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Thoughts and Progress:

Miniaturization of Mechanical Circulatory Support Systems

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Abstract

Heart failure (HF) is increasing worldwide and represents a major burden in terms of health care resources and costs. Despite advances in medical care, prognosis with HF remains poor, especially in advanced stages. The large patient population with advanced HF and the limited number of donor organs stimulated the development of mechanical circulatory support (MCS) devices as a bridge to transplant and for destination therapy. However, MCS devices require a major operative intervention, cardiopulmonary bypass, and blood component exposure, which have been associated with significant adverse event rates, and long recovery periods. Miniaturization of MCS devices and the development of an efficient and reliable transcutaneous energy transfer system may provide the vehicle to overcome these limitations and usher in a new clinical paradigm in heart failure therapy by enabling less invasive beating heart surgical procedures for implantation, reduce cost, and improve patient outcomes and quality of life. Further, it is anticipated that future ventricular assist device technology will allow for a much wider application of the therapy in the treatment of heart failure including its use for myocardial recovery and as a platform for support for cell therapy in addition to permanent long-term support.

Keywords

Miniaturization; Ventricular assist device technology; Mechanical circulatory support; Heart failure; Review

Heart failure (HF) is one of the largest unsolved problems in cardiac care today with more than five million patients in the USA alone. The number of patients is expected to double over the next 10 years. Among the three major forms of cardiovascular disease (HF, coronary artery disease, and stroke), only HF has shown a significant increase in hospitalization rates. Between 1980 and 2006, the number of patients over age 65 that were hospitalized for HF increased by 131%. The direct and indirect cost of HF in the USA was estimated to be \$34.8 billion in 2008 and projected to rise to \$44.9 billion by 2015 (1). Globally, the incidence of HF is also increasing with over one million new cases diagnosed annually. Current treatment options for HF include pharmacological therapy, cardiac resynchronization therapy (CRT), mechanical heart assist, and heart transplantation. Despite

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improvements in survival with medical therapy and CRT, the prognosis remains poor with 1-year mortality at 15.0% and 28.0% for New York Heart Association (NYHA) Class III and IV, respectively (2). Two-year mortality in the Randomized Aldactone Evaluation Study (RALES) trial was approximately 30% (3). In advanced HF, heart transplantation offers the best opportunity for long-term survival, but it is restricted to select patients based on multiple factors including age, prior surgeries, end-organ function, and even appropriate insurance coverage. Furthermore, the number of available donor organs (~2000/year in the USA) cannot meet the growing demand (up to 30 000 per year) (4). The availability of donor hearts is lower in other countries such as Canada (<200 heart donors/year) and Japan (11 heart transplants in 2009) (5,6).

The large patient population with advanced HF and the limited number of donor organs has stimulated the development of mechanical assist devices as permanent (destination therapy) or temporary (recovery therapy) support devices. Despite years of research and hundreds of millions of dollars in expenditures, it is estimated that less than 4000 patients receive mechanical circulatory support (MCS) each year. Current MCS devices usually require a major surgical procedure (sternotomy or thoracotomy) and the use of cardiopulmonary bypass (CPB) during implantation, device exchange, or explantation (transplant), which increases length of surgery and recovery, blood loss, and risk of exposure to donor blood products. While some MCS device implantations have been accomplished off-pump using smaller-sized incisions, implantation via thoracotomy (or sternotomy) and CPB is the current standard practice (7,8). The invasiveness and complexity of the surgical procedure(s) significantly increases mortality risk with 30-day postimplant mortality at 7% as reported in the Interagency Registry for Mechanical Assisted Circulatory Support (INTERMACS) registry (9). Furthermore, postoperative management of these patients can be challenging and costly. Due to the complexity and invasiveness of the surgical procedure(s) required, immediate complications are not insignificant, and include bleeding, thromboembolism, stroke, and infection. For these reasons, MCS therapy has not gained widespread clinical acceptance, has contributed to MCS devices not being approved for long-term use by government regulatory agencies in developing countries, and has been limited to use in advanced HF patients.

The miniaturization of MCS devices may provide the vehicle to overcome these limitations and usher in a new clinical paradigm in HF therapy. Specifically, miniaturized MCS devices will enable less invasive, “off-pump,” and sutureless surgical procedures to be the standard of care, which may improve patient outcomes to provide long-term support and/or promote myocardial recovery (10). Importantly, these emerging technologies may enable physicians to develop new strategies in the treatment of HF, such as partial ventricular unloading or use in less advanced stage HF patients, while also making it safe and more affordable in global markets. In this article, technological advances toward miniaturization of MCS devices and the potential clinical advantages they may provide are presented.

TECHNOLOGICAL INNOVATIONS

MCS devices include ventricular assist devices (VADs) with external drivelines, percutaneous catheter-based pumps, and counterpulsation devices. The main components of MCS devices may include a pump and inflow and/or outflow cannulae, driveline, driver, and power source. Technological advances for each of these components that will enable miniaturization are presented.

PUMPS

A principal design specification in the development of the first VAD was to create pulsatile flow physiologically similar to the native heart. These first-generation pulsatile flow pumps,

which include Novacor (World Heart, Ottawa, Ontario, Canada), HeartMate XVE, Thoratec Paracorporeal Ventricular Assist Device (PVAD) and Implantable Ventricular Assist Device (IVAD) (Thoratec, Pleasanton, CA, USA) used pneumatic or electrohydraulic drive mechanisms, were fitted with valves to provide unidirectional flow, and integrated pusher plates or diaphragms to fill and empty blood from the device (Table 1) (11–13). Design complexity and the additional space needed for device stroke volumes led to large sizes (>300 mL) and weights (>1000 g), lower reliability (0.51 device replacements/patient year), and the inability to be implanted in the thoracic cavity (Table 2). Rotary blood pumps including the HeartMate II (Thoratec), Jarvik 2000 (Jarvik Heart, New York, NY, USA), HeartAssist (MicroMed Cardiovascular, Houston, TX, USA), and HVAD (HeartWare, Miami Lakes, FL, USA) reduced the size (<100 mL) and weight (<300 g) as well as device complexity by eliminating the need for valves, pusher plates or diaphragms, and space for device stroke volume (Table 2) (14–17). These technological advances enabled preperitoneal and intrathoracic VAD placement and smaller pocket dissection, reducing the magnitude of surgical intervention and infection risk, while expanding application of MCS therapy to smaller patients (18). Device reliability was improved (0.06 device replacements/patient year) and frictional losses minimized by advances in bearing materials (ruby, ceramic), bearing technology (blood immersed, hydrodynamic), and the elimination of mechanical bearings (magnetically levitated) in new pump designs. The use of computational engineering tools (computational fluid dynamics, Solid-Works) led to improvements in impeller and stator designs with higher mechanical efficiencies (19,20). Advances in manufacturing methods, reduced manufacturing tolerances, and impeller designs enabled further reduction in rotary blood pump size for adults (<50 g, <40 mL) and spawned the development of pediatric MCS devices with support from National Institutes of Health PUMPKIN development initiative (21,22). These smaller adult rotary blood pumps, which include Miniaturized Ventricular Assist Device (MVAD) (HeartWare), HeartMate X (Thoratec), Synergy (CircuLite, Saddle Brook, NJ, USA), and Jarvik 2000 (Jarvik Heart), operate at higher rotational speeds (up to 26 000 rpm) and may be implanted in the pericardial space using less invasive surgical procedures without the use of cardiopulmonary bypass to provide partial/full VAD support chronically (Table 2) (23–25). The progression of miniaturization of Thoratec and HeartWare VAD is pictured in Fig. 1.

Significant miniaturization of impeller geometries enabled the development of catheter-mounted microaxial pumps, which include Impella 2.5 and Impella 5.0 (Abiomed, Danvers, MA, USA), and Percutaneous Heart Pump (Thoratec), as shown in Fig. 2. These pumps can be inserted percutaneously via a standard catheterization procedure and advanced into the ascending aorta, across the aortic valve, and into the left ventricle. The microaxial MCS devices have very high operational speeds of up to 50 000 rpm and provide short-term (hours to days), partial support (2–5 L/min) for patients with postcardiotomy low cardiac output syndrome, cardiogenic shock, and acute cardiac dysfunction (24,26).

Counterpulsation therapy with an intra-aortic balloon pump (IABP) is the most widely used form of MCS (160 000 patients/year). While the percutaneous access used for IABP is minimally invasive, IABP support is limited to short-term support (days to weeks), and patients are unable to ambulate (27,28). New pneumatically actuated devices that provide chronic counterpulsation have been developed and introduced clinically, which include Cardioplus (LVAD Technologies, Detroit, MI, USA), C-Pulse (Sunshine Heart, Eden Prairie, MN, USA), and Symphony (SCR, Louisville, KY, USA and Abiomed). Cardioplus is an inflatable aortic patch (Fig. 3A) and the C-Pulse (Fig. 3B) is an inflatable cuff that is wrapped around the aorta (29–34). A thoracotomy or sternotomy is required for Cardioplus and C-Pulse implantation. Symphony (Fig. 3C) is a pneumatically actuated sac that is implanted in the subclavicular space (pacemaker pocket) and anastomosed to the axillary artery (35–38).

CANNULAE

Inflow and outflow cannulae connect the MCS device to the patient's native circulation. Evolutions in cannula technology include material and surface modifications to improve biocompatibility, moderate reductions in cannula size to facilitate implantation, and location of attachment site to improve patency and local hemodynamics. The inflow cannulae were made out of plastic/polymer (Thoralon) (39). Current clinical VADs have inflow cannulae made out of titanium (HeartMate II, HVAD, MVAD) or stainless steel (HeartAssist), which provide higher rigidity, biocompatibility, and fracture resistance. Outflow grafts have transitioned from porous Dacron (PVAD/IVAD, HeartMate XVE, Novacor), which required preclotting to achieve hemostasis, to nonporous Hemashield (HeartMate II, HVAD, MVAD) (40–42). The inflow cannula size has decreased from 25 mm to 28 mm (HeartMate XVE, Novacor) to 21 mm (HeartWare HVAD). A smaller inflow size may adversely impact hemolysis rate, flow patency, and pump efficiency. The outflow graft size has been optimized from 20 mm to 10 mm to minimize blood stasis while maintaining flow patency.

Inflow cannula attachment to the ventricular apex is favored over atrial attachment (PVAD, IVAD, CircuLite) as it reduces the risk of suction and blood stasis in the ventricle (43). Outflow graft anastomosis to the ascending aorta is favored over descending aorta to prevent retrograde flow and stasis in the aortic arch (44–46). Recent VAD designs have integrated the rotor into the intraventricular housing (Jarvik 2000, HVAD, MVAD, HeartMate X), eliminating the need for an inflow cannula. The percutaneous VAD (Impella 2.5, Impella 5.0, PHP) and the completely intraventricular Longhorn VAD (HeartWare) have no inflow or outflow cannula attachment/ anastomosis, simplifying device implantation (47).

DRIVELINES

Drivelines are the connection between the externalized source of power and control for the internalized pump, and they have been considered a critical weakness of VADs for long-term therapy (defined as >5 years of support). There have been progressive improvements that have decreased driveline diameter in order to minimize the size of exit site, risk for driveline infection, and improve patient comfort. Pulsatile VADs required a channel for shuttling air (HeartMate IP) or an air vent (HeartMate XVE), which necessitated a large diameter driveline (48–50). The advent of rotary blood pumps eliminated the need for air channels or vents significantly diminishing the driveline diameter. The reduced diameter drivelines with continuous flow devices have been reported to have a lower device-related infection rate of 0.48 events/patient year compared to 0.90 events/ patient year associated with pulsatile flow devices (18). Following the introduction of rotary blood pumps with smaller diameter drivelines, only modest reductions in driveline diameter have been accomplished despite significant miniaturization of the pumps themselves. A reduction in driveline infection rates has been reported with the scalp driveline exit site (Jarvik 2000) compared to the traditional abdominal driveline exit site (51). Transcutaneous energy transfer system (TETS) technologies, which are currently in development, may eliminate VAD drivelines and significantly reduce infection rates (52).

DRIVERS

Early MCS pneumatic drivers for LVAD (>300 lbs) and IABP (>80 lbs) were very large, heavy, and unwieldy due to the size and weight of compressors, pressure and vacuum plenums, and analog controllers. Furthermore, these drivers required AC power and had limited battery reserve, which significantly restricted patient mobility. Miniaturization of compressor motors enabled the development of smaller, lightweight drivers for pulsatile LVAD (<30 lbs, Fig. 4) and counterpulsation devices (<4 lbs, Fig. 5).

The introduction of electromechanical pulsatile VAD reduced the size of the driver by eliminating plenums and compressors. The pulsatile VAD drivers were able to control filling and ejection pressures, beat rate, and filling and ejection times. In autonomous mode, these drivers initiated VAD ejection as soon as full fill of the blood sac was detected, imitating Starling's Law mechanism and preload sensitivity. Current rotary VAD drivers are smaller (Thoratec G1: 660 cc, Thoratec G2: 300 cc) and lighter (Thoratec G1: 635 g, Thoratec G2: 360 g) due to integration of microprocessors that can maintain a constant pump speed (rpm), and may be carried in a vest, backpack, or belt due to their ergonomic designs (24). The preload sensitivity is significantly diminished with rotary VADs and, currently, many drivers do not use physiologic control algorithms to alter VAD speed in response to physiologic demands due to physical activity or the patient's circadian rhythm (53–55). Modern rotary VAD drivers have incorporated algorithms for: (i) suction detection using motor current waveform and enabling autonomous decrease in pump speed as a response to suction events; (ii) display of pulsatility waveforms or pulsatility index; and (iii) estimation of VAD flow using motor power and rotor speed (56,57). However, it should be noted that the estimated VAD flow only provides qualitative value (HeartMate II) or requires input of blood viscosity/ hematocrit (HeartWare HVAD) for reasonably accurate estimation (15,58).

POWER SOURCES

The pulsatile VAD designs have several moving parts and require rapid acceleration and deceleration of blood during device filling and ejection, resulting in low mechanical efficiency and high power requirements (up to 20 W) (50). The rotary blood pumps have only one moving part (impeller) and deliver uniform flow, resulting in better mechanical efficiency and less power requirements (<10 W) (15,59). Magnetically levitated and miniaturized rotary blood pump designs that are currently in preclinical testing have even higher mechanical efficiencies and require less than 5 W of power.

The earliest pulsatile VAD drivers were required to be predominantly connected to an AC power source and had heavy lead acid batteries as backup. Coupled with the higher power requirements of early pulsatile VADs, the batteries could only power the VAD for short periods of time. Progressive improvements in battery technology (Ni/Cd, Ni MH, and currently Li ion) have led to batteries with higher energy density, increased cycle life, longer operational times, and reduced size and weight. Despite these improvements in battery technology, the patients need to be tethered to a battery pack, which can adversely affect the patient quality of life. TETS was first used with the LionHeart VAD to untether the patient briefly and to eliminate driveline infections (60). Free-range resonant electrical delivery wireless power systems (FREE-D, WiTricity) which are currently under development, aim to use magnetically coupled resonators to transfer power across a distance (2–3 m) (61,62). While significant challenges remain in implementing resonant power transfer technology for MCS, it has the potential to untether a patient from a battery pack for prolonged periods of time.

CLINICAL IMPLICATIONS

The implantation of the large, first-generation, pulsatile LVAD required a full median sternotomy and intra-abdominal placement or creation of a large pump pocket for preperitoneal placement. Additionally, use of cardiopulmonary bypass was required which increased the complexity of surgery, exposure to blood products, and significant risk of morbidity. The large size of these devices limited access to VAD therapy to patients with large body surface area ($>1.5 \text{ m}^2$), which effectively removed VAD therapy as an option for most women (63). Furthermore, adverse events associated with the size of the implantable components included pump pocket and driveline infection, thrombosis, and loss of appetite

(64–66). The introduction of smaller-sized rotary blood pumps eliminated the need for intra-abdominal placement, reduced the size of the preperitoneal pocket for implantation (HeartMate II), enabled VAD therapy in patients with BSA <1.5 m², reduced adverse events, and improved patient outcomes (2-year survival approaching 80%) (67,68). Despite these improvements, current VAD therapy is currently limited in its application to patients with severely advanced HF (NYHA Class IV). This patient cohort is subject to multiple comorbidities and is less likely to survive a highly invasive surgical intervention (69,70). Miniaturization of rotary VADs may enable implantation using less invasive non-sternotomy surgical approaches (HVAD, HeartMate III) or intraventricular placement (Jarvik, MVAD, HeartMate X, Longhorn) without CPB, potentially eliminating the need for pump pockets and sternotomy or thoracotomy (47,71). The minimally invasive surgical approach required to implant these smaller rotary VADs may reduce surgical time, infection risks, and adverse events. Exposure to blood products would be minimized without the use of CPB and “off pump” implantation which may improve patient outcomes. Furthermore, a less invasive surgical approach is more likely to gain greater acceptance by patients, referring physicians, and cardiac surgeons.

The current paradigm in HF treatment is that MCS devices are reserved for patients with end-stage HF that have failed medical therapy. Accordingly, current devices are usually adjusted to maximize flow with minimal ejection from the native heart. Clinically, very few patients demonstrate myocardial recovery with this treatment regimen (10). The potential of using smaller rotary VADs for partial circulatory support challenges the current paradigm. There is increasing interest in the field of partial circulatory support with early clinical evidence supporting the added benefits of this approach (72). The National Heart, Lung and Blood Institute (NHLBI) has recognized the need for innovative approaches to the treatment of HF with the NHLBI “Recovery from Heart Failure with Circulatory Assist” working group recommendations for the development of novel therapies for myocardial recovery, and elucidation of the mechanisms leading to reverse remodeling and myocardial recovery (73). It is possible that early intervention and partial support may increase sustained recovery rates. Thus, the ability to provide early intervention using miniaturized MCS device(s) that can be placed via a limited operative approach will represent a major clinical innovation. Specifically, partial circulatory support earlier in the disease process may promote native heart recovery, enable development of better medical management strategies, and/or slow the natural progression of the disease. In the event that a patient demonstrates myocardial recovery, MCS devices need to be easily explanted. This is in stark contrast to the need for repeat sternotomy required for replacement or removal of current implanted MCS systems. Expansion of MCS therapy to a larger HF patient population cannot occur until improved designs have achieved smaller, safer, and reliable devices, implanted and explanted using a less invasive surgical approach, with improved patient outcomes and quality of life.

SUMMARY

Current outcomes for patients with advanced HF supported with MCS continue to improve and are approaching results achieved with heart transplantation. Continuous flow pump design has enabled significant miniaturization in MCS technology and demonstrated 31–34% higher 2-year survival compared to larger pulsatile flow MCS devices. Additionally, these smaller devices have led to significantly lower rates of MCS-related infections, pump replacements, rehospitalization, and occurrences of sepsis, arrhythmias, respiratory failure, and renal failure (18,74). Additional design improvements, less invasive implant techniques, and the development of an efficient and reliable TET system will lead to further reductions in adverse events and improved long-term survival. We anticipate that future VAD technology will allow for a much wider application of the therapy in the treatment of HF

including its use for myocardial recovery and as a platform for support for cell therapy in addition to permanent long-term support.

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FIG. 1.

The progression of miniaturization of Thoratec and HeartWare VADs that are capable of providing full support (>5 L/min): (A) HeartMate XVE, (B) Thoratec PVAD, (C) Thoratec IVAD, (D) HeartMate II, (E) HeartMate III, (F) HeartWare HVAD, (G) HeartWare MVAD, and (H) HeartWare Longhorn. The maximum flow rate of the HeartWare MVAD and Longhorn are 6 L/min, while the other devices have a significantly higher maximum flow rate (>10 L/min).

FIG. 2.

Significant miniaturization of impeller geometries enabled the development of catheter-mounted microaxial pumps, which include (A) Impella 5.0, (B) Impella 2.5 (Abiomed), and (C) Percutaneous Heart Pump (Thoratec). The limitations of catheter-based pumps include lower maximum flow rates, shorter implantation periods, and higher risk of infection compared to VAD.

FIG. 3. Chronic counterpulsation devices include (A) Cardioplus (LVAD Technology), (B) C-Pulse (Sunshine Heart), and (C) Symphony (SCR, and Abiomed).

FIG. 4. The progression and miniaturization of Thoratec LVAD drivers include (A) VAD Pneumatic Drive System, (B) TLC-II driver, (C) HeartMate II/Thoratec G1 Controller, and (D) HeartMate III/ Thoratec G2 Controller.

FIG. 5. Miniaturization of counterpulsation device drivers include (A) CS 300 IABP system which measures 109 cm H $\times$ 56.6 cm D $\times$ 42.7 cm W and weighs over 80 lbs, and (B) Symphony driver which measures 5.5 cm H $\times$ 25.8 cm D $\times$ 17.1 cm W and weighs <4 lbs.

TABLE 1
Comparative data on MCS systems in clinical use or under development and their unique feature(s)

Device	Company	Flow type	Unique feature(s)	Status
1st and 2nd generation	PVAD	Pulsatile	Pneumatically driven pulsatile pump	CE Mark and FDA—BTT approval
	HeartMate XVE	Pulsatile	Textured surface for biocompatibility	CE Mark and FDA—BTT and DT approval
	HeartMate IVAD	Pulsatile	Thorolon blood-contacting surface	CE Mark and FDA—BTT approval
	Novacor LVAS	Pulsatile	First electrically powered LVAD	No longer clinically available
	HeartMate II	Axial	Ruby and ceramic bearings	CE Mark and FDA—BTT and DT approval
3rd generation	larvik 2000	Axial	Implanted completely in LV apex	Clinical Trials and CE Mark BTT
	HeartAssist 5	Axial	Direct flow measurements	CE Mark BTT and DT
	HVAD	Centrifugal	Rare earth magnet rotor	Clinical Trials BTT and DT
	HeartMate III	Centrifugal	Textured pump surface	Pre-Clinical Trials
	MiTiHeart	Centrifugal	Reduced number of controlled axes	Pre-Clinical Testing
	DuraHeart	Centrifugal	Three (X,Y,Z) position sensors	Clinical Trial BTT and DT
	MVAD	Axial	Smallest in generation	Pre-Clinical Trials
	Coraid	Centrifugal	Second impeller for balancing axial forces	Pre-Clinical Testing
	HeartMate X	Axial	Ruby bearings	Pre-Clinical Testing
	Incor	Axial	Only inline axial pump in generation	CE Mark—BTT
Levacor	World Heart	Centrifugal	Full magnetic levitation	Clinical Trial BTT (Halted)
EVAHEART	Evaheart	Centrifugal	Lubricating film of sterile water	Clinical Trial

Improvements in MCS technology have led to a significant reduction in pump size, displacement volume, and power requirements over time

TABLE 2

VAD	Flow (L/min)	Volume (cc)	Weight (g)	Operating rate	Power (Watts)	Battery (hours)
HeartMate XVE	Up to 10 L/min	390 cc	1255 g	Up to 120 bpm	5–15	4 each
Novacor	Up to 12 L/min	500 cc	1000 g	Up to 180 bpm	10–20	3.5 each
HeartMate II	Up to 10 L/min	63 cc	281 g	6000–15 000 rpm	<14	Up to 10 h
HeartWare HVAD	Up to 10 L/min	45 cc	145 g	2000–5000 rpm	<4.7	6 each
MicroMed DeBakey	Up to 10 L/min	38 cc	95 g	7500–12 500 rpm	<10	2–4 each
Jarvik 2000	Up to 12 L/min	25 cc	90 g	7000–13 000 rpm	6–9	8–10 each
HeartMate III	Up to 13 L/min	50 cc	200 g	2000–5500 rpm	N/A	N/A
HeartWare MVAD	Up to 10 L/min	15 cc	75 g	16 000–28 000 rpm	N/A	N/A
HeartMate X	Up to 8 L/min	N/A	N/A	N/A	N/A	N/A