Should Left Ventricular Assist Device Should Be Standard of Care for Patients With Refractory Heart Failure Who Are Not Transplantation Candidates?

Left Ventricular Assist Devices Should Be Considered Standard of Care for Patients With Refractory Heart Failure Who Are Not Transplantation Candidates

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The development of current mechanical circulatory support (MCS) systems began in the 1960s as an effort to provide a therapeutic option for patients with refractory advanced heart failure. Today, MCS represents a viable alternative to cardiac transplantation for the overwhelming majority of patients in whom age, comorbidities, or the profound shortage of donors makes transplantation infeasible.

Response by Owens and Jessup on p 3087

Painstaking work on the technique of orthotopic cardiac transplantation, coupled with advances in the knowledge of immunology, resulted in the improvements in survival and quality of life that make cardiac transplantation the treatment of choice for individuals with advanced heart failure. MCS has only recently become accepted for widespread clinical use.

Early MCS designs were based on the assumption that maintaining pulsatility of flow was a physiological necessity. These bulky devices were of limited durability and resulted in a great deal of morbidity in the form of hematologic, neurological, and infectious complications.

Current (second- and third-generation) devices deliver continuous flow (either axial [HeartMate II] or centrifugal [Heartware HVAD]) and have far fewer moving parts (only a rotor); as a result, they are smaller, quieter, and far more durable (estimated to last ≥10 years compared with 18 months) than the early pulsatile systems.

Although no longer in common use, early pulsatile-flow left ventricular assist devices (LVADs) provided the first proof of principle that MCS can extend life of well-selected patients with advanced heart failure refractory to traditional optimal medical therapy. The development of continuous-flow devices has made MCS a practical clinical tool, and outcomes with the newer devices provide a convincing rationale for LVADs as standard of care in well-selected patients with refractory heart failure in whom transplantation is not an option.

Advent of LVAD Therapy in Transplantation-Ineligible Advanced Heart Failure

Proof of Principle

Recognition that LVADs intended as a bridge to cardiac transplantation delivered durable support to some patients who were not transplanted provided rationale for the Ran-
were in the hospital.

ment was only 8 months, of which as many as 3 months
associated morbidity, and the median survival improve-
with the LVAD died within 2 years, there was extensive
use of pulsatile LVADs because nearly all of the patients
of Congestive Heart Failure (REMATCH) Trial. This
study, reported in 2001, was performed to determine whether
MCS with a first-generation pulsatile LVAD could improve
survival of end-stage heart failure patients compared with
medical therapy.

REMATCH enrolled patients who were not candidates for
transplantation who were in New York Heart Association
functional class IV heart failure for at least 90 days despite
standard medical therapy, had a left ventricular ejection
fraction ≤0.25, had peak oxygen consumption \( (\text{PVO}_2) \leq 12
\text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \), or had a clinical picture including symp-
tomatic hypotension, deteriorating renal function, or worsen-
ing pulmonary congestion. Later, the entry criteria were broadened to include \( \text{PVO}_2 \leq 14 \text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) and
patients in New York Heart Association class IIIb or IV
requiring intra-aortic balloon pump or inotropic support.
Patients were randomized to either LVAD implantation or
optimal medical therapy. A total of 129 patients were ran-
domized. The 1-year survival was 52% in the LVAD group
compared with 23% in the medically treated patients
\((P=0.002)\); the 2-year survival was 28% in the LVAD group
and 8% in the medically treated patients. There was also
improvement in quality of life in the LVAD patients com-
pared with the medically treated patients. This trial was
conducted with a first-generation LVAD that would now be
regarded as obsolete, but the study derives its fundamental
importance from being a proof of the principle that MCS
can improve the survival of late-stage heart failure patients
who had an expected 75% 1-year mortality rate. The
REMATCH trial was not followed by widespread clinical
use of pulsatile LVADs because nearly all of the patients
with the LVAD died within 2 years, there was extensive
associated morbidity, and the median survival improve-
ment was only 8 months, of which as many as 3 months
were in the hospital.

Progress in LVAD Technology
A major advancement in MCS technology occurred with the
introduction of the currently used continuous-flow LVADs
that are small-profile pumps that continuously draw blood
from the left ventricle and then propel it back to the aorta in
a nonpulsatile manner. These devices are simpler, quieter,
smaller, and more durable than the first-generation pulsatile-
flow device used in REMATCH. The Thoratec HeartMate II
was the first of these devices to be tested in a large
randomized trial against the older-generation device used in
REMATCH that achieved regulatory approval. To meet entry
criteria, Slaughter and colleagues\(^6\) enrolled transplantation-
ineligible patients with a left ventricular ejection fraction
<25\%, \( \text{PVO}_2 < 14 \text{mL} \cdot \text{kg}^{-1} \cdot \text{min}^{-1} \) or <50% of predicted,
New York Heart Association class IIIb or IV
symptoms for at least 45 of the 60 days before enrollment, or
intra-aortic balloon pump dependence for a period of 7 days
or on inotropes for at least 14 days before enrollment. A total
of 200 patients were randomly assigned in a 2:1 ratio to a
continuous-flow LVAD or a pulsatile-flow LVAD. The
primary end point of the study was the composite of 2-year
survival free of stroke and reoperation to replace the device.
Quality of life was also assessed. The mean left ventricular
ejection fraction was 0.17, and close to 80% of the patients
were on intravenous inotropes at entry; >20% were on an
intra-aortic balloon pump. In this study, 46% of patients in
the continuous-flow second-generation LVAD group and
only 11% of the pulsatile-flow first-generation LVAD group
reached the primary end point \((P<0.001)\). The quality of life
improved significantly from baseline in both groups. In
addition, there was a 38% reduction in the number of
hospitalizations in the continuous-flow patients compared
with the pulsatile device patients. Interestingly, the survival
curve of the older first-generation pulsatile LVAD group was
unchanged from that reported in the REMATCH trial. That
survival with medical therapy alone for late-stage heart
failure patients may not have changed substantially since
2001 is supported by the Investigation of Nontransplant-
Eligible Patients Who Are Inotrope Dependent (INTeEPiD)
study, reported in 2007.\(^7\) This observational study examined
a group of noncandidates for transplantation who could not be
weaned from inotropic therapy and were offered an LVAD.
Eighteen were not implanted because of either patient refusal
or unavailability of the LVAD. The important point here is
that the medical group survival (no LVAD) is extremely poor
and comparable to that of the medical treatment group in
REMATCH.

Real-World Outcomes and Trends
The Interagency Registry for Mechanically Assisted Circula-
tory Support (INTERMACS), a National Heart Lung and
Blood Institute–sponsored collaborative database, analyzes
US Food and Drug Administration–approved durable MCS
device implantations in the United States.\(^8\) This database now
includes >4000 MCS implantations from June 23, 2006,
through June 30, 2011. MCS centers in the United States
designated by the Centers for Medicare and Medicaid Ser-
dices as destination therapy (DT) centers are required to enter
all implantations for durable devices into the INTERMACS
database. The third INTERMACS report focused specifically
on DT patients, and the recently published fourth report
updated these analyses.\(^9\)\(^-\)\(^10\) The INTERMACS registry clas-
sifies patients as DT if they have no option to recover
end-organ function and will likely remain transplantation
ineligible. The third INTERMACS report in 2011 outlined
outcomes for 385 DT patients and reported that advanced age,
renal dysfunction, and a high body mass index were the
principal reasons for this classification.\(^9\) Available longer-
term follow-up of DT patients was mostly for those who
received the first-generation device and demonstrated a dis-
appointing 61% and 39% survival at 1 and 2 years, respec-
tively. However, for the continuous-flow device group, the 1-year survival was already approaching 75%, indicating the marked benefit of the newer technology. The more recent fourth INTERMACS report described a marked increase in device placement as DT. In the 4 years including 2006 to 2009, 135 DT devices were placed; 464 were placed in 2010; and 248 DT devices were placed in the first 6 months of 2011. This DT indication proportionally represents 34% of all devices placed in the United States from January to June 2011. The results at 1 year for those implanted with continuous-flow devices as DT (n=740) demonstrate that 74% are alive with a device in place, 3% transition to transplantation candidacy, and 1% recover.

Park and colleagues performed an observational investigation in 281 patients who underwent continuous-flow LVAD placement for DT from May 2007 to March 2009 and compared this cohort with an early group of 133 continuous-flow LVAD patients from March 2005 to May 2007. Patient entry criteria were the same during the 2 time periods. The more recent group had reduced adverse event rates for bleeding requiring transfusions (1.66 versus 1.13 events per patient-year; \( P<0.001 \)), sepsis (0.38 versus 0.27 events per patient-year; \( P=0.025 \)), device-related infections (0.47 versus 0.27 events per patient-year; \( P<0.001 \)), and hemorrhagic stroke (0.07 versus 0.03 events per patient-year; \( P=0.01 \)). Other event rates, including ischemic stroke (0.06 versus 0.05 events per patient-year; \( P=0.57 \)), were similar between groups. Survival at 1 year in the contemporary group was 73%, similar to that reported by the aggregate INTERMACS database.

Importantly, there is evidence of durability beyond the first year, as noted by the >70% survival at 2 years in the INTERMACS database. Thus, the Continuous Access Protocol and Post Marketing real-world experience points to the consistency of a large increase in survival in the patients with as much as an absolute improvement in survival of >10% compared with the index study cohort.

These outcomes with continuous-flow LVADs are clearly better than those with medical therapy alone, exhibit durability of benefit beyond 1 year, and are sufficient to consider this therapy the standard of care for patients with advanced refractory heart failure and no option for transplantation.

**Concept of Bridge to Candidacy**

One of the most vexing dilemmas encountered by clinicians is the “gray zone” in which current comorbidities render a patient ineligible for cardiac transplantation but there is the possibility of sufficient physiological improvement after hemodynamic support to make the patient a transplantation candidate. With LVAD-based hemodynamic unloading, patients exhibiting pulmonary hypertension or profound hepatorenal dysfunction often demonstrate recovery of these organ systems. In the absence of reasons for permanent ineligibility for transplantation such as advanced age or complex diabetes mellitus, patients are often classified into this category of bridge to candidacy. The INTERMACS report outlines that 38% to 40.5% of all devices placed in 2010 to 2011 (first 6 months) were in this category, making this the most commonly listed indication at the time of LVAD implantation. At 1 year, 56% remained on a continuous-flow device, 26% were successfully transplanted, and 17% died. Figure 1 depicts the dramatic advances in survival with LVAD therapy compared with treatment for advanced heart failure. Figure 2 outlines the proportion of MCS devices placed in transplantation-ineligible patients and their clinical outcomes.

**Selection of the Appropriate Patient for Lifetime MCS Therapy**

Today, permanently (DT) or currently (bridge to candidacy) transplantation-ineligible patients form the dominant indication groups for durable lifetime MCS in the United States.
Although the rate of MCS as a bridge to transplantation has not changed, 75% of all permanent MCS implantations in the US are now in the non-transplantation-eligible population at the time of decision.\textsuperscript{10} However, as this population of advanced heart failure patients continues to grow, the appropriate use of lifetime MCS will become an important decision as a standard of care. In this regard, it is vital that clinicians develop decision rules that allow them to select patients appropriately. A critical problem encountered early in the course of application of this therapy was the use in patients who were “crashing and burning,” those in cardiogenic shock. Such patients were uniformly less likely to benefit from MCS than more stable patients (INTERMACS 2 and 3 as opposed to INTERMACS 1).\textsuperscript{14} Similarly, the use of LVADs in “less sick” (INTERMACS 5 and above) patients is also not supported at this time. Although the HeartMate II trial enrolled New York Heart Association class IIIB patients, current data do not provide sufficient justification for use of permanent MCS in these patients.\textsuperscript{17–19} Such patients were difficult to classify, and although those enrolled in the clinical trials were often on chronic inotropic support, this treatment is not well supported for ambulatory non–inotropic therapy–bound patients with advanced heart failure.

Increasing survival and improving outcomes with the current generation of continuous-flow devices have led to sufficient equipoise that the National Heart, Lung, and Blood Institute has supported the Randomized Evaluation of VAD Intervention Before Inotropic Therapy (REVIVE-IT) study to investigate the feasibility and usefulness in ambulatory advanced heart failure patients who have not yet reached the point of inotropic support.\textsuperscript{15} We believe that the best outcomes will be achieved by appropriate referral of patients to specialized centers. There is evidence that centers with well-coordinated MCS teams that provide comprehensive care achieve the best outcomes. To avoid the poor results caused by preimplantation organ dysfunction, referral to an MCS center should be contemplated early.\textsuperscript{16} Clinicians must change their mindset typically from one focused solely on symptom-directed management to one that amplifies prognosis as a vital consideration, even when reasonable temporary symptom control is manifest. Thus, simple algorithms that facilitate early referral to specialized centers that offer team-based advanced therapy should be used\textsuperscript{16} (Figure 3).

### Economic Considerations

The use of LVADs is extraordinarily expensive and occurs in an era of great fiscal stress. In a recent analysis of MCS in DT indications, Rogers and colleagues\textsuperscript{20} constructed a Markov model to assess cost-effectiveness. Survival, hospitalization rates, quality of life, and cost data were obtained for advanced heart failure patients treated medically or with a continuous-flow LVAD. They demonstrated that compared with medically managed patients, the incremental cost-effectiveness ratio of the continuous-flow device was $198,184 per quality-adjusted life-year and $167,208 per life-year. Thus, the technology continues to be more expensive than the conventionally accepted incremental cost-effectiveness ratio threshold of $50,000 derived from data using chronic renal replacement therapy.\textsuperscript{21} However, medical expendi-
The Future of MCS in Transplantation-Ineligible Advanced Heart Failure

Improved Device Technology

Continued improvements in MCS systems are occurring and are likely to broaden the indications for implantation. Smaller devices are being developed. Systems that can be completely implanted would be a major advancement by reducing infection risk and improving the quality of patients’ lives. MCS that uses a wireless energy transfer will reduce the high risk of driveline infections and provide greater mobility and thus better quality of life for patients. Ultimately, a practical total cardiac replacement that is fully implantable, highly reliable, and responsive to changing patient cardiac output needs would complete the evolution.22 Perhaps the greatest challenge that remains of concern is in neurological outcomes with current MCS devices, a morbidity that has not improved despite the advent of newer devices. This requires further study.23

Alternatives to MCS

Heart failure represents the final common pathway of a number of diseases and will continue, despite advances in intervention, to be a major cause of disability and death with a large number of such patients transitioning to advanced heart failure syndromes.24 The size of the donor pool will not increase sufficiently to make allogeneic transplantation more than of limited public health significance.25 In fact, there has been no increase in the number of organ donors in the past decade; therefore, heart transplantation is never likely to offer...
a widespread solution for the continually increasing number of patients with advanced heart failure. Crossing the HLA barrier and allowing xenotransplantation is a distant goal, and stem cell–based cardiac regeneration remains in its infancy, although its apparent potential is exciting.26,27 It is conceivable that combining cell-based therapy with MCS devices may offer incremental hope for potential myocardial recovery, a concept under scrutiny as part of the Clinical Cell Trial Research Network, funded by the National Heart, Lung, and Blood Institute.

Thus, in the foreseeable future, advances in MCS will form the backbone of the standard of care in appropriately selected patients with advanced refractory heart failure.

Disclosures

Dr Mehra serves as chairman of the Data and Safety Monitoring Board for the REVIVE-IT Study, funded by the National Heart, Lung, and Blood Institute. In addition, he reports consulting income from St. Jude’s, Medtronic, Abbott Vascular, Johnson & Johnson, and the American Board of Internal Medicine. Dr Domanski reports consulting income from CardioMems.

References

Response to Mehra and Domanski

Anjali Tiku Owens, MD; Mariell Jessup, MD

We appreciate Drs Mehra and Domanski’s overview of the history and evolution of left ventricular assist devices. We agree that newer-generation devices have demonstrated increased durability compared with first-generation pulsatile devices and that purely medical management of advanced heart failure has remained disappointingly stagnant. However, as acknowledged by the authors themselves, mechanical circulatory support is successful only in “well-selected patients with refractory heart failure,” which is a far cry from stating that mechanical circulatory support is a substitute in all patients who are not eligible for heart transplantation. They further acknowledge the critical importance of distinguishing which patients have a need for permanent biventricular support, which is not feasible with current mechanical circulatory support device technology and Food and Drug Administration regulations. They outline the limited survival data for destination therapy patients, available in the latest Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) report, and the high societal cost of this therapy. Furthermore, they acknowledge the continued, unimproved rate of neurological complications with newer-generation left ventricular assist devices. In conclusion, although Drs Mehra and Domanski provide an accurate historical picture of the mechanical circulatory support landscape and an optimistic outlook for future advances, they do not provide convincing evidence that left ventricular assist devices should be standard of care for transplantation-ineligible patients. Heart failure is primarily a disease of elderly patients with multiple comorbidities; the majority of patients with heart failure would not be well served by either transplantation or left ventricular assist device implantation, but a renewed focus on quality of life.
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