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EDITORIAL

Mechanical Circulatory Support for the Failing Heart – Progress, Pitfalls and Promises

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Heart failure remains the dominant cause of death in industrialised countries, with most of the disease occurring in the elderly [1]. In Australia, it is the most common cause for hospitalisation and is associated with significant morbidity, mortality and immense costs for the hospital system. Efforts to shift care into the community have been successful with heart failure management programs, however more than $AUD1B is spent on inpatient hospital heart failure care annually [1]. However, a significant proportion of patients suffer heart failure throughout the entire span of life from infancy, through adolescence, into adulthood and older age. It is these younger patients with severe heart failure who remain the current focus of advanced therapies including mechanical circulatory support, with medical therapy having made significant inroads into the stabilisation and management of less severe forms. For suitable patients, heart transplantation remains the treatment of choice [2], but continues to be limited by donor shortages throughout the world despite focussed medical, societal and governmental efforts to increase awareness and donation rates [3]. With persistently high rates of waiting list deaths for those on the heart transplantation list despite implantable defibrillators, cardiac resynchronisation and optimal medical therapy, mechanical circulatory support (MCS) has been successful in bridging critically ill patients, who previously would have been expected to die, to subsequent transplantation [4,5]. The success of MCS and the shortage of organ donors, has resulted in most heart transplant waiting lists having 40-50% of patients waiting on a chronic mechanical support device [6]. Here we review the significant progress of MCS in the last decade and foresee that, with ongoing improvements, it is feasible that destination therapy will become an accepted part of advanced heart failure management in some patient groups and that the next decade will bring the first clinical trial of mechanical organ replacement versus human organ transplantation.

What devices are available for use? There have been significant changes in the MCS field with three generations of left ventricular assist devices (LVADs) on the market. As seen in Figure 1 (from [7]), first-generation pulsatile LVADs, such as the 1998 HeartMate XVE (Thoratec Inc, Pleasanton, Calif, US) which represented 80% of chronic implants in 2006, are no longer implanted. Rather, second and third generation continuous flow LVADs (cfLVADs) have increased from 1% in 2006 to 97% of chronic implants in 2013 [7]. They have proved to be more durable and reliable although not without their own problems, with the two most commonly implanted pumps worldwide being the centrifugal-flow HeartWare Ventricular Assist System (HVAD) (HeartWare International Inc, Framingham, MA, US) and the axial-flow HeartMate II (HMII_ (Thoratec Inc, US)). (The centrifugal flow VentraCor LVAD, designed and manufactured in Australia, failed as a result of financial stress rather than significant design flaws, and was largely superseded by the HeartWare HVAD pump.) Short term biventricular support is available with external pump drivers including the pulsatile Thoratec paracorporeal VAD (PVAD) or venopulmonary artery extracorporeal membrane oxygenation (VPA-ECMO) with external centrifugal pumps in combination with an LVAD, but make up less than1% of total pump implants. Chronic biventricular replacement is available with the Syncardia total artificial heart (TAH), with a gradual increase to nearly 3% of implants. The Syncardia is a pulsatile pump and uses an external pneumatic driver, recently updated for increased mobility. Recently the concept of implanting two cfLVADs has been suggested, with some promise, although a formal

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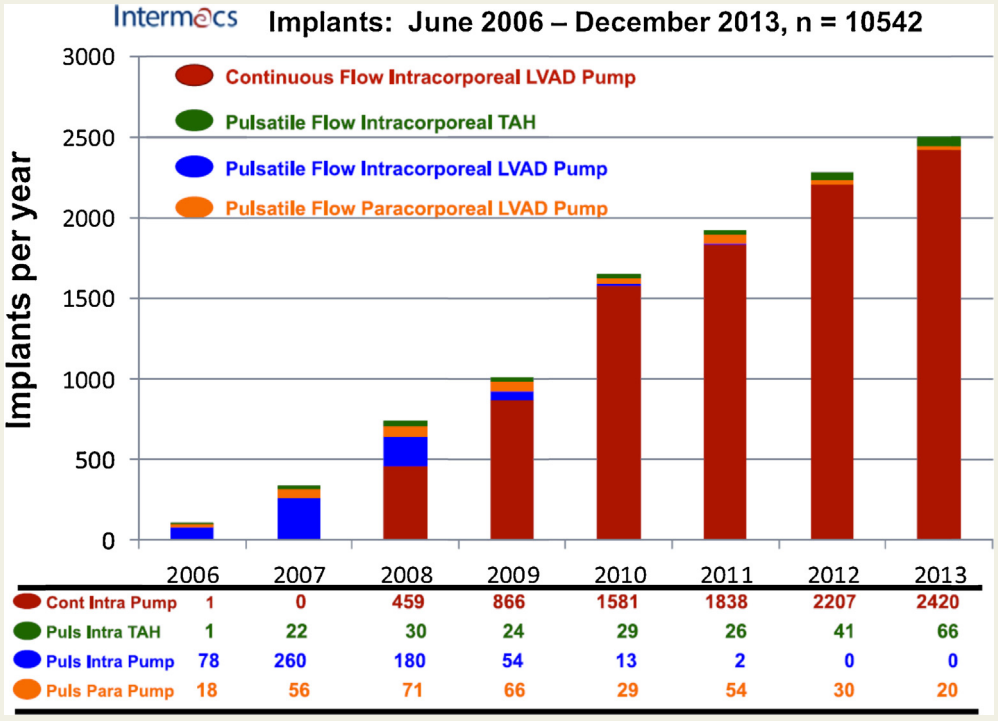

Figure 1 Primary adult implants in the INTERMACS registry by year of implant (from Ref [7]) (Kirklin et al., JHLT 2014).

trial of such configuration is yet to start. Devices implanted at St Vincent's over the last 30 years, since the inception of the mechanical and circulatory support program in 1994, are shown in Figure 2.

Most recently, LVADS have started down the route of miniaturisation with the recent development of the HeartWare Miniature Ventricular Assist Device (MVAD) and the centrifugal-flow HeartMate III. These newer devices are able to induce pulsatile fluctuations in flow through software manipulation of pump rotor speed, to try to, among other things, normalise vascular responses and encourage aortic valve opening [8].

What are the current indications for using these devices? Although LVADs were first approved for a bridge-to-transplant (BTT) indication, it was the landmark Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Cardiac Heart Failure (REMATCH) Trial in 2001 which suggested that these pumps could provide significant survival benefit compared with medical therapy in patients with end-stage heart failure (New York Heart Association Class IV) ineligible for transplantation [9]. This was followed up by a further study using the HeartMate II axial flow cfLVADs to show an even further improvement in outcomes [10]. Overall, the sixth INTERMACS annual report gives survival rates (for more than 10,000 patients in the database) of 80%, 70%, 59% and 47% after one, two, three and four years, respectively [7]. The subsequent approval for destination therapy (DT) by the United States Food and Drug Agency (FDA) in 2010 resulted in a massive uptake across the country, with non-transplant centres joining the more established programs to demonstrate excellent outcomes across a wide range of patients [7]. The almost exponential rate of increase in implantations has caused pause for thought from other countries, with the DT indication only approved specifically in USA. Other countries have tacit DT approval due to low transplant rates, meaning that patients are implanted with little realistic likelihood of transplantation. While both are approved for use in Australia, HMII and HVAD are indicated for BTT, they have a more general approval for management of severe heart failure without mention of transplantation. However, reimbursement for the cost of care for these patients is only linked to acceptance onto a transplant waiting list, meaning that DT therapy is not available in Australian public hospitals. An Australian destination clinical trial has been developed and is currently awaiting final approval to commence.

One of the indications that has proved challenging is ''bridge-to-candidacy'' for patients currently too unwell to be considered for heart transplant listing, but with the possibility of non-cardiac organ improvement, including rehabilitation, with subsequent reconsideration for transplant listing. Unfortunately these patients, by definition, have greater co-morbidities and are at greater risk of poor post-pump outcomes [7]. The hope of LVAD-induced ''recovery'' or remodelling has only been shown to occur in a very small cohort of carefully selected patients, despite aggressive medical therapies.

Which patients are selected for device implantation? With increased experience, many centres have developed strict eligibility criteria in considering potential LVAD patients.

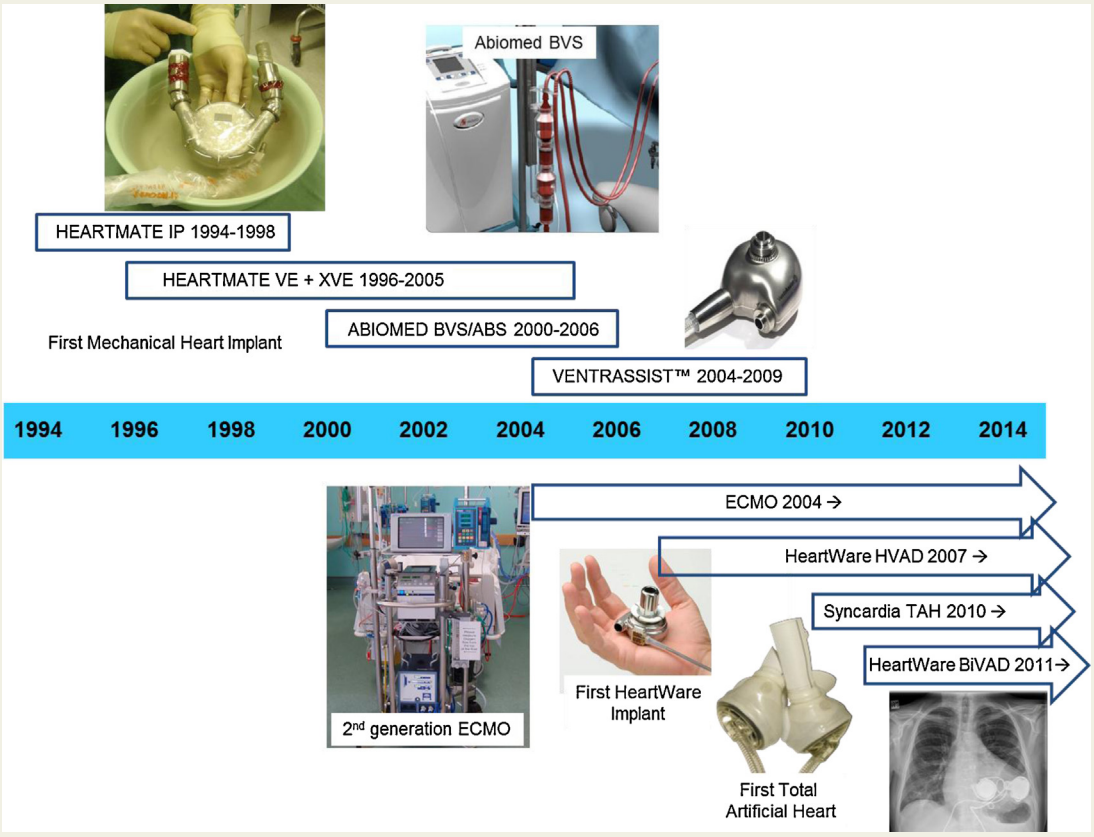

Figure 2 Milestones and devices implanted in St Vincent's Hospital since beginning of the mechanical circulatory support program.

To assist in classification of potential patients and monitoring outcomes of all chronically implanted pumps, the FDA developed an Interagency Mechanical Assist and Circulatory Support Registry (INTERMACS), which reports annually. This has been pivotal in demonstrating the impact of age, co-morbidities and device type on survival. Recently this has been extended to include worldwide implants in the International Mechanical and Circulatory Support (IMACS) registry, yet to report. Eligible patients would be expected to have severe irreversible heart failure, and unfortunately are at high risk of multi-organ dysfunction, particularly with renal impairment. Renal failure has been shown to be a persistently poor prognostic indicator [11], with most centres excluding patients with severe renal failure (eGFR<30 mL/min/1.73m^2), unless it can be demonstrated that improved cardiac output with short-term intra-aortic balloon pump or extra-corporeal membrane oxygenation can reverse renal dysfunction. Recently a more 'global' approach to patient assessment – that of ''frailty'' – has been recognised to be important in predicting outcomes post LVAD [12]. Using a combination of functional, strength based, cognitive and mood related assessments, we have recently shown significantly poorer outcomes in patients shown to be frail. Surprisingly, this index appears to be independent of age, and is a more powerful predictor than age or aetiology of LV impairment in predicting survival.

What are the pitfalls to be resolved for these devices? Despite improved survival, there remain significant barriers to widespread implementation of MCS. The requirement for ongoing anti-coagulation, most commonly with combination vitamin K antagonism and anti-platelet therapy to minimise thrombotic complications, contributes to increased bleeding rates seen in all implanted devices. One of the common areas for bleeding is the gastrointestinal tract, contributed to by shear stress-related acquired von Willebrand syndrome [13]. Although relatively common, this is more troublesome than life-threatening. A more significant bleeding complication, however, is intracranial haemorrhage [14]. Whether bleeding is related to the continuous flow with limited pulsatility provided by cfLVADs is not clear, although with newer devices re-introducing pulsatile flow, this will be able to be further studied.

The second major issue for MCS is the requirement for a transcutaneous driveline usually exiting just below the costal margin. This potential portal of entry for bacterial infections results in a cumulatively high rate of subcutaneous infection with occasional systemic complications [15]. One proposed solution for this is the development of transcutaneous energy

transfer systems (TETS) which will allow charging of internal batteries without the driveline. While these systems have been actively developed over the last decade, there remain significant hurdles to implementation. Improved battery technology will drive this forward but, at present, is limited by the sheer size of implanted material required.

Implicit in the discussion concerning availability of destination therapy for the increasing number of aging heart failure patients, is the barrier of cost. While the quality adjusted life year (QALY) cost has improved over the last decade, it remains significantly higher than acceptable within society-defined limits (usually set at around $60,000 / QALY) [16,17]. As durability of implanted MCS devices improves and costs of devices and technologies come down, it is likely that this threshold will be crossed within the next decade, supporting more widespread use including in patients with terminal heart failure acquired later in life. Destination therapy is already the commonest indication for LVADs in USA in the most recent INTERMACS report [7].

What other technologies hold future promise for the patient with terminal heart failure? Since last reviewed in this Journal 10 years ago [18], the C-PULSE device, an extra-aortic counterpulsation device, has completed a feasibility trial [19]. While the device does overcome some of the problems of anti-coagulation, it still requires an external driveline and provides only partial haemodynamic support, making it more suitable for NYHA Class III (than Class IV) patients. A further pivotal clinical trial will be required before it will achieve regulatory approval.

Ongoing development of MCS technologies and expansion into the less severe forms of advanced heart failure has focussed attention on other forms of 'partial' circulatory support. One such device has been the Circulite Synergy pump [20]. With the rationale that residual intrinsic left ventricular contractile function will support the patients at rest, and the pump providing additional support above that, it has been suggested that these devices may be suitable for the larger population of NYHA Class III heart failure patients. Further trials in that population are required. New pumps on the horizon include the smaller LVADs as mentioned. Both the MVAD and HMIII are in active clinical trials to achieve CE Mark approval. Improved accessories and peripherals are also being implemented in these trials, with an anticipated more patient-friendly pump-patient interface.

Although the SynCardia system has been the only approved total artificial heart over the last decade, there are some improvements in size to be implemented, with a smaller pump to come. While this remains a pulsatile pump, there are at least two continuous flow total artificial heart pumps under active development, with animal implants completed and plans for human studies most likely within the next five years. Both of these pumps rely on a moveable interventricular 'septum' to allow matching of right-left outputs, but use different control algorithms to adjust septal position. One of these, the Bivacor pump, was initially designed and developed in Australia, with further improvements in collaboration with the Texas Heart Institute.

Over the last 10 years, there have been significant improvements in the design and durability of mechanical support devices. There is now a stronger sense of appropriate patient selection for bridge-to-transplant patients, although cost-effectiveness issues remain a barrier for introduction into the larger destination market. Over the next decade, as costs decrease, patient selection is further refined, and technologies that remove the requirement for external driveline progress, it is likely that destination therapy will become an accepted part of advanced heart failure management. There will be an increase in the variety of chronic MCS available from partial support at one end of the severe heart failure spectrum, to complete heart replacement at the other. Although LVADs will remain the mainstay of temporary support for the majority of patients while waiting for transplant, with ongoing improvements in MCS, it is likely that the next decade will bring the first clinical trial of mechanical organ replacement versus human organ transplantation.

References

[1] Clark RA, McLennan S, Dawson A, Wilkinson D, Stewart S. Uncovering a hidden epidemic: a study of the current burden of heart failure in Australia. Heart Lung Circ 2004;13(3):266–73.

[2] Macdonald P. Heart transplantation: who should be considered and when? Intern Med J 2008;38(12):911–7.

[3] Organ and Tissue Authority. Annual Report 2013-2014 2014 [cited 2015 5 February]. Available from: http://www.donatelife.gov.au/sites/default/files/2013-2014 *OTA Annual Report.pdf*.

[4] Slaughter MS, Pagani FD, McGee EC, Birks EJ, Cotts WG, Gregoric I, et al. HeartWare ventricular assist system for bridge to transplant: combined results of the bridge to transplant and continued access protocol trial. J Heart Lung Transplant 2013;32(7):675–83.

[5] Starling RC, Naka Y, Boyle AJ, Gonzalez-Stawinski G, John R, Jorde U, et al. Results of the post-U.S. Food and Drug Administration-approval study with a continuous flow left ventricular assist device as a bridge to heart transplantation: a prospective study using the INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support). J Am Coll Cardiol 2011;57(19):1890–8.

[6] Australian and New Zealand Cardiothoracic Organ Transplant Registry. ANZCOTR Annual Report 2013 [cited 2015 January 14 2015]. Available from: http://www.anzcotr.org.au/.

[7] Kirklin JK, Naftel DC, Pagani FD, Kormos RL, Stevenson LW, Blume ED, et al. Sixth INTERMACS annual report: A 10,000-patient database. J Heart Lung Transplant 2014;33(6):555–64.

[8] Cheng A, Williamitis CA, Slaughter MS. Comparison of continuous-flow and pulsatile-flow left ventricular assist devices: is there an advantage to pulsatility? Annals of cardiothoracic surgery 2014;3(6):573–81.

[9] Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, et al. Long-term mechanical left ventricular assistance for end-stage heart failure. N Engl J Med 2001;345(20):1435–43.

[10] Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361(23):2241–51.

[11] Brisco MA, Kimmel SE, Coca SG, Putt ME, Jessup M, Tang WW, et al. Prevalence and prognostic importance of changes in renal function after mechanical circulatory support. Circ Heart Fail 2014;7(1):68–75.

[12] Dunlay SM, Park SJ, Joyce LD, Daly RC, Stulak JM, McNallan SM, et al. Frailty and outcomes after implantation of left ventricular assist device as destination therapy. J Heart Lung Transplant 2014;33(4):359–65.

[13] Muthiah K, Robson D, Macdonald PS, Keogh AM, Kotlyar E, Granger E, et al. Increased incidence of angiodysplasia of the gastrointestinal tract and bleeding in patients with continuous flow left ventricular assist devices (LVADs). Int J Artif Organs 2013;36(7):449–54.

[14] Wever-Pinzon O, Selzman CH, Drakos SG, Saidi A, Stoddard GJ, Gilbert EM, et al. Pulsatility and the Risk of Non-Surgical Bleeding in Patients Supported With the Continuous-Flow Left Ventricular Assist Device HeartMate II. Circ Heart Fail 2013.

[15] Zierer A, Melby SJ, Voeller RK, Guthrie TJ, Ewald GA, Shelton K, et al. Late-onset driveline infections: the Achilles' heel of prolonged left ventricular assist device support. Ann Thorac Surg 2007;84(2):515–20.
[16] Alba AC, Alba LF, Delgado DH, Rao V, Ross HJ, Goeree R. Cost-effectiveness of ventricular assist device therapy as a bridge to transplantation compared with nonbridged cardiac recipients. Circulation 2013;127(24):2424–35.
[17] Rogers JG, Bostic RR, Tong KB, Adamson R, Russo M, Slaughter MS. Cost-effectiveness analysis of continuous-flow left ventricular assist devices as destination therapy. Circ Heart Fail 2012;5(1):10–6.
[18] Esmore D, Rosenfeldt FL. Mechanical circulatory support for the failing heart: past, present and future. Heart Lung Circ 2005;14(3):163–6.
[19] Abraham WT, Aggarwal S, Prabhu SD, Cecere R, Pamboukian SV, Bank AJ, et al. Ambulatory extra-aortic counterpulsation in patients with moderate to severe chronic heart failure. JACC Heart failure 2014;2(5):526–33.
[20] Mohite PN, Sabashnikov A, Simon AR, Weymann A, Patil NP, Unsoeld B, et al. Does CircuLite Synergy assist device as partial ventricular support have a place in modern management of advanced heart failure? Expert review of medical devices 2015;12(1):49–60.