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EDITORIAL COMMENT

Evolution in Mechanical Circulatory Support

Are We at the Precipice of a Disruptive Innovation?*

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"It ought to be remembered that there is nothing more difficult to take in hand, more perilous to conduct, or more uncertain in its success, than to take the lead in the introduction of a new order of things."
—Niccolò Machiavelli (1)

The growing population with advanced stage heart failure (HF) is exemplified by a high disease burden, greater medical resource utilization, lack of responsiveness to traditional disease-modifying approaches, and an imperative for specialized therapy, including cardiac transplantation and durable mechanical circulatory support in selected individuals (2). In recent years, left ventricular assist devices (LVADs) have become increasingly entrenched into clinical practice as a result of transition from larger devices with displacement chambers that mimicked ventricular function to smaller, more durable devices with fewer moving parts that rely on axial or centrifugal continuous flow (3).

Continuous flow (CF) LVADs have been adopted widely as a bridge to transplantation or for permanent lifetime therapy. Compared with medical therapy, clinical outcomes with CF-LVADs increase 1- and 2-year survival (2). Yet, morbidity from device-related complications remains high, characterized predominantly by complications related to the interface between bleeding and thrombosis as well as the patient-device interface. Principal hemocompatibility-related adverse events encountered include bleeding, thrombosis, and stroke, whereas right ventricular HF (early and late) as well as infections (especially driveline infections) constitute the foremost patient-device related interactions (3–6). Thus, novel devices with the aim of enhancing biocompatibility are needed to move this rapidly evolving field forward.

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In this issue of the *Journal,* Netuka et al. (7) report on the first-in-human experience of a new durable LVAD, the HeartMate 3 (St. Jude Medical, Pleasanton, California) in 50 patients from 10 centers within Europe, Australia, and Canada. The HeartMate 3 LVAD is a new-generation device, engineered with the promise of enhanced hemocompatibility. This centrifugal flow device is miniaturized, uses magnetic levitation to spin the rotor, and has large gaps between the pump housing and perimeter of the rotor. The magnetic levitation allows the rotor to stay in a stable position at wide ranges of speed, while the enhanced gaps are designed for improved blood flow without encumbering increased shear stress on blood elements. Two additional technical properties are embedded in this device: internal sintering with textured titanium microspheres to allow for a biocompatible surface, and interestingly, an internal pulsatility function at a rate of 30 beats/min with automatic speed changes.

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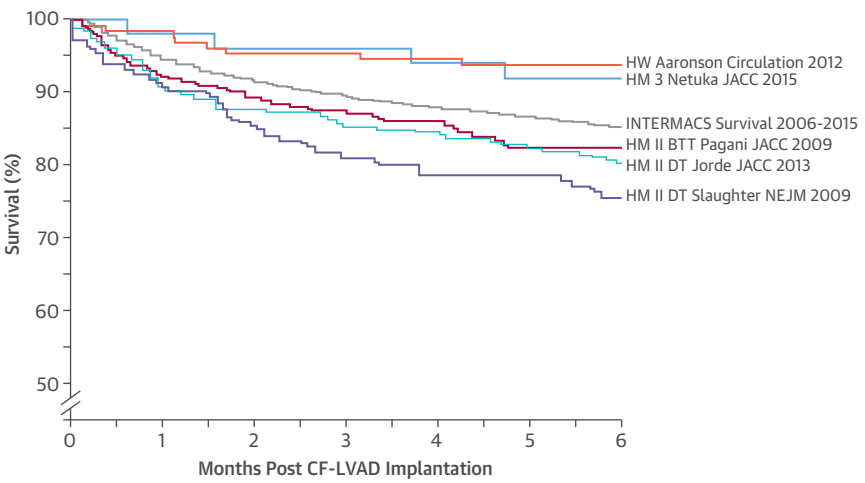
The primary reasoning behind this intrinsic pulse is to reduce pump stasis. Whether this phenomenon provides systemic benefits as a circulatory pulse mimic and decreases the incidence of gastrointestinal bleeding secondary to arterial venous malformations remains unknown.

The primary objective of this first-in-human experience was to evaluate the early performance and safety of this new left ventricular assist system. The study met its pre-specified survival goal, with excellent 1- and 6-month survival of 98% and 92%, respectively. These findings are outlined in the context of other similar experiences with currently available LVADs as well as from the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) registry (**Figure 1**).

Although we tend to classify patients into discrete categories by intent of bridge to transplant or permanent support, we recognize that such segregation in the advanced-stage HF patient can be rather arbitrary. It has been demonstrated that 30% of patients listed with the initial intent to undergo heart transplant remain on LVAD support for longer than 2 years, and as many as 44% of such individuals are delisted from requiring transplantation (8). As such, the initial HeartMate 3 LVAD experience was uniquely constructed to enroll an "all-comers" population of advanced stage HF. It is also known that transplant ineligible patients tend to have modestly inferior outcomes compared with the typically younger population of transplant candidates (with fewer comorbidities) who undergo LVAD implantation (2).

FIGURE 1 Progressive Improvement in Outcomes of Patients Supported With CF-LVADs for Advanced Heart Failure



Study	Patients	Device	Indication	1 Month Survival	6 Month Survival
Netuka et al. 2015	50	HM 3	BTT + DT	98%	92%
Aaronson et al. 2012	140	HW	BTT	99%	94%
INTERMACS 2006-2015	14,037	HW + HM II	BTT + DT	94%	85%
Pagani et al. 2009	281	HM II	BTT	92%	82%
Jorde et al 2013	247	HM II	DT	90%	80%
Slaughter et al. 2009	133	HM II	DT	91%	75.5%

Kaplan-Meier curves of the HeartMate (HM) II bridge-to-transplantation (BTT) study (Pagani et al.), HM II post-approval study (Jorde et al.), HVAD BTT study (Aronson et al.), INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) report, and the current HM 3 study (Netuka et al. [7]). Shown are 1- and 6-month survival. CF = continuous flow; DT = destination therapy; HW = HeartWare; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; LVAD = left ventricular assist device.

Thus, the clinical outcomes of the HeartMate 3 experience should be judged in light of the unique "all-comer" population enrolled. In the INTERMACS registry, 6-month survival in bridge to transplant is 90% and decreases to 83% in those designated as destination therapy (2).

As we move the field of mechanical circulatory support forward, diminishing the reliance on segregated indications and employing the use of LVAD therapy as a step in the clinical journey of an advanced-stage HF patient, tipping will be crucial. In this regard, the pivotal U.S.-based MOMENTUM 3 (Multi-center Study of MagLev Technology in Patients Undergoing MCS Therapy With HeartMate 3) clinical trial purports to move this thought forward by evaluating 1,028 patients and randomizing them to the HeartMate 3 versus the HeartMate II device with the intent of evaluating any advanced-stage HF patient deserving of such therapy to an evaluation endpoint of freedom from death, pump exchange, or disabling stroke at short-term (6 months) and long-term (2 years) support (9).

More recently, the spotlight has been cast upon the development of LVAD pump thrombosis that requires pump exchanges, with consequent reduction in survival and increased disability from neurological complications (8,10–12). The frequency of pump thrombosis has been noted to increase between 6% to 12% in patients supported with HeartMate II LVAD and 8% in those with an HVAD (HeartWare, Framingham, Massachusetts) (8,11,12–15). Encouragingly, no device thrombosis or pump exchanges were seen to occur by 6 months in the HeartMate 3 experience. Coupled with this observation is the finding of stability in parameters of hemolysis, all providing evidence of a trend toward enhanced hemocompatibility with this LVAD. One must be cautious in exercising excessive ebullience with this finding, because we are looking at a small sample size of 50 patients with limited duration of follow-up.

Neurological events, characterized by ischemic and hemorrhagic strokes, are an "Achilles heel" of LVADs, with a 2-year incidence of disabling stroke ranging from 9 to 27 events/patient/year (16,17). Our understanding of this complication remains rudimentary, with correlations of the type of device (higher incidence with the HVAD), control of blood pressure (better outcomes with lower pressure), and use of antithrombotic therapy (6,17). Whether enhanced hemocompatibility with the HeartMate 3 will also serve in reducing this critical complication remains uncertain. The observed rate of stroke in the current study cohort was 12% (8% ischemic and 4% hemorrhagic stroke), and there was another 8% rate of milder neurological events such as seizures and transient ischemic episodes within 6 months. It is sobering to observe this higher than expected risk of stroke; however, 1 stroke was related to an unusual complication (contrast agent anaphylaxis) and another to the learning curve of the surgical implant technique (apical cuff bleeding and hypotension). It is too scant an experience to provide conclusive direction in this regard, and the larger experience in MOMENTUM 3 will be pivotal in enhancing our understanding of neurological complications with CF-LVADs.

As new technology is introduced, it is not unusual to observe a learning curve in its early application. Evidence of this phenomenon is noted in the HeartMate 3 series by the observation of a high rate of early bleeding events, many of which required surgical reintervention. It is also difficult to predict whether the standard anticoagulation protocols are required, even as enhanced hemocompatibility is observed. Thus, the learning curve is equally operational in the surgical technique as it is in the medical management of the anticoagulation profiles, and other factors such as blood pressure and blood volume control. Curiously, the rates of gastrointestinal bleeding observed in this cohort appear to be lower than those demonstrated in larger experiences with conventional LVADs (18,19). It is known that atrioventricular malformations and hemostatic aberrations by degradation of large multimers of von Willebrand factor as a result of low systemic pulsatility induced by CF-LVADs account for a significant predilection to gastrointestinal bleeding (18,19). Whether enhanced hemocompatibility decreases this outcome with the HeartMate 3 LVAD remains uncertain. We urge caution in the interpretation of the trend toward a lower gastrointestinal bleeding rate in the current experience with the HeartMate 3, because mechanistic insight about reduction of acquired von Willebrand disease due to the reduced shear stress or reduction the development of arterial venous malformations and the effect of the intrinsic device artificial pulse program is not provided.

As the field of LVAD therapy advances, advanced-stage HF patients tend to be referred before end-organ failure sets in. In the current study, 40% of the patients were in INTERMACS profile 4 (those with resting symptoms but not requiring inotropic support). Previous trials have enrolled a greater proportion of patients that are in a higher INTERMACS profile with inotropic therapy dependency (20–22). One could argue that the excellent 6-month survival observed in the HeartMate 3 series is due to this phenomenon. However, there is little difference in

the quality-of-life parameters of INTERMACS 4 patients compared with profile 3, and furthermore (23), analyses of the INTERMACS registry suggest that the outcome for an INTERMACS profile 3 and 4 patient appears similar with device intervention (3). It is in the cardiogenic shock patients (INTERMACS 1) or those unstable on inotropic support (INTERMACS 2) that the early hazard of worse outcome is noted. As outcomes with available technology improve over time, we may see earlier referral for evaluation and consideration for therapy.

A gradual evolution, rooted in perseverance and tolerance for clinical imperfection, has allowed the field of mechanical circulatory support to become a clinical reality. As engineering pursuits face clinical reality, we are once again on the precipice of a new technological advance in the field. Whether this promise becomes a clinical reality remains to be proven. As Jean Piaget commented, "Scientific thought, then, is not momentary; it is not a static instance; it is a process" (24).

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