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Current and Future Considerations in the Use of Mechanical Circulatory Support Devices: An Update, 2008–2018

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Abstract

Our review in the 2008 volume of this journal detailed the use of mechanical circulatory support (MCS) for treatment of heart failure (HF). MCS initially utilized bladder-based blood pumps generating pulsatile flow; these pulsatile flow pumps have been supplanted by rotary blood pumps, in which cardiac support is generated via the high-speed rotation of computationally designed blading. Different rotary pump designs have been evaluated for their safety, performance, and efficacy in clinical trials both in the

United States and internationally. The reduced size of the rotary pump designs has prompted research and development toward the design of MCS suitable for infants and children. The past decade has witnessed efforts focused on tissue engineering–based therapies for the treatment of HF. This review explores the current state and future opportunities of cardiac support therapies within our larger understanding of the treatment options for HF.

Contents

1. INTRODUCTION

Heart failure (HF) is one of the largest public health problems in the United States. The mainstays of treatment are lifestyle modification and medications. Medical and surgical treatment of HF has advanced considerably over the past 20–30 years. At the time of our review in the 2008 volume of this journal (1) mechanical circulatory support (MCS) was reserved for patients with severe, refractory HF failing medical therapy and as a bridge to cardiac transplantation. With the maturation of rotary blood pump technology over the past 10 years, more and more MCS is being used for destination therapy, for example, as long-term support in patients who are not candidates for transplant. This updated review explores the current state and future opportunities of MCS within the overall treatment option paradigms for HF.

2. HEART FAILURE: SCOPE OF THE PROBLEM

Cardiovascular disease is highly prevalent and remains the leading cause of death in the United States, with 26.7 million American adults (11.5% of the population) carrying the diagnosis. Among

these, 6.5 million have HF, which is broadly defined as the clinical syndrome of fatigue, breathlessness, and/or fluid retention that results from impaired cardiac output. According to the American Heart Association, the prevalence of HF will increase by 46% from 2012 to 2030, resulting in more than 8 million people 18 years of age or older with HF. The estimated total annual cost in the United States for HF in 2012 is $30.7 billion. While treatments have improved mortality rates for HF, the rate is still 50% at 5 years (2). The number of patients receiving a left ventricular assist device (LVAD) for advanced HF has continued to grow as well, now with almost 2,500 implants annually in the United States (2).

These numbers indicate that while multiple HF therapies have been developed and improved outcomes over the past 30 years, they are generally not curative. This fact, along with the large scope of the problem, dictates that definitive therapy, particularly for end-stage disease, is needed. MCS reverses many of the adverse physiological changes occurring in HF, but its link to clinical recovery of cardiac function is still poorly understood. A stepwise approach to the treatment of HF is generally employed, predicated on the symptoms and response to therapy, and includes medications; implantable defibrillators or pacemakers, including cardiac resynchronization therapy (e.g., biventricular pacing); transplant; and left ventricular assist devices (LVADs) (**Figure 1**) (3). Below, we present the current status of clinical-use LVAD technologies, along with future designs undergoing preclinical testing. We describe the advantages and disadvantages of current LVAD technologies, particularly with relation to the requisite design improvements required to meet the increasing clinical need for the devices.

3. MECHANICAL CIRCULATORY SUPPORT

3.1. Current Indications

LVADs have a long history as a support for postcardiotomy failure (i.e., inability to intraoperatively wean a patient from cardiopulmonary bypass), as a bridge to transplant for patients with end-stage HF, and more recently as a chronic destination therapy for nontransplant candidates (4, 5). For transplant candidates, LVAD bridge therapy can improve survival post transplantation (6–8). The current criterion for LVAD implantation remains severe HF [i.e., class IIIb or IV HF, according to the New York Heart Association (NYHA)]. Many recent trials have included NYHA class IIIb along with class IV, although the vast majority of enrollments have been NYHA class IV (e.g., class IIIb patients represent ~5% of enrollments in the ENDURANCE Trial for HeartWare destination therapy and in the MOMENTUM 3 Trial for HeartMate III). Interestingly, the US Food and Drug Administration (FDA) generally does not specify NYHA class but rather tends to use language such as "advanced, refractory left ventricular heart failure" (9, p. 1).

Other considerations for LVAD implantation include an assessment of factors that may place a patient at greater risk. The number of such factors is extensive and includes right ventricular function (because the right ventricle remains unsupported and can be at high risk for failure), pulmonary hypertension (which generally improves on mechanical support), age, frailty, and other comorbidities ranging from other organ function or failure to poor nutritional status, lack of psychosocial support, and inability to maintain the paracorporeal components of an implantable LVAD system (10–13).

3.2. Current Devices: Rotary Blood Pumps

Rotary blood pumps, sometimes referred to as second- or third-generation pumps, have taken the place of their larger, first-generation, positive-displacement, pulsatile flow predecessors. Rotary

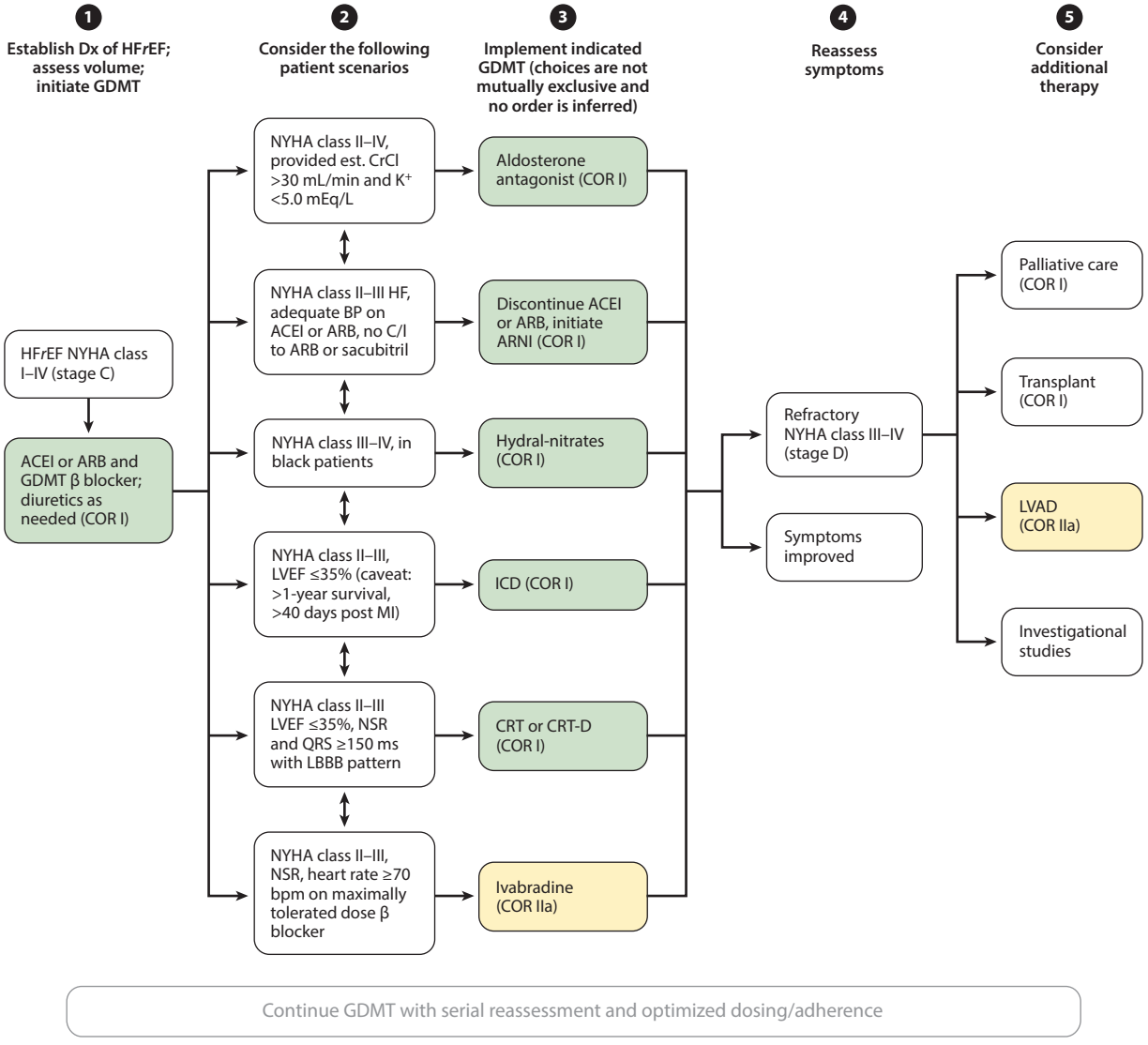


Figure 1

Guidelines for the management of heart failure. Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor neprilysin inhibitor; BP, blood pressure; bpm, beats per minute; C/I, contraindication; CrCl, creatinine clearance; CRT, cardiac resynchronization therapy; CRT-D, cardiac resynchronization therapy with defibrillator; GDMT, goal-directed medical therapy; HFrEF, heart failure with reduced ejection fraction; ICD, implantable cardioverter/defibrillator; LBBB, left bundle branch block; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; NSR, normal sinus rhythm. Adapted with permission from the American Heart Association (3).

blood pumps have a single rotating part, called the impeller, which generates continuous (non-pulsatile) flow. Clinical rotary blood pumps use either axial or centrifugal configurations, each of which is capable of delivering >5 L/min output, which can support the circulation of adult HF patients. For both axial and centrifugal blood pumps, the rate of generated flow is a function of pump speed (revolutions per minute) and the pressure difference (also called pressure rise) across

the pump from the inlet to the outlet. Second-generation rotary pumps operate with bearings immersed in blood or plasma, whereas third-generation rotary pumps operate with fluid-suspended or magnetically suspended impellers.

This shift in design paradigm (to the generation of nonpulsatile versus physiologic pulsatile flow) drastically reduced pump size by removing the need for blood sacs and one-way flow valves, while increasing durability and patient mobility. However, the nonphysiologic nature of these pumps poses additional design challenges, such as impeller position control, pump flow rate estimation, and ventricular wall suction detection (14). These and other challenges associated with the clinical use of rotary versus pulsatile flow blood pumps are discussed in detail in the following sections.

3.3. Current Devices: INTERMACS

For 13 years, investigators in the field benefited from a key source of clinical-use VAD information, namely the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), managed by the University of Alabama at Birmingham under the directorship of James J. Kirklin, MD, PI. On January 1, 2018, INTERMACS became part of the Society of Thoracic Surgeons (STS) National Database, joining the Adult Cardiac Surgery Database, the Congenital Heart Surgery Database, and the General Thoracic Surgery Database. There are currently 193 active clinical sites, enrolling more than 25,000 patients, in the STS INTERMACS Database (15). INTERMACS, which was in an early stage of development at the time of our 2008 review, classifies patients according to their level of limitation at the time of implant (16).

Table 2 summarizes these profiles at time of implant for more than 19,000 INTERMACS patients (17). As expected, those patients whose HF was most severe (Levels 1–4, according to the INTERMACS levels of limitation) (**Table 1**) were the primary recipients of MCS devices. In 2008, the use of first-generation blood pumps delivering pulsatile blood flow (positive displacement pumps) was waning, with a concomitant increase in the use of second-generation MCS devices and third-generation MCS devices, which can deliver diminished pulsatile or continuous blood flow. **Figure 2** demonstrates that intracorporeal axial and centrifugal flow pumps have

Table 1 Patient profile at time of implant by implant period[a]

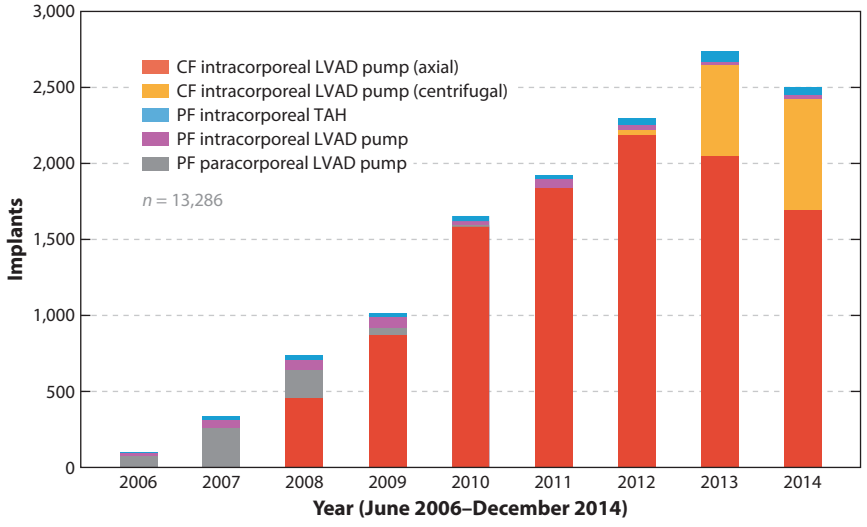
Patient profile at time of implant	Implant period						Total	
	Before 2010		2010–2011		2012–2016			
	n	%	*n*	%	*n*	%	*n*	%
1. Critical cardiogenic shock	637	29.2	529	14.8	2,091	15.7	3,257	17.1
2. Progressive decline	925	42.4	1,406	39.5	4,641	34.9	34.9	36.6
3. Stable but inotrope dependent	333	15.2	954	26.8	4,436	33.4	5,723	30.1
4. Resting symptoms	197	9.0	475	13/3	1,710	12.8	2,382	12.5
5. Exertion intolerant	42	1.9	107	3.0	267	2.0	416	2.1
6. Exertion limited	23	1.0	64	1.7	76	0.5	163	0.8
7. Advanced New York Heart Association (NYHA) III	20	0.9	22	0.6	46	0.3	88	0.4
Unspecified	None	NA	None	NA	12	0.0	12	0.0
Total	2,177	100.0	3,557	100.0	13,279	100.0	19,013	100.0

[a]Patient profile status provides a general clinical description of the patients at the time of implantation. Implants: June 23, 2006 to December 31, 2016.
Abbreviation: NA, not applicable.
Table adapted from INTERMACS (17).

Table 2 INTERMACS levels of limitation

Level	Description
Level 1: Critical cardiogenic shock	Critical cardiogenic shock describes a patient who is "crashing and burning," that is, has life-threatening hypotension and rapidly escalating inotropic pressor support.
Level 2: Progressive decline	Progressive decline describes a patient who has been demonstrated to be dependent on inotropic support but nonetheless shows signs of continuing deterioration.
Level 3: Stable but inotrope dependent	Stable but inotrope dependent describes a patient who is clinically stable on mild to moderate doses of IV inotropes.
Level 4: Resting symptoms	Resting symptoms describe a patient who is at home on oral therapy but frequently has symptoms of congestion at rest or with activities of daily living.
Level 5: Exertion intolerant	Exertion intolerant describes a patient who is comfortable at rest but unable to engage in any activity, living predominantly within the house or household.
Level 6: Exertion limited	Exertion limited also describes a patient who is comfortable at rest without evidence of fluid overload, but who is able to do some mild activity.
Level 7: Advanced New York Heart Association (NYHA) III	Advanced NYHA III describes a patient who is clinically stable with a reasonable level of comfortable activity, despite history of previous decompensation that is not recent.

Table adapted from Reference 16.



	2006	2007	2008	2009	2010	2011	2012	2013	2014
CF intracorporeal LVAD pump (axial)	0	0	459	867	1,580	1,838	2,183	2,044	1,695
CF intracorporeal LVAD pump (centrifugal)	0	0	0	0	0	0	38	598	728
PF intracorporeal TAH	1	22	30	24	29	26	41	74	54
PF intracorporeal LVAD pump	76	260	180	54	13	2	0	1	0
PF paracorporeal LVAD pump	18	55	72	65	29	54	31	21	24

Figure 2

Distribution of device types by year of implant from June 2006 to December 2014. Abbreviations: CF, continuous flow; LVAD, left ventricular assist device; PF, pulsatile flow; TAH, total artificial heart. Adapted from Reference 18 with permission.

dominated the MCS field during the past decade (2). One second-generation blood pump, the Abbott–Thoratec HeartMate II Left Ventricular Assist System (LVAS), is the most widely used blood pump worldwide. Its clinical use statistics, based on clinical trial and device-tracking data as of December 22, 2017, according to the manufacturer (A. Baumberger, personal communication), are as follows:

- patients implanted: >26,000 worldwide;
- 2,325 patients on support for more than 5 years;
- 44 patients on support for more than 10 years;
- age range: 10–91 years;
- body surface area (BSA) range: 1.0–3.4 M^2; and
- transplanted, recovered, or supported to 6 months: 91%.

The HeartWare–Medtronic HVAD MCS device is a widely used third-generation blood pump (19). According to its manufacturers, this centrifugal HVAD has been implanted in more than 13,000 patients in 47 countries worldwide.

Another third-generation device that is anticipated to see widespread clinical use is the centrifugal Abbott–St. Jude Medical HeartMate III LVAD (20). The HeartMate III incorporates a fully magnetically levitated design, thereby eliminating the need for bearings or seals to support impeller rotation.

Both the HVAD and the HeartMate III have been evaluated in comparison to the most widely used device, the HeartMate II LVAD. **Table 3** and **Figure 3** summarize these comparative trials (19, 20). In their assessment of these two comparison trials, Hetzer & Delmo Walter (21,

Table 3 Comparison of centrifugal LVAD designs versus HeartMate II

	Medtronic–HeartWare HVAD (19)	St. Jude–Abbott HeartMate III (20)
Pump design	Centrifugal-flow pump	Fully magnetically levitated centrifugal-flow pump
Impeller positioning	Hydrodynamic bearing	Fully magnetic levitation
Approval	BTT	Investigational
Pivotal study	Endurance trial	Momentum 3 trial
***n* (study versus control)**	297 versus 148	151 versus 138
Primary endpoint definition	2-year survival free from stroke with patient alive on original device having undergone elective transplant or with the device explanted due to LV recovery	6-month survival free of disabling stroke with patient alive on original device
Failure definition	Death or stroke within 2 years Urgent transplant or surgery required for LVAD removal or replacement due to failure of original device	Death or stroke within 6 months Reoperation to replace or remove device (for nonrecovery) Emergency transplant
Noninferiority achieved?	Yes	Yes
Superiority achieved?	N/A	Yes
Findings as compared to HeartMate II	Higher risk of stroke Higher risk of RV failure Higher risk of sepsis Lower risk of mechanical failure Lower risk of emergency transplant	Less likely to require replacement at 6 months

Abbreviations: BTT, bridge to transplantation; LV, left ventricle; LVAD, left ventricular assist device; RV, right ventricle.

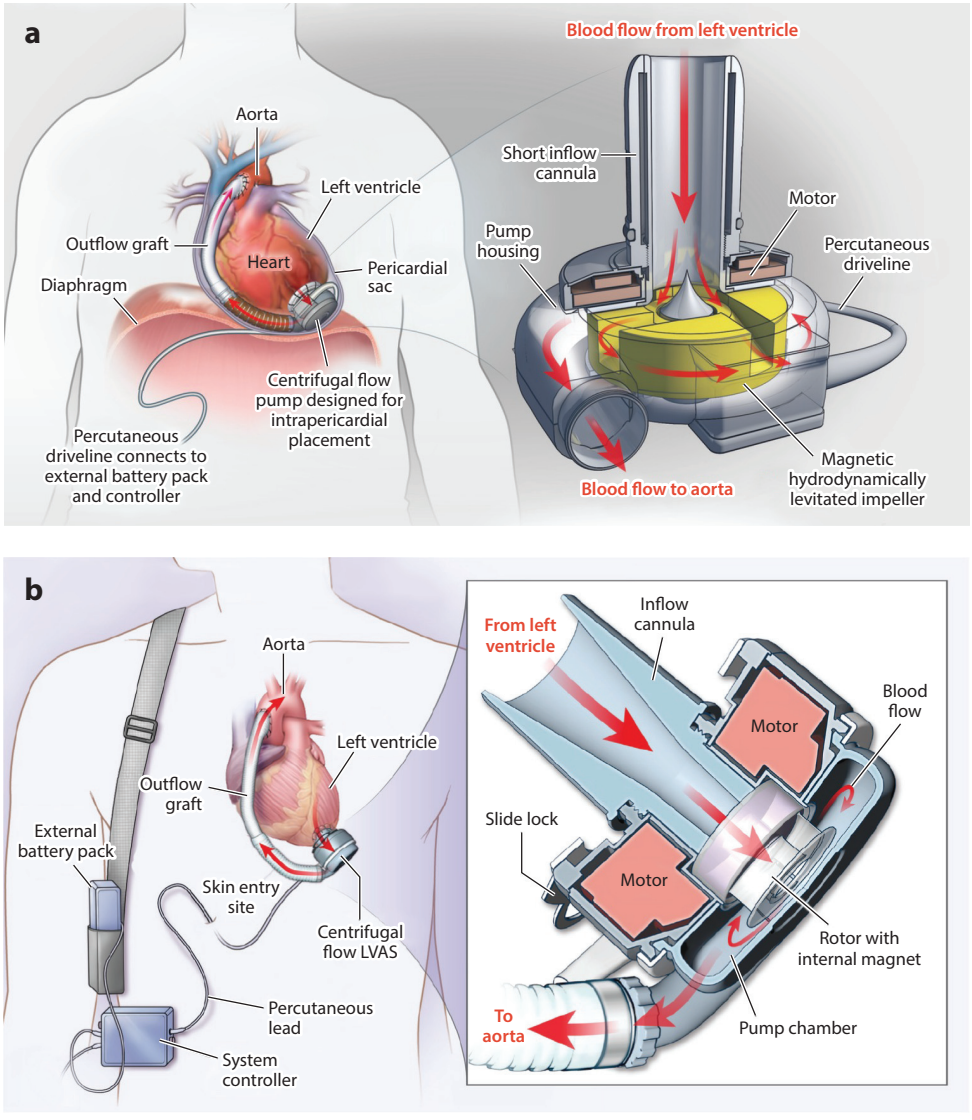


Figure 3

Images of (*a*) a centrifugal flow pump (Medtronic HeartWare HVAD) (19) and (*b*) a fully magnetically levitated centrifugal flow pump (St. Jude–Abbott HeartMate III) (20). Abbreviation: LVAS, left ventricular assist system. Adapted with permission from the Massachusetts Medical Society.

p. 488) note that "continued concerns about device complications, particularly pump thrombosis requiring device replacement led to the two trials in which the HeartMate II is compared with two newer pumps, HeartMate III (MOMEMTUM 3 Trial) and HVAD (ENDURANCE Trial)." These authors conclude that "it is clear that the newer devices have not yet resolved some of the most important problems with LVAD support…bleeding, sepsis, the risk of right heart failure, risk of stroke…. The perfect approach to mechanical circulatory support in advanced heart failure has not yet been achieved" (21, pp. 488–89).

As we note in our 2008 review (1), identifying the origins and solutions to the key adverse events of bleeding, infection, and thrombosis are of highest priority. To that end, there have been numerous investigations into the role of von Willebrand factor (vWF) in adverse events observed in patients using LVADs. Welden et al. (22) reported that gastrointestinal bleeding (GIB) in patients using LVADs is a significant problem leading to high rates of readmission. In a complementary study, Sakatsume et al. (23, p. 841) determined that "patients with GIB exhibited a more significant loss of vWF multimers…which may dictate the risk of GIB after an LVAD implantation." In a study comparing outcomes of patients using the HeartMate III versus historical controls using the HeartMate II, Zayat et al. (24) reported that in HeartMate III patients for whom no thromboembolic events were noted, there was a lower incidence of platelet-type von Willebrand disease. The authors concluded, however, that "bleeding events remain a serious postoperative complication" (24, p. S366).

Looking at bleeding from the point of view of pump flow dynamics, Vincent et al. (25, p. 2107) "demonstrated that the vWF defect reflects the balance between degradation induced by the shear stress and the endothelial release of new vWF triggered by the pulsatility. This modulation of vWF levels could explain the relationship between pulsatility and bleeding observed in continuous flow–MCS recipients. Preservation of pulsatility may be a new target to improve clinical outcomes of patients." In an accompanying editorial, Badimon & Santos-Gallego (26, p. 2121) stated that the "utmost caution should be taken when speculating that the development of continuous flow—mechanical circulatory support generating pulsatility could mitigate this acquired vWF, reduce bleeding and improve clinical outcomes" without further investigations in "larger sample sizes incorporating clinically relevant endpoints."

Patients supported with MCS devices achieve an enhanced quality of life (QoL) compared with HF patients without assisted circulation. According to Grady et al. (27), overall QoL improves to similar levels after MCS regardless of the severity of HF before implantation. This finding is borne out by the eighth annual INTERMACS report, published in 2017 (28). QoL assessments of more than 22,000 pump patients determined that "on average, important improvement in quality of life is noted in the first 3 months and is maintained out to at least 24 months postimplant" (28, p. 1085). Importantly, when patients were queried about their decision to have VAD therapy, "approximately 80% of responding patients ha[d] a favorable impression of their VAD experience during the first 2 years" (28, p. 1086).

In addition to the introduction of the aforementioned chronic-use, continuous flow–generating LVADs and their ongoing evaluations for safety, efficacy, and performance, the past decade has witnessed the introduction of a number of short-term-use, continuous flow–generating LVADs intended for treatment of cardiogenic shock. Several recent articles have described these various devices and their clinical use in detail. Nagpal et al. (29) identify various MCS devices available to treat medically refractory cardiac and cardiopulmonary failure. The devices from US-based manufacturers include CentriMag® (Thoratec Corp., Pleasanton, CA/St. Jude Medical, St. Paul, MN/Abbott Laboratories, Abbott Park, IL), the TandemHeart (CardiacAssist, Inc., Pittsburgh, PA), and the Impella (Abiomed, Danvers, MA) family of microaxial pumps. According to the manufacturer (30), the CentriMag Extracorporeal Blood Pumping System "provides hemodynamic stabilization in patients in need of cardiopulmonary support for 6-hours (acute support)." The CentriMag comprises a single-use centrifugal pump, a motor, and a primary drive console, which operate via magnetic levitation of the impeller (third-generation design). Nagpal et al. (29, p. 114) report that the CentriMag has been approved by the FDA "for up to 6-hours in a left sided support indication, up to 30-days in a right-sided support indication, and CE [Conformité Européenne]-marked for up to 30 days of use in any indication." A preliminary seven-center study of the safety, effectiveness, and outcomes of the CentriMag in 38 patients in cardiogenic shock

by John et al. (31) determined a mean duration of support for the entire cohort of 13 days, with 18 of 38 patients (47%) surviving 30 days after device removal. The authors conclude that "the CentriMag provided short-term support with an acceptable survival for patients with cardiogenic shock with a low incidence of device-related complications and no device failures" (31, p. 932).

The TandemHeart was introduced in 2005 as a temporary percutaneous LVAD technology, in which, as noted by Nagpal et al. (29, p. 113), "a 21-Fr drainage catheter is inserted into the femoral vein, and traverses the right atrium into the left atrium via a trans-septal puncture, a centrifugal pump, and a 15- to 19-Fr arterial catheter are inserted into the common femoral artery." Similar to the CentriMag designation, the TandemHeart has been approved by the FDA for 6 h of use for treatment of medically refractory cardiogenic shock (32); in Europe, the TandemHeart has been CE-marked for up to 30 days (29).

Many clinical reports are available regarding the use of the TandemHeart for treatment of cardiogenic shock. An early report by Tempelhof et al. (33, p. 254) investigated the use of TandemHeart in a series of 25 patients requiring percutaneous ventricular assist device support and concluded that "the TandemHeart device is a safe therapeutic option as a bridge-to-recovery or bridge-to-bridge for patients with hemodynamic compromise regardless of the etiology." Very recent single center reports on the use of TandemHeart for the management of cardiogenic shock employ retrospective database review of patients receiving left ventricular support via TandemHeart (34). A recent, comprehensive single-center assessment of the TandemHeart for management of severe cardiogenic shock has been reported by Berg et al. (35, p. 108), who evaluated "65 consecutive patients between 2006 and 2014, analyzing demographic, clinical, laboratory, hemodynamic, and survival data." Thirty-two patients (49.2%) survived to hospital discharge. The median duration of TandemHeart support for these patients was 5.9 days.

The Impella family of microaxial pumps includes three pump sizes for support of the left ventricle (Impella 2.5, Impella 3.5/CP, and Impella 5.0/LD) and one size for support of the right ventricle (Impella RP). The pumps consist of 9–11 French catheters that contain the inlet, impeller, outlet, and power cord. A dextrose flush solution/purge flow is maintained by a secondary pump, located within the device controller, to decrease hemolysis and potential for thrombus formation. Implantation of the Impella 5.0 for left ventricular support is performed via either percutaneous insertion or cut-down. In operation, the Impella (see **http://www.medicalexpo.com/prod/abiomed/product-77758-468918.html**) provides a pump rate of ~2.5–5.0 L/min into the ascending aorta (**Figure 4**). Accordingly, the Impella increases cardiac output and mean arterial pressure, analogous to an intra-aortic balloon pump (IABP), improving perfusion of coronary arteries and end organs. The Impella RP is inserted from the femoral vein into the pulmonary artery, thereby unloading the right ventricle into the pulmonary artery. **Table 4** details the cardiac support applications provided by the Impella family of microaxial pumps. According to this information, the Impella 2.5 is typically used to provide mechanical support for high-risk percutaneous coronary intervention (PCI); indications for use of the Impella 3.5/CP and Impella 5.0/LD are left ventricular failure due to cardiogenic shock and other etiologies. A retrospective record review of 47 patients who were implanted with the Impella LVAD between January 1, 2006 and December 31, 2011 (36) shows that the duration of Impella support can range from <1 week to >2 weeks. In 2017, Abiomed introduced a third-generation Impella microaxial pump. Among the attractive features of this new pump is its capability to generate peak flow rates above 4 L/min in patients requiring additional pump support (37).

Numerous single-center case reports utilizing various Impella microaxial pumps have been published. Particular attention has focused on comparison of Impella devices and IABPs in patients with cardiogenic shock. In the PROTECT II Trial (38), a prospective randomized trial

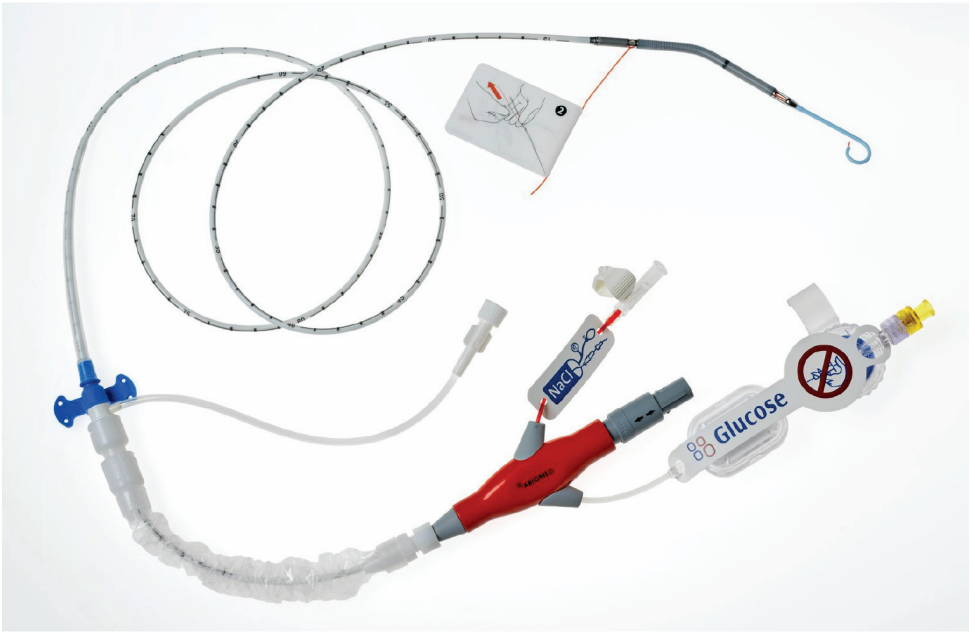


Figure 4

Impella 2.5 catheter-based microaxial temporary left ventricular assist device. Adapted from **http://www.abiomed.com/impella/impella-25**. Copyright Impella 2.5, ABIOMED.

comparing the hemodynamic support of the Impella 2.5 with that of an IABP in 452 high-risk patients with PCI, the 30-day incidence of major adverse events was similar between the two groups (35.1% for Impella versus 40.1% for the IABP). More recently, data supporting the use of the Impella 5.0/LD pump for support of patients with cardiogenic shock were provided, in

Table 4 Impella catheter-based microaxial ventricular assist devices

Impella device	Placement	Intended use	Pump motor size, level of support	Duration
2.5	Standard catheterization via femoral artery; across aortic valve	LV support for high-risk PCI; CS	12 FR, 2.5 L/min	≤6 hrs (PCI), ≤4 days (CS)
3.5/CP	Standard catheterization via femoral artery; across aortic valve	LV support for high-risk PCI; CS	14 FR, 3.5 L/min	≤6 hrs (PCI), ≤4 days (CS)
5.0	Femoral cutdown; across aortic valve	CS	21 FR, 5.0 L/min	≤6 days
LD	During open chest procedures; across aortic valve	CS	21 FR, 5.0 L/min	≤6 days
RP	Standard catheterization via femoral vein; inlet placed in RA, outlet located in PA	Acute right heart failure or right heart failure post-LVAD implantation, myocardial infarct, transplant, or other surgery	22 FR, 4.0 L/min	≤14 days

Abbreviations: CS, cardiogenic shock; FR, French; LV, left ventricle; LVAD, left ventricular assist device; PA, pulmonary artery; PCI, percutaneous coronary intervention; RA, right atrium.

part, by the RECOVER I study, a nonrandomized, prospective, single-arm (Impella 5.0) study of 16 patients with postcardiotomy shock (39). According to the authors, "the results of this study demonstrated that the use of the Impella enabled immediate restoration of hemodynamics with a gradual reduction in the need of inotropic support" (39, p. 552).

While these three short term–use, continuous flow–generating blood pumps are employed widely in medical centers both in the United States and internationally, a significant drawback is that a paucity of randomized controlled studies are available to assist with "clinical decision making" regarding the use of these pumps to treat cardiogenic shock. In a recent article, Miller (40, p. 1882) addresses this point in terms of the selection of one of these pumps versus an IABP:

> To date, there have been few clinical trials conducted with temporary mechanical support (TMS). Their largely nonrandomized design with small numbers of patients makes them underpowered to demonstrate a survival benefit. There are several factors that help explain the reason why there is not more clinical trial data to demonstrate the superior mortality benefit of TMS over IABP in acute myocardial infarction (AMI) due to cardiogenic shock. This includes that fact that patients with the diagnosis of AMI shock are a heterogeneous group, with varying degrees of shock, previous infarction, and/or heart failure, and therefore variable potential for improvement, and are often very unstable, and therefore challenging to enroll in clinical trials. It will be very important going forward to conduct (randomized) prospective trials to better define the optimal patient who might benefit from this therapy and develop the much-needed criteria for when to initiate TMS and when to transition to other LVAD devices. These efforts will be aided by the creation of a registry for their use, which is currently being developed.

3.4. Devices Under Development

In addition to the aforementioned devices, R&D is under way on other cardiac support technologies for patients with HF and cardiogenic shock.

3.4.1. NuPulseCV IVAS. The NuPulseCV Intravascular Ventricular Assist System (IVAS) (NuPulseCV, Inc., Raleigh, NC) uses counterpulsation via an intra-aortic balloon that is placed via the left subclavian artery (**Figure 5**) (41). The driveline exits the abdomen and connects to a drive unit that includes a small compressor. This device provides partial support as a bridge to transplant, eliminates the need for a full sternotomy or thoracotomy, and allows patients to ambulate. The NuPulse was approved by the FDA in 2015 for a first-in-human clinical trial, and as of September 2016, six patients with advanced HF had been implanted with the NuPulse at the University of Chicago (42).

3.4.2. TORVAD. Windmill Cardiovascular Systems (Austin, TX) has developed a synchronous (or asynchronous) pulsatile toroidal VAD called the TORVAD. The goal of this device is to preserve normal aortic flow while partially unloading the left ventricle under low-shear conditions. Flow is generated by two independent pistons that travel in a circular path. The pistons are magnetically coupled to two separate motors that are controlled with a system that permits independent optimization of stroke volume, timing, and output. Additional details regarding the TORVAD principle of operation can be found elsewhere (43, 44).

TORVAD is currently undergoing preclinical testing in preparation for first-in-human testing (45). According to the manufacturer, in vitro tests have demonstrated preservation of vWF and low hemolysis.

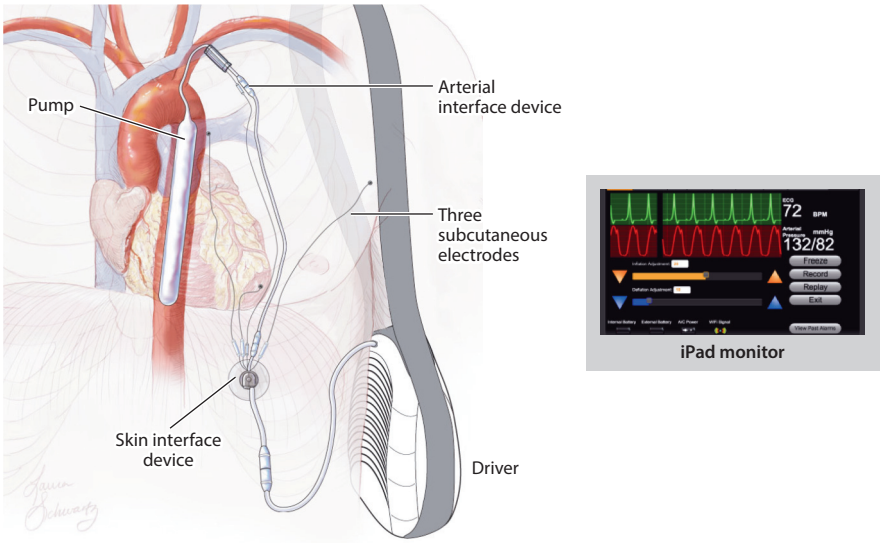


Figure 5

The NuPulseCV Intravascular Ventricular Assist System (IVAS) uses counterpulsation via an intra-aortic balloon, which is placed via left subclavian artery. Adapted from Reference 41 with permission from Elsevier.

4. TOTAL ARTIFICIAL HEARTS

4.1. Cleveland Clinic Foundation and Texas Heart Institute

Since 2008, the total artificial heart (TAH), first implanted in Dr. Barney Clark in 1982, has been the only such device approved by the FDA. The eighth annual INTERMACS report (28) updated the clinical use of the TAH; 373 TAH implants have been entered into the INTERMACS database, with 1-year survival <60%, which is consistent with VAD patients requiring biventricular support. According to the manufacturer, SynCardia Systems (Tucson, AZ), more than 1,600 TAHs have been implanted since 1982.

Other research groups are pursuing the development of next-generation TAHs. Both the Cleveland Clinic Foundation (CCF) and the Texas Heart Institute (THI) are applying lessons learned from the continuous flow rotary LVADs described above to novel TAH designs that are smaller than their pulsatile predecessors. Both CCF and THI have designed a dual-chamber device with a single shaft that drives two separate rotors. These rotors rotate at the same speed and produce the same output. However, the blade designs for the right side and the left side are optimized for the vastly different afterloads that are found in the pulmonary and systemic vasculature, respectively. The CCF TAH, 6 cm in diameter and 10 cm long, has a single moving part supported by hydrodynamic bearings with no valves or sensors. The current THI TAH prototype, BiVACOR, which also has a single moving part, has a diameter of 75 mm and a length of 90 mm.

A major difference between the designs of these two devices is in their approach to rotor positioning. The BiVACOR uses a fully magnetically levitated rotor design to stabilize position (46). The CCF device incorporates a different approach, in which the rotor position is determined mainly by the pressure differential between the right and left sides (47).

Both the CCF TAH and the BiVACOR are undergoing preclinical testing, both on the bench and in animals. A recent report by Karimov et al. (48) indicates that the CCF TAH has been

implanted in 17 calves, 2 of which were intended for 90-day studies. For these long-term animals, the findings indicate good biocompatibility, with no thromboembolism in organs. According to a recent report by Cohn et al. (49), the BiVACOR TAH has been implanted in three calves for 3 weeks, 1 month, and 3 months. Notably, acceptably low hemolysis levels were documented, and the animals were well perfused.

Dr. Richard Wampler and colleagues at Oregon Health & Science University reported on design and development of a novel TAH with the following characteristics (50):

- Pulsatile rotary pump with no valves, a single moving part, and zero mechanical contact.
- Excellent blood compatibility, which minimizes blood damage and reduces the risk of thrombosis.
- Adjustable settings to allow clinicians to best meet patient-specific physiology.
- Made of proven, FDA-approved materials, translating into lower risk and cost.
- Includes wearable components designed to be relatively compact and lightweight, enabling patient mobility (movement and exercise); similar to LVADs for improved QoL and medical outcomes.

4.2. CARMAT

The CARMAT® TAH (CARMAT, Vélizy-Villacoublay, France), which is under development by Carpentier et al. (51) for destination therapy and not bridge-to-transplant applications, uses two reciprocating rotary gear pumps to alternately shuttle hydraulic fluid between two blood sacs with compressible diaphragms. The CARMAT TAH has four pericardial tissue valves; the blood-contacting surfaces of the blood sacs are lined with a microporous biocompatible material intended to obviate the need for anticoagulation. Pulsatile flow pump output ranges from 2 to 9 L/min. Sensors embedded in the device provide autonomous regulation of the pump rate and output in response to activity level and physiological factors. The microprocessor that controls the device is integrated into the pump housing. In an attempt to decrease the incidence of pump-related infections, and analogous to the approach taken by Dr. Robert Jarvik (see **https://www.jarvikheart.com/products/post-auricular-cable/**), a percutaneous power lead enters through the posterior scalp and is affixed to a skull-mounted pedestal. **Figure 6** displays the CARMAT TAH system components (see the schematic at **https://www.carmatsa.com/en/our-product/**).

In December 2013, the CARMAT TAH began first-in-human trials in Europe with implantation in five patients. According to Carpentier et al. (51), the first patient died after 74 days as the result of device failure. The second patient survived 9 months, spending the last 4 months at home, with a wearable system without technical assistance, until suffering low cardiac output. A change in the CARMAT TAH was attempted, but the patient died as a result of multiorgan failure. The third and fourth patients also died—the third at home, 9 months post operation, from respiratory and kidney failure, and the fourth from medical complications related to pre- and postoperative clinical conditions.

The CARMAT TAH has received approval from the French National Agency for the Safety of Medicines and Health Products to undertake a 20-patient pivotal trial of the fully implantable system (52). The primary goal is 6-month survival.

In a recent article, Cohn et al. (53) commented on efforts over the past half-century to develop total cardiac replacements for patients with HF. These authors noted that success during the past decade in the use of continuous flow LVADs has "paved the way for new approaches to total heart replacement leveraging two rotary LVADs as a TAH" and that a rotary TAH "has the potential of

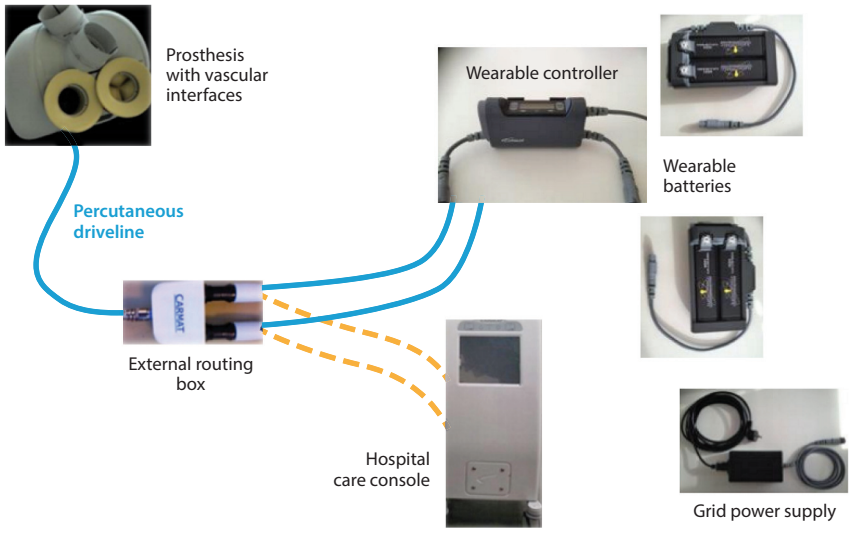


Figure 6

CARMAT system components. Adapted from Reference 51 with permission from Elsevier.

succeeding where previous attempts have failed to provide a practical replacement for the human failing heart" (53, p. 616).

4.3. Left Ventricular Assist Device Pump and Component Malfunctions: Bioengineering Considerations

As described above (**Figure 2**) and by Kirklin et al. (2), continuous flow LVADs have been implanted in thousands of patients during the past decade, with survival of 80% at 1 year post implantation and 48% at 4 years post implantation. Complications associated with VAD implantation are described in the 2015 INTERMACS report (2). Of particular interest to bioengineers is the hazard function, or risk of death from device malfunction. Kirklin et al. (2, figure 10) note that the instantaneous risk of death from device malfunction "appears to be low and constant over time" at 0.0006 deaths/month. The authors (2, tables 6 and 7) provide further details, namely that among 9,781 continuous flow LVAD/BiVAD (biventricular assist device) implants for Level 1–3 INTERMACS patients (**Table 1**) during the period 2008–2014, there were 2,596 deaths, of which 92 (3.5%) were caused by device malfunction (2, table 6). A total of 2,194 Level 4–7 INTERMACS patients received continuous flow LVAD/BiVAD implants during the same period. Of these patients, 579 died; 23 (4.0%) of these deaths were caused by device malfunction. Numerous published reports during the past decade have investigated device malfunction in continuous flow blood pumps. John et al. (54) reported on the freedom from pump exchange (for any reason) in their single-center retrospective analysis of 278 consecutive patients who underwent a total of 302 HeartMate II implants from June 2005 through June 2014: 1 year, 95% freedom from pump exchange; 2 years, 92%; 3 years, 84%; 4 years, 82%; and 5 years, 72%. Interestingly, pump exchange was statistically more common in bridge-to-transplant recipients versus destination therapy patients. Wever-Pinzon et al. (55) analyzed 3,821 heart transplant candidates supported by continuous flow LVADs whose names were on the United States waiting list from 2008 to 2014. One of the evaluations included the incidence of LVAD malfunction. This study defined LVAD malfunction as "failure of one or more of the electrical or mechanical components of the

VAD system that could lead to a state of inadequate circulatory support or death" (55, p. 885); 85% of the patients were supported by the HeartMate II and 15% by the HVAD. LVAD malfunction occurred in 210 patients (5.5%) for an overall incidence of 0.06 events per patient year. According to the authors, their data suggest that "surgical and anatomic factors, as represented by the history of previous cardiac surgery, are important contributors to the development of LVAD malfunction" (55, p. 890). Furthermore, according to the authors, "patients with higher functional capacity are at increased risk for LVAD malfunction, which could be the result of excessive wear and tear of the different peripheral LVAD components in a highly active patient" (55, p. 890).

In a retrospective study, Soltani et al. (56) analyzed pump malfunctions associated with cable damage in patients supported with implanted HeartMate II ($n = 191$) devices. This study considered HeartMate II pumps implanted both prior to and following modifications made to the cable strain relief. These authors defined cable damage as being "present with any pump malfunction caused by acute or chronic damage to the leads or connector, leading to pump exchange, high urgency heart transplantation or death before admission to hospital" (56, p. 985). According to the authors, "following introduction of the new cable design strain relief, incidence of cable damage in HeartMate II patients dropped from 0.06 events per patient-year (18 patients) to 0 ($P = 0.03$)" (56, p. 985).

When LVAD malfunction occurs, repairs are made to allow pump operation to continue. Pal et al. (57, p. S27) reported their experience and outcome of all attempted external lead repairs for the HeartMate II between initiation of repairs in 2008 through 2014:

> A total of 321 repairs were undertaken in 297 patients. The median duration of mechanical support prior to the repair procedure was 2.0 years (range 7 days–8.7 years). 202 of the 297 (68%) patients had resolution of pump dysfunction with no recurrence of lead problems. The median duration of support after lead replacement was 189 days, with 11 patients greater than two years. Twenty-seven of 297 (9.2%) patients had minor additional problems such as abrasions of the insulation without electrical damage that were repaired with tape and external reinforcement. Thirty-seven (12.5%) patients had unsuccessful external replacement of the percutaneous lead due to concomitant intracorporeal lead damage. Thirty-one (10.4%) patients continued with serious malfunctions after lead replacement. Of these, 17 patients underwent repeat repair, and 14 continued on ungrounded cables. Fourteen of these 31 patients ultimately underwent pump exchange. One patient required emergent pump exchange due to catastrophic failure during the external lead replacement procedure. There were three deaths within 14 days of attempted lead repair due to ongoing lead damage and electrical malfunction of the LVAD.

On the basis of these data, the authors concluded that "lead repair by replacement of the external distal percutaneous lead can be performed by trained personnel in a standardized fashion and may provide a durable solution in select patients with isolated external lead damage, thus avoiding the need for surgical exchange" (57, p. S27).

Two recent single-center reports describe device malfunction in clinically used rotary blood pumps. Kerk et al. (58) report their experience at Singapore National Heart Center with device malfunction in long-term MCS devices from May 2009 to October 2013. A total of 41 patients were implanted with either the HeartMate II ($n = 31$) or the HeartWare HVAD ($n = 10$). According to the authors, "there were a total of 77 device component malfunctions related to long-term MCSD, including controller ($n = 21$, 27%), external battery (11, 14%), cable (10, 13%), battery charger (13, 17%), driveline (8, 10%), battery clips (3, 4%), pump (2, 3%), power module (3, 4%), monitor (2, 3%), power adapter (2, 3%), and power connector (1, 1%)" (58, p. S260). The authors concluded that "there is a need to make the device especially its peripheries more reliable, rugged and durable for long-term use" (58, p. S260).

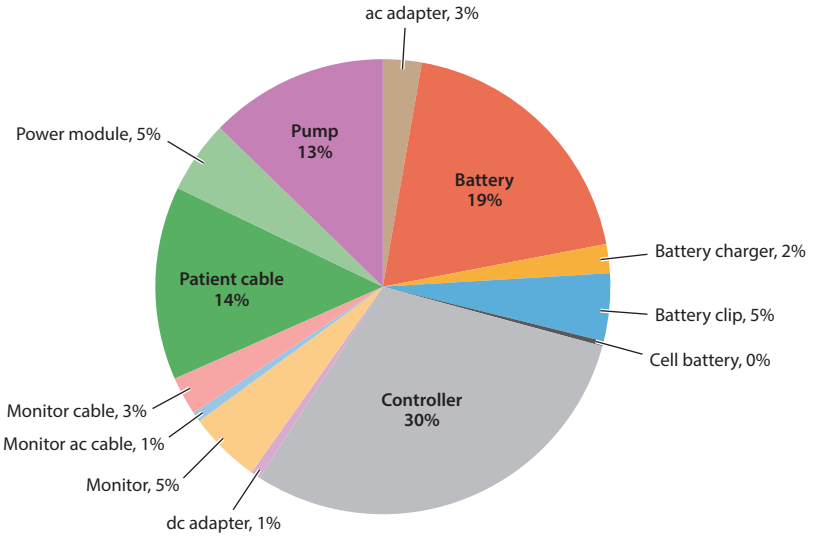


Figure 7

Distribution of types of device malfunction as a percentage of total malfunctions, according to Kormos et al. (60). Adapted with permission from Wolters Kluwer Health.

Kormos et al. (59) reached a similar conclusion on the basis of their examination of all device malfunctions for the HeartMate II and the HVAD LVAD implanted as a bridge to transplantation or destination therapy from January 2, 2001 until December 31, 2013 at the University of Pittsburgh Medical Center. This study categorized device malfunction as primary pump failure (PF), controller failure (CF), or peripheral component failure (PCF). CF included controller replacement due to failure of either the controller itself or its connectors. PCF included premature battery failure or failure of other cables, monitors, or chargers. The authors reported that, of 134 device malfunctions in 92 HeartMate II patients, PCF accounted for 67% of malfunctions, CF for 19%, and PF for 12%. For the HVAD, there were 35 device malfunctions in 49 patients, with PCF accounting for 65% of them, CF for 26%, and PF for 9%. On the basis of these data (**Figure 7**), Kormos et al. (60, p. 1714) concluded that "device malfunction remains common after VAD, most commonly in the peripheral components, while true pump failure is less common."

4.4. Cardiac Recovery with Continuous Flow Ventricular Assist Devices

Continuous flow LVADs have been used in tens of thousands of patients with end-stage HF as a bridge to cardiac transplantation or destination therapy. One of the goals of LVAD use is to allow the patient to recover physiologic status as quickly as possible so that he or she can be discharged from the hospital.

Cardiac recovery with left ventricular assistance has long been a topic of interest. In 2006, Birks et al. (61, p. 1873) reported that "sustained reversal of severe heart failure secondary to nonischemic cardiomyopathy could be achieved in selected patients with the use of a pulsatile flow left ventricular assist device and a specific pharmacologic regimen." In a follow-up study, Birks et al. (62, p. 381) reported that "reversal of end-stage heart failure secondary to nonischemic cardiomyopathy can be achieved in a substantial proportion of patients with nonpulsatile flow through the use of a combination of mechanical and pharmacological therapy." These authors'

reports were recently substantiated by Jakovljevic et al. (63, p. 1924), who "evaluated whether patients undergoing a continuous flow LVAD bridge-to-recovery protocol can achieve cardiac and physical functional capacities equivalent to those of healthy controls." According to these authors, "a substantial number of patients who recovered sufficiently to allow explanation of their LVAD can even achieve cardiac and physical functional capacities nearly equivalent to those of healthy controls."

4.5. Exercise Recovery with Continuous Flow Ventricular Assist Devices

Exercise is imperative for cardiac health and recovery. In normal physiology, the native heart responds to meet metabolic demands during exercise. Recent articles have described this response in patients suffering from end-stage HF following implantation of continuous flow LVADs (HeartMate II and HVAD). Jung & Gustafsson (64) reviewed the different components of exercise physiology in LVAD patients. Their review strategy consisted of "conducting a systematic literature search in PubMed by identifying studies on exercise capacity in LVAD patients" (64, p. 489). Exercise capacity was characterized according to the usual clinical measurements, including the 6-min walk test, NYHA functional classification, peak oxygen uptake, percent of predicted peak oxygen uptake, anaerobic threshold, ventilator equivalent ratio for carbon dioxide, and respiratory exchange ratio. Results from numerous studies cited in their article led to the conclusion that "[m]aximal exercise capacity remains severely reduced in heart failure patients, even after continuous flow LVAD implantation. In the maintenance phase of LVAD support, the majority of studies showed exercise tolerance to be stabilized at a consistently severely reduced level" (64, p. 495). Interestingly, the authors proposed a possible approach to enhancing exercise capacity in these continuous flow LVAD patients via the incorporation of closed-loop speed control, which would "respond to various loading conditions and enable the pumps to provide sufficient support even during strenuous exercise" (64, p. 495).

Reiss et al. (65, p. 457) reached similar conclusions:

> During physical exertion cardiac output increases to a certain degree—partly through the assist device, partly through the residual function of the left ventricular myocardium. Ultimately, the cardiopulmonary capacity of LVAD patients is restricted to a higher degree during exercise. Further information is needed to investigate how an increase in the number of pump rotations can lead to increased physical capacity in LVAD patients.

Haufe et al. (66) hypothesized that pulse pressure augmentation could be achieved through regular physical exercise in patients implanted with continuous flow LVADs. In their pilot study involving patients implanted with four continuous flow LVADs (HVAD, HeartWare) supported for between 5 and 24 months, these authors assessed beat-to-beat pulse pressure by finger photoplethysmography. The results documented that "exercise elicits a marked pulse pressure increase in all patients, even in those with very low resting pulse pressure" (66, p. 1568). According to Haufe et al. (66, p. 1569), the importance of this preliminary finding is that "the human cardiovascular system is tuned to operate with pulsatility…and patients implanted with continuous flow LVADs exhibit marked arterial pulse pressure reductions that could adversely affect cardiovascular health." Thus, an increase in pulse pressure (in response to physical exercise training) could have beneficial effects on cardiovascular structure and function.

The three reports described above highlight the need for research regarding the importance of pulsatility and adaptive control in response to physiologic activity/loading conditions for greater recovery of functional exercise capacity in patients with continuous flow LVADs.

5. PEDIATRIC VENTRICULAR ASSIST DEVICES

The use of MCS devices, primarily LVADs, in pediatric patients with advanced HF has progressed over the past 20 years and is poised to change significantly in the near future. Clinical reports, although few in number, have been encouraging. Ihnat et al. (67, p. 234) described the "deployment and successful weaning from LVAD in young children with severe heart failure." Between 2004 and 2009, 13 children with severe HF received LVADs; 8 survived with recovered native hearts, and 1 underwent transplantation.

The progress and interest in the use of LVADs in pediatrics resulted in the creation of an offshoot of INTERMACS in September 2012 specifically for pediatric patients. The first annual report from this voluntary registry, known as the Pediatric Interagency Registry for Mechanical Circulatory Support (PEDIMACS) (68), revealed that 200 patients underwent durable device implants in the United States in the first 33 months of the Registry's existence. These numbers indicate that the rate of chronic MCS use in US children is 73 patients per year (69). This number certainly underestimates the number of children who received chronic MCS because, as a voluntary registry including a portion of the sites implanting LVADs in pediatric patients, PEDIMACS does not capture all pertinent implants. The United Network for Organ Sharing (UNOS) database can also provide an estimate of current usage; using this database, Villa et al. (70) reported that 284 children were supported by LVADs and transplanted over the 3.5 years spanning January 2011 to June 2014. This corresponds to a rate of approximately 81 children per year receiving LVADs leading to heart transplant. However, that number does not include those children who recovered or died while on LVAD support or those who were implanted with TAHs. Given these limitations, a reasonable estimate of the number of pediatric patients utilizing chronic MCS in the United States is 100 per year. This rate is similar to that given in the second annual PEDIMACS report, which revealed that 364 patients were supported by temporary and/or chronic MCS devices in 42 US hospitals over the 4 years spanning September 2012 to September 2016 (68), which corresponds to a rate of 91 pediatric MCS patients per year. The number of children in the United States who could benefit from MCS is greater. For the decade spanning 2008–2017 (since the publication of our earlier review), the UNOS database indicates that 525 children per year younger than 18 years were listed for a heart transplant, and 429 children per year received them (see **https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/**). More than half (301 listings and 224 transplants per year) were for children 5 years of age or younger. The difference between listings and transplants (which indirectly indicates waiting-list mortality) is much greater for the children younger than 6 years, accounting for 77 of the average 96 per year. Because some of these patients did not require MCS before transplant and some children may require MCS, recover, and never need a transplant, it is uncertain how many children in the United States would benefit from chronic MCS use. However, these data provide a rough estimate that the need for chronic MCS may be up to 500 per year for all pediatric patients and 300 per year for children younger than 6 years.

The data in the first two annual PEDIMACS reports reveal that (*a*) continuous flow MCS devices are used predominantly in older, larger pediatric patients, and (*b*) pulsatile MCS devices are used almost exclusively in younger, smaller pediatric patients. Of the 200 implants recorded in the first report, 91 were pulsatile flow and 109 were continuous flow devices. Of the pulsatile devices used, 93% were LVADs and 70.4% were used in children aged 5 years or younger. Of the continuous flow devices (all of which were LVADs), 97.2% were used in children 6 years of age or older. The continuous flow LVADs are clearly the preference for these older children, since they account for 77% of the devices implanted into children 6 years of age or older. The second annual PEDIMACS report confirms these trends. Note that continuous flow LVADs are being used in

smaller and smaller patients; the HeartWare HVAD has been used in patients weighing as little as 13 kg and with a BSA as low as 0.6 m^2 (71). Considering the available devices and their sizes, this is not surprising. The only options for chronic support in children with a BSA of 1.2 m^2 or lower are the Berlin Heart EXCOR VAD (Berlin Heart, The Woodlands, TX) and the HeartWare HVAD, which, although designed and clinically used in adults, as noted above, may be small enough to fit into and work well enough in some of these small patients, with a BSA as low as ~0.6 m^2.

As noted above, the use of MCS in children is a relatively new development. Prior to the introduction of the Berlin Heart EXCOR VAD in the United States in 2000, extracorporeal membrane oxygenator (ECMO) circuits were the only means available for supporting young children with HF, and the use of ECMO was and still is limited to a few weeks of cardiac support. In 2000, the FDA made the EXCOR VAD available on a case-by-case basis, known as compassionate use, and its use grew at centers across the country since it provided the only means to bridge these young patients for months and even years while awaiting cardiac transplantation. From 2007 through 2011, Berlin Heart conducted a single-arm trial of the EXCOR device and received FDA humanitarian device exemption (HDE) approval in late 2011 for use of the device to bridge pediatric patients to cardiac transplantation (71). In June 2017, after reviewing evidence gathered from additional clinical studies of the EXCOR VAD, the FDA granted premarket approval (PMA) for the same use of the device. The PMA eliminated some reporting and site approvals required for HDE approval.

The greater availability and outcomes of the EXCOR VAD and the HeartWare HVAD in pediatric patients with HF have resulted in more widespread use of LVADs in this population. Recent data on the worldwide experience of the Berlin Heart EXCOR indicate that more than 1,800 patients, in 37 countries and more than 164 pediatric heart centers, have been implanted with this device. The longest time to date on the EXCOR exceeds 3.5 years (J. Woodard, personal communication). However, similar to adults on VADs, pediatric patients with these devices experience significant rates of adverse events. Clinical trial reports and individual case reports reveal that pediatric patients, especially the smaller recipients, experience bleeding and thrombosis at rates similar to or greater than those observed in adults on LVADs (72–74). While the HeartWare HVAD has more limited pediatric use than the EXCOR due to its size, as noted above, it has been used in children with a BSA as low as 0.6 M^2. However, some data indicate that while the survival rate is quite good in patients with a BSA ranging from 0.6 to 0.9 M^2, pump thrombosis appears to occur at a higher rate in smaller patients (72). The Berlin Heart EXCOR trial that led to HDE approval reported that 29% of children had a neurologic event. To address this issue, a new anticoagulation protocol for the use of the EXCOR, known as the Stanford Anticoagulation Protocol, has been developed and is being implemented, with favorable early results (74).

Several newer LVADs have incorporated recent technology and, if successful, may reduce the rate of serious adverse events in pediatric patients with LVADs, especially those with a BSA of 1.0 M^2 or lower (75). One such device is the pediatric version of the TORVAD technology, discussed above (75). This device, still at an early stage of development, is designed to minimize blood shearing and provide adaptive pumping to optimize blood output. Another promising LVAD for pediatric use is the Jarvik 2015 (Jarvik Heart, New York, NY) (76). It is the first continuous flow LVAD designed specifically for use in small children and, as such, may be better able to provide the advantages of continuous flow pumps in pediatric patients versus pumps designed for use in adults. The Jarvik 2015, which is approximately the size of an AA battery, will soon be evaluated in the Pumps for Kids, Infants, and Neonates (PumpKIN) clinical feasibility trial, a study sponsored by the National Heart, Lung, and Blood Institute that is designed to include children with a BSA as low as 0.4 M^2. If successful, a pivotal trial could follow.

In another example of ongoing development in pediatric VADs, the principle of magnetic levitation has been applied to a miniaturized, continuous flow pump (PediaFlow®; HeartWare International, Inc., Framingham, MA) for infants and small children, also approximating the size of an AA cell battery. The PediaFlow has an operating range of 0.5–1.5 L/min with minimal hemolysis in vitro and excellent hemocompatibility (e.g., minimal hemolysis and platelet activation) in vivo. The pump and implantable components have demonstrated 60-day acceptable preclinical hemodynamics and excellent biocompatibility suitable for pediatric application (77).

6. FUTURE CONSIDERATIONS

6.1. Future Therapies: Cell Transplantation and Tissue Engineering

Since 2008, the research community has gained a more mature perspective regarding the potential of cell transplantation and tissue engineering approaches to HF, particularly for ischemic cardiomyopathy. There has been extensive research, including multiple clinical trials, utilizing a variety of cell types and approaches, and reports and reviews of the topic are quite frequent in the literature (78, 79). Although progress has occurred, the dichotomy invoked in our 2008 review (1) between cell transplantation and tissue engineering (i.e., cells combined with biomaterials) continues to apply to this field.

6.2. Cell Transplantation

In many ways, from the clinical translation perspective the past decade has been a disappointment with regard to the potential of cell transplantation. A general summary of the broad literature in this area is that the functional benefits measured have been modest; the survival of transplanted cells has been lower than originally envisioned; and we now know that the primary effects related to the transplanted cells come not from their integration as functional cardiomyocytes but rather from their role as cellular drug delivery vehicles, delivering cytokines and exosomes beneficial to the diseased ventricular wall (80, 81). As was the case in 2008, concerns remain that, should a large number of cells survive to form functional islands of new cardiomyocytes, these islands would introduce a nidus for arrhythmias. This issue has not been adequately addressed in the clinical model, since high cell survival and differentiation have generally not been observed (81).

On the positive side, as clinical studies have expanded, the types of HF being targeted have increased to include hypoplastic left heart syndrome, adriamycin-induced cardiomyopathy, and idiopathic dilated cardiomyopathy (81). Also, an ever-increasing set of cell types are being evaluated along the translational pathway, with a transition from studies that initially heavily favored mesenchymal stem cells or circulating mononuclear cells to investigations of inducible pluripotent stem cell (iPSC)-derived cells, adipose-derived stem cells, cardiosphere-derived cells, and genetically modified cells that seek to specifically address issues of cell survival, differentiation, and stimulation of local cardiomyocyte proliferation (78, 82). Substantial advances in our understanding of the mechanisms of inherent cardiac regeneration are strongly influencing the approach to cell selection, cell manipulation, and delivery strategies, including concurrent or independent pharmacologic therapy (78). Investigators are also considering the value in delivering an appropriately mixed cell population to assist better engraftment (83). Finally, there has been encouraging progress made with in situ cell transformation (e.g., cardiac fibroblasts to cardiomyocytes) to increase contractile tissue mass, which may provide an alternative to direct cell delivery (84).

6.3. Tissue Engineering

Tissue engineering approaches to HF, while numerous and varied, frequently fall into two categories: (*a*) efforts focused on the development of a cardiac patch to be applied to the failing ventricle and (*b*) a combination of cell therapy and a designed biomaterial milieu for injection therapy. In both patch and injectable approaches, there is substantial interest in acellular approaches on the basis of the mechanical benefits each of these methods can provide to reduce wall stress in the remodeling infarcted ventricle, as well as the potential to incorporate an array of bioactive factors with the biomaterial (85, 86). The combination of each approach with cells remains attractive, leading to the hope that either additive or synergistic benefit from cells and passive mechanical support might be realized.

In the patch approach, a variety of materials, both synthetic and natural, have been examined (87), most commonly with epicardial placement in open-chest animal models. There have also been efforts to generate cell sheets lifted from their culture substrate and ultimately placed onto the epicardium (88). In all cases, vascularization is a concern. While rodent models minimize this challenge due to the thin cardiac wall geometry, large animals requiring thicker patches will require vascularization to support high cell densities beyond metabolite diffusional limits. The coseeding of multiple cell types, including endothelial cells, has been attempted to help address vascularization needs. Three-dimensional printing has attracted increasing attention in recent years as a means to dictate cellular placement, provide vascular pathways, and prescribe construct mechanics (89, 90). In seeking injectable approaches, investigators have examined natural and synthetic hydrogels and incorporated a variety of bioactive agents, usually growth factors, to influence the local target environment as well as codelivered cells (91, 92). A recent review article by Hernandez & Christman (93) discusses acellular injectable biomaterial–based therapies for treatment of myocardial infarction. Finally, we note that the potentially revolutionary concept of whole-organ engineering has gained traction over the past decade. In whole-organ engineering, a large animal organ is decellularized and repopulated with precursor cells, commonly neonatal cells, but with a practical vision for iPSCs, which may allow functional organs with autologous cells to be created. This approach presents many challenges, and the heart is arguably among the most challenging organs to engineer (94), but the impact of success in this area would be profound.

7. CONCLUSIONS

While the field of MCS has advanced significantly since 2008, next-generation breakthroughs require an infusion of new talent along with bold scientific and engineering concepts that recognize the MCS limitations of today and will create the "pulseless" innovations of tomorrow. Initially, the concept of pulseless MCS blood flow was viewed as irrational. Through exploratory engineering research supported by the National Institutes of Health, axial flow MCS devices were proven feasible in laboratory and animal studies (95). Adult continuous flow MCS systems were developed using the same clinical translational steps as first-generation MCS pulsatile devices, demonstrating their readiness for clinical trials (96). Randomized clinical trial results showed that the second-generation HeartMate II performed better than the first-generation HeartMate I in essentially all aspects. As the MCS field embraced rotary blood pumps, important and surprising innovative advances resulted. The design of axial and centrifugal blood pumps underpinned the development of second- and third-generation MCS systems. However, as covered in this review, many adult (as well as pediatric) patients still face severe adverse events, such as bleeding, infection, and thrombosis.

Today, MCS malfunction generally occurs with paracorporeal engineered equipment. This equipment needs to be designed out of the systems. Around 2–4 W of power are needed at the level of the blood. There are solutions waiting to be discovered that will simplify the MCS peripherals, improving QoL for both patients and caregivers. How can we provide the needed power seamlessly? Such innovations would meaningfully reduce MCS malfunctions and may also result in a lower rate of infection and related thrombotic events.

Recovery of daily-living function for patients with advanced HF is paramount. MCS provides the required safety net for exploring experimental cell, protein, and tissue engineering adjunctive treatments in both adults and children. A patient provides his or her own best regenerative capacity, which can be activated by signals from biologics such as exogenous extracellular matrix or, perhaps, energy patterns produced from pacemaker-like devices. For INTERMACS patients at Levels 4–7, one can envision a low-cost 3-year MCS system backing up staged adjunctive therapy that could regenerate cardiac functionality in 12–18 months, followed by removal of the implanted device. The potential impact of such an innovation on cardiac care would be profound.

HF is a global medical condition. MCS holds the potential to have a global impact on understanding basic mechanisms while mitigating the symptoms of HF. MCS is now practiced in 35 countries with equivalent outcomes for men and women (97). This wide translation of MCS highlights the robust nature of the technology and patient management arising from close collaboration among engineers, clinicians, and scientists. MCS patient studies designed to understand the basic mechanisms of HF will provide insights into the specifications of future generations of MCS systems and novel approaches for early diagnosis and treatment of pre-HF patients.

At the current stage of the evolution of MCS systems, 36 years after the historic first implant of Dr. Barney Clark in Salt Lake City, Utah, it is important that proposed design changes show clear evidence that the modifications will benefit clinical outcomes. For example, scientific findings that are likely to reduce infection must be translated through engineering research into the design specifications required for clinical MCS systems. Funding agencies must recognize that industry alone does not have the research capacity and environment to develop the innovative science and engineering needed for future MCS systems and for reducing the scourge of HF in adults and children. Rather, close collaboration among industry, academia, and government will be required in order to achieve the requisite outcomes in the quest for optimum therapies to treat patients with HF.

DISCLOSURE STATEMENT

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