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Mechanical Circulatory Support: Registering a Therapy in Evolution

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Introduction

The development of durable mechanical circulatory support systems paralleled the expansion of cardiac transplantation. The National Institutes of Health sponsored grants in the 1980s to develop implantable left heart assist systems; 20 years later they contracted for a national registry to track the clinical evolution of this new technology, INTERMACS (Interagency Registry for Mechanical Assisted Circulatory Support). INTERMACS has refined the classification of NYHA Class IV heart failure, standardized adverse event definitions, and explored outcomes of device type, location and strategy. The majority of mechanical circulatory support patients are between the ages of 50 and 70 years, and about 90% of patients prior to implant are in the highest levels of clinical instability. Six month survival following device implant is 75%, but increases to 80% among those not in shock at implant. Patients who require bi-ventricular support have decreased survival. As longer term outcomes are analyzed, improved outcomes may justify triage of high risk patients awaiting heart transplantation to chronic mechanical circulatory support.

Developmental History of Mechanical Circulatory Support

The application of mechanical circulatory support in animal experiments can be traced back to the work of Carrel and Lindberg in the 1930s. (1,2) With the initial foray into open-heart surgery in the 1950s (3,4), the stage was set for application of more prolonged mechanical support for myocardial recovery in situations of failure to wean from cardiopulmonary bypass. Although initial reports of successful recovery utilized roller-pump technology (5), their applicability was limited by issues of blood trauma and difficulties in modulation of pump speed in response to changes in left atrial and left ventricular pressure. The first clinical application of a pneumatically driven ventricular assist device (VAD) is attributed to DeBakey in 1966, in which a 37-year old woman was successfully supported for 10 days with a paracorporeal circuit following complex cardiac surgery (6).

The NHLBI artificial heart program has invested more than 400 million dollars over 4 decades in targeted contracts and grants pursuing durable mechanical circulatory support (10). Establishment of the program in 1964 called for the development of short and long-term circulatory assist devices as well as cardiac replacement pumps. During the 1970s,

targeted requests for proposals were issues for the development of specific components for ventricular device systems. Disappointing results of the first total artificial hearts and the increasing problem of deaths on the heart transplant waiting list shifted the focus to the development of devices that could support patients awaiting appropriate donor hearts. In 1980, the NIH invited proposals to develop an “implantable, integrated, electrically powered left heart assist system” that could allow extensive patient mobility.

These collaborative efforts between scientists, device engineers, and the heart transplant community culminated in the successful application of the Novacor (World Heart Corp., Oakland, CA) left ventricular assist system as a bridge to cardiac transplantation in 1984 (7). This was followed by the Pearce-Donachey paracorporeal pneumatic VAD system (8) and in 1992 the successful bridging with the implantable pneumatic HeartMate VAD (ThermoCardiosystems Thoratec, Pleasanton, CA) (9). Despite the clinical focus on bridging therapy to transplantation, the circulatory support scientific community was clearly targeting the development of devices capable of long-term circulatory support. The Randomized Evaluation Of Mechanical Assistance For The Treatment Of Congestive Heart Failure (REMATCH) provided the scientific impetus for FDA approval of the HeartMate Vented Electric ventricular assist device as so-called “Destination” therapy in 2002, followed by Medicare approval of this device in 2003 for reimbursement as a permanent implant. The stage was set for multiple clinical trials of devices introduced for the purposes of long term durable mechanical circulatory support.

As newer generation devices were introduced into clinical trials, an entire vocabulary surfaced to describe the evolution of these devices. The term “first generation” refers to the pulsatile, positive displacement pumps introduced into clinical practice during the decade of the 1990s. “Second-generation” blood pumps (rotary pumps with contact bearings or seals) included such devices as the Jarvik 2000 introduced in 1999, the HeartMate II axial flow pump introduced in 2000, and the DeBakey Micromed pump, which entered clinical trials in 1998. “Third-generation” (rotary pumps without mechanical touching bearings) pumps currently entering clinical trials include both axial flow and centrifugal flow devices.

Framing the Current Challenge

As early as 1991, the Institute of Medicine recognized the importance of detailed longitudinal data on patients receiving long-term mechanical circulatory support, “Patients should be followed through a registry for the remainder of their lives...Maintaining a registry of recipients should be considered a routine aspect of this care. The committee recommends that NHLBI support long-term follow-up studies...(11)”. Once FDA had approved a left ventricular assist device for long-term support, the dawn of ventricular assist devices as a serious therapy for advanced heart failure had arrived.

With this development, the challenge of allocating therapies for patients with truly advanced heart failure was confounded by additional choices. The scientific community had long appreciated the need for thorough evaluation of such devices over a prolonged period in order to judge not only their utility but also the associated adverse outcomes. Unfortunately, collection of rigorous outcomes data with unified definitions for adverse events lagged behind device development.

With the clinical reality of durable devices, the design of prospective studies to define their role is complicated by the complex decision-making process that is required in the application of expensive, potentially life-threatening as well as life-saving therapies to higher risk patients. The experience at one or even a few institutions is too small for meaningful analyses, and the relevant variables describe a complex and diverse patient population, which further confounds trial design.

The critical need for secure information about this evolving therapy generated the demand for rigorous data collection which included the following elements: a core group of variables that are collected over time at all institutions; uniform definitions of adverse events that are agreed upon and applied at all centers; and methods of assuring that essentially all patients are entered at each institution to minimize bias.

NIH Initiative

The NHLBI issued a Request for Proposals to develop a national database for durable mechanical circulatory support devices. In 2005, the 5-year contract was awarded to a collaborative group including the University of Alabama and a broad panel of experts previously assembled under the sponsorship of the Mechanical Circulatory Support Device section of the International Society for Heart and Lung Transplantation. Lessons gleaned from a preliminary Mechanical Circulatory Support Database were instrumental in guiding the design of the database. (12). The contract led to the formal creation of INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support), a United States national registry for patients who receive durable mechanical circulatory support device therapy to treat advanced heart failure. The rapidly evolving intersection of needs for scientific progress, individual program development, and quality assurance for both centers and industry is reflected in the unprecedented collaboration of multiple agencies. The registry was thus devised as a joint effort among the National Heart Lung and Blood Institute, the Centers for Medicare and Medicaid Services, the Food and Drug Administration, clinicians, scientists, and industry representatives. The goals of the INTERMACS registry are listed in Table 1. Through the broad committee structure and the commitment of its participants and partners, the potential exists to define the totality of mechanical circulatory support device experience, including durable devices intended for long-term therapy, bridge-to-transplantation, and bridge-to-recovery.

Candidates for Mechanical Circulatory Support

For patients reaching the advanced stages of heart failure, three general categories of therapy have emerged, with evolving indications for each: medical and standard surgical procedures, including electrical therapies; cardiac transplantation; and durable mechanical circulatory support. Only for cardiac transplantation is there currently an inclusive database from which outcomes can reliably be predicted for individuals as well as populations. For this overall population, a survival approaching 60% at 10 years is now anticipated, and more specific predictions can be generated for individual patients based on age, renal function, other parameters, and donor characteristics. Estimates of survival with medical and electrical therapies for heart failure largely derive from small selected populations for randomized trials, which are not representative of broader populations, particularly those with more advanced disease. Ongoing trials of surgical reconstructive therapies will be characterized by similar limitations. As the field of circulatory support progresses, the decision-making process for its application will likely require a database of comparable advanced heart failure patients treated medically for whom data is collected that would mirror the data elements collected longitudinally in device and transplant recipients.

Profiles of Disease Severity

Current indications for mechanical circulatory support relate generally to the adequacy of perfusion and organ function, with specific criteria when devices are implanted as long-term therapy in patients not anticipated to be eligible for cardiac transplantation (Table 2). Class IV New York Heart Association symptoms of heart failure have been a major descriptor of disease severity for VAD consideration, but it has become recognized that this encompasses different levels of clinical compromise. As a first step in refining the severity of heart failure

which triggers application of mechanical circulatory support, INTERMACS has incorporated a sub-classification of clinical profiles that provides more description of the time course and acuity of decompensation at the time of implantation (Table 3).

Device Strategies

Although the device industry has always targeted the development of devices capable of long-term circulatory support, patients requiring support for a limited period of time until transplantation provided an opportunity for devices to be introduced first as temporary therapy, to “bridge” to transplantation. Nearly 20 years would elapse before FDA and subsequently CMS issued approval of the first device (Heartmate XVE) for so-called “destination therapy”. Some patients receiving these devices as destination therapy later became suitable candidates for transplantation. On the other hand, some transplant candidates receiving devices may become ineligible, and thus retain their devices as permanent therapy. Thus the ambiguities of device strategy become apparent. Although currently required for reimbursement purposes, the clinical distinction between specific pre-implant strategies becomes obscure since many patients do not clearly fit one strategy or the other, and may receive devices as “bridges to decision”. These gradations in strategy are captured before and at intervals after implantation, as shown in Table 4. Furthermore, the initial intent at the time of implantation has not been seen to have a major impact on the actual outcome of survival during the time the device is in place (Figure 2).

Current VAD Outcomes

Survival

During the first 18 months of data collection, over 300 patients were entered into the INTERMACS database. The age distribution, initial strategy of implant, and the patient profile level are depicted in Tables 3,4,5. The majority of mechanical circulatory support patients are between the ages of 50 and 70 years of age and about 90% of patients are at INTERMACS level 1,2,3 (Class IV on intravenous inotropic therapy). The 6 month survival while supported on a device was approximately 75% (Figure 1) with no difference whether initial strategy was bridge to transplant or as permanent therapy (Figure 2). Survival with circulatory support devices increases to about 80% at 6 months for patients not in critical cardiogenic shock (level 1) at time of implant (Figure 3). However, patients who required support of both ventricles fared significantly worse than those receiving isolated left ventricular support (Figure 4). It is not yet known to what extent this results from worse underlying disease or from increased morbidity due to two devices.

Standardizing Adverse Event Definitions

Every therapy designed to increase survival must be judged in part not only by those events or complications that diminish survival but also by those that help define the quality of life anticipated. For device therapy, the critical adverse events include device malfunction or failure, neurologic events, and infections. During the developmental years of mechanical circulatory support, outcome analyses were confounded by the absence of uniform definitions among all investigators and industry sponsors. During the development of the INTERMACS database, surgeons experienced with mechanical support devices, advanced heart failure cardiologists, industry stakeholders, and the FDA worked in concert to pioneer precise definitions of all major adverse events collected in the INTERMACS database. The 17 adverse events defined and collected are listed in Table 6. From the early analyses, about 10% of patients developed significant device malfunction within the first 6 months. The most frequent causes implicated in deaths were cardiovascular failure, central nervous system events, infection, liver failure, and respiratory failure (13). It is hoped that the

precision and consensus underlying these definitions will level the playing field and accelerate the reduction of complications for current and future device development.

Triage From Transplantation

Based on current information, some patients might be triaged from the heart transplant waiting list to long-term mechanical circulatory support. A secure recommendation awaits longer-term followup of current mechanical circulatory support devices, particularly axial flow and centrifugal flow pumps not yet FDA-approved. The presence of multiple non-cardiac co-morbidities impairs long-term survival following cardiac transplantation, as quantified in analyses from the cardiac transplant research database (CTRD) (Figure 5). When longer term follow-up is available on axial flow and centrifugal flow pumps now in clinical trials, triage of some patients from transplant lists to long-term device therapy may be considered. This may provide an avenue for the rational allocation of certain patients away from transplantation toward long term mechanical circulatory support. This would potentially provide an important benefit for sensitized patients who endure very long waiting times while continuing to suffer from advanced heart failure symptoms. Furthermore, allocation of donor hearts to recipients with fewer life-limiting co-morbidities would increase the survival utility of the precious and limited resource of donor hearts.

Future Device Development

One of the stated goals of the INTERMACS initiative is the facilitation of new effective device development. Some of the durable devices approved or in development are listed in Table 7. Although the accepted approach for evaluation of new therapies includes a randomized clinical trial, many aspects of durable device therapy complicate the design and interpretation of such trials. The evolution of new devices, changing medical therapy for advanced heart failure, the importance of patient-specific variables on outcome, and the considerable expense of randomized trials all argue for a rigorous database that could be used to generate objective performance criteria in non-randomized studies or to provide concurrent patients to serve as a control arm for direct comparisons. To that end, INTERMACS has been designed to include elements of study quality which approach that of a good clinical trial, including inclusion criteria, all-inclusive patient enrollment, adverse event definitions and adjudication, complete data entry and follow-up, local certification of investigators, a study monitoring board, and prospectively planned analyses. Outcomes affecting both survival and quality of life lie at the core of new device evaluation. For example, it remains to be determined whether adverse effects will result from the chronic effects of low pulsatility with new rotary pumps. Will the lack of a bail out hand-pumping system be a major deterrent? Will drive-line failure or accidental damage become a serious Achilles' heel of new rotary pumps? Only with detailed formal long-term data collection can these issues be answered with confidence.

Since the initiation of the NHLBI sponsored INTERMACS program to collect comprehensive data on durable mechanical circulatory support devices in the United States, the number of participating centers has steadily increased. (Figure 6). This has been facilitated by the requirement of CMS that all designated designation therapy centers must enter their mechanical circulatory support data into INTERMACS. However, longer-term follow-up will be crucial. The obligatory delay between the introduction of new devices into clinical trials and their subsequent FDA approval will further delay the aggregate data analyses necessary to demonstrate appropriate survival with device therapy for specific patient subsets, and to match the appropriate device to an individual patient's physiologic and functional needs.

Finally, it is increasingly recognized that certain pathophysiologic consequences of truly advanced heart failure are harbingers of high subsequent mortality with more than one approach to therapy. Just as pulmonary hypertension can increase the risk of mortality with both medical therapy and heart transplantation, right ventricular failure increases mortality with medical therapy and mechanical circulatory support. The cardio-renal syndrome is increasingly central to patient evaluation, as renal dysfunction that does not reverse is a major predictor of increased complications and mortality with all medical and surgical therapies for advanced heart failure. Thus, a major focus of current and future research will be the clinical indicators in advanced heart failure which portend a poor survival with standard heart failure therapies, and should trigger the timely consideration of device therapy in order to maximize the benefit realized from this rapidly evolving technology.

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INTERMACS Implant Dates: June 23, 2006 – August 31, 2007

Figure 1.

Kaplan-Meier survival curve after device implant. Patients are censored at time of transplant or explant. (12)

INTERMACS Implant Dates: June 23, 2006 – August 31, 2007

Device Strategy at Implant

Figure 2.

Kaplan-Meier survival stratified by device strategy at implant. BTT = device implantation intended as “Bridge to transplant”; Dest = device as permanent or “destination” therapy. Patients are censored at transplant or explant. (12).

INTERMACS Implant Dates: June 23, 2006 – August 31, 2007

Patient Profile at Implant

Figure 3.

Kaplan-Meier survival stratified by patient profile at implant, defined as in Table 3.

Depiction is as in Figure 2. Patients are censored at transplant or explant. (12).

INTERMACS Implant Dates: June 23, 2006 – August 31, 2007

Device Type

Figure 4.

Kaplan-Meier survival stratified by device type. Depiction is as in figure 2. Patients are censored at transplant or explant. (12).

Figure 5. Survival after cardiac transplantation in the Cardiac Transplant Research Database (CTRD) for four patients transplanted as UNOS Status II (stable outpatient). The curves represent solutions of the multivariable risk factor analysis for death. One goal of the INTERMACS registry is to generate similar curves for VAD outcomes according to similar baseline profiles.

INTERMACS: Patient Accrual

Figure 6.

Graph depicting projected patient accrual in the INTERMACS database of approved devices.

Table 1
GOALS of the Registry

-
- Facilitate the refinement of patient selection to *maximize outcomes* with current and new device options.
 - Identify predictors of good outcomes as well as risk factors For adverse events after device implantation.
 - Develop consensus “best practice” guideline to improve clinical management by reducing short and long term complications of MCSD therapy.
 - Utilize Registry information to guide improvements in technology, particularly as next generation devices evolve.
 - Guide clinical testing and approval of new devices.

Table 2
Common Indications* for Mechanical Circulatory Support[#]

1	Bridge to transplantation (for patients with such severe reductions in cardiac output or non-cardiac co-morbidities that survival and successful cardiac transplantation are unlikely without mechanical circulatory support)
	<ul style="list-style-type: none"> • Impending cardiogenic shock despite inotropic support $\pm$ IABP • Acute renal dysfunction (creatinine >2.0) that is deemed secondary to insufficient renal blood flow and is poorly responsive to inotropic support. • Pulmonary hypertension (PA systolic pressure >60) that persists despite optimal medical and inotropic therapy and is presumed to have a reactive component that would respond to prolonged normalization of left atrial pressure (with MCS therapy)
2	Bridge to Recovery (for patients with otherwise fatal low cardiac output in situations where recovery is possible or probable)
	<ul style="list-style-type: none"> • Acute myocardial infarction complicated by cardiogenic shock • Acute myocarditis with shock • Acute cardiac failure following cardiac surgery
3	Long-term device therapy (for patients with 1 or more major contraindications to cardiac transplantation)
	<ul style="list-style-type: none"> • Class IV heart failure with chronic, refractory and disabling heart failure symptoms despite optimal therapy
	<ol style="list-style-type: none"> 1. Peak oxygen consumption < 12-14 ml/k/min with cardiac limitation 2. Dependence on intravenous inotropic support
	<ul style="list-style-type: none"> • Class IV heart failure with expected mortality exceeding 50% in 1 year.

• IABP, intra-aortic balloon pump; PA, pulmonary artery;

• MCS, mechanical circulatory support

* The final patient disposition (permanent mechanical support, transplantation, or explant for recovery) after a given indication for implant may change over time due to evolving patient circumstances or condition.

[#] This table applies to durable devices with the potential for longer term implant and active patient ambulation.

Table 3
Patient Profile of Disease Severity at Implant (3/1/06 – 8/31/07) n=334

Intermacs Level (Pre-Implant)	n	% of 334
Critical cardiogenic shock	141	42%
Progressive decline	128	38%
Stable but inotrope dependent	29	9%
Recurrent advanced HF	20	6%
Exertion intolerant	5	2%
Exertion limited	4	1%
Advanced NYHA III	7	2%
Total	334	100%

Modified from INTERMACS Quarterly Report (13)

- 1. Critical cardiogenic shock**
- 2. Progressive decline**
- 3. Stable but inotrope dependent**
- 4. Recurrent advanced HF**
- 5. Exertion intolerant**

↖ Degrees
of Class
IV

Table 4
Intended Device Strategy at Implant (3/1/06 – 8/31/07)

Device Strategy at Implant	n	% of 334
Bridge to Recovery	18	5%
Bridge to Transplant	248	74%
Listed	137	41%
Likely to be listed	61	18%
Moderate likely to be listed	32	10%
Unlikely to be listed	18	5%
Destination Therapy	66	20%
Other	2	1%
Total	334	100%

Modified from INTERMACS Quarterly Report (13)

Table 5
Age of VAD Recipients (3/2/06-8/31/07)

Age at Implant (years)	n	% of 334
10 – 19	10	3%
20 – 29	26	8%
30 – 39	31	9%
40 – 49	59	18%
50 – 59	99	30%
60 – 69	91	27%
70 – 79	18	5%
Total	334	100%

Table 6
Major Adverse Events After VAD Implantation

-
- Arterial Non-CNS Thromboembolism
 - Bleeding
 - Cardiac Arrhythmia
 - Device Malfunction
 - Hemolysis
 - Hepatic Dysfunction
 - Hypertension
 - Major Infection
 - Myocardial Infarction
 - Neurological Dysfunction
 - Pericardial Collection
 - Psychiatric Episode
 - Renal Dysfunction
 - Respiratory Failure
 - Right Heart Failure
 - Venous Thrombosis
 - Wound Dehiscence
-

Modified from INTERMACS Quarterly Report (13)

Table 7
Examples of the Durable Mechanical Circulatory Support Devices (Approved or Emerging)

Device	Positive Displacement (Pulsatile)	Rotary		Total Artificial Heart
		Axial Flow	Centrifugal	
Extracorporeal				
Abiomed AB 5,000	x			
Thoratec PVAD	x			
Berlin Heart *	x			
Intracorporeal				
Heart Mate XVE	x			
Novacor	x			
Thoratec IVAD	x			
Heart Mate II		x		
Jarvik 2000 *		x		
Micromed DeBakey *		x		
CorAide *			x	
EvaHeart *			x	
HeartMate III *			x	
Heart Ware *			x	
Incor		x		
Terumo Dura Heart *			x	
VentrAssist *			x	
Abiocor *				x
CardioWest SynCardia				x

Devices that allow active ambulation and/or hospital discharge

* Not yet FDA approved in U.S.