Heart transplantation vs long-term mechanical assist devices: clinical equipoise?

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Heart transplantation became a clinical entity in 1967, but reached clinical viability in the early 1980s. Since the first heart transplant the donor’s age has increased, as has the recipient’s. The length of stay for the initial hospitalization has decreased. The time to the first rejection episode has increased. Long-term survival has also improved [1]. The current generation of mechanical assist devices was born in the early 1990s, if we exclude the experience with an artificial heart in 1982. Their clinical usage has steadily increased since the REMATCH trial was published in 2001 [2]. The criteria for destination therapy continue to evolve as we learn more about patient selection and management.

For this editorial, let us exclude total artificial hearts, as the experience is limited. There are certain patients who cannot benefit from placement of a left ventricular assist device (LVAD) alone. These are patients with pronounced right ventricular failure, as well as patients with protracted arrhythmias. Those with a restrictive cardiomyopathy do not have a large enough left ventricular chamber to receive an LVAD. Hypertrophic cardiomyopathy patients have too-thick a left ventricle to receive a functioning LVAD. Finally, what about patients who have received various palliative procedures for a single ventricle? Heart transplantation is the appropriate procedure for them [3].

At the University of Minnesota, there have been patients who required temporary biventricular support as a bridge to an implantable LVAD. They underwent eventual LVAD explant and heart transplantation, but then required temporary right ventricular assist support. How long will insurance companies pay for this much surgery? How many patients will recover from this much time in the hospital? All of these operations increase the patient’s exposure to blood products. This increases the number of patients who are sensitized. Sensitized patients increase the challenges of suppressing rejection and infection after heart transplantation.

The patient with multiple cardiac operations as well as multiple cardiac catheterizations may develop complications from these treatments such as heparin-induced thrombocytopenia. All programmes are becoming more experienced in dealing with this problem. Plasmapheresis or bivalirudin offer solutions, but it is better to avoid the condition entirely. With obese patients, there is a patient-heart mismatch that contributes to the development of heart failure. Dealing with the obesity epidemic in terms of prevention would cut down on the number of patients requiring a heart transplant or LVAD.

There are patients with significant fixed pulmonary hypertension or recent malignancy who are not candidates for heart transplantation. A transpulmonary gradient of ≥15 would mean that the patient should be considered for LVAD over heart transplantation. A patient with a malignancy within the past 5 years should also be considered a candidate for LVAD over heart transplantation. Any evidence of ongoing infection makes the patient a poor candidate for either procedure. The very-sensitized patient is also one who should be considered for a destination LVAD.

According to the most recent report of the Registry of the International Society for Heart and Lung Transplantation, the median survival of 96 273 adult and paediatric heart recipients is 10 years [4]. Those who survive 1 year have a 63% chance of living 10 years and a 27% chance of living 20 years. Recipients of ventricular assist devices are significantly fewer in number and post-procedure years. Dr Kirklin presented the Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) data on patients who received a continuous-flow LVAD as destination therapy [5]. The patients who were not in cardiogenic shock at the time of implantation were the most favourable group for good outcomes. These patients had survival of 88 and 80% at 1 and 2 years, respectively. The mortality rate for these patients was ~10% per year. After heart transplantation, it is ~6% per year.

Moreno et al. [6] used a probabilistic Markov model to estimate the cost-effectiveness of the HeartMate II LVAD (Thoratec, Pleasanton, CA, USA). They found that the HeartMate II had a mean cost per quality-adjusted life-year of $414 275. The cost of the device alone was $150 720. Medical management of patients awaiting transplant has improved since the REMATCH trial. At least in the UK, the HeartMate II LVAD is not judged to be cost-effective as a bridge to transplantation. According to OPTUM health, in the USA a heart transplant hospitalization costs $550 000. The hospitalization for a patient receiving an LVAD is $400 000, beginning on the day that the LVAD is implanted. Length of stay depends on how sick the patient is at the time of transplant or implant.

Clinical equipoise suggests that there is true uncertainty about which of two potential clinical treatments is appropriate for a
given individual with end-stage heart disease [7]. Heart transplantation remains the gold standard, but there are a finite number of donor hearts that are available in any given year. The number appears to be \( \sim 3000 \) worldwide. The greatest number of donor hearts peaked \( \sim 1994 \).

The main complications of heart transplantation have been well defined. Acute rejection, particularly antibody-mediated rejection, continues to be a vexing problem. Infection can be treated with our rich supply of antibiotics, antivirals and antifungals. Primary graft dysfunction can be fatal, or rescue can be achieved with extracorporeal membrane oxygenation or biventricular assist devices. Chronic rejection continues to limit long-term survival. With heart transplantation, there are the myriad side effects of immunosuppression. Long-term use of cyclosporine or tacrolimus can lead to renal insufficiency. Older patients may develop malignancies, particularly skin cancers. Younger patients are at risk for post-transplant lymphoproliferative disorders. Patients >55 years should have their immunosuppression scaled back unless they have some other reason to keep it at the same level as the younger patients. Graft atherosclerosis is what all immunosuppression is directed against. It is still the biggest obstacle to long-term survival.

What about infectious complications after placement of VADs? Recent data from the INTERMACS were collected on 2006 patients receiving continuous-flow LVADs between 2006 and 2010 [8]. Of these patients, 20% developed sepsis. Percutaneous driveline infections occurred in 9.8% of the patients receiving a continuous-flow device. Freedom from LVAD-related infection was 56% at 2 years in this study.

Recently, in the Journal of Heart and Lung Transplantation, the group at Columbia looked at preoperative and postoperative risk factors for neurological complications in patients receiving LVADs [9]. The main preoperative risk factors were: previous stroke, persistent malnutrition, persistent inflammation and severity of heart failure. Patients with persistent malnutrition are poor candidates for heart transplantation. Perhaps a history of previous stroke should put that patient on a pathway of fewer operations and transplantation over device implantation.

Right heart failure that persists after LVAD placement can lead to vasoplegia and multiorgan system failure. These patients can have a temporary right ventricular assist device placed, but bleeding can be a substantial problem. Inotropic support with norepinephrine and the use of pulmonary vasoconstriction therapy have proved helpful in some of these cases.

There is a delicate balance that must be achieved when anticoagulating patients after LVAD placement. Gastrointestinal bleeding can occur as well as pump thrombosis [10]. According to a paper by John et al. [11], there are \( \sim 0.02 \) events per patient year, of pump thrombosis in patients who are being bridged to transplantation. In destination therapy patients, there are 0.04 events per patient year [12]. Infection seems to put patients at greater risk of thrombotic complications. At the University of Minnesota, we recently reviewed our experience with 193 patients who received HeartMate II LVADs from 2005 to 2012. Thirty-nine patients had haemolysis or pump thrombosis, and 22 had neurological events. The incidence of haemolysis or pump thrombosis was 13.4%. The incidence of neurological events was 9.8% (B.A. Whitson et al., submitted for publication).

The patient’s native aortic valve can complicate the success of an LVAD implant. Trace to mild aortic insufficiency is not a problem at implant. When there is moderate to severe aortic insufficiency, it is necessary to close off the aortic valve or do a patch closure. When there is a pre-existing mechanical valve, again patch closure is necessary. This means that the device stop working, the patient will experience sudden death. Perhaps these are patients who would be better served by heart transplantation alone. About 25% of all VAD patients will develop moderate or greater aortic insufficiency at 1 year [13].

There are donor-rich and donor-poor organ procurement organizations in the USA. Currently, 25.4% of heart transplant recipients do not require inotropic or mechanical support. At the University of Minnesota, that number is 23.3%. At the University of Minnesota, 53.3% of our heart transplant recipients have required mechanical circulatory support. In the USA, that number is 43% [Dr Monica Colvin-Adams, personal communication]. The lack of available donors drives the need for devices.

There are situations when a potential heart transplant recipient is at risk of primary graft dysfunction. Multiparous females may be better off with a VAD rather than a donor heart. Perhaps they should always have a prospective crossmatch. The very-sensitized patient may be another case when heart transplantation poses a greater risk. If the patient has risk factors for acute rejection or multiple transfusions are anticipated with a heart transplant, perhaps a device would be better. Multiple transfusions after heart transplantation can lead to right heart distension, and the right heart is already delicate after a period of cold ischaemia.

In a recent review, 10-year survival in heart transplant recipients was associated with age <55, white race, younger age of the donor, and shorter organ ischaemia times [14]. The chance of long-term survival is reduced when the status I recipient has diabetes, renal impairment or requires preoperative ventilation. Predictors of early death after a heart transplant include: preoperative mechanical ventilation, valvular cardiomyopathy, United Network of Organ Sharing status Ia, creatinine >1.5 mg/dl, the presence of an intra-aortic balloon pump, age >60, use of inotropes, weight <70 kg and pulmonary capillary wedge pressure <20 mmHg [15].

In terms of lifestyle, it is important to continue to evaluate patients who have VADs with quality of life measurements. Repeated infections, operations and hospitalizations affect recipients of VADs and heart transplants. As the durability of VADs increases, it will be an easier choice for patients and surgeons. Though not currently available, the development of totally implantable VADs may change the decision-making algorithm.

It takes a village or network of people to care for the patient with advanced heart failure. The first decision should be, are they a candidate for heart transplantation? The next decision should be, are they a candidate for a device? Then, if a device is indicated, what device? Any device is placed as a bridge to decision except for the destination patients. The patient with pulmonary hypertension should receive a VAD, as should the patient with recent malignancy. Older patients should be considered for VADs to save the hearts for younger patients. Whenever possible, patients should demonstrate their compliance with medical regimens before receiving heart transplants. Patients who receive VADs should be willing to consider another device implant should the VAD fail or develop pump thrombosis or persistent haemolysis.

With VADs the continuing challenge is the appropriate amount of anticoagulation. Haemolysis and pump thrombosis are to be avoided. Neurological events can happen, as well as gastrointestinal bleeding. We are still learning how to appropriately anticoagulate these patients, particularly when infection occurs, as there might be an increase in the risk of thromboembolic events at the time of an infection.
Multiple transfusions may occur in patients receiving heart transplants and LVADs. Multiple transfusions can act to immunosuppress the patient. This may lead to fatal infection in the already immunosuppressed heart recipient. It may set up the LVAD patient to develop sepsis, vasoplegia or a later driveline infection. It does not help that so many patients have had previous heart surgery or are already anticoagulated at the time of the LVAD or heart transplant.

In the future, the genetic tea leaves will allow us to determine a person’s susceptibility to malignancy. Perhaps on that basis, patients will be given a device or a transplant. There are many more people who require surgical management of their heart failure than there are heart donors. Each day this number continues to grow. The right choice for each patient continues to require further investigation so that we may optimize the best course of treatment for patients, particularly when one considers the severely limited amount of acceptable donors. Mandatory donation would also help.

REFERENCES