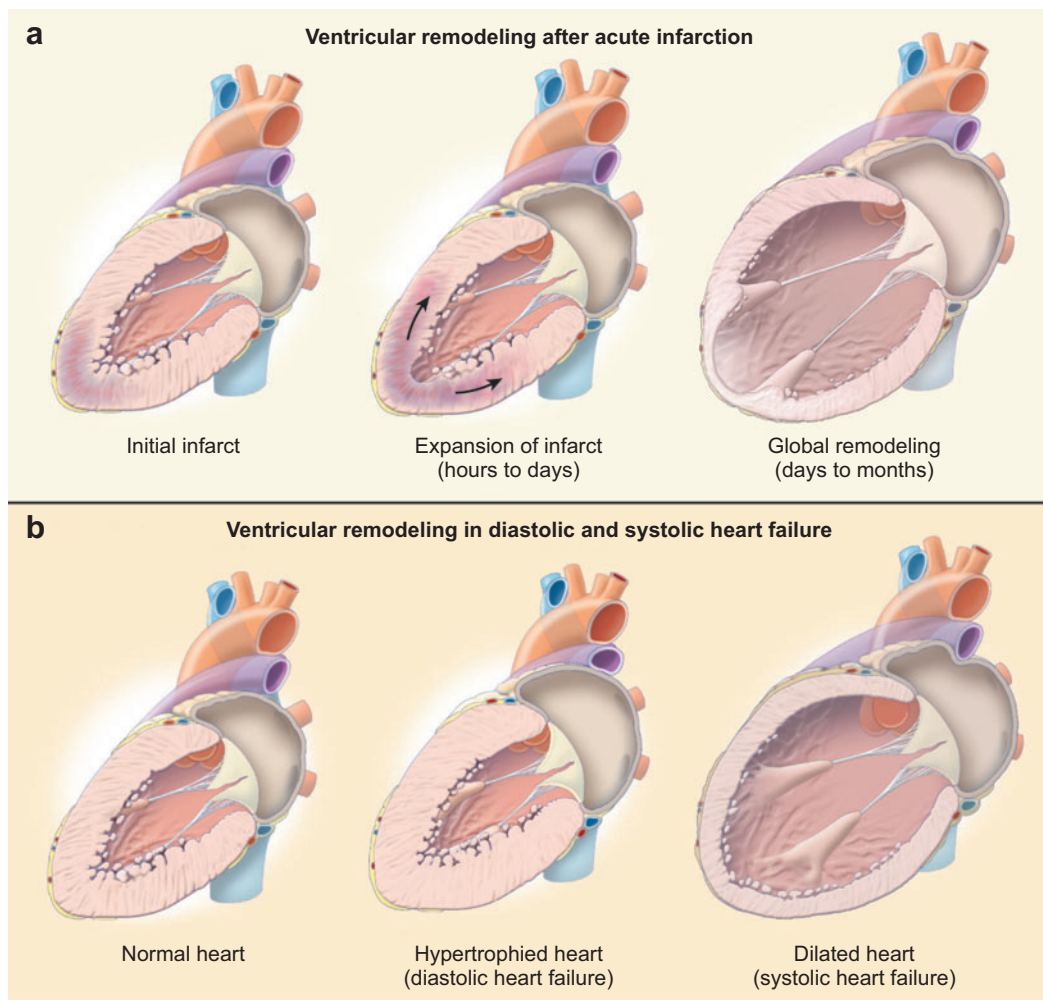


Figure 1

Ventricular remodeling in heart failure. From Reference 13.

reduced coronary flow reserve, and decreased compliance. Increased wall stress, decreased compliance, and coronary flow reserve reduce oxygen delivery to the myocardium, causing diastolic dysfunction. Such chronic oxygen supply/demand mismatch further contributes to deterioration in stroke volume and systolic ventricular function (8, 9).

Ventricular hypertrophy and remodeling is a process involving cells as well as the extracellular matrix (ECM). Cardiomyocytes hypertrophy while the ECM undergoes profound changes thought to be induced by paracrine response to myocyte stretch (9). Local inflammatory response is frequently seen acutely and involves oxygen free radical formation, leading to apoptosis and loss of myocytes (9). Tumor necrosis factor (TNF) has been particularly implicated in this maladaptive cascade (10). Matrix metalloproteinases (MMPs), whose function is predominately to break down the ECM, are upregulated leading to increased turnover of the ECM, which is a critical biochemical step in ventricular remodeling and cardiac fibrosis (11). Collagen content increases and its subtype distribution is altered as well as its cross-linking (11). Alterations in collagen and MMP expression, as well as tissue inhibitors of metalloproteinases (TIMPs), are influenced by a wide variety of cytokines (including TNF, interleukin-1 β , transforming growth factor- β ₁), whose expression is also altered in HF (9, 11).

The neurohormonal system responds to HF in an attempt to physiologically compensate for a low cardiac output state. Activation of the sympathetic nervous system (SNS) and the renin-angiotensin-aldosterone system (RAAS) causes increased heart rate and myocardial contractility, vasoconstriction in arterial and venous beds to preserve end-organ perfusion, sodium retention in the kidney to facilitate volume expansion, and improved stroke volume via the Frank-Starling pressure-volume relationship. Plasma levels of norepinephrine, epinephrine, angiotensin II, and aldosterone positively correlate with mortality (12). Natriuretic peptides cause sodium retention in an effort to maintain tissue perfusion pressure. Endothelin, a strong vasoconstrictive hormone, is also upregulated. Although these multiple feedback mechanisms can result in improved cardiac function and/or tissue perfusion acutely, they can also cause a vicious cycle of ventricular remodeling, further stimulating their expression, which chronically worsens HF.

MEDICAL TREATMENT OF HEART FAILURE

The goals of medical therapy are to improve survival, decrease symptoms, and maximize functional status. There is now a sizable list of medical interventions to treat HF (see **Table 3**). A step-wise approach to the treatment of HF is generally employed, predicated on the stage of disease (see **Figure 2**) (13). Each successive therapy has been evaluated clinically, resulting in a progressive decline in the absolute risks of morbidity and mortality. Addition of angiotensin-converting enzyme (ACE)-inhibitors and beta-blockers has dropped mortality to as low as 12% at one year in NYHA functional class IV HF patients (see **Table 1**). Most medications are approved for either the treatment of symptomatic HF in general or, more specifically, for post-MI ventricular dysfunction. The existence of a specific indication for post-MI ventricular dysfunction speaks to the high likelihood with which this can progress to overt clinical HF. The future of HF pharmacotherapy is likely pharmacogenetics, in which medications are prescribed based on genetic predisposition to respond to therapy. Current investigations of pharmacogenetics are underway and have already shown promising results (14).

NON-MECHANICAL CIRCULATORY SUPPORT SURGICAL TREATMENT OF HEART FAILURE

There are several cardiac surgeries for HF that may delay progression of disease and the need for MCS. Coronary artery bypass graft surgery (CABG) (43, 44), valve surgery (45), ventricular

Table 3 Medical treatment of HF

Nonpharmacologic	Patient education of low sodium/fluid diet, symptoms, daily weights, avoidance of nephrotoxic agents (such as nonsteroidal antiinflammatory drugs). Multidisciplinary approach to care.
Diuretics (furosemide, bumetanide, etc.)	Volume control. Chronic use may stimulate the renin-angiotensin-aldosterone system (RAAS) and increase mortality (15). Current investigations of mechanical fluid removal (ultrafiltration) (16).
Digitalis	Block sodium-potassium ATPase. Improve symptoms and decrease hospitalizations but not mortality (17). Reserved for patients that remain symptomatic despite other treatments.
Hydralazine/nitrates	Vasodilation, volume control. Improve survival but inferior to ACE-inhibitors (18). Of particular benefit for self-identified black patients likely due to genetic resistance to ACE-inhibitors (19).
ACE-inhibitors (lisinopril, enalapril, etc.)	Block conversion of angiotensin I to angiotensin II in the RAAS pathway. Improve survival, symptoms, quality of life and decrease hospitalizations in asymptomatic LV dysfunction and HF of any severity (18, 20–23). Prevent adverse remodeling, particularly post-MI; promote reversal of remodeling (8, 24). First choice for medical management of HF.
Beta-blockers (carvedilol, metoprolol succinate)	Prevent SNS activation of cardiomyocytes and vascular smooth muscle by blocking cellular catecholamine β -receptors. Improve survival, symptoms, LVEF, NYHA functional class, and decrease hospitalizations, regardless of HF severity (25–27). Prevent adverse remodeling, particularly post-MI, promote reversal of remodeling (28–30).
Angiotensin-receptor blockers (valsartan, candesartan)	RAAS blockade, prevent ACE-inhibitor escape phenomenon, block kininase II to inhibit bradykinin degradation. Bradykinin may have a beneficial role in HF due to its vasodilatory properties and positive effects on endothelial function (31). Improve survival, reduce hospitalizations (32, 33). Similar results for acute MI with LV dysfunction, promote reversal of remodeling (35, 36).
Aldosterone-receptor blockers (sprinolactone, eplerenone)	RAAS blockade, prevent ACE-inhibitor escape phenomenon, block aldosterone-induced perivascular inflammation (37). Improve survival, reduce hospitalizations in severe HF and post-MI (38, 39).
Inotropes (dobutamine, milrinone)	Adrenergic stimulation (dobutamine) to increase cyclic adenosine monophosphate production (or block cAMP degradation in the case of milrinone), which increases intracellular calcium and contractile force. Improve hemodynamics and symptoms, but increase tachyarrhythmias and mortality (40–42). Few clinical trials. Reserved for end-stage HF. MCS traditionally considered in inotrope-dependent patients.

surgical remodeling (46), or some combination thereof (47, 48) have all been shown to benefit appropriately selected HF patients. Percutaneous coronary interventions are now a reasonable option to CABG owing to the advent of coronary stents, specific antiplatelet therapies such as glycoprotein IIb/IIIa inhibitors or clopidogrel, and lipid-lowering therapies that greatly improve percutaneous coronary procedural outcomes (49, 50). Drug-eluting stents, which have a lower incidence of recurrent stenosis (51, 52) hold even more promise and a trial is underway to compare drug-eluting stents to CABG (53). Other advances in percutaneous management of HF include valves designed for percutaneous implantation, which are in the early stages of clinical investigation and may be of benefit in patients with too great an operative risk for a surgical approach (54–56).

Transplant

For severe refractory HF, the gold standard for treatment is orthotopic heart transplantation. Currently, posttransplant survival rates are approximately 85% at 1 year, 80% at 2 years, and 75%

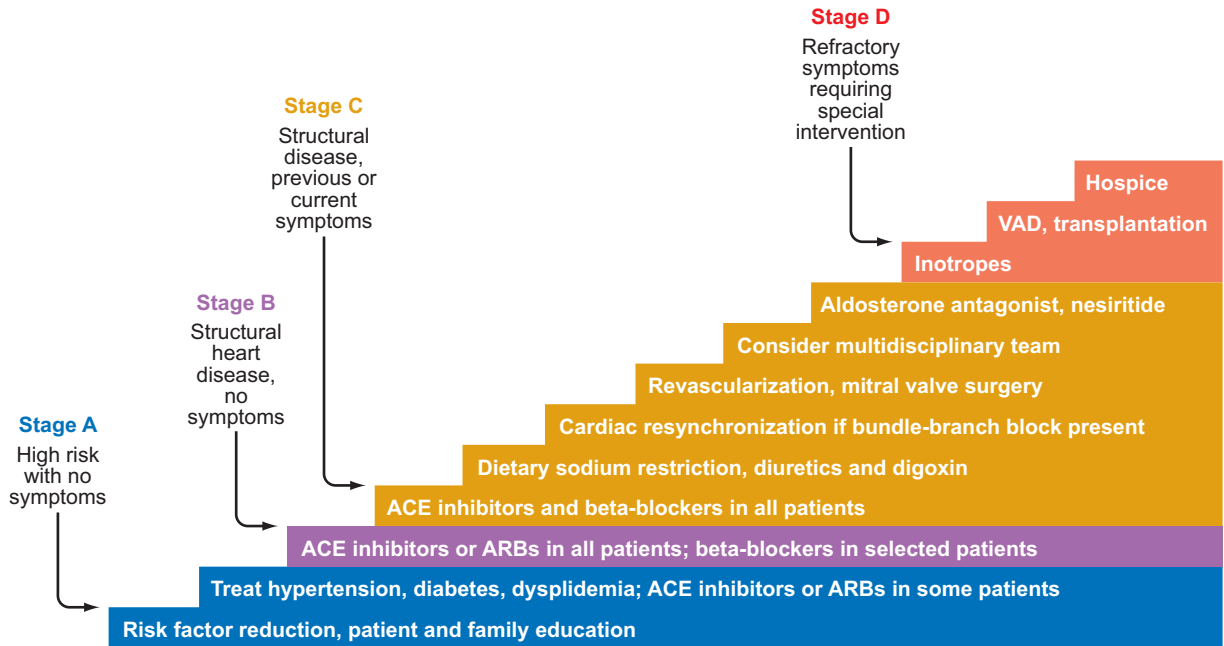


Figure 2

The current paradigm for the treatment of HF. From Reference 13.

at 5 years (57). This is at least as good as any medical HF trials in NYHA class III-IV patients, and is particularly better than outcomes associated with inotropes, which are needed in up to half of HF patients awaiting transplant. However, the number of donors has continuously declined over the past 10 years. Currently, 3000–4000 candidates are listed annually in the United States but only approximately 2000 cardiac transplants are performed (58). Furthermore, it is estimated that 20,000 patients per year could benefit from cardiac transplantation (59). Although patient status on the transplant list has become more ill, deaths on the transplant list have declined, likely as a result of improved therapy for HF, including MCS as a bridge to transplant. Despite this, 8%–10% of patients on the transplant list die each year.

NON-MECHANICAL CIRCULATORY SUPPORT DEVICES FOR THE TREATMENT OF HF

Implantable Cardioverter-Defibrillators

Arrhythmic death causes 30%–60% of all HF deaths (60). Implantable cardioverter-defibrillators (ICDs) as primary prevention of sudden cardiac death for HF patients improve survival by 25%–30% (61, 62). ICDs are indicated for any stable symptomatic HF patient (NYHA class II or greater) with an LVEF <35%. Medical therapy for HF (including beta-blockers, ACE-inhibitors, and aldosterone antagonists) also has been shown to decrease the incidence of sudden cardiac death (25, 38, 39). MCS can be used for intractable life-threatening ventricular arrhythmias in the setting of severe HF.

There are several caveats to defibrillator therapy for HF patients. First, complications from ICD implantation occur in 5% of the HF population and include infection, bleeding, lead dislodgement,

and pneumothorax requiring hospitalization or surgery (62). Second, there is always the risk of recurrent or inappropriate shocks from an ICD that could worsen quality of life and survival. Third, the optimal method of tachyarrhythmia termination with an ICD is unknown (antitachycardia pacing versus defibrillation, or some combination or progression in the programming). Fourth, defibrillation can exacerbate HF, as can defibrillation threshold testing, which is commonly performed to determine the amount of energy necessary for successful arrhythmia termination. Finally, all defibrillators function as pacemakers and right ventricular pacing has been associated with progression of HF and adverse remodeling (61, 63).

LV: left ventricle

Cardiac Resynchronization Therapy

Cardiac resynchronization therapy (CRT), or biventricular pacing, is based on the observation that ventricular conduction delay on an electrocardiogram (defined as a QRS interval greater than 120 ms) was frequently associated with HF (up to 25% of cases) and particularly with poor outcomes in HF patients (64, 65). Subsequent investigations found an association between electrical conduction delay (or dyssynchrony) and mechanical dyssynchrony, defined as delayed contraction of one ventricular wall relative to another during systolic contraction. By synchronously pacing the septum and free wall of the left ventricle (LV), initial studies found acute hemodynamic improvement, decreased mitral regurgitation, and decreased myocardial oxygen consumption (66, 67). With the advent of percutaneously placed left ventricular pacing leads (see **Figure 3**), large-scale

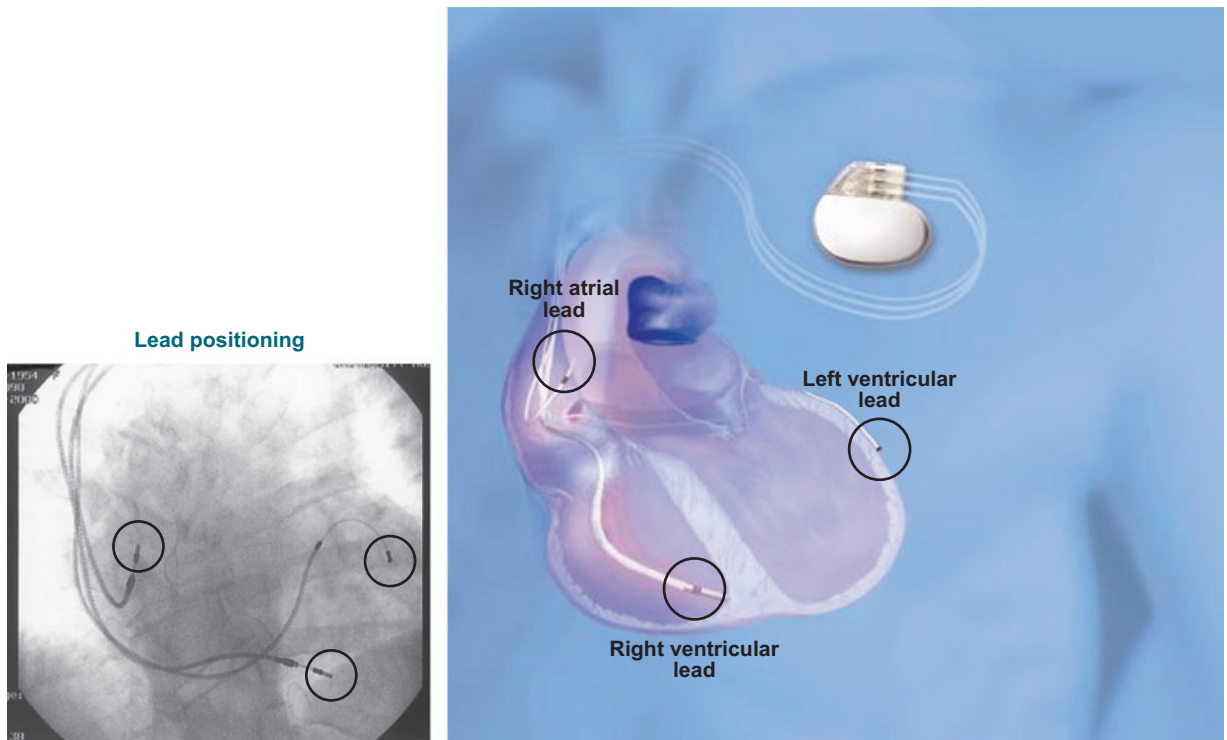


Figure 3

Cardiac resynchronization therapy device and anatomical positioning of leads. Inset demonstrates the positioning of the leads in the heart as seen on fluoroscopy as is typically used to guide implantation. Courtesy of <http://www.medtronicconnect.com>.

clinical trials have now shown CRT, with or without an ICD, for HF patients with reduced LVEF and wide QRS reduces death by as much as 36%. HF hospitalizations also are reduced and quality of life is improved (68, 69). Furthermore, CRT has been shown to improve such endpoints as distance walked in 6 min (although MCS improves function an additional several-fold), NYHA functional class, LVEF, and peak oxygen consumption. CRT reduces left and right ventricular dimensions (reverse remodeling) (70, 71). CRT devices are now approved by the Food and Drug Administration (FDA) and covered by the Centers for Medicare and Medicaid Services (CMS).

Some unresolved issues include the use of CRT for NYHA class IV HF patients, particularly those on inotropic support; better definitions of dyssynchrony; use in the setting of atrial fibrillation; and use for dyssynchrony induced by chronic right ventricular pacing. Overall, ICDs and CRT are examples of implantable technology to treat HF with excellent risk/benefit profiles that MCS technology must eventually emulate.

Cardiac Restraint Devices

Several devices under evaluation have addressed the problem of progressive ventricular remodeling via mechanical restraint to decrease wall stress by Laplace's law. The Acorn CorCap is a knitted polyester device that is surgically fitted over the exterior of the heart (72). This device decreases LV dimensions and improves functional status (NYHA class, 6-min walk distance), although at the expense of right ventricular function (73). The Myocor Myosplint reduces the LV radius of curvature. It consists of a flexible load-bearing tension member with epicardial pads on either end. Three are implanted across the diameter of the LV chamber (74). The Coapsys is similar to the Myosplint and is implanted just below the mitral valve to treat mitral regurgitation (75). Implantation of these devices has been limited to HF patients undergoing other cardiac surgeries.

Annuloplasty Rings

In patients with substantial mitral regurgitation in the setting of severely symptomatic HF (NYHA class III-IV) and LVEF <25%, surgical implantation of a ventricular annuloplasty ring to decrease the dimensions of the mitral opening can result in significant reduction in symptoms with reasonable operative mortality (5%) and survival (70% at 2 years) (76). The type of annuloplasty ring used may be significant. There is at least some retrospective data suggesting that a nonflexible ring is associated with reduced risk of recurrent surgery (77).

FUTURE THERAPIES: TISSUE ENGINEERING AND CELL TRANSPLANTATION

There is considerable active research into biological regeneration of the damaged myocardium in situ. One such method that has received considerable media attention is the implantation of cells into the heart (into or near the scar of a prior infarct, for example). Cells are generally taken from the same individual (autologous transplantation). Two broad types of cells have been studied: skeletal myocytes from a muscle, such as the quadriceps, and undifferentiated stem cells harvested from bone marrow or peripheral blood. There is also initial evidence in an animal model that stem cells harvested from the heart via percutaneous right ventricular endomyocardial biopsy are capable of regenerating myocardium (78). There is some evidence of cell engraftment in the heart and differentiation into functional cardiomyocytes. However many questions persist, including the rate of engraftment, the exact cell type that is most beneficial (myocytes, mesenchymal stem cells, angioblasts, etc.), the best method to introduce the cells (direct surgical injection, injection

through the coronary arteries in the cardiac catheterization laboratory), and the extent to which arrhythmias are induced. Clinical data from several modest-sized clinical trials (30–100 patients) in which stem cells were introduced via cardiac catheterization at the time of an acute MI revealed modest results, generally with an improvement in LVEF of 0%–6% at follow-up of 4–18 months (79–83). A successful biological solution to HF could represent a new paradigm in the use of MCS as a bridge to augmented myocardial recovery, and at least one such trial is underway (see Mechanical Support for Myocardial Recovery, below).

Patches made from decellularized extracellular matrix may be another useful solution to biological regeneration of myocardium. The patch retains biologically active substances such as growth factors providing paracrine as well as mechanical support for regrowth of cardiomyocytes. These devices are still in preclinical testing but have shown improvements in regional function in an MI model (84). Synthetic patches are also under development. These would act as temporary, degradable scaffolds to alter wall stresses during the remodeling period and might also be used for stem cell or tissue construct delivery (85).

TAH: total artificial heart

VAD: ventricular assist device

MECHANICAL CIRCULATORY SUPPORT

History

The first substantial efforts to develop mechanical circulatory support devices began in the 1960s and were stimulated by the space race between the United States and the former Soviet Union. The initial efforts were focused on the development of a total artificial heart (TAH) and are well chronicled in a review by Frazier (86). In 1964, the then National Heart Institute of the National Institutes of Health (NIH) invested funds into efforts to produce a TAH (87, 88). The wisdom then was that a concerted effort was needed to duplicate the pumping function of the heart, as an alternative to cardiac transplantation, and was mainly an engineering problem. Success was expected within 5–10 years. This was a serious underestimate to the effort required, and research and development continue today.

As with most technical/scientific advancements, circulatory support systems, including the TAH and ventricular assist device (VAD), could not have been developed without many successes in different fields, especially in engineering. Function, clinical application, operating principles, or other logical breakdown may conveniently categorize these systems. A distinction is usually made between a TAH and VAD. Currently, several VADs are approved for clinical use and routinely used in many centers, mainly as a bridge to cardiac transplantation. TAHs, however, are used more sparingly; they are currently limited to the relatively few centers that implant them in patients awaiting cardiac transplant.

Although TAH research predates VAD research, the latter developed more quickly. A VAD typically consists of a pump, energy converter, and energy source. The pump is intended in most cases to aid the natural LV in pumping blood throughout the systemic circulation. The blood flow capacity of the pump is variable. Clinically, the VAD was first intended to perform temporarily until either the natural heart recovered or until a donor heart became available. Intensive research and development by many industry and academic investigative teams led to the first clinically usable systems in the late 1980s. Support for these research and development efforts in the United States was provided almost entirely by the National Heart, Lung, and Blood Institute (NHLBI) through contract and grant programs.

After the first enthusiastic endorsement of circulatory assist devices in the 1960s, mainly focusing on the TAH, it became increasingly evident that success could not be achieved by concentrating solely on engineering a good pumping machine. Major unanticipated complexities included

compatibility between artificial surfaces and blood, frequently leading to thromboembolic events. Other critical obstacles to success included infection, which has been exacerbated by electrical or pneumatic connections through the skin, and design of a pump that could function reliably for months or years in the body without inducing damage to surrounding body tissues thermally or mechanically, and without continuous tethering to an external energy source. NHLBI-supported efforts nurtured research and development of individual VAD components to overcome or at least reduce these problems. Separate, parallel subprograms were formed dedicated to advancing the state of the art in pumps, energy converters, and energy transmission techniques and to enhancing our knowledge of biomaterials and biocompatibility. Following this, programs were established to integrate the resulting improved components into complete VADs and, ultimately, to demonstrate performance and reliability in both bench tests and animal studies. Government support led to increased investments of funds by both industry and university partners. Currently, several VAD designs are available for different clinical applications, predominantly for use as a bridge to transplant, although the focus today is on the development of VADs to be used as alternatives to cardiac transplantation or for contributing to direct cardiac recovery.

Current Indications

VADs have a long history as support for postcardiotomy failure (inability to intraoperatively wean a patient from cardiopulmonary bypass), bridges to transplant for patients with end-stage HF, and more recently as chronic destination therapy for nontransplant candidates (89, 90). For transplant candidates, VAD bridge therapy can improve survival posttransplantation (91, 92). The current criteria for VAD implantation is severe NYHA class IV HF (see **Table 4**). This limits the utilization of devices to the 40,000–50,000 new cases of end-stage HF diagnosed in the United States each year (93).

Permanent support for severe NYHA class IV HF patients ineligible for cardiac transplant (destination therapy) is the most recently approved indication for VAD implantation based on the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial (90), which demonstrated significant survival benefit for NYHA Class IV HF patients deemed not to be cardiac transplant candidates compared with medical therapy (2-year survival 23% versus 8%). CMS approved Medicare coverage of VADs for use as destination therapy on October 1, 2003, based on very specific patient selection criteria (94, 95).

Table 4 Current indications for the implantation of a ventricular assist device

<ul style="list-style-type: none"> ■ Failing hemodynamics, defined as any of the following: <ul style="list-style-type: none"> - Low cardiac index ($<1.5 \text{ liters min}^{-1} \text{ m}^{-2}$) - Low systolic blood pressure ($<80 \text{ mm Hg}$) - Requiring intra-aortic balloon pump - Requiring continuous inotropic therapy or multiple inotropic agents - Elevated pulmonary capillary wedge pressure ($>25 \text{ mm Hg}$) ■ Persistent pulmonary edema off of a mechanical ventilator ■ Neurologic or renal failure due to low flow that is reversible ■ Fluid and electrolyte imbalance clearly related to HF and low cardiac output ■ Severe arrhythmias despite medical therapy
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Adapted, in part, from Reference 93.

Current Devices Used and Under Development

In a recent editorial, Olsen categorized blood pumps into first-, second-, and third-generation designs (96). The more commonly known and commercially available pumps described as first generation include the VADs of Thoratec, WorldHeart, Arrow, and ABIOMED and TAH or biventricular assist of SynCardia Systems, Thoratec, and ABIOMED. These devices are based on design concepts developed in the 1970s. They deliver pulsatile blood flow and are usually positive-displacement pumps. Several are approved by the FDA for use in the United States.

Second-generation pumps are mostly rotary pumps with bearings immersed in blood or plasma that can deliver diminished pulsatile or continuous blood flow. These devices are in different stages of development and testing. They include those of Thoratec (HeartMate® II), Jarvik (Jarvik 2000®), and MicroMed (MicroMed DeBakey®). The Baylor Gyro VAD, and the Arrow CorAide™, which use centrifugal pumps to deliver either diminished pulsatile or continuous flow, also are second-generation systems.

Third-generation pumps are those with magnetically suspended impellers that can deliver continuous or diminished pulsatile blood flow. Examples are the Terumo DuraHeart™, Thoratec HeartMate® III, Ventracor VentrAssist™, WorldHeart Levacor®, and the HeartWare HVAD™.

Research and development of several of the aforementioned second- and third-generation designs were stimulated in the United States by a program of the NHLBI of the NIH beginning in 1995. In particular, the Thoratec HeartMate® II, the Jarvik 2000®, and the Arrow CorAide™ (see **Figure 4**) were developed in response to an NHLBI request for proposals for innovative ventricular assist systems (IVAS). It was largely due to this NHLBI program that continuous-flow blood pumps were developed. Continuous-flow blood pumps represent a significant advance in mechanical circulatory support, particularly due to the enhanced mechanical longevity when compared with pulsatile systems. There is some question as to the long-term physiological effect of continuous blood flow given that the body is designed as a pulsatile biological system. Despite this theoretical concern, clinical experience to date has been encouraging (97–102).

Pulsatile VADs used today are based on designs initiated 20–30 years ago, although their performance has steadily improved as better and more reliable components substitute for those that were available earlier. Such components include diaphragms, bearings, magnetic materials, and motors. In more recent years, researchers have begun working toward eliminating or drastically reducing the more common causes of failures, decreasing size and weight, increasing efficiency, and advancing several new concepts. These new concepts include (*a*) non-blood contacting systems, (*b*) biological augmentation, and (*c*) small volume centrifugal and axial flow pumping (rotary blood pumps). The latter are characterized by continuous or diminished pulse flow and blood-lubricated, plasma-lubricated (103), or magnetically levitated bearings. Even with rotary blood pumps, there will be a pulse associated with the native ventricular waveform propagation, breathing, and muscle movements. By the nature of their operation, rotary blood pumps eliminate the need for venting gas from the system, resulting in a smaller diameter percutaneous driveline. Smaller caliber drivelines are believed to reduce the risk of infection, which is the most frequently occurring clinical adverse event associated with VADs.

Current Device Limitations

Despite the many advances in technology and patient care, adverse events are common. This may be due as much to the extraordinarily ill patients currently implanted as to the technology. In the REMATCH trial, such complications included bleeding (42%), infection (28% at 3 months, with 25% dying of sepsis), stroke (24% with neurological event), and peripheral thromboembolism

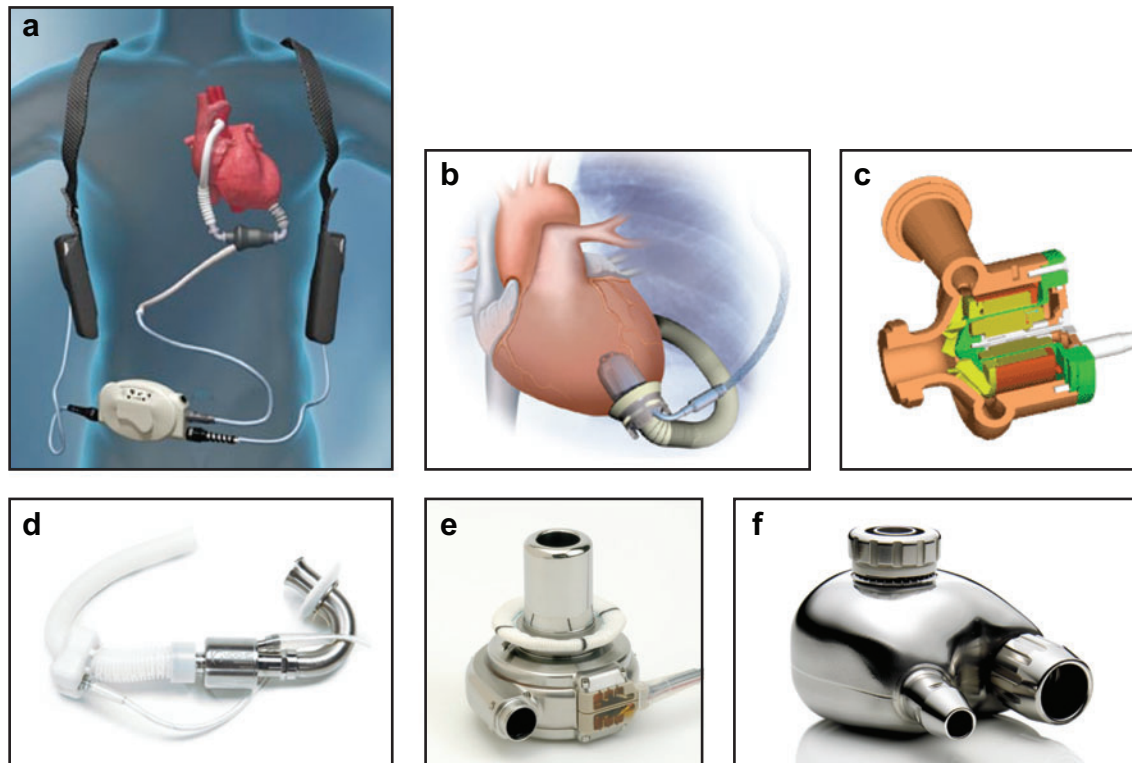


Figure 4

The Thoratec HeartMate[®] II (a), the Jarvik 2000[®] (b), the Arrow CorAide[™] (c), MicroMed DeBakey[®] (d), HeartWare HVAD[™] (e), and VentrAssist[™] LVAD (f) are examples of second- and third-generation pumps that are in clinical trials and/or pending approval from the Food and Drug Administration (FDA). Courtesy of <http://www.thoratec.com>, <http://www.jarvikheart.com>, <http://www.lerner.ccf.org/bme/golding/lab/design.php>, <http://www.micromedtech.com>, <http://www.heartware.com>, and <http://www.ventracor.com>, respectively.

(90). Despite the high adverse event rate, REMATCH showed a survival and quality of life benefit for severe HF patients (in fact, the most severe HF patients ever studied) compared with optimal medical therapy.

Historically, the infection and stroke rates have been even higher (104, 105, 109). Other known complications of blood-contacting pumps include hemolysis and mechanical pump failure, as well as psychosocial and emotional strains (106, 107). Although mechanical failure requiring pump replacement or pneumatic pump actuation has been reported to be 64% at 2 years in a mixed cohort of patients receiving the HeartMate[®] electric (vented electric or XVE) or implantable pneumatic, or Thoratec paracorporeal ventricular assist device (108), this is expected to be considerably less in the second- and third-generation pumps. Additionally, adverse outcomes are decreasing with increased experience but still remain worse than transplantation (89, 109–111). Adverse event rates may be lower with continuous flow devices, as suggested by recent reports about the HeartMate[®] II and MicroMed DeBakey[®] pumps (112–114); however, experience with these devices is still considerably less than pulsatile devices.

To better document current clinical experience, a national registry for all MCS patients has been established (Interagency Registry for Mechanically Assisted Circulatory Support, INTERMACS)

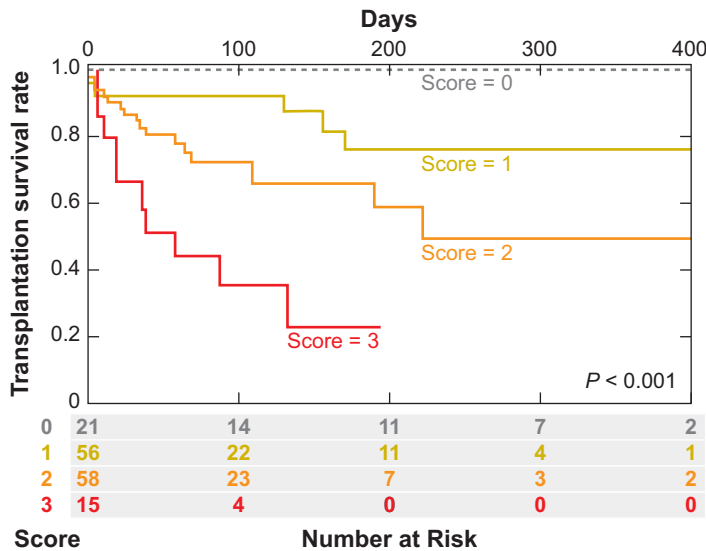


Figure 5

Survival to cardiac transplantation while on VAD support, stratified by number of risk factors identified by multivariate analysis. The four clinical preoperative variables independently predictive of survival while supported with VAD are ischemic etiology, lack of implantable cardioverter-defibrillator (ICD), antiarrhythmic medication other than amiodarone, and blood urea nitrogen >40 mg dl^{-1} . (M.A. Simon, J.J. Teuteberg, R.L. Kormos, M.A. Dew, unpublished data.)

as a joint effort of the NHLBI, CMS, and the FDA (115). This registry will track clinical indications, function, patient quality of life, adverse events, and cost.

Patient Selection

Current candidates are severely ill with end-stage HF and numerous comorbidities. In most cases, these patients have no other options for survival (that is, they are refractory to pharmacologic intervention and the various other aforementioned HF therapeutic options). Methods to identify the subset of patients most likely to benefit from VAD support can improve overall outcomes. Many preoperative risk factors have been identified (89, 116–124). Survival time incrementally decreases as the total number of risk factors present increases (see **Figure 5**).

Limitations of the Current Paradigm of Indications for Ventricular Assist Device Implantation

Despite greater numbers of HF patients, growing clinical VAD experience, improved outcomes, and greater number of devices and centers implanting, the overall number of implants has not grown tremendously and has certainly not met estimated needs (93). There are many factors contributing to this trend. For one, medical treatment with use of ICD and CRT has progressed considerably, as described above, creating higher expectations for clinical benefit that devices must now meet to justify their use, while postponing patient referral for VAD support. Furthermore, most HF patients are older with more comorbidities (and thus risk factors for poor outcomes) than those entered into clinical trials. For example, while the average age of patients in the REMATCH trial was 66 years, the average age of hospitalized HF patients is 74 (125).

Improvements in identification of currently unrecognized HF patients who may benefit from mechanical support are needed. Additionally, many implanting centers are struggling with current indications for device implantation. Waiting times for cardiac transplantation continue to increase and patients frequently are supported with a VAD for 1–2 years prior to receiving a donor heart. During such extended waiting times, many events can occur that would alter the appropriateness of transplantation. Conversely, patients supported as destination therapy can subsequently become transplant-eligible. Thus, the initial indication for mechanical support is not fixed, but can change over the course of support. Further, as our knowledge of the physiology of MCS continues to grow, new applications beyond postcardiotomy support, bridge to transplant, or destination therapy, such as promotion of myocardial recovery (see below), are beginning to be appreciated. Altering the implanting indication paradigm may eventually be needed to realize broader utilization of devices to match estimated public health needs (125).

Mechanical Support for Myocardial Recovery

Although MCS is efficacious for prolonged support for the most critically ill, there is very likely a broader applicability that has yet to be realized. Over the past several years, data has emerged on the utility of mechanical support as a temporary option until recovery of native cardiac function such that the patient can be weaned from VAD support and the device explanted without the need for transplant. Such an indication has the potential to be applied to a much broader patient population because the outcome would no longer be limited to death or cardiac transplant. Three compelling reasons to pursue VAD weaning and removal include (*a*) to avoid cardiac transplantation and its ultimate restrictions placed on quality of life (126), (*b*) to avoid the current high morbidity and mortality of destination therapy (90), and (*c*) to eliminate the risk of complications associated with prolonged VAD support. Furthermore, the life expectancy of patients with significant myocardial recovery who undergo VAD removal may be longer than those who have transplantation. However, currently no MCS is designed to support and encourage myocardial recovery and implant removal.

There have been multiple anecdotal reports of hemodynamic unloading and myocardial rest after VAD placement leading to recovery of native cardiac function and allowing for removal of the device without cardiac transplantation (127–131). Biological evidence of recovery of native cardiac function during VAD support includes decreases in neurohormonal activation, alterations in myocyte calcium handling, and improvement in the proinflammatory cytokine milieu (132–138). Histologic analysis of the explanted heart at the time of transplantation (in patients bridged to transplantation) demonstrates decreased fibrosis, improvements in matrix metalloproteinase activity, and decreased myocyte size after VAD placement (135, 139–141).

Most reports indicate 5%–10% of all adult patients implanted with a VAD for planned long-term support recover ventricular function sufficient for device removal. These patients tend to be nonischemic, with most having acute myocarditis or peripartum cardiomyopathy (127). Clinical measures of acute illness, in particular, short duration of symptoms and less dilated LV diameter, were significant predictors of recovery, whereas histologic evidence of myocardial inflammation was not.

Despite the extensively documented physiologic improvements evident with VAD support, the numbers of bridge to recovery (BTR) patients reported to date are low. This may be, in part, due to inadequate screening as well as a lack of understanding of optimal device operational parameters (e.g., pump speed and phase relative to the cardiac cycle) to maximize the chance of recovery. Recovery of function appears to be an early phenomenon occurring within 2 months of VAD support (127). Beyond 2–3 months of mechanical support, there is concern for myocyte atrophy on prolonged support and lower chances of myocardial recovery (142, 143). Routine assessment

by transthoracic echocardiography after 1–2 months appears to be the most useful clinical tool for more generalized screening for BTR. The finding that BTR subjects have shorter durations of symptoms is consistent with the finding in nonischemic cardiomyopathy that dynamic recovery is common in recent onset disease (144) but extremely rare in more chronic disease. Additional data are needed to better define patients most likely to benefit from a BTR strategy and to predict long-term outcomes of BTR patients and the extent to which observed ventricular recovery is sustained.

Methods to maximize myocardial recovery on mechanical support could vastly broaden the utilization of devices as well as potentially offer a cure for many people with life-threatening end-stage HF. Methods to maximize myocardial recovery on mechanical support could fall into two categories: (a) protocols controlling the regimen of mechanical support and (b) adjunctive therapies to be delivered while on mechanical support.

Design principles for mechanical support to encourage myocardial recovery include several considerations. First, the pump output necessary needs to be studied, as there is evidence for myocardial atrophy with extended mechanical support that may be related to the level of support (magnitude of pump output) (145). Perhaps 2–3 LPM pump flow rates are all that is required and the current philosophy of 4–10 LPM is detrimental to the goal of recovery. Perhaps less support, either continuously or intermittently, over time would encourage myocardial recovery. Another consideration is pump ejection phase in relation to the cardiac cycle for pulsatile devices. Perhaps cycling the pump to 180° out of phase (synchronous counterpulsation) with native rhythm could stimulate myocardial recovery. The physiologic impact of long-term continuous versus pulsatile MCS is unknown, widely debated, and deserves further investigation. Will the decreased pulsatility with continuous flow devices alter the amount of recovery that has been observed with pulsatile devices? Is there a degree of pulsatility (pulse pressure) that could maximize recovery?

Adjunctive therapies currently under investigation fall into two categories: pharmacologic agents and biological therapies. It is widely accepted that treatment with beta-blockers and ACE-inhibitors while on mechanical support maximizes the chances of myocardial recovery based on the large amount of data in the HF literature showing reverse remodeling. However, this theory has never been studied. The most studied adjunctive pharmacologic agent to promote myocardial recovery while on mechanical support is the β_2 -receptor agonist clenbuterol. When used in conjunction with a very aggressive medical regimen of a selective β_1 -receptor blocker, an ACE-inhibitor, an ARB, and the aldosterone-receptor blocker spironolactone, 11 of 15 patients had their VAD explanted due to myocardial recovery as evidenced by normalization of LVEF (146). Importantly, this approach treats the heart and peripheral circulation as a system. A multicenter confirmatory trial is currently being planned.

Adjunctive biological therapies to promote myocardial recovery while on mechanical support include myoblast and stem cell transplant (see Future Therapies: Tissue Engineering and Cell Transplantation, above). Cells can be introduced either by direct injection at the time of VAD implantation (one such study is currently underway) or percutaneously via injection into the coronary arteries. Given that cardiac function is being mechanically supported during these experimental cell therapy trials, this patient group is of particular relevance both to assess a future adjuvant therapy to MCS and for the implications to cell therapy for the HF population as a whole.

FUTURE CONSIDERATIONS AND CONCLUSIONS

In spite of optimal medical management, HF remains the largest public health problem, and with aging U.S. and European populations, this problem will continue to grow. As we look ahead, the future clinical utilization of MCS will evolve based on clinical outcomes and device design. Certainly long-term therapy (DT) is an option, yet its clinical implementation has been limited by a high

incidence of comorbidities, as discussed above. The potential utility of MCS to promote or bridge to myocardial recovery in otherwise end-stage HF, either by itself or with adjunctive therapies, is currently under investigation and holds promise but may be limited to acute cardiomyopathies. Chronic stage D HF may be forever limited to the current MCS indications. From a public health perspective, the most pressing concern of the HF epidemic is the extraordinary number without overt disease that are at risk of developing it, as well as those with early-stage disease that are at risk for progression. Given evidence of reverse remodeling, it would be reasonable to presume that utilization of devices could be adapted for secondary prevention of HF, i.e., to prevent disease progression after it has started (stage C HF). This would truly impact the vast numbers of people with HF frequently quoted in the literature, but as yet not nearly addressed with current devices. To begin to address this possibility, there first must be a definable stage of reversibility in the pathologic process of the HF syndrome, specifically with regard to mechanical unloading of the ventricle. One such stage could be after initial MI. Next, the devices used would have to be newer generation, smaller, highly reliable, biocompatible, and designed for recovery of cardiac function. It is likely that clinical management should address the heart and the peripheral circulation. Systems implanted percutaneously, or at least minimally invasively, to minimize surgical and infection risks will allow for more widespread use. Finally, issues related to duration of support and optimal adjunctive therapies need to be solved, preferably in randomized clinical trials.

SUMMARY POINTS

1. HF is a large and growing public health problem. MI is one of the most common risk factors for developing HF. Medical management strategies continue to improve outcomes.
2. MCS is currently reserved for the most severe HF, due to morbidity and mortality of patients implanted with certain pulsatile flow-generating devices. Much of this risk may be due to the critically ill status of those implanted.
3. Newer devices, particularly continuous-flow devices (centrifugal and axial flow, which incorporate state-of-the-art ceramic bearings or support the spinning rotor by magnetic levitation), have much lower failure rates, but have only begun to address common MCS problems such as infection and thromboembolism.
4. As technology and our understanding of the mechanical-biological interface advance, the risk-benefit profile of MCS will favor implanting in less severely ill HF patients.
5. Adjunctive strategies to promote myocardial recovery during MCS are currently being investigated and offer promise for a growing indication for MCS.
6. MCS for temporary support during acute myocardial injury (e.g., MI) may prevent progression to overt HF.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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