Long-term mechanical circulatory support: could it really have a public health impact?

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Cardiovascular disease is a leading cause of death in North America and Europe, and heart failure represents a major component, affecting about 2.5% of the adult population [1, 2]. Ten percent of the heart-failure population experiences truly advanced heart failure, with limited long-term survival. For patients with New York Heart Association (NYHA) Class IV heart-failure symptoms poorly responsive to medical therapy, cardiac transplantation has dramatically improved the survival and quality of life, with a 2-year survival of 80% or more, and a median survival of >10 years [3].

Although cardiac transplantation represents the standard of care for eligible NYHA Class IV heart-failure patients, the limited availability of suitable donor hearts has restricted its application to about 2500 patients annually in North America and <1500 in Europe [3]. In Europe, in particular, despite the ongoing epidemic of heart failure, heart transplant activity has decreased since 2000 [3]. Thus, from a public-health perspective, cardiac transplantation exerts a minor impact on refractory Stage D heart failure.

Durable mechanical circulatory support (MCS), originally introduced clinically as bridge-to-transplant (BTT) therapy, gained acceptance as long-term ‘destination therapy’ (DT) in the USA following the REMATCH trial, in which the HeartMate XVE (Thoratec, Pleasanton, CA, USA) pulsatile pump produced superior survival compared with medical therapy for terminal heart-failure patients [4].

With the emergence and evolution of continuous-flow (CF) technology, these small, durable pumps have nearly completely replaced the bulky, noisy, infection-prone pulsatile systems. Europe, and Germany in particular, has led the way in the introduction and maturation of CF technology in clinical practice. The evolving landscape of MCS in the USA has been chronicled through Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), a database sponsored by the National Heart, Lung, and Blood Institute in a partnership with the Center for Medicare Services and the US Food and Drug Administration (FDA) [5].

Since the approval of HeartMate II by the FDA, pulsatile pumps have essentially disappeared from clinical practice for isolated left ventricular support. Following FDA approval of HeartMate II for BTT in 2008 and DT in 2010, the HeartWare ventricular assist device (HeartWare Corp., Framington, MA, USA) was approved for BTT in 2012. Since 2010, >99% of left ventricular assist devices (LVADs) implanted in the USA have employed CF technology [6]. In 2012 alone, nearly 2500 CF pumps were implanted in the USA, essentially equaling the total number of heart transplants [7]. The dramatic increment in survival with CF pumps compared with pulsatile systems is reflected in the US INTERMACS experience since 2006 (Fig. 1). The 1- and 2-year survivals in the current era approach 80 and 70%, respectively.

Of course, the majority of these pumps are currently implanted as BTT and therefore, do not directly expand the surgical support/replacement options for end-stage heart failure. The spectrum of intended use of MCS is perhaps more easily examined in the USA than Europe because of the US regulatory requirement (possibly a disadvantage to clinicians) to commit to a strategy of either long-term permanent LVAD support (DT) or BTT at the time of implant. The approval of a CF pump for DT in the US set the stage for an increased surgical impact on advanced heart failure over that of heart transplantation alone. Between 2006 and 2011, DT implants represented only 18% of total LVAD implants in the USA; but in 2012, over 40% of implants were DT! [7]

The artificiality of such designations is highlighted by the spectrum of ‘commitment’ to transplantation among centers/physicians implanting ventricular assist devices (VADs) for BTT over the past 4 years in the USA. Table 1 depicts the varying levels of commitment to transplant under the general category of BTT [7], so much so that a totally ‘unofficial’ category of bridge to candidacy has emerged as a new part of the strategy repertoire. Even more indicative of the fluid nature of these designations is the movement of patients from one category to another as time elapses since implant, consistent with the well-known tendency for comorbidities to be modified by the haemodynamic impact of the VAD itself [5].

The platform for the expansion of long-term MCS is currently limited by the requirement for such patients in the USA to be transplant ineligible, a stipulation appropriate for a technology whose mid-term survival has never been competitive with cardiac transplantation. Recently, however, the door for including transplant-eligible patients has at least been unlocked, if not yet actually opened. Analyses from INTERMACS have identified patient subsets within the current DT population (generally poorer risk patients who have contraindications to transplantation) whose survival is 80% at 2 years, representing about 20% of non-urgent DT implants [8].

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Despite the improving survival, device complications continue to challenge clinicians. Major adverse events associated with MCS include stroke, driveline, pump, pocket infection and gastrointestinal bleeding. Device malfunction is uncommon, with continuous-flow pumps experiencing an event rate about half that of earlier pulsatile iterations [7]. Approximately 95% of CF device patients remain free from major device malfunction at 2 years [7].

The rare event of pump thrombosis may begin insidiously as recurrant then increasing haemolysis, spikes in power utilization and, if not reversed, can lead to pump thrombosis and cessation of function. The precise delineation of risk factors and the possible circumstances that may facilitate this catastrophic event are incompletely understood.

A major neurological event is perhaps the most devastating complication, potentially destroying the coveted opportunity to replace the suffocating symptoms of the heart-failure malady with a greatly improved quality of life. Since all current CF pumps are inherently thrombogenic, neurological events may relate to intracavitary thrombosis or anticoagulation-associated intracerebral haemorrhage.

INTERMACS studies in 2010 revealed that patients fared less well when durable pumps were implanted in the throes of cardiogenic shock [9]. To examine the impact of varying levels of NYHA Class IV heart failure, INTERMACS investigators introduced a grading system that included five levels of Class IV heart failure and two additional levels characterizing advanced NYHA Class III symptoms [10]. More recent studies have verified the independent incremental risk introduced by implanting these devices in the presence of rapid circulatory decline or shock [7]. These findings support the current evolution towards the initial support of patients in shock with temporary MCS systems, which can provide initial stabilization before converting to a durable device.

Although the quality of life and functional outcomes after VAD implantation remain under-evaluated, available data from INTERMACS indicate major benefit in overall life satisfaction, self-care and activities of daily living during the first year [7]. The degree to which the signature of the ‘adverse event burden’ for patients receiving MCS therapy differs qualitatively from the adverse event profile after cardiac transplantation or the symptom complex of recurrent advanced heart failure will also influence patient and physician acceptance.

So, the heart-failure world is poised to open the clinical ‘laboratory’ to studies that explore, scrutinize and analyse trials and protocols that apply this technology to patients with somewhat

**Figure 1:** Actuarial survival for primary LVAD implants, stratified by continuous-flow pumps vs pulsatile-flow pumps. INTERMACS: Interagency Registry for Mechanical Assisted Circulatory Support; BiVAD: biventricular assist device; DT: destination therapy; BTT: bridge to transplant.

**Table 1:** VAD implants: INTERMACS: June 2006–June 2012

<table>
<thead>
<tr>
<th>Device strategy at time of implant</th>
<th>Implant date period</th>
<th>Total, n (%)</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Pre-2011, n (%)</td>
<td>2011, n (%)</td>
</tr>
<tr>
<td>BTT listed</td>
<td>1545 (39.8)</td>
<td>421 (22.6)</td>
</tr>
<tr>
<td>BTT likely</td>
<td>994 (25.6)</td>
<td>417 (22.4)</td>
</tr>
<tr>
<td>BTT moderate</td>
<td>392 (10.1)</td>
<td>186 (9.9)</td>
</tr>
<tr>
<td>BTT unlikely</td>
<td>127 (3.2)</td>
<td>75 (4.0)</td>
</tr>
<tr>
<td>Destination therapy</td>
<td>714 (18.4)</td>
<td>725 (38.9)</td>
</tr>
<tr>
<td>BTR</td>
<td>57 (1.4)</td>
<td>16 (0.8)</td>
</tr>
<tr>
<td>Rescue therapy</td>
<td>33 (0.8)</td>
<td>9 (0.4)</td>
</tr>
<tr>
<td>Other</td>
<td>14 (0.3)</td>
<td>12 (0.6)</td>
</tr>
<tr>
<td>Total</td>
<td>3876 (100.0)</td>
<td>1861 (100.0)</td>
</tr>
</tbody>
</table>

Modified from Kirklin et al. [7].

VAD: ventricular assist device; BTT: bridge to transplant; BTR: bridge to recovery.
less-than end-stage heart failure (US REVIVE-IT Trial) [11] and those transplant-eligible patients whose comorbidities elevate the transplant risk or the expected wait time.

All stakeholders in the world of MCS share the excitement and commitment to extend the virtues of added duration and quality of life established through cardiac transplantation to patients treated with current- and future-generation pumps. If these goals can be even partially realized, MCS therapy can stand side-by-side with cardiac transplantation in a synergism of surgical therapies for advanced heart failure.

If we are good shepherds of the appropriate expanded application of this expensive therapeutic paradigm, the next decade may, for the first time, witness a real surgical public health impact on patients suffering from refractory advanced heart failure.

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REFERENCES


