

The Next Wave of Mechanical Circulatory Support Devices

Next-generation mechanical circulatory support devices in different phases of development and clinical use are anticipated to improve outcomes and quality of life in patients with advanced heart failure.

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The recent success of continuous-flow (nonpulsatile) circulatory support devices has markedly increased long-term artificial circulation as a treatment option for patients with advanced heart failure. Multiple continuous-flow devices are clinically approved as a bridge to transplant and destination therapy. However, morbidities related to device implantation via median sternotomy with cardiopulmonary bypass and frequent adverse events, such as acquired von Willebrand syndrome, gastrointestinal bleeding, device thrombosis, progressive aortic insufficiency, and stroke, complicate management and impose further morbidity and mortality. As a result, therapy with these devices is still limited to only the sickest patients. The number of patients referred for durable circulatory support device implantation is small compared to the number of patients with advanced heart failure who could benefit from prolonged circulatory support with fewer adverse events. Therefore, there is an urgent need for next-generation devices with less-invasive implantation approaches, novel mechanisms of blood flow, physiologic performance, improved hemocompatibility, and fewer adverse events. This article highlights next-generation mechanical circulatory support (MCS) devices in different phases of development and clinical use that are anticipated to improve outcomes and quality of life in patients with advanced heart failure.

BACKGROUND

Survival with advanced heart failure remains poor. Cardiac transplantation offers the best opportunity for long-term survival. However, limited availability of donor hearts, strict selection criteria, insurance constraints, and complications of lifelong immunosuppression restrict

heart transplantation to only 7,000 patients annually worldwide. As a result, over the past 20 years, MCS has emerged as a standard long-term therapy for adult patients with intractable heart failure.^{1,2}

Over the past decade, first-generation pulsatile devices, which mimic native cardiac function, were replaced by rotary blood pumps that continuously unload the failing heart.³ So-called continuous-flow left ventricular assist devices (LVADs) have markedly improved patient outcomes.^{1,2} Continuous-flow devices are smaller, more reliable and durable, more energy efficient, and less traumatic to implant than first-generation devices. However, continuous-flow devices have introduced a new nonpulsatile physiology with unforeseen complications. Blood trauma from supraphysiologic shear stress in these devices causes acquired von Willebrand syndrome in all continuous-flow LVAD patients,⁴ gastrointestinal angiodysplasia and bleeding in 20% to 40% of patients,⁴⁻⁶ and device thrombosis in 2% to 13% of patients.^{7,8} Nonpulsatile flow also contributes to progressive de novo aortic valve insufficiency in 37%⁹ and stroke in close to 15% of patients.¹⁰ To reduce adverse events and improve patient outcomes, refinement of current pump designs¹¹ and development of novel devices¹² are needed.

The following sections discuss next-generation LVADs and total artificial hearts (TAHs) that are in various phases of development and clinical use. We hope that increased awareness of the relationships that exist between circulatory support device implantation strategy, design features, operational and flow characteristics, and adverse events stimulate enthusiasm in the community for further development and availability of less-invasive, safer devices.

NEXT-GENERATION CONTINUOUS-FLOW LVADs DESIGNED TO REDUCE ADVERSE EVENTS

Continuous-flow LVADs have achieved overall survival of 80% at 1 year and 70% at 2 years.¹³ However, the current profile and frequency of adverse events restrict these devices to only the sickest patients. Better clinical outcomes are necessary before prolonged LVAD support is more widely accepted.

Continuous-flow devices contain an impeller that rotates at 1,500 to 30,000 rpm to generate forward flow. Blood courses through narrow gaps (50–500 μm) at high velocity. As a result, shear stress may exceed physiologic values by one to two orders of magnitude.¹² For example, the industry standard, HeartMate II (Abbott Vascular), generates peak shear stress $> 1,500 \text{ Pa}$ ¹⁴ (normal physiologic intravascular shear stress is approximately 2–8 Pa ¹⁵). Supraphysiologic shear stress causes blood trauma. The foremost types of LVAD-associated blood trauma with known clinical consequences include von Willebrand factor degradation³ (which contributes to bleeding), platelet activation⁴ (which contributes to thrombosis), and subclinical hemolysis⁵ (which contributes to thrombosis). As a result, LVAD hemocompatibility, a term used to characterize the clinical impact of biophysical interactions and blood trauma at the device-blood interface, is gaining attention as a major area for improvement of future-generation LVADs.



Figure 1. The Evaheart 2 device.

Also problematic, current-generation continuous-flow LVADs operate at a fixed rpm without physiologic control. Devices do not sense physiologic feedback to adjust pressure and flow according to preload, afterload, intracardiac hemodynamics, or metabolic demands. Other major areas of focus for next-generation LVADs are design features and physiologic control algorithms to promote load sensitivity, optimize unloading, and facilitate device weaning.

Currently approved LVADs and TAHs contain polymeric valves and diaphragms or mechanical contact bearings that wear down. To counter this limitation and increase device durability, third-generation devices include a hydrodynamically or magnetically suspended bearingless impeller that does not wear over time or generate frictional heat.¹⁶

Lack of pulsatile blood flow has also raised concerns. Consequently, continuous-flow pulsation algorithms are being developed to generate pulsatility.^{17,18} As device companies address these issues associated with new systems, continuous-flow LVAD therapy is likely to further increase in clinical success and prevalence.

Evaheart 2

Evaheart, Inc. has developed a novel centrifugal-flow LVAD (Figure 1). The original Evaheart device has been available in Japan since 2010. Outcomes in the initial clinical trial were favorable.¹⁹ Recently, the next-generation Evaheart 2 device was implanted in a patient in Japan, and it is poised for clinical trial in the United States.

Evaheart devices have an open-vane hydrodynamic impeller design with large blood flow gaps. The result is preserved aortic pulsatility, low operational rpm, low shear stress, minimal blood trauma, and low likelihood of thrombosis. Ex vivo experiments demonstrated significantly less blood trauma than with currently approved continuous-flow LVADs.¹¹ As a result, patients with the Evaheart device experience a remarkably low incidence of gastrointestinal bleeding.¹⁹ This is a clear demonstration of the impact of device design on clinical outcomes.

Evaheart 2 is a smaller version of the first-generation device with the same open-vane centrifugal-flow design and a novel inflow cannula. The new inflow cannula was redesigned with a double cuff to minimize protrusion into the left ventricle, eliminate local blood stagnation, and prevent inflow cannula malposition. This inflow cannula may provide a complete solution to inflow thrombus formation and ventricular wall suction, which are root causes of ischemic stroke and pump thrombosis. Further clinical experience with this device will define potential advantages of preserved pulse pressure, minimal blood trauma, and improved cannula design.



Figure 2. The HeartMate 3 device.

HeartMate 3

The HeartMate 3 device (Abbott Vascular) is a magnetically levitated centrifugal-flow LVAD (Figure 2). A recent multicenter, randomized clinical trial, MOMENTUM 3, compared the HeartMate 3 to its predecessor, the HeartMate II. At 6 months²⁰ and at 2 years,² rates of death or disabling stroke were the same with each device. However, there were significantly fewer pump malfunctions and no device thrombosis with the HeartMate 3 device.

HeartMate 3 is implanted via median sternotomy or a less-invasive sternal-sparing approach²¹ on cardiopulmonary bypass. Favorable design features include a magnetically suspended impeller that is intended to provide continuous support for a decade with low power consumption. An artificial pulse mode may have numerous beneficial effects that include improved myocardial reverse remodeling, prevention of aortic valve thrombosis, leaflet fusion, de novo aortic insufficiency, reduced arterial stiffening, better end-organ function, and reduced bleeding.^{17,22}

LESS-INVASIVE CONTINUOUS-FLOW LVADS

If combined, the benefits of a minimally invasive surgical approach and durable flow augmentation may expand the potential patient population for LVAD therapy. As LVADs are miniaturized, minimally invasive implantation may increase acceptance by physicians, who are more likely to refer patients for less-invasive surgical therapies.²³ As a result, earlier intervention in less-sick patients may increase the public health impact of MCS. Novel surgical approaches include limited thoracotomy, subxiphoid access, placement of support devices in the infraclavicular fossa, or percutaneous implantation.

Furthermore, certain minimally invasive and percutaneous operative approaches do not require cardiopulmonary bypass.²⁴ As a result, less coagulopathy may reduce postoperative bleeding and blood transfusions, which play a role in right ventricular failure and infection with LVADs.²⁵

Impella 5.5

The Impella family of devices (Abiomed, Inc.) have been developed and approved by the FDA to provide acute circulatory support for high-risk percutaneous coronary intervention (PCI) and cardiogenic shock (Figure 3). These catheter-based devices are percutaneously placed retrograde across the aortic valve with the pump inflow in the left ventricle and the pump outflow in the proximal ascending aorta.

Recently, the Impella 5.5 device underwent initial human implantation in Europe (n = 4). This device is implanted through the subclavian artery and provides up to 6 L/min of flow for up to 30 days. Early ambulation and discharge to home are possible. Optical sensors in the device display real-time aortic and left ventricular pressure waveforms to confirm appropriate device placement and optimize hemodynamics and device weaning. Design modifications to extend the duration of support to > 1 year are in advanced developmental stages.

The potential advantages of a full-support device implanted without a sternotomy or cardiopulmonary bypass and provides real-time intracardiac hemodynamic data to guide weaning and myocardial recovery are significant.

Aortix

Aortix (Procyron, Inc.) is a catheter-deployed, intra-aortic, continuous-flow device for the management of acute decompensated heart failure with cardiorenal syndrome. It features a miniature rotary pump that

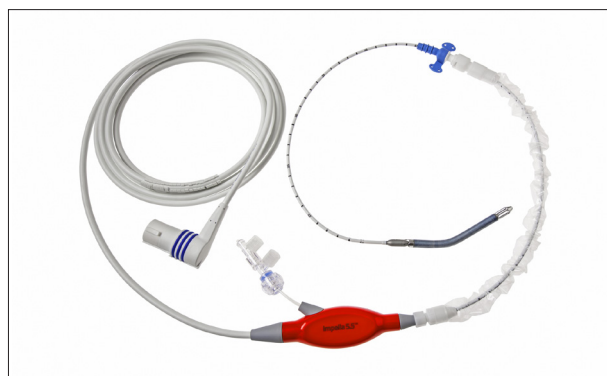


Figure 3. The Impella 5.5 device.

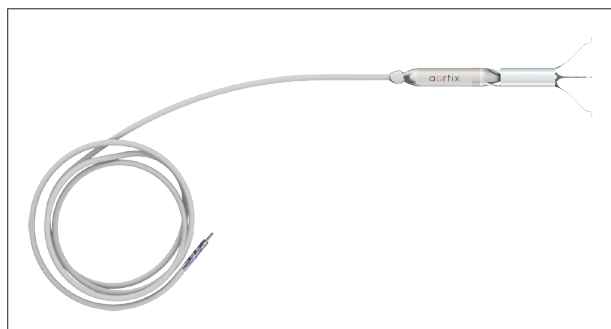


Figure 4. The Aortix.

is caged within a catheter-based nitinol strut system (Figure 4). The device is percutaneously deployed in the descending aorta and unloads the left ventricle by decreasing proximal aortic resistance while providing distal aortic flow augmentation.

Preclinical studies demonstrated effective deployment and retrieval. In an ovine heart failure model, the Aortix device decreased cardiac energy consumption and improved cardiac and urine output.¹² Initial patients supported during high-risk PCI ($n = 6$) also demonstrated significant increases in cardiac and urine output (J. Heuring, PhD, written communication, December 2018). Further clinical studies will define the role of the Aortix device in acute and chronic heart failure.

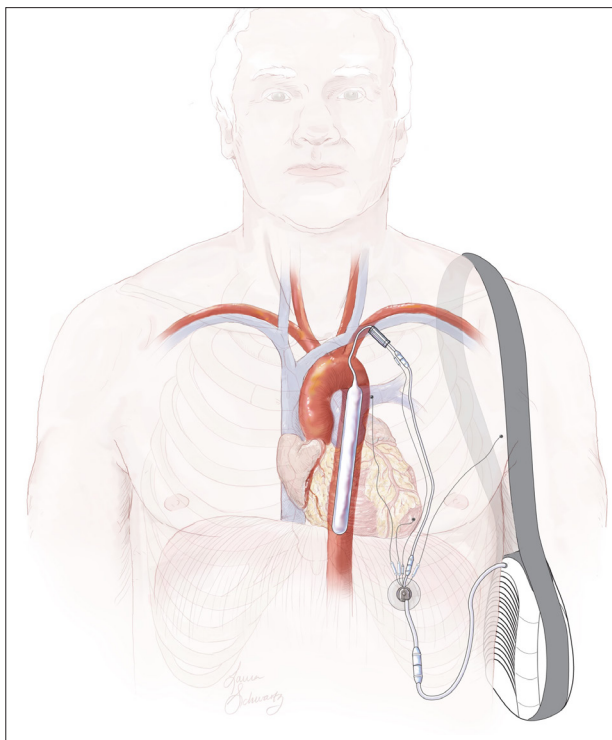


Figure 5. The iVAS device.

iVAS

The iVAS intraventricular assist system (NuPulseCV, Inc.) is a novel, counterpulsation device similar to an intra-aortic balloon pump (Figure 5). An FDA-approved feasibility study was performed in patients with advanced systolic heart failure. All participants ($n = 13$) were successfully bridged to cardiac transplantation with no deaths or neurologic events.²⁶ Improved biventricular function was observed.²⁷

The iVAS balloon is implanted in the aorta via left axillary artery cutdown. The 50-mL balloon inflates during diastole to augment coronary blood flow and deflates during systole to reduce afterload. A limited operative approach combined with the proven benefits of counterpulsation therapy is desirable and may have significant clinical impact for ambulatory support in patients with less-advanced heart failure.

NEXT-GENERATION CIRCULATORY SUPPORT DEVICES WITH NOVEL FLOW MECHANISMS AND BETTER HEMOCOMPATIBILITY

Strong evidence suggests that limited hemocompatibility with current-generation LVADs contributes to LVAD-associated bleeding, thrombosis, and stroke.⁵⁻⁹ These complications cause significant morbidity and mortality and have limited the role of LVADs in patients with less-advanced stages of heart failure.¹⁰ As such, it is becoming increasingly clear that next-generation LVADs with less blood trauma (better hemocompatibility) are urgently needed to reduce adverse events.

Additionally, current-generation continuous-flow LVADs operate at a fixed rpm. Devices are unable to automatically respond to changing hemodynamics and metabolic demands. Toward this goal, next-generation devices described in this section have been specifically designed to improve hemocompatibility and physiologic responsiveness.

TORVAD

The TORVAD toroidal ventricular assist device (Windmill Cardiovascular Systems, Inc.) is a novel, positive-displacement, toroidal-flow LVAD (Figure 6).²⁸⁻³⁰ The toroidal-flow mechanism creates pulsatile blood flow and allows physiologic device control with low shear stress²⁸ and minimal blood trauma.³¹ At 40 to 260 rpm, the 30-mL stroke volume generates 1 to 8 L/min of flow. Synchronous counterpulsation or asynchronous modes may be used to optimize ventricular unloading and facilitate device weaning in the setting of myocardial recovery.

The pumping mechanism of TORVAD is distinctly different from first-generation, sac-type, pulsatile LVADs. To simultaneously fill and eject, TORVAD spins one of

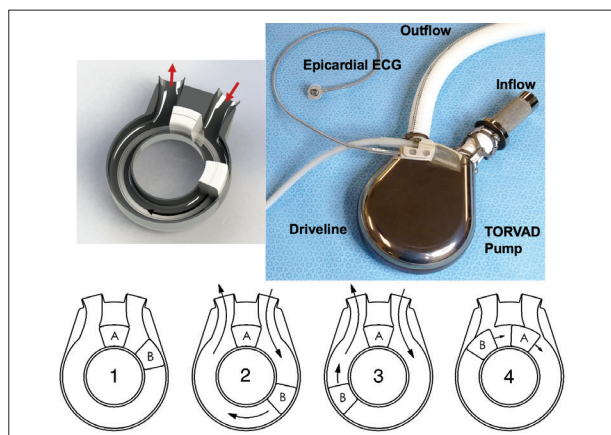


Figure 6. The TORVAD device.

two magnetic pistons within a torus (doughnut-shaped) chamber to generate unidirectional pulsatile flow. While one piston is temporarily fixed as a “virtual valve,” the other spins around the torus to generate flow through a 1.7-cm-wide path comparable to a large artery. At 5 L/min and 70 mm Hg, TORVAD generates shear stress of approximately 10 Pa,²⁹ which is near physiologic values.

In *ex vivo* experiments with human blood, TORVAD caused no platelet activation or hemolysis and minimal von Willebrand factor degradation.³¹ These data are consistent with findings from 60-day bovine implants in which hemolysis and von Willebrand factor degradation were not significant.³² Animals were not anticoagulated, and thromboembolism was not observed.

Furthermore, TORVAD senses pressures within the pump and can automatically adjust pump output to optimize hemodynamic support. For these reasons, toroidal flow is a promising new LVAD design with pulsatile flow, physiologic device control, and significantly less blood trauma.

Neptune

Neptune (CorWave) is a novel device that employs wave membrane physics to generate pulsatile blood

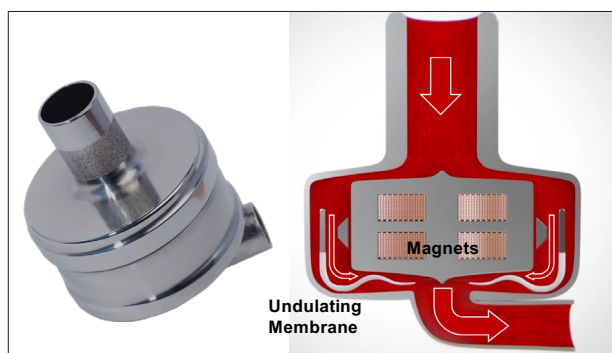


Figure 7. The Neptune device.

flow (Figure 7). The wave membrane (a flexible biomimetic polymer) mimics the undulating motion of a fish tail. The membrane is driven by electromagnets that create membrane oscillations to generate forward propulsion of blood. Physiologic pulsatility (> 35 mm Hg) and shear stress are observed.

The Neptune device is a full-support device implanted via median sternotomy that generates 5 to 6 L/min of blood flow. Acute and chronic animal studies demonstrated cardiac output of 5 L/min at physiologic blood pressures when the pump was synchronized with native heart function. After 9 days of support, no evidence of pump thrombus or thromboembolism was observed (C. Botterbusch, written communication, December 2018). Final design of the pump and external components will be followed by additional preclinical implants. First-in-human implantations are planned for 2020.

NOVEL TOTAL ARTIFICIAL HEARTS

Despite recent advancements in LVAD technology, the management of biventricular failure continues to be a major challenge. Although survival with LVADs continues to improve, there remains significant early morbidity and mortality due to right ventricular failure.^{33,34} In select patients, a TAH may be the best treatment option. The CardioWest (SynCardia Systems, LLC) is the only artificial heart available for clinical use in the United States. However, a major limitation is that the CardioWest does not fit in many men and most women.

The shift from volume displacement pumps to continuous-flow devices has progressively decreased size and increased the durability of LVADs. Not surprisingly, the development of continuous-flow TAHs is underway.

BiVACOR

BiVACOR, Inc. has developed a novel, continuous-flow TAH (Figure 8). Unlike previous-generation TAHs, the BiVACOR TAH uses rotary pump technology to provide biventricular support. BiVACOR consists of a single, magnetically levitated spinning disc positioned between separate right and left ventricular chambers. On either side of the disc are impeller blades that simultaneously generate independent flow from each ventricle. A unique feature of the device allows the disc's relative axial position to change according to the loading conditions of each ventricle. This design allows for passive-flow adaptation with a Frank-Starling-like response and dynamic control of right-left output balance.³⁵ For example, an increase in right ventricular preload pushes the disc to the left and increases right ventricular output and vice versa. Magnetic levitation eliminates contact bearings, and the continuous-flow mechanism

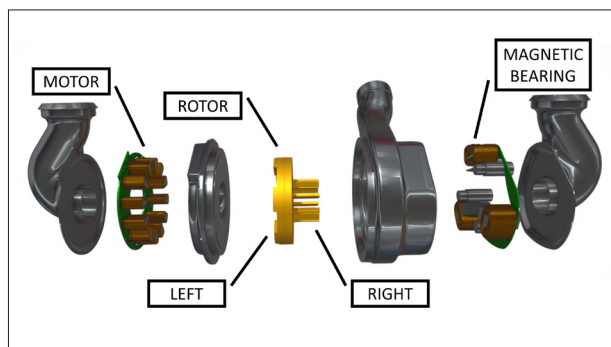


Figure 8. The BiVACOR TAH.

precludes unidirectional valves for an expected durability of 10 years of support.

BiVACOR is orthotopically implanted after native cardiectomy. Unlike previous-generation TAHs, the smaller BiVACOR will accommodate smaller patients (body surface area > 1.2 m²). In chronic calf implantations, the BiVACOR generated peak and mean flows of 17 and 10 L/min, respectively. A pulsatile flow algorithm generated a pulse pressure of 40 mm Hg.³⁶ Animals exhibited normal end-organ function. Additional animal studies are underway to support an application for a human clinical trial.

Biventricular replacement with physiologic hemodynamics, right-left balance, and physiologic control for prolonged circulatory support may have a significant impact for patients with life-threatening biventricular failure.

RealHeart

RealHeart (Scandinavian Real Heart AB) is a novel, pulsatile TAH designed to mimic native heart function (Figure 9). RealHeart consists of two independently operated piston pumps. Each pump has an atrium and a ventricle separated by an atrioventricular valve. Movement of the atrioventricular plane toward the atria decreases ventricular pressure, which opens each valve and fills each ventricle. Movement of the atrioventricular plane toward the ventricles closes each atrioventricular valve and triggers ventricular ejection.

Extensive anatomic fit studies have been performed. In an acute porcine model, RealHeart delivered a wide range of cardiac outputs with a pulsatile waveform similar to the flow pattern of the native heart.³⁷

Carmat

Carmat has developed a novel, pulsatile TAH. The Carmat device consists of two chambers in which a bovine pericardium membrane separates a blood compartment from a hydraulic fluid compartment. Electrohydraulic pressurization of the membranes ejects blood through unidirectional bioprosthetic valves. Bioprosthetic blood-contacting surfaces are anticipated to improve hemocompatibility and preclude systemic



Figure 9. The RealHeart TAH.

anticoagulation. Embedded sensors interact with a control algorithm that responds to changes in preload and afterload to accommodate physiologic demands.

Preclinical bovine implantations with the Carmat device demonstrated the absence of significant blood trauma with a normal profile of von Willebrand factor and normal levels of clotting factors.³⁸ Initial clinical implantations (n = 4) allowed two patients to be discharged home.³⁹ The clinical trial is ongoing in Europe.

CONCLUSION

Continuous-flow MCS devices have significantly improved outcomes in patients with end-stage heart failure. However, frequent device-related complications still occur. Refinement of device design is needed to improve outcomes. Miniaturization and less-invasive surgical approaches may expand the role of MCS devices. Pulsatility and physiologic device control are needed to improve device performance, recreate native physiology, promote myocardial recovery, and facilitate device weaning. Lower shear stress and less blood trauma may improve hemocompatibility and reduce adverse events. Smaller, more durable TAHs may expand the treatment options for patients with end-stage biventricular failure. Careful examination of experiences with next-generation circulatory support devices will determine the relative utility of each device. ■

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