Review Article

Advancements in mechanical circulatory support for patients in acute and chronic heart failure

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Cardiogenic shock (CS) continues to have high mortality and morbidity despite advances in pharmacological, mechanical, and reperfusion approaches to treatment. When CS is refractory to medical therapy, percutaneous mechanical circulatory support (MCS) should be considered. Acute MCS devices, ranging from intra-aortic balloon pumps (IABPs) to percutaneous temporary ventricular assist devices (VAD) to extracorporeal membrane oxygenation (ECMO), can aid, restore, or maintain appropriate tissue perfusion before the development of irreversible end-organ damage. Technology has improved patient survival to recovery from CS, but in patients whom cardiac recovery does not occur, acute MCS can be effectively utilized as a bridge to long-term MCS devices and/or heart transplantation. Heart transplantation has been limited by donor heart availability, leading to a greater role of left ventricular assist device (LVAD) support. In patients with biventricular failure that are ineligible for LVAD implantation, further advancements in the total artificial heart (TAH) may allow for improved survival compared to medical therapy alone. In this review, we discuss the current state of acute and durable MCS, ongoing advances in LVADs and TAH devices, improved methods of durable MCS implantation and patient selection, and future MCS developments in this dynamic field that may allow for optimization of HF treatment.

Keywords: Cardiogenic shock (CS); heart failure; left ventricular assist device (LVAD); mechanical circulatory support (MCS)

Submitted Aug 26, 2017. Accepted for publication Sep 16, 2017.
doi: 10.21037/jtd.2017.09.89
View this article at: http://dx.doi.org/10.21037/jtd.2017.09.89

Introduction

Cardiogenic shock (CS), defined as acute cardiac hemodynamic instability and end organ hypoperfusion resultant from a primary cardiac disorder, continues to have high mortality and morbidity despite advances in pharmacological, mechanical, and reperfusion approaches to treatment (1). The etiology of CS varies with the most common etiology (~75%) being secondary to an acute coronary syndrome (ACS). Other causes include acute exacerbation of chronic heart failure (HF) (10–15%), valvular and other mechanical causes (5–10%), stress-induced cardiomyopathy (Tako-Tsubo; 1–5%), and myocarditis (1–5%) (2). Despite routine use of reperfusion therapy, ACS complicated by CS continues to have an impressive short term mortality of 35% (3). Initial treatment of CS from severe acute HF includes oxygen, diuretics, vasodilators, non-invasive ventilation, and inotropes. When CS is refractory to medical therapy, patients should be evaluated for percutaneous mechanical circulatory support (MCS) candidacy by a multi-disciplinary heart care team consisting of intensivists, cardiologist, and

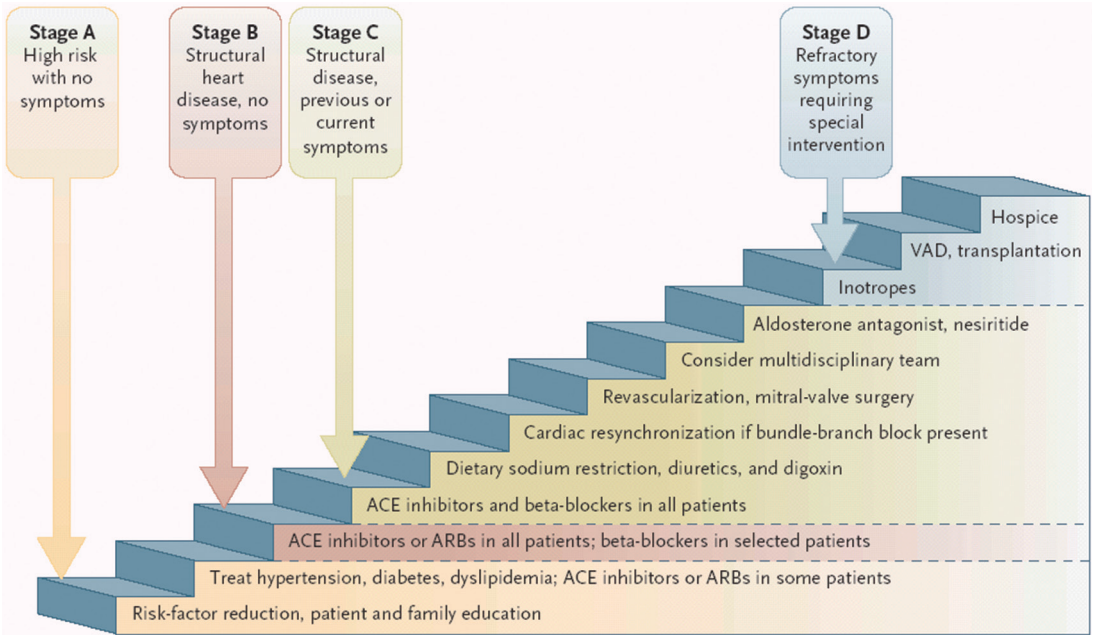

Figure 1 Stages of chronic heart failure and treatment. Adapted with permission from Jessup *et al.* N Engl J Med 2003;348:2007-18.

cardiothoracic surgeons. The degree of hemodynamic support given by various MCS therapies can vary with the gamut of devices ranging from intra-aortic balloon pumps (IABPs), to percutaneous temporary ventricular assist devices (VAD) to extracorporeal membrane oxygenation (ECMO). These various devices can aid, restore or maintain appropriate tissue perfusion before the development of irreversible end-organ damage. Some of the devices can provide either uni- or bi-ventricular support with the added benefit of respiratory support when combined with an oxygenator. Undoubtedly, technology has improved patient survival to recovery from CS, but in patients whom cardiac recovery does not occur, acute MCS can be effectively utilized as a bridge to long-term MCS devices and/or heart transplantation.

Treatment options for American College of Cardiology (ACC) Stage D HF patients are limited to the use of continuous inotropes, LVAD implantation, heart transplantation, and ultimately hospice and palliative care (4) (*Figure 1*). Heart transplantation remains the gold standard treatment for advanced chronic HF, but a limited availability of transplant hearts for a growing population of end-stage HF patients has led to a greater role of left ventricular assist device (LVAD) support. In 2001, the REMATCH trial demonstrated a significant increase in one year survival of end-stage HF patients implanted with pulsatile HeartMate XVE LVAD (Abbott, Lake Bluff, IL, USA) *vs.* medical therapy alone (52% *vs.* 25%) (5). The next generation continuous axial flow HeartMate II (Abbott, Lake Bluff, IL, USA) pump demonstrated one year survival of 68% (6), and became the first pump fully approved device with the intent of destination therapy (DT) (7). The HeartMate II remains the most widely implanted LVAD with the most recent INTERMACS report (8) showing an increasing use of smaller, continuous centrifugal flow pumps designed to decrease barriers of LVAD implantation including pump failure, pump thrombosis, and stroke events. This new generation of pumps include the HeartWare HVAD (Medtronic Inc., Fridley, MN, USA), which was approved for bridge to transplant (BTT) in 2012 (9), the HeartMate III (Abbott, Lake Bluff, IL, USA) (10) and HeartAssist 5 (ReliantHeart, Inc., Houston, TX, USA) (11), which are currently in clinical trial. In patients with biventricular failure that are ineligible for LVAD implantation, further advancements in the total artificial heart (TAH) may allow for improved survival compared to medical therapy alone. Importantly, barriers to durable MCS remain, and future technological advances in LVAD designs are needed to enhance treatment outcomes of chronic HF.

In this review, we discuss the current state of acute and durable MCS, ongoing advances in LVADs and TAH devices, improved methods of durable MCS implantation

and patient selection, and future MCS developments in this dynamic field that may allow for optimization of HF treatment.

Acute MCS

IABP

IABPs are the most widely used MCS device since its introduction in the 1960s, but recent studies have questioned its potential benefit. Theoretically, pump inflation at the onset of diastole increases coronary perfusion, and pump deflation at the end of diastole results in reduction in aortic end-diastolic and systolic pressures, allowing for decreased afterload, decreased cardiac work, decreased myocardial oxygen consumption and increased cardiac output. Prior to 2012, the American and European guidelines supported IABP use in CS with a class I recommendation. In the randomized prospective IABP-SHOCK II trial, IABP was not found to be associated with reduction in 30 day mortality in patients with CS complicating ACS (12) or 12 month all-cause mortality (13). Given these trials and potential adverse events of IABP including limb ischemia, bleeding, thrombocytopenia, infection, and aortic dissection, IABP was downgraded to class III (harm) by the European Society of Cardiology, advising against the use of IABP in CS patients (14). However, AHA/ACC guidelines recommend IABP as class IIa in CS (15), and the most recent Society for Cardiovascular Angiography and Interventions expert consensus on PCI without on-site cardiac surgery maintain IABP support during transport of unstable patients a requirement (16). Given the controversy surrounding its benefit, the use of IABP is decreasing (17), and its future role in the treatment of CS may continue to decline as superior devices such as ECMO, percutaneous MCS, and isolated RV support become more commercially available with data arising from clinical trials and clinical experience.

Percutaneous MCS

Current available percutaneous VADs offering temporary circulatory support include the non-pulsatile microaxial Impella 2.5, 5.0, and CP (Abiomed Europe, Aachen, Germany), and the Tandem Heart (Cardiac Assist, Inc., Pittsburgh, PA, USA). Other pumps under investigation include the pulsatile iVAC 2L (PulseCath BV, Arnhem, Netherlands), HeartMate percutaneous heart pump (Abbott, Lake Bluff, IL, USA) and the Impella RP (Abiomed Europe, Aachen, Germany), which is designed for univentricular RV support. The device specifications regarding mode of action, implant technique, cannula size, and flow are summarized (18) in *Table 1* and *Figure 2*.

Data regarding percutaneous MCS devices in CS is limited. A meta-analysis of three randomized trials comparing percutaneous LVADs (two with TandemHeart and one with Impella 2.5) compared to IABP, percutaneous LVADs were associated with higher cardiac index, higher mean arterial pressure, lower pulmonary capillary wedge pressure (PCWP) but increased bleeding complications and no difference in 30-day mortality (19). In a recent randomized prospective trial of 48 patients, the Impella CP was not associated with decreased 30-day mortality in CS complicating ACS compared to IABP (20). Results from the USpella Registry show that Impella 2.5 use prior to PCI is associated with more complete revascularization and improved survival in the setting of refractory CS complicating ACS (21). Recently, the iVAC 2L pulsatile pump was shown to offer support in high risk PCI with 100% angiographic success in a prospective pilot study of 14 patients by den Uil *et al.* (22), but no trial results are currently available. An additional percutaneous LVAD under investigation has been the HeartMate percutaneous heart pump. A trial comparing this device to Impella support during high risk PCI began in 2014, but was paused in 2017 due to mechanical issues leading to pump stoppage (23).

Isolated RV failure has become more recognized in recent times, leading to development of devices specific for this cardiac dysfunction. The Impella RP is an intracardiac microaxial blood pump designed for the management of right ventricular failure (RVF) that can be inserted through the femoral vein. The prospective RECOVER RIGHT study showed that the safe, easily deployed, and reliable pump resulted in immediate hemodynamic benefit in patients with life-threatening RVF, leading to approval for use through a humanitarian device exemption (24).

Surgically placed temporary MCS

Surgically-implanted temporary MCS devices include the CentriMag (Abbott, Lake Bluff, IL, USA) and Abiomed (Abiomed Inc., Danvers, MA, USA) pumps. The CentriMag ventricular assist system can be used for univentricular or biventricular support for patients with CS, and was the first FDA-approved implantable VAD with biventricular capability (7,25). This system is typically

Table 1 Technical features of currently available percutaneous and surgically implanted short term mechanical circulatory support devices

Feature	Impella 2.5	Impella 5.0	Impella CP	Tandem Heart	iVAC 2L	Centrimag	Abiomed	ECMO
Catheter size (F)	9	9	9	–	11	–	–	–
Cannula size (F)	12	21	–	21 venous; 12-19 arterial	17	Variable	36 or 42	17–21 venous, 16–19 arterial
Flow (L/min)	Max. 2.5	Max. 5.0	3.7–4.0	Max. 4.0	Max. 2.8	Max. 9.9	Max. 6	Max. 7.0
Pump speed (RPM)	Max. 51,000	Max. 33,000	Max. 51,000	Max. 7,500	Pulsatile, 40 mL/beat	Max. 5,500	Pulsatile, 80 mL/beat	Max. 5,000
Insertion/ placement	PC (femoral artery)	PS (femoral artery)	PC (femoral artery)	PC (femoral artery + vein for LA)	PC (femoral artery)	Midline sternotomy/mini-thoracotomy	Midline sternotomy	PC (femoral artery + vein)
LV unloading	+	++	+	++	+	+	+	–
Anticoagulation	+	+	+	+		+	+	+
Recommended duration of use	10 days	10 days	10 days	14 days	+	30 days (CE), 6 hours (FDA)	up to 60 days	7 days
CE-certification	+	+	+	+	+	+	+	+
FDA approval	+	+	+	+	–	+	+	+

–, no; +, for LV unloading means some; for CE and FDA means yes; ++, for LV unloading means significant. Max., maximum; F, French; FDA, US Food and Drug Administration; LA, left atria; LV, left ventricle; PC, percutaneous; PS, peripheral surgical; RPM, rotations per minute. Adapted with permission from Thiele *et al.*, Eur Heart J 2015;36:1223-30.

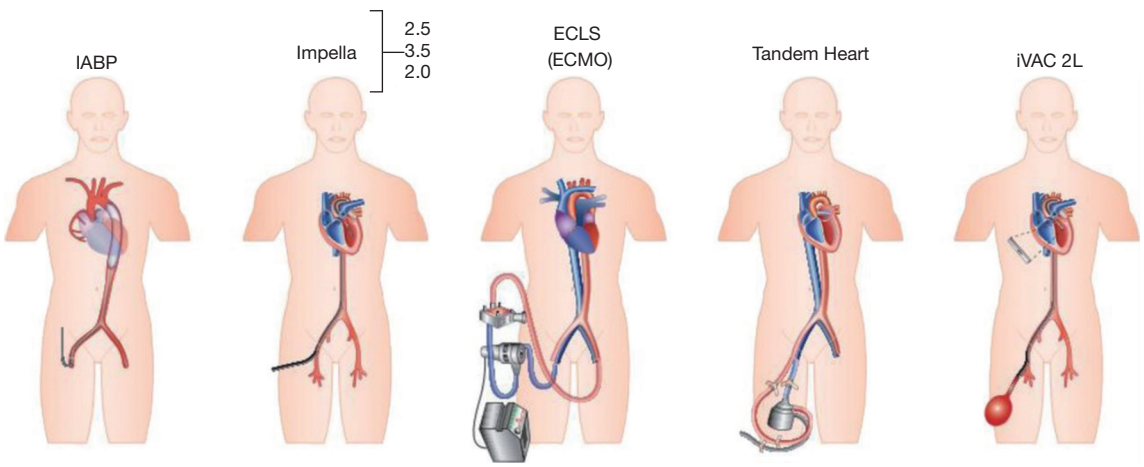

Figure 2 Schematic drawings of current percutaneous mechanical support devices for CS. ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; IABP, intraaortic balloon pump. Adapted with permission from Thiele *et al.*, Eur Heart J 2015;36:1223-30.

implanted via median sternotomy. Recently, Takeda *et al.* (26) have developed a minimally invasive surgical approach combining ECMO with CentriMag VAD for short term CS treatment. The major advantage of this system in addition to full hemodynamic support is the ability to add an oxygenator to the right side of the configuration, thus providing complete right, left, and pulmonary support. This system showed non-inferior 30 day and overall 1 year survival *vs.* CentriMag BiVAD alone, but eliminated the need for cardiopulmonary bypass and reduced blood

product utilization and bleeding events. The Abiomed ventricular assist system is another device with uni- or biventricular capabilities that is placed via sternotomy, but no randomized trials assessing its effectiveness are available.

ECMO

ECMO provides gas exchange as well as cardiac support and is used in patients suffering from respiratory failure, cardiac failure or both. Veno-venous ECMO is reserved for patients in isolated respiratory failure with no significant cardiac dysfunction, while veno-arterial ECMO (VA-ECMO) is considered in patients with cardiopulmonary collapse and is used to support patients in CS (27). In patients who fail to wean from cardiopulmonary bypass after open heart surgery, central VA-ECMO has been applied as bridge to recovery. However, in non-post-cardiotomy failure patients requiring urgent cardiac support, peripheral VA-ECMO through the femoral artery and vein is the most common approach. Peripheral VA-ECMO has limitations, including retrograde blood flow leading to LV afterload mismatch and inadequate LV decompression. To counteract this in addition to the traditional addition of a surgical LV vent, some centers utilize concurrent IABP (28) or Impella 2.5 (29) support to reduce the LV afterload and hence pulmonary edema. Recently, Naito *et al.* (30) describe a rotation speed modulation system that changes rotational speed in synchrony with the cardiac cycle of the native heart to offer the effects of VA-ECMO and IAPB in a single device, thus decreasing LV work load and afterload in CS patients, but these results from an *in vivo* goat model are yet to be applied in clinic.

The latest Extracorporeal Life Support Organization (ELSO) registry report shows ECMO use as well as the number of centers utilizing ECMO is increasing (31). Adults receiving ECMO for cardiac support from 1989–2015 show 41% survival to hospital discharge, with survival only increasing to 42% in the year 2015. Survival to discharge was dependent on VA-ECMO indication as CS (42%), cardiomyopathy (51%), myocarditis (65%), and congenital defect (37%). Absolute contraindications to VA-ECMO use include advanced age, chronic organ dysfunction (emphysema, cirrhosis, renal failure), compliance (financial, cognitive, psychiatric, or social limitations), and prolonged CPR without adequate tissue perfusion, while contraindications for anticoagulation, advanced age, and obesity are relative contraindications (ELSO Guidelines, 2013). Adverse events during the course of VA-ECMO are common (31), and it requires appropriately trained physicians and requisite healthcare infrastructure to prevent or mange these events. However, in the appropriate patient population, VA-ECMO is recommended as a useful tool that aids in acute HF treatment.

Durable MCS

Patients who are refractory to hemodynamic stability from CS and who continue to need mechanical support should be considered for transition to durable MCS. Temporary MCS restores hemodynamics and reverses end-organ dysfunction, but these patients have high residual risk with postoperative morbidity and mortality that parallels that of critical CS patients without temporary MCS (32). Although the use of temporary MCS is associated with considerably worse post-transplant survival compared to heart transplant without, overall post-transplant survival following temporary MCS is improving. While incidence for durable LVAD implantation in the CS patient population is increasing, the most common reason for durable LVAD implantation is chronic heart failure.

LVADs

LVADs were FDA-approved for BTT in 1998, and the landmark REMATCH trial that followed demonstrated a significant increase in one year survival in patients receiving pulsatile HeartMate I LVAD *vs.* medical therapy alone (52% *vs.* 25%) (5). However, due to device replacement in 21% of patients from limited durability, continuous-flow pumps were developed (33), and the HeartMate II LVAD was shown to have greater survival post implant compared to first generation pumps when implanted as BTT and DT (6,7,34). In these pumps, limitations including stroke, driveline infections, and RVF persisted, and an abrupt increase in pump thrombosis from 2011–2013 (35,36) highlighted the need for improvements in LVAD device design, perioperative management, and patient selection (37).

Recent innovations

To address the growing concern of pump thrombosis and stroke in chronic HF support, as well as the large proportion of patients implanted as DT and the need for devices that were more durable long-term, new LVAD devices with noncontact bearings via magnetic levitation have been developed to allow for rotation without friction

Table 2 Technical features of currently available durable mechanical circulatory support devices

Device	Stage/approval	Unique features
Continuous flow		
Axial flow		
HeartMate II (Abbott)	BTT/DT	IA, most widely studied, >200 publications
HeartAssist 5 (Reliant Heart)	Undergoing clinical trial	IP, remote monitoring of direct flow measurements, adaptive control options
Jarvik 2000 (Jarvik Inc.)	Undergoing clinical trial	IP, documented survival 7.5 years, pediatric application
Centrifugal flow		
HVAD (Medtronic Inc.)	BTT/DT*	IP, ML, uni/biventricular capabilities, flow estimations derived from motor power and speed
HM III (Abbott)	Undergoing Clinical Trial	IP, ML, artificial pulse generator, sensorless flow estimator
TAH		
Available		
Syncardia 70cc (SynCardia Systems, Inc., Houston, TX, USA)	BTT/DT**	pulsatile pneumatic pump, physiologically responsive blood flow regulation
Undergoing development		
SynCardia 50cc (SynCardia Systems, Inc., Houston, TX, USA)	Undergoing clinical trial	pulsatile pneumatic pump, pediatric and female patient application
Carmat (Velizy, France)	Under investigation	pulsatile electrohydraulic pump, no thrombus formation observed in 3 implanted patients
BiVACOR (Houston, TX, USA)	Under investigation	pulsatile centrifugal flow, intrinsic adjustment and maintenance of systemic and pulmonary balance
Cleveland Clinic Heart (Cleveland, OH, USA)	Under investigation	intrinsic adjustment and maintenance of systemic and pulmonary balance, bovine pericardium lining

*, approved for BTT. Clinical trial for DT was completed in 2015 and is now waiting for FDA approval. **, approved for BTT. Clinical trial for DT is ongoing. BTT, bridge to transplant; DT, destination therapy; IA, intra-abdominal; IP, intrapericardial; ML, magnetic levitation.

or wear. Furthermore, these pumps are being designed to allow for remote monitoring capabilities to optimize flow to the body's demand and give clinicians an additional non-invasive tool to monitor device function and optimize treatment. Currently, the only FDA-approved device employing this design is the HeartWare HVAD, while other devices under investigation include the HeartMate III and HeartAssist 5. Currently available devices as well as those undergoing trials are summarized in *Table 2*.

The HeartWare HVAD is a small intrapericardial centrifugal-flow pump approved for BTT in 2012. The ENDURANCE trial (9) was designed to evaluate the HVAD as DT and compared survival free from disabling stroke at two years between this device vs the HeartMate II control. Overall survival at two years did not differ significantly between the study group *vs.* control group (60.2% *vs.* 67.6%), while the study group had decreased device failure requiring replacement, increased stroke, and increased occurrence of sepsis. Given these results, non-inferiority of the device compared to the control was established.

The MOMENTUM 3 clinical trial is designed to evaluate the HeartMate III device for BTT and DT, comparing survival free of debilitating stroke or reoperation to replace the pump at 6 months and 2 years to the axial continuous flow HeartMate II pump (10). At six months, there were no significant between-group differences in rates of death or disabling stroke, but reoperation for pump malfunction was less frequent in the centrifugal-flow pump group (n=1, 0.7%) than axial flow (n=7, 7.7%). Secondary analysis of the trial showed the HeartMate III demonstrated greater freedom from hemocompatibility-related clinical

adverse events *vs.* the HeartMate II at 6 months (38) and 1 year (39), and the trial is ongoing.

In addition to the potential benefits of a smaller, intrapericardial design and decreased device malfunction, new generations of LVADs may allow for noninvasive monitoring of pump function and flow. The HVAD allows for flow waveforms that provide information about HVAD function and patient hemodynamics. Recently, Grinstein *et al.* (40) describe that the slope of ventricular filling phase of HVAD waveforms is correlated with PCWP and can discriminate elevated versus normal or low PCWP. The HeartAssist 5 pump is currently undergoing clinical trial for use as BTT and takes this monitoring one step further by providing direct flow measurements through remote monitoring. In addition to flow data, the HeartAssist 5 tracks speed and electrical current usage by the pump motor, providing information about the volume of blood flow and its fluidity. Automated noninvasive tracking of pump function and flow offers an additional tool clinicians may use to help in the clinical assessment and management of patients.

Importance of patient selection and timing of LVAD implantation

New device designs and future innovations offer great potential to enhance treatment outcomes in advanced HF patients. Alternatively, appropriate patient selection and timing of LVAD implant offer additional routes toward maximization of therapy outcomes. The Randomized Evaluation of VAD InterVEntion before Inotropic Therapy (REVIVE-IT) pilot study began in 2009 to investigate the benefits of a more "aggressive" LVAD implant strategy *vs.* medical management in DT older patients with end stage HF. However, patient enrollment was delayed multiple times due to new studies showing increased incidence of LVAD pump thrombosis, and the trial was discontinued without ever beginning in 2015 (41,42). Similarly to the REVIVE-IT study, the Risk Assessment and Comparative Effectiveness of Left Ventricular Assist Device and Medical Management in Ambulatory Heart Failure Patients (ROADMAP) study sought to assess the outcomes of early LVAD implantation in less sick (INTERMACS 4-7) patients (43). Twelve month (80%±4% *vs.* 63%±5%; P=0.022) and two year (70%±5% *vs.* 41%±5%; P<0.001) (44) survival was greater in the LVAD *vs.* medical management group, as was health-related quality of life, while the LVAD group experienced more frequent adverse events and hospitalizations. These studies provide risk-benefit information to assist patient and physician decision making for elective LVAD therapy as a treatment for HF in non-inotrope dependent patients, but making an informed clinical choice between LVAD and medical therapy remains a challenge.

Improvements in perioperative management and implantation technique

The advancement of device technology and improved patient selection will continue to offer potential improvements in patient survival and freedom from adverse events (8). At the same time, careful perioperative management of LVAD patients and technique of LVAD implantation has been associated with better patient outcomes. The PREVENTion of HeartMate II Pump Thrombosis Through Clinical Management (PREVENT) (37) recommendations on implant technique, anti-coagulation and anti-platelet strategy, pump speed management, and blood pressure management were offered to address risk of early (<3 months) pump thrombosis with HeartMate II LVADs. Investigators found that full adherence to implant techniques, heparin bridging, and pump speeds >9,000 RPMs resulted in significantly lower risk of pump thrombosis (1.9% *vs.* 8.9%; P<0.01) and risk of suspected thrombosis, hemolysis, and ischemic stroke (5.7% *vs.* 17.7%; P<0.01) at 6 months. This stark decrease in early pump thrombosis associated with adherence to this set of recommendations supports the impact of surgical implant technique and clinical management practice in limiting pump thrombosis.

The smaller size of new pumps in combination with their intra-pericardial placement has led to the investigation of less invasive off-pump implantation techniques via mini-sternotomy and thoracotomy to limit surgical trauma and allow for early postoperative ambulation to optimize patient outcomes. This technique offers a surgery with potentially decreased bleeding, blood product transfusion, sternal wound infection, ventilation time, and intensive care unit stay. As the sternum is left largely intact, mechanical respiratory physiology is preserved, favoring downloading of the RV and decreased RVF (45). Additionally, it has been hypothesized that the largely intact pericardium may support the right ventricle and prevent distention (46). The first LVAD to be implanted off pump via thoracotomy and ministernotomy was the HeartWare HVAD (45-47), and similar techniques have since been described in the

implantation of the CentriMag BiVAD system (48), and HeartMate 3 LVADs (49,50). Despite the advantages offered by a noninvasive and off-pump surgical technique, limitations remain (51,52). In surgeries requiring concomitant valve repair or replacement, this ministernotomy and thoracotomy approach is not feasible. Furthermore, the LVAD placement in the pleural space may create adhesions to the lung, phrenic nerve and/or diaphragm, complicating future operations. Given these risks and lack of clinical trials comparing the techniques, the advantage of minimally invasive off-pump surgical techniques over standard median sternotomy procedures remains unproven.

RVF and TAH developments

While RVF and right ventricular assist device (RVAD) use in LVAD patients have declined with better patient selectivity and utilization of intra-operative maneuvers (53) to reduce the strain on the right ventricle, RVF remains a serious complication associated with decreased survival (54). Univariate predictors of RVF such as DT intent of therapy, INTERMACS profile, preoperative hemodynamic profile, and baseline lab values have been proposed (55-57), and while a number of risk scores have been developed to predict RVF (55,58-60), appropriate selection and prediction of the RV prior to LVAD implementation remains imperfect (41). Current treatment options in patients with significant concomitant RV dysfunction to LVAD implantation include permanent LVAD with planned temporary right-sided RVAD. However, in patients with acute RVF post-LVAD implantation, as well as in patients with severe biventricular cardiomyopathy, complex congenital heart disease, failed transplantation, or acquired structural heart defects that have failed or remove the patient from conventional surgical treatment, TAH and off-label use of long-term RVAD offers a final alternative for survival while waiting for a donor transplant.

The idea of a TAH replacing the human heart has long been an intriguing challenge, with the first TAH implanted in a human in 1969 by Cooley *et al.* (61). Since this first TAH implantation, a number of devices and designs have been investigated (62), but none have been as successful as the Jarvik 7, later renamed CardioWest and now SynCardia TAH (SynCardia Systems, Inc., Houston, TX, USA), which relies on an external pulsatile pneumatic pump attached to the TAH through reinforced polyurethane drivelines. In 2004, CardioWest (now SynCardia 70cc) became the first and only TAH to get FDA approval for BTT (63,64), and clinical trial began in 2014 to evaluate the device for DT in biventricular patients ineligible for heart transplantation (65). Furthermore, the smaller SynCardia 50cc received FDA approval for an Investigational Device Exemption clinical study in 2015 to address the need for a smaller device in female and pediatric patients unable to receive the larger SynCardia 70cc device (66). Currently, INTERMACs registry data for biventricular HF patients receiving MCS as BTT shows one year mortality for SynCardia TAH is 59% *vs.* 56% for BiVADs (9). Despite the development of the SynCardia pumps, the pumps are still underutilized and only implanted in 50–80 patients per year (*Figure 3*) due to a ~59% post-implant one year survival (*Figure 4*) (9) but markedly decreased survival further past one year due to mechanical parts prone to malfunction, high incidence of thrombosis and hemoincompatibility (62). Other limitations include the need for a large and loud external motor, and dependency on an external energy supply.

The challenges to outcomes in patients implanted with the SynCardia TAH have led to continued developments of bioprosthetic TAHs to reduce anti-coagulation therapy and thrombosis-associated complications (67). The Carmat TAH (Carmat, Velizy, France) is a pulsatile electrohydraulic TAH that has been implanted in three patients, supporting one for 74 days before electronic failure, another for 270 days before mechanical device failure, and a third for 254 days (68,69). In all cases, autopsy did not detect any relevant thrombus formation within the bioprosthesis nor other organs. Two other TAH devices, the Cleveland Clinic continuous flow TAH (70) and the pulsatile BiVACOR TAH (71), have recently undergone *in vivo* calf studies, showing potential applicability to the clinical setting. These initial findings provide optimism of the use of bio-prosthetic materials in the construction of TAH going forward, but more study is required before these designs are prepared for widespread clinical use.

Future directions and technological advances of MCS

Over the last few decades, important improvements to MCS devices have allowed for improved patient survival and outcomes. Notwithstanding, the steady increase in patients requiring these devices, the large number being implanted as DT, and the continued occurrence of driveline infection, pump thrombosis, pump failure, cerebrovascular accidents,

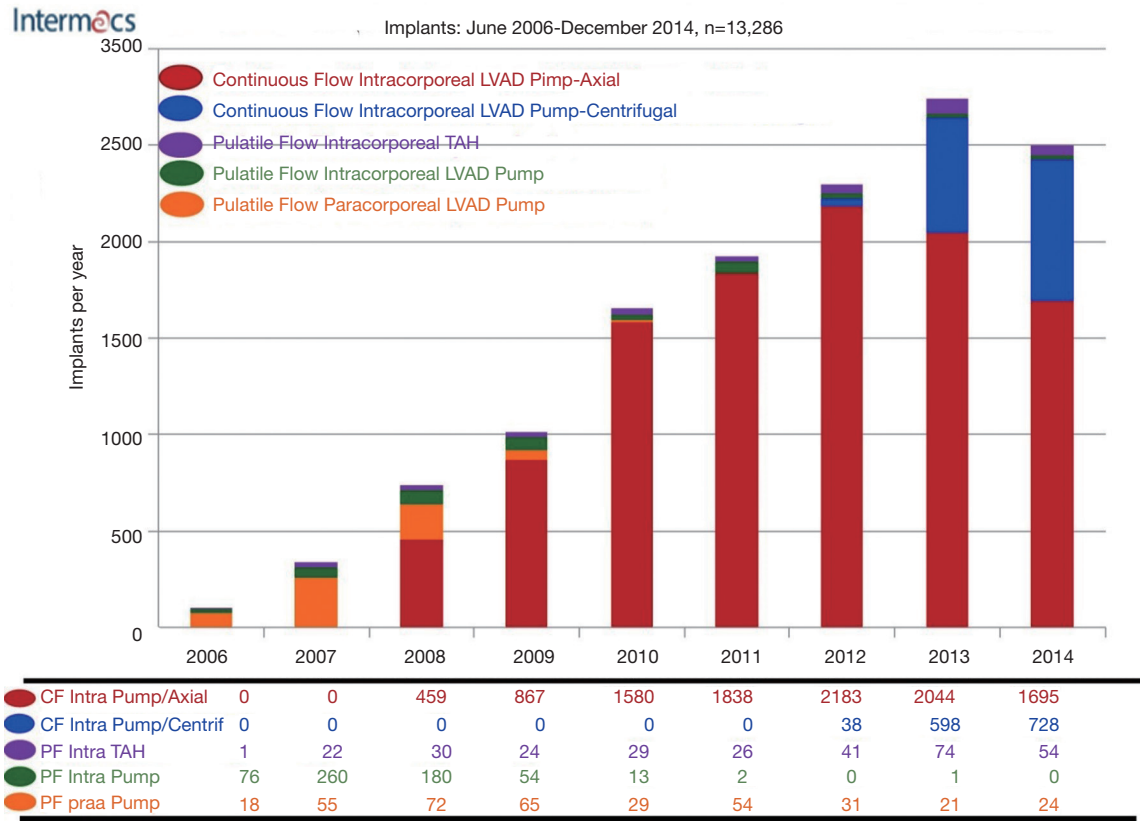

Figure 3 Distribution of device types by year of implant. CF, continuous flow; PF, pulsatile flow; LVAD, left ventricular assist device; TAH, total artificial heart. Adapted with permission from Kirklin *et al.*, J Heart Lung Transplant 2015;34:1495-504.

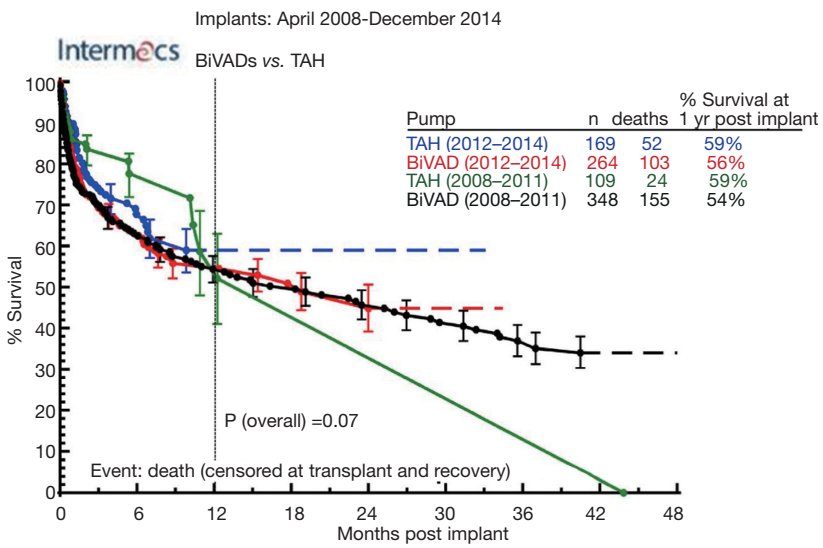

Figure 4 Actuarial survival curves stratified by BiVAD *vs.* total artificial heart (TAH). BiVAD, biventricular assist device. Adapted with permission from Kirklin *et al.*, J Heart Lung Transplant 2015;34:1495-504.

and RVF calls for further improvements for long-term sustainable and reliable LVAD support. Transcutaneous energy transfer (TET) has long been a potential option to eliminate driveline infections. TET would allow for the complete implantation of a device with a battery that can be recharged through intact skin of the patient, therefore removing the need for an external driveline. Although the LionHeart (72) (Arrow International, Inc., Research Triangle Park, NC, USA) and previously the AbioCor (73) (Abiomed, Inc., Danvers, MA, USA) devices utilized this technology, its impact in eliminating driveline infection has not been viewed as a great enough benefit at this point to overcome disadvantages in safety, economics, and administrative aspects (74).

As described earlier, HVAD flow waveforms potentially give physicians a non-invasive approach to analyze PCWP, while the new HeartAssist 5 LVAD offers direct flow measurement to precisely monitor blood flow and assist in the clinical assessment and management of patients supported by an LVAD (40). Importantly, future development of a smart LVAD pump that can adapt to changes in a patient's physiology and respective perfusion demand may rely on similar pump measurements and analysis provided by these devices. Furthermore, new inflow cannulae designs may allow for decreased ventricular suction events while mitigating complications associated with hemolysis, as evidenced in an *in vitro* model by Pauls *et al.* (75). In vivo evaluation of a system combining a compliant outflow and inflow cannula with a sensor-based controller that altered left and right VAD speed based on pressure and flow showed promising results in preventing suction and pulmonary venous congestion in a sheep RVF model (76). Application and testing of these developments to LVADs and BiVADs in the human is a logical future step that may allow for decreased suction events, hemolysis, and RVD in patients.

To decrease thrombosis-associated complications and reduce anti-coagulation therapy, decellularized pericardium is being used in the construction of new generation TAH designs (67,70,71). Other approaches have been proposed, including titanium surfaces (77) and engineered gratings allowing for the migration and adhesion of endothelial cells leading to a fully confluent endothelial monolayer (74,77-79). The application of this type of material and these surfaces to future LVADs could further assist in pump hemocompatibility and allow for decreased pump thrombosis, cerebrovascular accidents, and bleeding.

Conclusions

CS refractory to medical therapy has high mortality and morbidity, and temporary MCS devices are seen as a last option in treatment of these patients. IABP remains the most widely used device for temporary MCS, but recent trial results have led to a decline in its use, while at the same time ECMO use and the number of centers utilizing ECMO is increasing. Percutaneous VAD pumps and surgically placed temporary MCS have been shown to be beneficial in observational trials, but randomized clinical trial data supporting their effectiveness is lacking. While these devices have increased HF patient survival to recovery, those in whom cardiac recovery does not occur require a heart transplantation or long-term MCS support via LVAD or TAH depending on whether or not biventricular failure is present. New LVAD devices are being designed to reduce the rate of adverse events. Undoubtedly with improvements in perioperative management, patient selection and timing of implant improvements to quality of life offered with these devices should continue to improve. However, complications including pump thrombosis, stroke, bleeding events, driveline infection, and RVF remain a major concern to wider adoption of device therapy. Future device innovations including remote monitoring of flow, new blood-contacting materials to promote pump hemocompatibility, and the use of TET to remove the need for a percutaneous driveline may aid in the reduction of these events and augment chronic HF treatment.

Acknowledgements

This work was supported in part by the American Association for Thoracic Surgery's Summer Intern Scholarship.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Csepe TA, Kilic A. Advancements in mechanical circulatory support for patients in acute and chronic heart failure. J Thorac Dis 2017;9(10):4070-4083. doi:10.21037/jtd.2017.09.89