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Mechanical Device–Based Methods of Managing and Treating Heart Failure

Donna Mancini, MD; Daniel Burkhoff, MD, PhD

Abstract—Despite advances in pharmacological treatments aimed at neurohormonal blockade for heart failure in the setting of left ventricular pump dysfunction, there is still a growing number of patients with advanced symptoms who suffer significant morbidity and mortality. Mechanical stresses and chronic neurohormonal activation conspire to propagate maladaptive ventricular remodeling responsible for the insidious nature of this disease. Recent studies suggest that further pharmacological neurohormonal blockade may not be safe or effective, which has driven development of devices for this patient population. Furthermore, such devices may target fundamental pathophysiological abnormalities that are largely hemodynamic and mechanical in nature that are not addressed by available pharmacological agents. The profound reverse remodeling routinely associated with left ventricular assist device use, reviewed in detail, further validates device-based approaches and should inspire research to find ways to make this recovery more complete and permanent. Accordingly, this review focuses on the multitude of mechanical device–based approaches currently being investigated to manage and treat this population. From devices for monitoring patient status to anticipate congestive heart failure exacerbations and preemptively adjust therapy to devices to support preterminal patients with end-stage disease, it is recognized that these device-based approaches will assume an increasingly important role in treating the growing number of patients with advanced heart failure. (*Circulation*. 2005;112:438-448.)

Key Words: heart failure ■ transplantation ■ disease management

There have been several important advances in pharmacological treatments for heart failure resulting from decreased ventricular pump function that have significantly reduced mortality—namely ACE inhibitors,¹ β -blockers,^{2,3} and aldosterone inhibitors.⁴ Nevertheless, the progression from asymptomatic left ventricular dysfunction to symptomatic heart failure is still common. The number of hospitalizations for heart failure exacerbations continues to increase, and most patients will ultimately die of complications related to heart failure.⁵ There is a need for treatments that prolong life and enhance exercise tolerance.

Many of the major advances achieved over the past 2 decades came with the recognition that the progression of heart failure is due to neurohormonal activation and abnormal mechanical stresses on the myocardium (increased preload and afterload; Figure 1). This vicious cycle of progressive pump enlargement and dysfunction is collectively referred to as ventricular remodeling. The structural and functional aspects of remodeling can be illustrated on a ventricular pressure-volume diagram (Figure 2A). With sustained neurohormonal activation and its consequences, the pressure-volume relations gradually shift toward larger volumes so that ejection fraction is reduced with marked myocardial hypertrophy. The goal of many heart failure treatments is to prevent, slow, or reverse this process (Figure 2B). Randomized studies have shown that pharmacological blockade of the

key neurohormonal pathways interrupts the vicious cycle, retards progression, and improves survival (Figure 1, blue). However, results of several recent trials suggest that attempts to block additional neurohormonal pathways may be detrimental.⁶ This finding has led to the concept that we may have reached the limit to which neurohormonal and cytokine mechanisms can be blocked in heart failure patients.⁷

Accordingly, there have been intensive efforts to develop and test device-based therapies for patients with both acute and chronic heart failure. For example, cardiac resynchronization therapy⁸ has been approved by the US Food and Drug Administration (FDA) for NYHA class III and IV chronic heart failure (CHF) patients with abnormal electric conduction, and recent clinical trials support broader use of implantable cardiac defibrillators in patients with ventricular dysfunction.^{9,10} Such devices have significantly affected the treatment of CHF patients. Other experimental forms of therapy such as myogenesis (eg, stem cell, myoblasts)¹¹ and other electrical therapies such as cardiac contractility modulating nonexcitatory electrical impulses¹² and less invasive defibrillators are under active investigation. These classes of devices are the topic of a recent review in this series. The focus of the present review is on mechanical devices to treat various stages of heart failure that are currently available or are under development. Not included for the sake of brevity, but still noteworthy, are classes of devices under development

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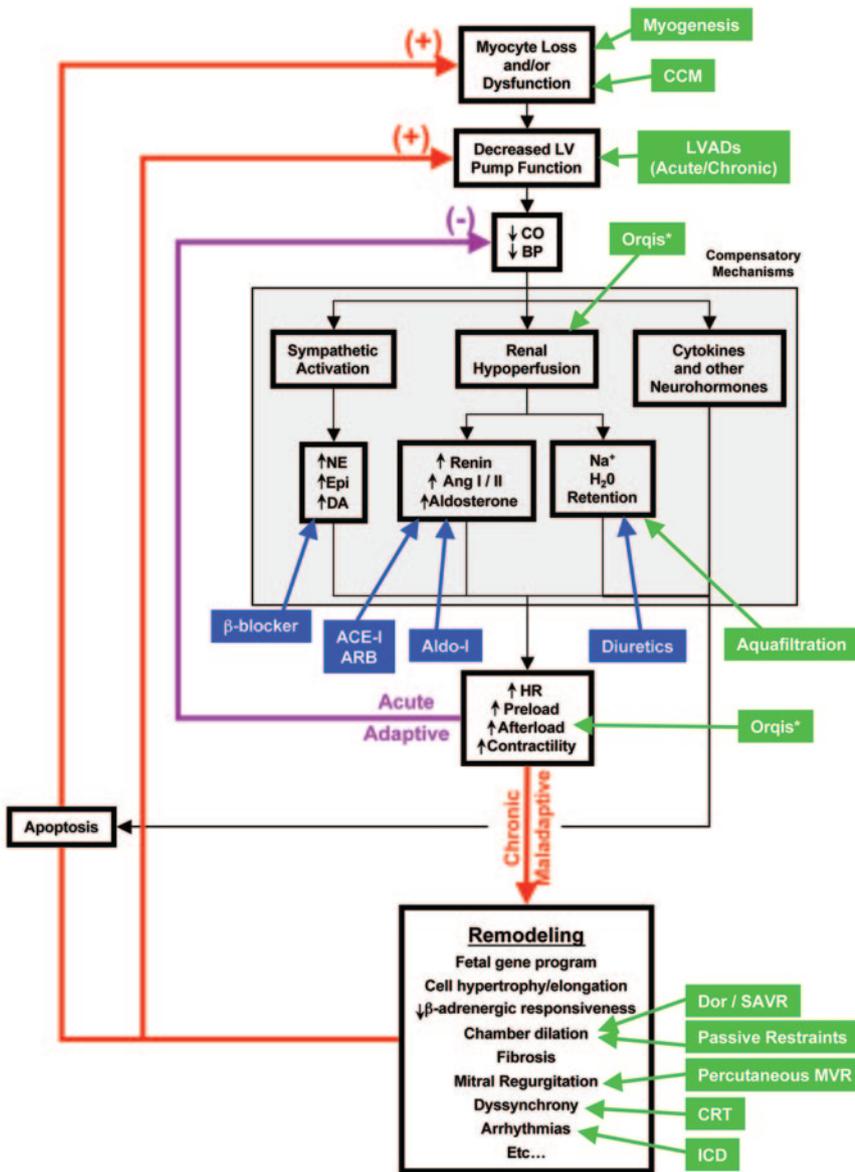


Figure 1. Vicious cycle of ventricular remodeling. Myocyte loss and/or dysfunction results in pump dysfunction. In acute setting, neurohormonal activation attempts to restore cardiac output and blood pressure via mechanisms considered adaptive in short term. If sustained, neurohormonal activation and increased mechanical stresses conspire in maladaptive process to drive multitude of abnormal processes, including apoptosis. Blue boxes show pharmacological treatments and where they block the vicious cycle. Green boxes show device-based therapies and where they intervene. CO indicates cardiac output; BP, blood pressure; NE, norepinephrine; EPI, epinephrine; DA, dopamine; Ang I/II, angiotensin I and II; CCM, cardiac contractility modulating; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter-defibrillator; HR, heart rate; and LV, left ventricle. *Orqis, continuous aortic flow augmentation with femoral-to-aorta blood shunting.

to aid in comprehensive disease management programs and chronic hemodynamic monitoring systems aimed at prevention and early detection of heart failure exacerbations to reduce hospitalizations and increase longevity.

Surgical Approaches to Treatment of CHF

Surgical reshaping of the dilated heart, a topic of significant research in recent years, is relevant to the topic of device-based heart failure treatments. One class of procedures that has received significant attention is generically referred to as ventricular reduction surgery. The concept behind these procedures is to reduce the increased radius of curvature present in a dilated heart, which increases systolic myocardial wall stress via Laplace's law. A reduction in radius of curvature would decrease wall stress, in principle allowing for reverse remodeling. The technique for reducing radius of curvature conceptually involves excluding a portion of the ventricular wall and reconstructing a smaller (preferably more normally elliptical) chamber. The surgical procedure differs in technique and physiolog-

ical effect, depending on the properties of the muscle removed. The Batista operation¹³ was intended to treat patients with idiopathic cardiomyopathy, so the muscle removed was functional but weak. However, it was prospectively predicted¹⁴ and later proven that this approach worsened overall pump function (as indexed by the relation between filling pressure and cardiac output) and did not generally provide benefit to patients.¹⁵ This procedure is no longer practiced.

In ischemic cardiomyopathy, myocardium affected by infarctions can heal in different ways, generating either an akinetic scar or a dyskinetic scar (ie, aneurysm). Ventricular reduction surgery in this setting therefore removes noncontractile material. The effects of these ventricular reduction surgeries on ventricular pressure-volume relations has not been studied, and clinical studies of these procedures are generally confined to reports of nonrandomized registries. Removal of dyskinetic scar (aneurysmectomy) is clinically accepted and reported to be associated with satisfactory outcomes.¹⁶ The effects of removing akinetic scar (often referred to as the Dor procedure¹⁷ or surgical

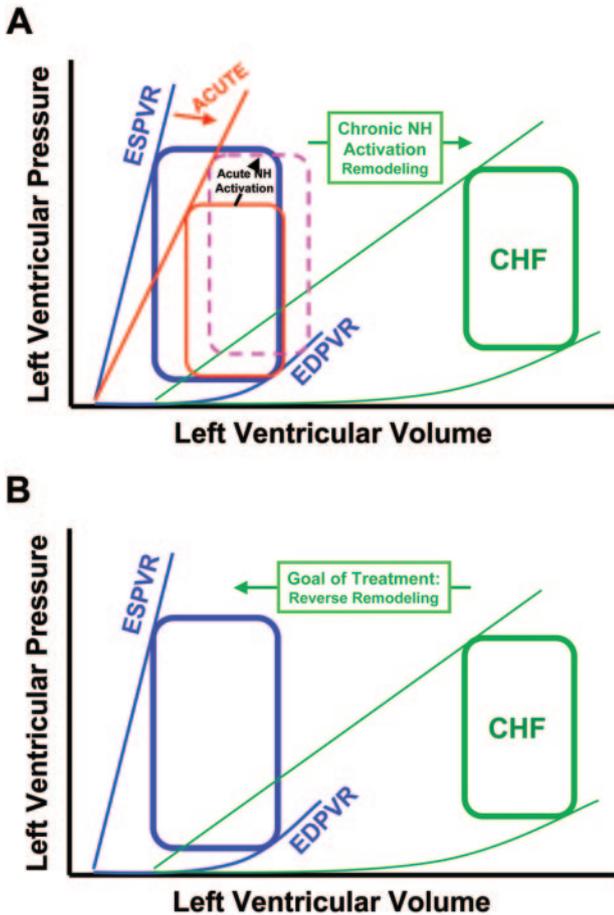


Figure 2. A, Ventricular remodeling represented on pressure-volume diagram. Systolic and diastolic properties shown by end-systolic and end-diastolic pressure-volume relations (ESPVR and EDPVR, respectively) with normal pressure-volume loop (blue). Acute decrease in contractility causes shift of ESPVR with reduced stroke volume and blood pressure (red solid line). Acute neurohormonal (NH) activation increases heart rate and constricts arteries and veins, which increases arterial, venous, and ventricular end-diastolic pressures (dashed purple line). When compensation is incomplete and neurohormonal activation persists, remodeling manifests as progressive shifts toward larger volumes of both ESPVR and the EDPVR (green). B. Goal of many drug- and device-based treatments for heart failure is to prevent, slow, or reverse remodeling so that ESPVR and EDPVR return toward normal.

anterior ventricular restoration [SAVR]¹⁸) are less clear. The same theoretical modeling that correctly predicted detrimental effects of the Batista operation predicts that aneurysmoplasty significantly improves pump function (which matches most of the data in the literature) and predicts that pump function will not be significantly improved by SAVR (Figure 3).¹⁹ The SAVR operation is now being studied prospectively as part of the NIH-sponsored Surgical Treatment of Ischemic Heart Failure (STICH) trial (<http://www.stichtrial.org/disclaimer/index.cfm>). Without firm scientific evidence that proves the benefits of such surgery, many physicians are reluctant to refer patients.

One limitation of these surgeries that could potentially confound the study is the lack of a uniform method of performing the procedure. Thus, the amount of tissue removed and the ultimate size and geometry of the reconstructed chamber are

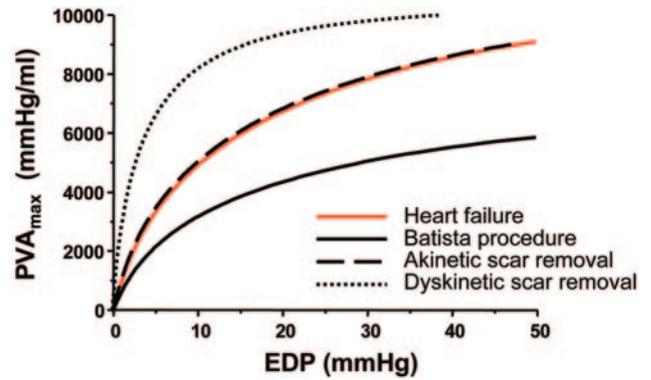


Figure 3. Results of theoretical model that predict effects of surgical ventricular remodeling on overall left ventricular pump function assessed by relationship between ventricular end-diastolic pressure (EDP) and pressure-volume area (PVA), which is measure of total ventricular work. This model, which prospectively predicted that Batista operation would be detrimental compared with baseline heart failure state (red line), suggests that removal of aneurysm will significantly enhance ventricular pump function, whereas removal of akinetic scar (as with SAVR) will not significantly enhance pump function. Randomized study of SAVR is currently underway within context of STICH trial.

more or less at the discretion of the surgeon, with no firm guidelines. Two devices under development provide a model (CHF Technologies and Chase Medical) that is inserted into the chamber to provide a guide for both resizing and reshaping the left ventricle. These devices are being studied independently outside the STICH trial.

Another method proposed to decrease wall stress and to induce reverse remodeling is by passive ventricular restraint devices (ACORN Cardiovascular Inc; Paracor Medical, Inc; Myocor Inc). This concept evolved from an earlier investigational approach called cardiomyoplasty²⁰ that tested the concept that the latissimus dorsi muscle could be freed, wrapped around the heart, and stimulated to contract in synchrony with the native heart, providing a boost to ventricular performance. However, it was discovered that after a relatively short time, continual stimulation of the skeletal muscle caused fatigue so that the graft no longer contracted with each stimulation.^{21,22} Rather, the skeletal muscle ultimately became a passive wrap around the heart. Although the overall clinical trial failed to show benefit, some patients appeared to benefit, and there was a reduction in heart size with some improvement in function. This led to the concept that the same effect could be readily achieved with a passive material appropriately tailored and fit snug to the heart.²³ Studies in animals in which CHF was induced by repeated coronary artery microembolization have indeed shown reverse remodeling, including a leftward shift back toward normal of the end-systolic pressure-volume relationship (Figure 4), improved pump function and reversal of the fetal gene program associated with heart failure, which is interpreted as being a beneficial consequence of reduced wall stress.²³ Importantly, despite the fact that the heart is wrapped to slightly decrease volume acutely, there is no induction of a restrictive physiology. A recently completed multicenter, randomized study of this technology with ≈300 patients has suggested that this approach improves NYHA functional

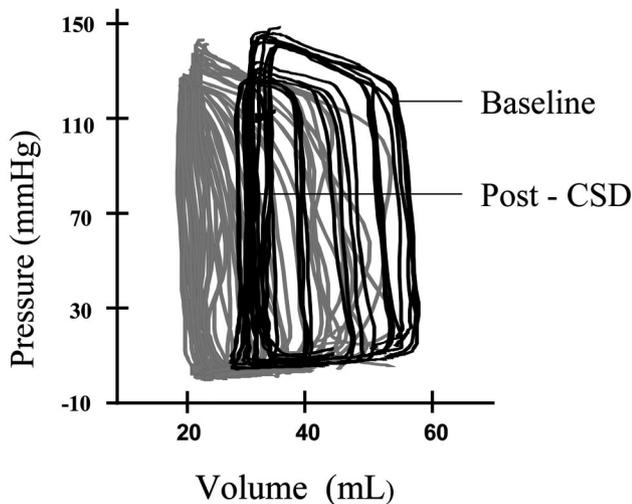


Figure 4. Pressure-volume relations measured in dogs with heart failure induced by repeated coronary microembolizations before (black) and 3 months after heart is wrapped with thin polyester mesh. Leftward shift of loops indicates reverse ventricular remodeling.²³ CSD indicates cardiac support device.

class and reduces the requirement for subsequent major cardiac procedures such as cardiac transplantation and ventricular assist device insertion. Another device intended to perform similarly is constructed of nitinol, which may more readily permit placement of the device via port access.

Still another form of ventricular reshaping involves use of transventricular struts to bring opposite sides of the dilated left ventricle toward each other to reshape the ventricular circumference from 1 large circle to 2 circles, each with a smaller radius of curvature (in a kind of figure 8 configuration; Myocor, Inc).²⁴ This device is currently under investigation for its potential use in treating heart failure and as a means of less invasively reducing the severity of mitral regurgitation.

For all these forms of surgical heart failure treatments, mitral valve repair or replacement is an important yet potentially confounding factor during clinical trials. Although mitral repair is typically effective at eliminating or reducing the regurgitant volume, it remains controversial as to whether and when to perform such surgery as a sole treatment in patients with low ejection fraction.²⁵ Accordingly, numerous catheter-based devices are being developed to perform mitral valve repair percutaneously to reduce risk and allow it to be performed as a sole therapy to treat symptoms of heart failure.^{26,27} It is proposed that availability of such devices will allow treatment of more patients, including those at high risk, with reduced procedural morbidity and mortality.

Devices to Treat Acutely Decompensated Heart Failure

As patients deteriorate into more severe decompensation and cardiac output and blood pressure decline, patients become increasingly resistant to high doses of diuretics, and fluid overload ensues. Reduced renal perfusion resulting from relative hypotension and renal artery constriction are contributing factors. Because diuretics reduce glomerular filtration rate, their use, although necessary to treat symptoms, may contribute to further diuretic refractoriness. Accordingly,

devices aimed at improving renal perfusion, directly dealing with fluid overload, and/or attempting to improve systemic perfusion have been developed.

One such strategy is local renal artery vasodilator drug delivery.²⁸ Local renal vasodilator therapy can potentially improve renal blood flow and glomerular filtration rate while acting synergistically with diuretics to effect a diuresis with fewer effects on arterial blood pressure than the same drugs delivered systemically. Devices are currently under development for such local drug delivery that would allow testing of this strategy (Flowmedica, Inc).

A direct means of dealing with fluid overload in patients who have inadequate response to diuretic therapy is aquapheresis with a specialized system that provides efficient salt and water removal by a new form of ultrafiltration (Aquadex System 100, CHF Solutions).²⁹ This system uses peripheral or central venous access and requires a low volume of extracorporeal blood to prime the system (33 cm³) compared with standard hemofiltration devices. This system removes isotonic salt and water at rates between 100 and 500 cm³/h without clinically significant changes in serum electrolytes,

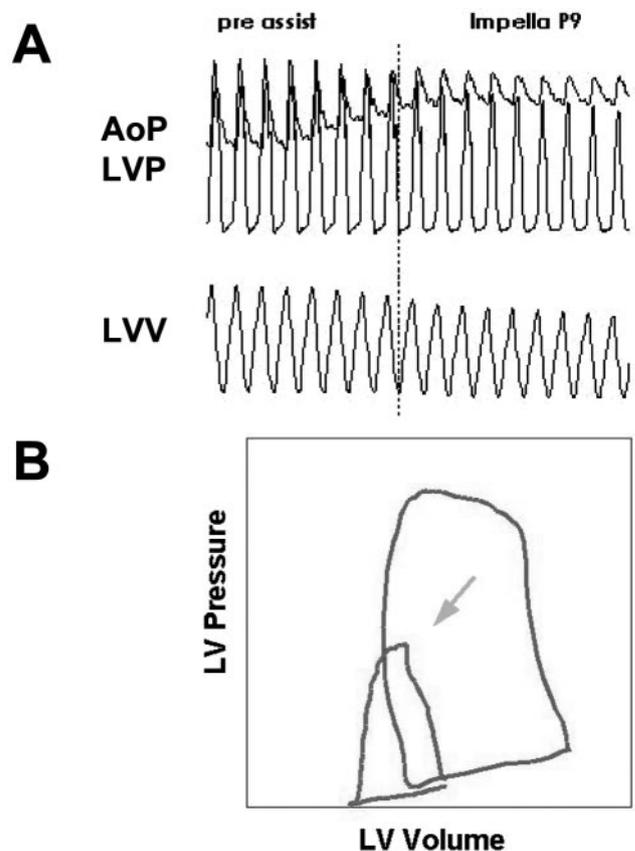


Figure 5. A, Aortic (AoP) and left ventricular pressure (LVP; top) and left ventricular volume (bottom) obtained in animal before and with initiation of hemodynamic support with catheter-based axial flow pump (Impella). This continuous flow pump reduces systolic arterial pressure with little effect on diastolic pressure; left ventricular volume is markedly reduced. B, Left ventricular pressure-volume loops corresponding to tracing in A. Loops demonstrate pressure and volume unloading provided by pump that is associated with markedly reduced oxygen demands of left ventricle. Tracing provided courtesy of Dr F.H. van der Veen, PhD, Department of Cardiothoracic Surgery, Maastricht, the Netherlands.⁶⁹

TABLE 1. Current Guidelines for the Placement of LVAD as a Bridge to Transplantation³⁹

Inclusion criteria	
1. Patient is a transplantation candidate	
2. Hemodynamic parameters	
Cardiac index	$<2.0 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$
Systolic blood pressure	$<80 \text{ mm Hg}$
Pulmonary capillary wedge	$>20 \text{ mm Hg}$
Exclusion criteria	
1. Technical considerations	
Body surface area	$<1.5 \text{ m}^2$
Aortic insufficiency	
Right-to-left shunt	
Abdominal aortic aneurysm	
Prosthetic valves	
Left ventricular thrombus	
2. Severe right-side heart failure	
3. Factors increasing the risk of perioperative complications	
Right atrial pressure	$>16 \text{ mm Hg}$
Prothrombin time	$>16 \text{ s}$
Reoperation	
White blood count	>15
Urine output	$<30 \text{ cm}^3/\text{h}$
Mechanically ventilated	
Temperature	$>101.5^\circ\text{F}$

heart rate, or blood pressure. Because of the relative simplicity of operation, this system can be administered in inpatient settings and outpatient care centers. Four clinical trials of this system have indicated the ease, safety, and efficacy of this strategy to remove fluid. The UNLOAD trial, a prospective, randomized, multicenter, 200-patient trial, is currently underway and is testing the short-term efficacy with respect to fluid and symptoms and 30- to 90-day clinical impact of aquapheresis compared with usual diuretic strategies.

Another novel investigational approach for treating patients with acute heart failure exacerbations who are dependent on or resistant to intravenous inotropic agents involves continuous aortic flow augmentation.³⁰ The Cancion system (Orqis Medical) consists of an extracorporeal, magnetically levitated centrifugal pump that withdraws blood from the femoral artery and returns it to the descending thoracic aorta in a continuous, nonpulsatile manner at rates between 1.1 and 1.5 L/min. Studies in experimental animals with CHF and results of preliminary clinical studies in patients with heart failure exacerbations demonstrate that this continuous flow loop results in increased cardiac output, improved renal function (decreased creatinine) and diuresis, and reduced pulmonary capillary wedge pressure. The suggested mechanisms of action include direct ventricular afterload reduction, stimulation of nitric oxide production (resulting from increased aortic shear stress) that leads to vasodilation, and increased renal perfusion. Randomized, controlled studies are currently underway.

Catheter-Based Pumps for Acute Cardiogenic Shock

As a result of either the progression to end-stage heart failure in patients with longstanding cardiomyopathy or severe ventricular dysfunction in the setting of acute myocardial

infarction, cardiogenic shock (inadequate blood pressure and cardiac output to meet the metabolic needs of the body) occurs in many patients surviving to hospital admission. Medical treatment with intravenous inotropes, followed by use of the intra-aortic balloon pumping (IABP), is considered the first line of treatment for such patients.³¹ However, these strategies are frequently not effective. Several devices are under development for treating such patients.

Approved for short-term (6 hours) hemodynamic support is the TandemHeart percutaneous ventricular assist device (CardiacAssist). This device consists of an extracorporeal centrifugal (continuous flow) pump that withdraws blood from the left atrium via a cannula introduced transeptally via the femoral vein. Blood is then pumped (at up to $\approx 3.5 \text{ L/min}$) by a centrifugal pump through cannulas in 1 or both femoral arteries.³² Preliminary results showed that this device can improve hemodynamics in patients with cardiogenic shock. Studies also showed a reduction in serum lactate levels, an indication of improved tissue oxygenation and thus reversal of the cardiogenic shock state. In a more recent study, patients with cardiogenic shock resulting from acute myocardial infarction failing medical treatment were randomized to treatment with either an IABP or the TandemHeart assist device.³³ The IABP had almost no effect on hemodynamics, but the TandemHeart device significantly increased cardiac output and

TABLE 2. Columbia Presbyterian Criteria for LVAD Destination Therapy Patients

Inclusion criteria	
Class IIIB or IV CHF	
Inotrope dependent (failed ≥ 1 attempt at weaning, ie, documented hypotension, end-organ failure, refractory CHF with downtitration)	
Maximal medical therapy with $\dot{V}_{O_2} < 10 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ (if not able to tolerate β -blockers, then $\dot{V}_{O_2} < 12 \text{ mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$)	
Exclusion criteria	
Transplantation candidates	
Acute cardiogenic shock	
Renal dysfunction: dialysis, CVWH, or Cr $>3 \text{ mg/dL}$	
Hepatic failure: ALT, AST >3 times normal, INR >2.5	
BMI <18 or $>35 \text{ kg/m}^2$	
Prolonged ventilatory support	
$\text{FEV}_1 < 1$	
PVR >8 and/or severe RV dysfunction with anticipated RV support	
Comorbidity with life expectancy $<2 \text{ y}$	
Acute condition: GI bleed, infection	
Neurological: Mini Mental Exam score <20 , prior CVA with significant residua	
High surgical risk (ascending aortic carotid artery, > 2 prior cardiac surgeries)	
Severe PVD (limb ulcers, amputation)	
Heparin-induced thrombocytopenia	
Psychosocial factors	

CVWH indicates continuous venovenous hemofiltration; Cr, creatinine; ALT, alanine transaminase; AST, aspartate transaminase; INR, international normalized ratio; BMI, body mass index; PVR, pressure-volume relationship; RV, right ventricular; GI, gastrointestinal; CVA, cerebrovascular accident; and PVD, peripheral vascular disease.

TABLE 3. Mechanical Bridges to Transplantation

	Pump Mechanism	Pulsatile	Anticoagulation	Approval Status
Extracorporeal devices				
IABP	Pneumatic	No	Yes	Available
TandemHeart (CardiacAssist)	Centrifugal	No	Yes	Available
IMPELLA Recover	Axial flow	No	Yes	Clinical trials
AMed pVAD	Axial flow	No	Yes	Clinical trials
Extracorporeal membrane oxygenation	Centrifugal	No	Yes	Available
Abiomed BVS 5000 (single or biventricular)	Pneumatic pulsatile	Yes	Yes	Available, postcardiotomy
Pierce-Donachy Thoratec VAD (single or biventricular)	Pneumatic pusher plate	Yes	Yes	Available, postcardiotomy
Intracorporeal devices				
Univentricular support				
HeartMate IP	Pneumatic	Yes	No	Available, bridge to transplantation
HeartMate XVE	Vented electric	Yes	No	Available, bridge to transplantation and destination
Novacor	Electric dual pusher plate	Yes	Yes	Available, bridge to transplantation; destination trial ongoing
Lion Heart (totally implantable)	Pusher plate	Yes	Yes	Clinical trials, destination
HeartMate II	Axial flow	No	Yes	Clinical trials, destination/bridge
Jarvik 2000	Axial flow	No	Yes	Clinical trials, destination/bridge
MicroMed DeBakey VAD	Axial flow	No	Yes	Clinical trials, destination/bridge
HeartMate III	Centrifugal	No	Yes	Preclinical trials, destination/bridge
Kriton	Centrifugal	No	Yes	Preclinical trials, destination/bridge
Biventricular support (TAH)				
Cardiowest	Pneumatic	Yes	Yes	Bridge to transplantation
Abiocr	Hydraulically coupled, asynchronous			Clinical trials, destination

blood pressure while significantly decreasing pulmonary capillary wedge pressure. However, mortality was comparable in both groups.

Other devices are being developed to provide acute hemodynamic support. They include 2 axial flow pumps (Impella CardioSystem AG,³⁴ A-Med System, based on a prior system called the Hemopump³⁵). These systems have helical propellers at the tip of catheters that are positioned retrograde across the aortic valve. Motors rotate the propellers, which draw blood from the left ventricle through the distal end of the catheter and discharge it into the aorta. These catheters can be inserted percutaneously via a femoral artery or surgically into the proximal aorta. Like the TandemHeart, these devices unload the left ventricle, thus reducing oxygen demand while improving systemic perfusion (Figure 5). Studies are underway to assess the safety and efficacy of these devices in a variety of settings in which IABPs are now used, including cardiogenic shock.

Devices for Chronic Decompensated CHF

Because of the limited availability of donor organs and the urgency for cardiac support in the setting of severe hemodynamic decompensation, ventricular assist devices capable of completely supporting the circulation are taking on an increasingly important role in heart failure therapy.

Several FDA-approved devices provide short-term circulatory support for postcardiotomy failure or bridge to trans-

plantation. Those who might benefit from device placement for acute cardiac failure include patients unable to be weaned from cardiopulmonary bypass, those experiencing acute myocardial infarction with cardiogenic shock, patients with myocarditis, and patients who deteriorate while awaiting transplantation. In the last group, assist devices can be especially helpful before transplantation by providing a period for recovery of heart failure–related end-organ impairment, thus reducing the risk of transplantation.^{36,37}

Following the results of the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial, use of left ventricular assist devices (LVADs) as destination therapy is now approved for some patients ineligible for transplantation.³⁸ Use of the HeartMate vented electric device was shown to improve survival over a 2-year period in this population. Although this landmark study ushered in the era of destination therapy, adverse effects related to infection, stroke, bleeding, device failure, and other factors all call for technological advances to improve outcomes.

Tables 1 and 2 outline LVAD patient selection criteria for a bridge to transplantation and destination therapy, respectively. The main hemodynamic criteria include systolic blood pressure <80 mm Hg, pulmonary capillary wedge pressure >20 mm Hg, and a cardiac index <2.0 L · min⁻¹ · m⁻² despite maximal inotropic and/or IABP support.³⁹ In practice, however, the clinical judgment of experienced surgeons and

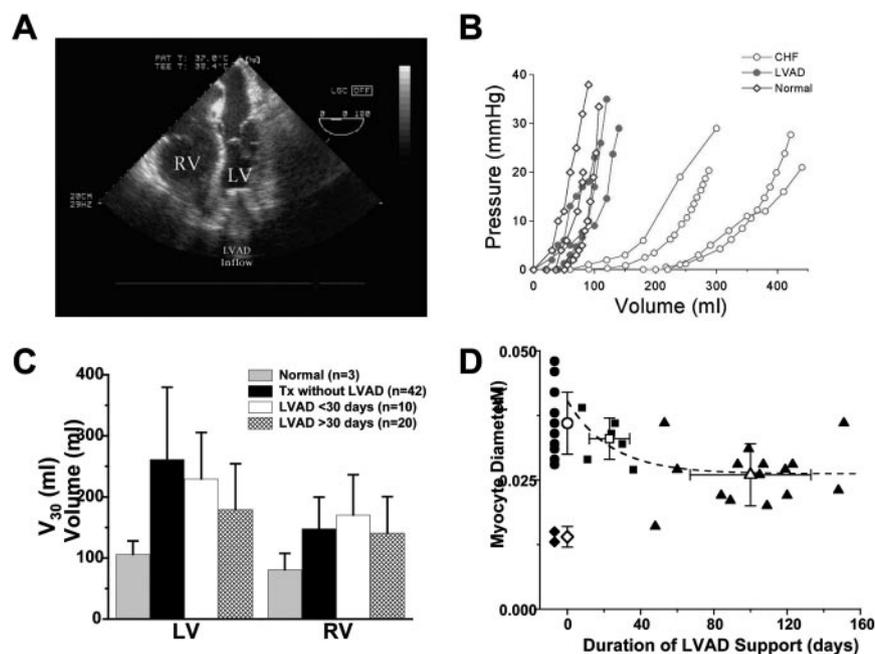


Figure 6. A, Transesophageal echocardiogram of patient with HeartMate vented electric LVAD showing volume unloading of left atrium and left ventricle (LV), whereas right-sided chambers remain volume loaded. B, Ex vivo LV end-diastolic pressure-volume relations (EDPVR) measured from normal hearts (blue), failing hearts (purple), and end-stage failing hearts supported with LVAD explanted at time of transplantation (red).⁵⁵ C, With heart size indexed by V₃₀, volume on EDPVR at which pressure is 30 mm Hg, it is seen that LV reverse structural remodeling occurs and is more prominent after than before 30 days of support.⁶¹ In contrast, there is no significant reverse remodeling of right ventricle (RV).⁶⁰ D, Time course of regression of cellular hypertrophy during LVAD support.⁶¹

cardiologists influences the timing of implantation on the basis of estimated waiting time for transplantation and other comorbidities that complicate device insertion.

Many devices are available to provide temporary support, either as a bridge to another treatment or until recovery of heart function. Selecting the appropriate device is dependent on a number of considerations, including the anticipated duration of patient support, the need for right-sided support, and the patient's size (Table 3).

Extracorporeal Devices

Centrifugal pumps are commonly used to propel blood for standard cardiopulmonary bypass,⁴⁰ and systems based on these pumps are available for short-term support of critically ill patients. Left- and/or right-sided support can be obtained with these systems. If necessary, an oxygenator may be spliced into the circuit to allow extracorporeal membrane oxygenation. Cardiovascular support with extracorporeal membrane oxygenation in adults, however, has yielded poor results.

support and in patients weighing >60 kg. The device has a percutaneous lead that serves as both a vent and an electrical connection. The blood contacting surface of the system requires anticoagulation, which needs to be started soon after implantation if bleeding is relatively well controlled. Patients are able to ambulate and participate in many activities. Despite anticoagulation, the incidence of thrombotic stroke remains relatively high. Like all other devices with a percutaneous line, there is a significant risk for infection. The advantages of this system are the excellent mechanical reliability (few device failures) and successful outpatient experience. Results from the US multicenter trial of 129 patients satisfying all criteria for inclusion demonstrated a transplantation rate of 77%, despite a 30% systemic infection rate and a 26% embolic stroke rate. The global experience has demonstrated support times as long as 4 years. This device is currently under evaluation for destination therapy.

The Arrow Lionheart-2000 is an experimental LVAD that can pump up to 8 L/min. Unlike other LVADs, however, this device is totally implanted. The battery, controller, and a gas compliance chamber are implanted with no lines crossing the skin. The pump is powered via continuous transcutaneous energy transfer that maintains charge on the battery. The battery can operate the device for \approx 1 hour when not being charged, but only 20 to 30 minutes daily is recommended. The device was designed for destination therapy. A 260-patient study in Europe, the CUBS trial, demonstrated reliability of the device over an average of \approx 1 year, with survival and adverse events similar to those reported in the REMATCH trial. Additional testing is underway.

Total Artificial Hearts

Currently, 2 devices are being developed as total artificial hearts. The AbioCor Artificial Heart is a total artificial heart that is implanted in the orthotopic position. It is driven by an internal motor using hydraulically coupled chambers so that, while the left side is ejecting, the right side is filling. The device is completely implantable and has an internal battery and a transcutaneous energy transfer system that permits recharging the battery or running the device with an external coil. Several patients have received the device, and reports of initial experiences have appeared.⁴⁷

The Cardiowest Total Artificial heart was recently approved by the FDA as a bridge to transplantation in patients in need of biventricular support.⁴⁸ This is a biventricular, pneumatic, pulsatile pump that totally replaces the native ventricles and all 4 cardiac valves. Like the AbioCor, it is implanted in the orthotopic position. Eighty-one patients treated with this device had a rate of survival to transplantation of 79%. This device is currently powered by a large console that precludes hospital discharge and thus widespread applicability. Development of a smaller console that will allow greater patient mobility is underway.

New Devices

The newest generation of devices includes axial flow and centrifugal pumps. Many devices include magnetically levitated rotating propellers or plates that eliminate a failure mode related to wear on bearings. These pumps are smaller than the devices discussed above but generally have flow rates >5 L/min. Flow

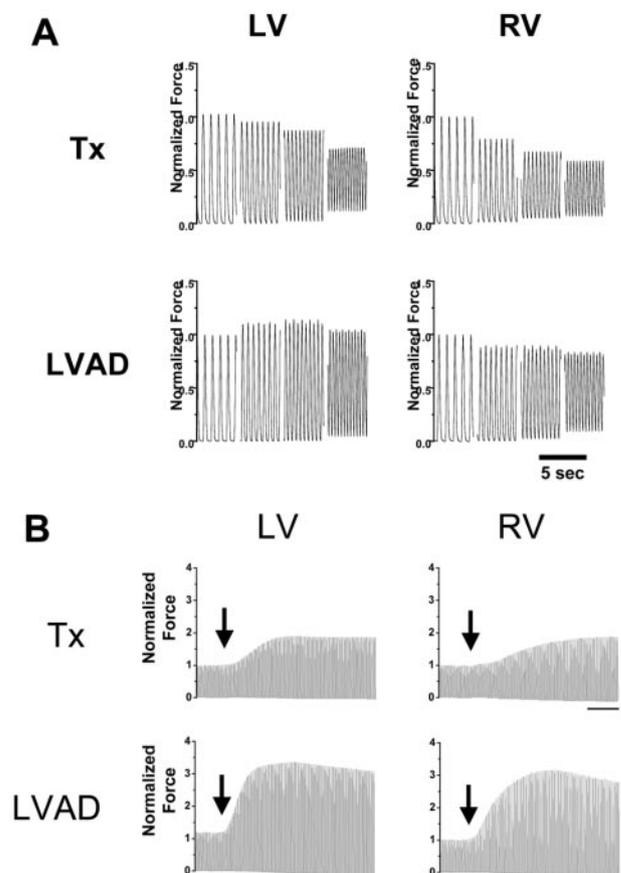


Figure 7. A, Force-interval relationship (FIR) in right ventricular (RV) and left ventricular (LV) trabeculae. In transplant (Tx) hearts, force declines as contraction frequency is increased in both RV and LV.⁶⁰ However, after LVAD support, contraction force increases with increasing frequency in LV (positive FIR) but not RV. B, In contrast, compared with transplanted hearts, LVAD support improves myocardial contractile response to β -adrenergic stimulation in both RV and LV myocardium. After baseline force is recorded, isoproterenol (1 μ g/mL) is added to muscle bath of each preparation at arrow. Force is normalized to respective baseline value before isoproterenol infusion.

is nonpulsatile with all these devices. Potential advantages of these devices include their durability, small size, simpler mechanics, quiet function, and lack of valves (Table 3).⁴⁹

The smaller size of these pumps is expected to facilitate placement and explantation, with some pumps being placed by lateral thoracotomy incision without the need for cardiopulmonary bypass. The small size should also permit use in smaller patients. Because they have fewer moving parts and points of friction, it is expected that, once perfected, they will have improved longevity. Unfortunately, if device failure occurs, there are few options other than replacement.

Ventricular Assist Devices as a Bridge to Recovery

Early in the course of LVAD use as a bridge to transplantation, it became evident that some patients exhibit substantial recovery of ventricular function.^{50,51} This prompted explanation of some devices in lieu of transplantation, so-called bridge to recovery therapy.^{52–54} However, outcomes after these early experiences were poor, with many patients pro-

gressing rapidly back to heart failure or dying of heart failure–related complications.^{50,52} Therefore, LVADs are not generally used with the intention of bridging patients to recovery except in relatively rare, potentially reversible situations (eg, postcardiotomy failure and fulminant myocarditis). However, many insights have been obtained into the mechanisms of remodeling through studies of hearts supported by LVADs.^{55–66}

LVADs provide profound unloading of the left ventricle, although the right ventricle remains hemodynamically loaded (Figure 6A).⁵⁵ LVADs normalize the circulating neurohormonal and cytokine levels⁶⁶ which would be expected to affect right and left ventricles equally. The effects of LVAD support on the left ventricle include (but are not limited to) near normalization of the passive left ventricular pressure–volume relations (Figure 6B and 6C),^{55,60} regression of left ventricular free wall mass and cellular hypertrophy (Figure 6D), normalization of the force–frequency relationship (Figure 7A), normalization of β -adrenergic responsiveness (Figure 7B), normalized phosphorylation of the calcium release channel (ryanodine receptor),⁶² normalized expression of key genes encoding for proteins involved in calcium cycling,⁶⁰ and normalized tissue levels of norepinephrine (unpublished). These observations are collectively referred to as reverse remodeling.⁵⁵ However, in the right ventricle (Figure 6C and 7B),⁶⁰ only normalization of β -adrenergic responsiveness, calcium release channel phosphorylation, and tissue norepinephrine levels are observed.⁶⁷ These observations indicate that some aspects of reverse remodeling are regulated primarily by hemodynamic stress, whereas other aspects are regulated by neurohormonal milieu.⁶⁰

Although most characteristics improve toward normal during LVAD support, this trend is not ubiquitous. Interstitial fibrosis and total, cross-linked, and type I and III collagen contents are all increased beyond the already abnormal levels found in the heart failure state.^{61,68} The implications and mechanisms of these changes are under investigation.

Summary and Conclusions

A broad range of devices (many investigational) for treating patients with heart failure have been reviewed. Such devices, along with other classes of devices reviewed elsewhere, attempt to address aspects of the vicious cycle of heart failure not treated or incompletely treated by already available pharmacological therapies (Figure 1). We suggest that some of the fundamental abnormalities not addressed by available pharmacological agents are largely hemodynamic and mechanical in nature (Figure 1) and may most readily lend themselves to device-based solutions. The emphasis in the present medical device era is on less invasive treatments made possible by technological and engineering advances. The profound reverse remodeling routinely associated with LVAD use further validates device-based approaches and should inspire research to find ways to make this recovery more complete and permanent.

Because this field is moving so quickly, it is likely that by the time this review appears in press, new information about several of the devices discussed will already be available, some of the approaches may already have been abandoned, and new ap-

proaches will have appeared. It is therefore hoped that the enduring message of this review relates to fundamental concepts learned over the recent decades about why and what types of device-based approaches are likely to play an increasing role in the management of patients with heart failure in the future.

Disclosure

Dr Burkhoff is employed by Impulse Dynamics, which is investigating an electrical-based treatment for CHF that is not related to the subject of this article. Dr Burkhoff also has an ownership interest in Abiomed and has served as a consultant to Acorn and Cardiac Assist.

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