Continuous flow blood pumps: the new gold standard for advanced heart failure?

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Consider the familiar phrase ‘cardiac transplantation sets the gold standard for the treatment of severe heart failure’. Does this still ring true? For the advanced heart failure (AdHF) patient, the primary objective is to provide symptomatic relief from intolerable breathlessness, lethargy and fatigue [1]. The secondary aim, conditional upon the primary objective being met, is to extend life. Neither is accomplished easily in refractory Stage D heart failure (New York Heart Association (NYHA) IV). Conventionally, at this stage, only cardiac transplantation or palliative care options remain. The former may offer symptomatic relief and extended life for a carefully selected minority [2]. In contrast, opiates or inotropes may accelerate death for the great majority. These patients typically experience at least three periods of hospitalization during their last 6 months of life. The costs of dying are considerable, and the end-of-life/dying trajectory notoriously difficult to predict for any individual [3].

Of >7 million heart failure patients in both North America and Europe, 60% have systolic dysfunction, 10% of whom are categorized Stage D. Twenty percent of these are younger than 65 years of age [4]. This amounts to between 100,000 and 150,000 potentially transplant-eligible patients in each of these continents with access to fewer than 2500 donor hearts per annum [5]. Also, because of the comorbidities, renal failure and pulmonary hypertension, few AdHF patients fulfill stringent cardiac transplant criteria [5]. For the individual who receives a donor heart, the outcome may prove miraculous. The UK’s first transplanted infant recently enjoyed her 25th birthday. Because of positive early results, there have been no randomized trials of cardiac transplantation vs the improved treatment strategies of the modern era [7]. Important evidence has emerged from registry data [8]. Transplant candidates are carefully selected for preserved renal function and pulmonary vascular resistance <2.5 Wood units [9]. Most centres have an age limit of 65 years, and waiting list mortality ranges between 8 and 10%. Increasingly, borderline-quality donor organs are being accepted, but may compromise outcomes [10]. United Network for Organ Sharing (UNOS) data question the value of transplantation for ambulatory patients who have yet to deteriorate to a critical low cardiac output state [8]. Given the improvements in medical and non-transplant surgical treatment, a clear survival advantage can only be defined for UNOS Status I patients who are hospitalized on inotropes or mechanical circulatory support (MCS) (Inter-Agency Registry for Mechanically Assisted Circulatory Support (INTERMACS) 1 or 2). Deng et al. [11] showed that Status II waitlisted patients who did not receive a donor heart had similar survival rates to those transplanted. One-year survival of UNOS Status II candidates exceeds the outcome of transplantation. Around 30% of Status II patients improved symptomatically and prognostically when managed by a specialist heart failure team. Shah et al. [12] showed that 1- and 3-year survival for Status II patients removed from the transplant waiting list were 100 and 92%, respectively. In a recent analysis of 22,385 transplanted patients, Kilic et al. [8] showed a 1-year survival of 85% and an overall median survival of 12.2 years. However, 58% died within 10 years, and for this group, mean survival was only 3.7 ± 3.3 years. Clear predictors of longevity were age <55 years, white race, younger donor age and short donor heart ischaemic time [8]. Factors associated with hospital mortality included the need for preoperative ventilation, a borderline donor heart, donor/recipient sex mismatch and prolonged donor heart ischaemic duration. Predictors of limited long-term outcome included diabetes, renal impairment, obesity and hypertension. These are characteristics found in the majority of patients with ischaemic cardiomyopathy [13]. This suggests that transplantation conveys only limited benefit for those with the commonest cause of heart failure. Therefore, given the rarity of the procedure, the bar is set low against a new gold standard.

Long-term (destination or lifetime) MCS has the potential to supersede transplantation by at least 20:1. The first-generation pulsatile left ventricular assist devices (LVADs) were designed to produce stroke volume at similar pulse rates to the native heart [14]. Originally intended as an alternative to transplantation, these now-obsolete pumps had limited mechanical reliability and unacceptable complication rates. Nevertheless, they successfully established an evidence base for symptomatic and survival advantages in comparison with medical treatment in NYHA IV patients [15]. Pump technology then changed markedly with the revelation that the pulse pressure is not a fundamental requirement for the human circulation [16]. It also became clear that modest increases in blood flow in the range of 3–4 l/min were effective in relieving symptoms and reversing both the humoral and cytokine changes of heart failure [17]. The new continuous flow blood pumps are miniaturized and more patient friendly, with lower complication...
rates (Fig. 1). Surgical methods have also improved, with considerably less perioperative bleeding or mortality. Implants can be done without cardiopulmonary bypass or with the use of minimal extracorporeal circulation [18]. As such, they provide an unrestricted ‘off-the-shelf’ approach to provide symptomatic relief and improved quality of life for those without access to transplantation.

One of the most dramatic LV AD effects is on pulmonary hypertension. Pulmonary artery pressure falls with secondary unloading of the right ventricle. Reduced central venous pressure relieves organ congestion and abdominal discomfort. Wieselthaler et al. [19] demonstrated that preoperative pulmonary vascular resistance up to 10 Wood units begins to decline after 3–4 days and reaches normal values <2.5 Wood units in all patients within 6 weeks. In parallel, the LVAD induces ventricular reverse remodeling with reduced dimensions and improvement in contractility [20]. This reversal of myocyte and myocardial dysfunction is critically important for selected patients with myocarditis and idiopathic dilated and post-partum cardiomyopathy where sustained improvement may allow LVAD removal [21].

Heart failure symptoms are so distressing that it is unreasonable and justifiably unethical to withhold any treatment with proven benefit [22]. In the proof of concept Randomised Evaluation of Mechanical Assistance for the Treatment of Congestive Heart failure (REMATCH) trial, the median survival for medically treated patients was 150 days [15]. Only 8% were alive at 2 years and remained housebound with breathlessness and fatigue in the interim. Since REMATCH, LVAD survival has improved progressively with better devices, appropriate patient selection and management strategies based on broad experience [23]. The continuous-flow LVADs are mechanically reliable, while new approaches are lessening the risk of thromboembolic and infective complications. The single most important difference to outcome has been made by employing elective low-risk surgery in chronic heart failure patients before presentation with cardiogenic shock [24]. Recent evidence from the INTERMACS annual report (2012) showed that continuous flow LVAD patients up to 70 years without shock, diabetes or renal failure had 1- and 2-year survival of 85%, at least as good as cardiac transplantation [25]. Survival between 3 and 5 years is achieved consistently and for as long as 7.5 years also [26]. Risk factors for poor outcome include implantation during cardiogenic shock, established right heart failure with secondary liver dysfunction as evidenced by elevated bilirubin, high body mass index, diabetes, older age and previous coronary bypass surgery [27]. The majority of these risk factors relate to terminal heart failure in INTERMACS Level 1 or 2 patients (hospitalized with inotropes or temporary MCS) who historically account for the vast majority of LVAD implants [28]. As the mechanical reliability and safety of LVADs improves, their unfortunate image as the last-chance and last-minute therapy for impending death is changing. When low-, medium-, high- and very high-risk category preoperative patients were reviewed in the pulsatile LVAD era, 1-year mortalities of 19, 38, 72 and 89% were recorded [27]. Again, in a more recent analysis of rotary blood pump patients from the INTERMACS database, Boyle et al. [24] showed a dramatic difference in 3-year survival between those operated urgently in cardiogenic shock (INTERMACS I) vs severely symptomatic but electively implanted ambulatory patients in INTERMACS Profiles 4–5 (51 vs 96%, P = 0.01). For inotrope-dependent patients in Profiles 2 and 3, the survival difference appeared substantial but failed to achieve statistical significance (69 vs 96%, P = 0.065). Electively implanted patients left hospital at a mean of 14 days vs 49 days for the cardiogenic shock survivors (P < 0.001). These and other studies emphasize that carefully considered patient selection together with well-timed surgery has an important impact on LVAD implant outcome and is the key to cost effectiveness.

Figure 1: Plain chest X-rays showing rotary blood pumps in clinical use. (A) Jarvik Flowmaker with skull pedestal power delivery. (B) Heartware VAD. Implantable defibrillator in place. (C) HeartMate II LVAD. Implantable defibrillator in place. (D) Berlin Incor. (E) MicroMed De Bakey VAD in a child. (F) Terumo LVAS.
Currently, the preferred candidates for lifetime circulatory support are those who are not yet hospitalized on inotropic therapy but are severely symptomatic and virtually housebound, with poor survival prospects [29]. For these patients, the wish for symptomatic relief from intractable symptoms is more important than uncertain prolongation of life.

With data accumulated from the UNOS and INTERMACS registries, well-defined patient criteria are emerging in relation to suitability for heart transplantation or lifetime LVAD recommendations to the patient [9, 29] (Table 1). In clinical practice, the ‘end-of-life’ for a given heart failure patient is not easily forecast by symptomatic status [3] (Fig. 2). Levels of breathlessness and fatigue do not differentiate between NYHA III and IV patients at imminent risk of death vs those who will survive for 1–2 years. Objective findings such as peak maximum oxygen uptake test or risk models such as the Seattle Heart Failure Score, may identify patients at high likelihood of death within the next 6–12 months, but most terminal patients managed by heart failure specialists experience multi-organ dysfunction syndromes with metabolic derangement, coma or sudden death, not congestion or dyspnoea [30]. By the time of metabolic derangement and cardiogenic shock, such patients are at prohibitive risk for any surgical procedure.

Goodlin’s graphic depiction of the unpredictability of AdHF (Fig. 2) serves to emphasize the difficulties of timing in cardiac transplantation given that only established Status I patients manifest survival benefit in the current era [11, 30]. The timing of elective LVAD implantation is far less critical since the native heart is preserved and continues to contribute to systemic blood flow.

Table 1: Severe heart failure refractory to medical management. Evidence based preferred patient characteristics for the treatment options cardiac transplantation, mechanical circulatory support and end-of-life palliative care (derived from references [8, 9, 11, 13, 24, 29, 31, 34, 35, 40])

<table>
<thead>
<tr>
<th>Demographic</th>
<th>Cardiac transplant</th>
<th>Rotary blood pump</th>
<th>Palliative care</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical candidate (frailty index)</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>[30, 35]</td>
</tr>
<tr>
<td>Age (years)</td>
<td>&lt;55</td>
<td>&lt;80</td>
<td>All age groups</td>
<td>[8, 25, 35, 40]</td>
</tr>
<tr>
<td>INTERMACS profile</td>
<td>1–2</td>
<td>3–5</td>
<td>1–6</td>
<td>[24, 25, 28, 29]</td>
</tr>
<tr>
<td>UNOS status</td>
<td>I</td>
<td>II</td>
<td>N/A</td>
<td>[9, 11]</td>
</tr>
<tr>
<td>Body mass index &gt;35 kg/m²</td>
<td>Contraindation</td>
<td>Acceptable</td>
<td>N/A</td>
<td>[8, 13, 25, 29]</td>
</tr>
<tr>
<td>Pulmonary vascular resistance (Wood units)</td>
<td>&lt;3</td>
<td>&lt;7.5</td>
<td>N/A</td>
<td>[31, 34]</td>
</tr>
<tr>
<td>Right heart failure (CVP &gt;20 mmHg)</td>
<td>N/A</td>
<td>Contraindation</td>
<td>N/A</td>
<td>[25, 29, 31, 34]</td>
</tr>
<tr>
<td>Renal impairment (creatinine &gt;2.5 mg/dl)</td>
<td>Contraindation</td>
<td>Acceptableα</td>
<td>N/A</td>
<td>[25, 29, 31]</td>
</tr>
<tr>
<td>Type 1 diabetes with endorgan dysfunction</td>
<td>Contraindation</td>
<td>Acceptable</td>
<td>N/A</td>
<td>[13, 31]</td>
</tr>
<tr>
<td>Previous malignancy with limiting life expectancy</td>
<td>Contraindation</td>
<td>Acceptable</td>
<td>N/A</td>
<td>[25, 29, 31]</td>
</tr>
<tr>
<td>Advanced vascular disease</td>
<td>Contraindation</td>
<td>Acceptable</td>
<td>N/A</td>
<td>[29, 31]</td>
</tr>
<tr>
<td>Coagulation disorders</td>
<td>Acceptable</td>
<td>Contraindation</td>
<td>N/A</td>
<td>[29]</td>
</tr>
</tbody>
</table>

αNot when dialysis dependent.

N/A: not applicable; UNOS: United Network for Organ Sharing; CVP: central venous pressure.

Figure 2: The unpredictable course of AdHF. (A) Symptomatic onset, diagnosis and initiation of medical treatment. May need acute hospital admission for fluid retention and breathlessness. Some die suddenly at this stage. (B) Stable on medical management + cardiac resynchronization therapy. Exercise limitation and risk of sudden death persist (NYHA II–III). (C) Periods of instability related to dysrhythmia or renal dysfunction. Worsening exercise tolerance and increasing dependence (NYHA III–IV). May receive implantable cardio-defibrillator (INTERMACS Profiles 5–7). (D) Poor response to treatment (NYHA IV) and requiring multiple hospital admissions. High risk of rapid decompensation or sudden death (INTERMACS Profiles 3–4). (E) Terminal phase often with cardiogenic shock, cardiac cachexia, Modified from Goodlin [30], Copyright JACC (2009), with permission from Elsevier.
Equally, an LVAD implanted for symptom relief does not rule out transplantation as the definitive solution for selected patients. On the contrary, the physiological consequences of left ventricular unloading serve to increase transplant candidacy [19,29].

Established indications for LVAD therapy include NYHA IV status despite maximum tolerated medical therapy or inotropic dependence with left ventricular ejection fraction <25% and cardiac index <2 l/min/m² [31] without advanced right heart failure [32], indicated by the ability to generate pressure and forward flow [33]. Thus, high pulmonary artery pressure is favourable, whereas high central venous pressure with preoperative tricuspid regurgitation, hepatomegaly and acites are detrimental. Although the LVAD decreases left ventricular filling pressures and pulmonary vascular resistance, thereby improving right ventricular function, earlier implantation before right heart failure leads to better outcomes [34]. A potential LVAD patient must be able to manage the equipment, preferably with immediate family support. While age cannot be used as a contraindication, overall frailty (where surgical survival is in doubt) should be taken into account [35]. Given careful selection, it is reasonable to anticipate between 3 and 5 years of good quality life without threat of death from comorbidity.

A huge body of registry evidence now supports the decision-making process between lifetime MCS or heart transplantation from a prognostic and economic standpoint. Transplantation remains a rare commodity that benefits a small selective group of younger patients. The ideal candidate for transplantation is <50 years of age, UNOS Status I (INTERMACS 1–2), without metabolic risk factors or peripheral vascular disease, with recoverable renal and hepatic dysfunction and low pulmonary vascular resistance [29]. For prolonged survival, a young donor heart (<40 years) with short-ischaemic time is preferable. In contrast, a continuous flow blood pump candidate has no strict age limit, should be UNOS Status II (INTERMACS 3–5) without right heart failure, hepatic dys- function, metabolic risk factors, dialysis-dependent renal failure or contraindication to anticoagulation. The patient should undergo an elective implant for symptomatic relief in the presence of a functional family or equivalent support system [29]. Thus, in regard to preferred patient characteristics, the treatment options are complementary rather than competitive (Table 1).

Because heart failure is a dynamic, unpredictable illness, attempts to distinguish between bridge to either transplant, recovery or candidacy vs destination therapy are of little practical importance and no longer useful [30,36]. Data from INTERMACS show that 20% of patients designated ‘bridge to transplant’ remain on their LVAD 18 months later, while 20% of the younger ‘destination therapy’ patients switch to cardiac transplantation following resolution of pulmonary hypertension and renal impairment [25]. Patients classified as bridge-to-candidacy are similar to those for bridge-to-transplantation, but with more intermediate risk factors (obesity, diabetes and chronic obstructive airways disease). Enduring recovery is largely limited to patients with inflammatory cardiomyopathy or postischaemic stunning, both within the sphere of temporary (non-implanted) assist devices. A single indication for ‘long-term’ mechanical support has practical merit in that it may shorten the development time and the costs of introducing new devices. This approach will require only one clinical trial to investigate prolonged support rather than committing industry to the expense of several trials to establish multiple indications for a single device [36]. Furthermore, given the increasing complexity of donor heart allocation processes in Europe and the USA, Krabatsch et al. [37] from a leading transplant centre now suggest LVAD implantation as the primary treatment for all suitable heart failure patients. Their well-reasoned argument is based upon the unlimited availability of LVADs when needed, together with their suitability for at least 90% of candidates. The authors highlight the 1-year waiting time for a donor heart in Germany during which 20–30% die unoperated. This is followed by a 22% 1-year post-transplant mortality through the increasing use of liberal donor criteria. As a result, outcomes of transplant and LVAD implantation are essentially the same at 3–5 years postoperatively. Urgent transplantation can be used in reserve to address LVAD complications. This approach may have merit for the USA, where issues regarding the duration of specific treatments may inconsistently prevent appropriate candidates from receiving an implantable LVAD. Current ‘Centres for Medicare and Medicaid Services’ criteria for destination therapy require demonstration of NYHA IV class symptoms for 45 of 60 days or continuous inotrope therapy for 14 days or continuous treatment with an intra-aortic balloon pump for 7 days. Should clinical deterioration continue despite these therapies and the patient has not met the duration of symptomatic or treatment guidelines, the patient would not be a candidate for LVAD therapy [36]. In the USA, it is now proposed that LVADs be evaluated, approved and reimbursed simply for short- or long-term (implantable and permitting patient discharge with untethered mobility) circulatory support indications [36].

With regard to ‘Gold Standards’, a lifetime LVAD implanted electively at low risk provides the best symptomatic relief, the best prospects for improved prognosis and the best quality of life for the severely symptomatic patient whose only other option is medical management (Table 2). LVAD safety profile, clinical management and outcomes continue to improve, providing good quality of life with acceptable complications rates [38–40]. The debate about the best team recommendation to the patient who is the ultimate decision-maker about her/his preferred option, then, appears less between LVAD and cardiac transplantation but increasingly between LVAD and palliative care for many thousands of patients at the ceiling of symptomatic relief who remain fit for a surgical procedure (Table 2). With the prediction for >40 000 long-term LVAD implants per year in the USA and a similar number throughout Europe, we have to face an emerging controversy with enormous economic implications [36]. Should blood pump support be discussed with all severely symptomatic NYHA IV systolic heart failure patients who fit eligibility criteria? Is an ‘off-the-shelf’ device now the ‘gold standard’ for these patients? The emerging strategic health-care dilemma is: should there be a

<table>
<thead>
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<th>Table 2: Selection criteria for heart failure outpatients who should be considered for an elective LVAD</th>
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<tr>
<td>Chronic systolic heart failure &gt;60 days</td>
</tr>
<tr>
<td>Severe refractory symptoms despite optimum medical therapy</td>
</tr>
<tr>
<td>Exercise tolerance &lt;100 ft</td>
</tr>
<tr>
<td>Dependent for ≥3 activities of daily living</td>
</tr>
<tr>
<td>Two hospital admissions for decompensation in last 6 months</td>
</tr>
<tr>
<td>Low risk of right heart failure*</td>
</tr>
<tr>
<td>Suitable for elective surgery at acceptable risk</td>
</tr>
</tbody>
</table>

*Risk manifest by CVP >18 mmHg, pulmonary vascular resistance >8 Wood units, moderate to severe tricuspid regurgitation, low right ventricular stroke work index.
heart transplant centre for every 5–10 million of the population supported by VAD centres for every 2–5 million of the population based upon centre eligibility criteria and population need [41, 42].

REFERENCES


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