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# Horizon scanning technology
# Horizon scanning report

# Continuous flow ventricular assist devices for bridge to transplantation

## November 2008

ASERNIP-S

Australian Safety and Efficacy Register of New Interventional Procedures - Surgical

Royal Australasian College of Surgeons

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The production of this horizon scanning report was overseen by the Health Policy Advisory Committee on Technology (HealthPACT), a sub-committee of the Medical Services Advisory Committee (MSAC). HealthPACT comprises representatives from health departments in all states and territories, the Australia and New Zealand governments, MSAC and the New Zealand District Health Boards. The Australian Health Ministers' Advisory Council (AHMAC) supports HealthPACT through funding.

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# Executive Summary

The severe disparity between available donor hearts and the number of end-stage heart failure patients who require cardiac transplantation has resulted in the adoption of left ventricular assist devices (LVADs) which function as a bridge to transplantation. The randomised REMATCH trial has shown that LVADs confer significant survival advantage compared to medical therapy, and is therefore a viable option for ventricular support. Current LVADs are pulsatile devices, which utilises various moving parts to mimic normal physiological blood flow. This has major implications towards mechanical reliability, and mechanical failure has been shown to increase significantly over time. The use of pulsatile LVADs (P-LVADs) is also associated with high infection rates.

Continuous flow LVADs (C-LVADs) were developed as an alternative to P-LVADs, and has been touted as "next generation" LVADs with greater mechanical reliability complemented with a much smaller design, which translates to easier implantation. Despite some variability in the measured parameters between studies, the retrieved evidence indicates that C-LVADs support is mostly comparable to the haemodynamic and echocardiographic results achieved by P-LVADs. In addition, exercise performance and organ function parameters were comparable for both types of LVADs. However, there is evidence that improvements in organ function, although significant at first, did not persist up to the day of transplantation.

As expected, the use of C-LVADs resulted in significantly lower infections rates compared to P-LVADs. However, one study highlighted that C-LVAD support significantly elevated specific inflammatory markers, while others remained similar to P-LVADs. The reason for this remains unclear, and may be associated with the materials used to construct the C-LVAD. Meanwhile, studies examining neurological injury and neurocognitive functions revealed that both pulsatile and continuous flow LVADs achieved similar outcomes and do not appear to have adverse events towards the brain. One of the key concerns associated with the use of C-LVADs is the fact that the long-term implications of continuous blood flow remains unclear. Two of the retrieved studies revealed that vascular reactivity and pulsatility is compromised during C-LVAD support. Vascular impedence readings also revealed that C-LVAD support results in loss in vascular compliance, which indicates vascular stiffening.

The evidence available is generally supportive of C-LVADs and demonstrates that key outcomes are mostly comparable to P-LVADs. However, many questions remain unanswered. The long-term mechanical reliability of C-LVADs have not been adequately investigated, uncertainties regarding continuous flow support remains and the increase in specific inflammatory markers during C-LVAD support warrants further investigation.

While Australia and New Zealand have some of the highest transplant success rates in the world, the ageing population and stagnant donor organ availability is leading to a higher incidence and prevalence of heart failure. Unfortunately, this scenario is increasing heart transplant waiting lists and waiting times for suitable candidates, with more people inevitably dying while on the waiting list. While it is anticipated that the work of the new Australian Organ and Tissue Donation and Transplantation Authority will assist in reducing transplant waiting lists, demand pressures mean that there will be a need for VADs as a component of the system of care for people with advanced heart failure.

VADs confer significant survival advantage for those with severe heart failure. The newer continuous flow VADs not only appear to be as effective as pulsatile VADs but also have a greater safety profile, a consequence of fewer moving parts. This design feature also supports their use in women and children. Use of, and continued research into, continuous flow VADs is expected to grow as the population ages, although their long-term reliability and effectiveness is not known at present.

## Introduction

The Australian Safety and Efficacy Register of New Interventional Procedures – Surgical, on behalf of the Medical Services Advisory Committee (MSAC), has undertaken a horizon scanning report to provide advice to the Health Policy Advisory Committee on Technology (Health PACT) on the state of play regarding the introduction and use of continuous flow ventricular assist devices for bridge to transplantation.

Continuous flow ventricular assist devices may be a viable alternative to pulsatile devices, and may provide a safer and more effective means of bridging to transplantation. These devices are currently in limited use in Australia, and are still in the early stages of development.

This horizon scanning report is intended for the use of health planners and policy makers. It provides an assessment of the current state of development of continuous flow ventricular assist devices, its present use, the potential future application of the technology, and its likely impact on the Australian healthcare system.

This horizon scanning report is a preliminary statement of the safety, effectiveness, cost-effectiveness and ethical considerations associated with continuous flow ventricular assist devices.

# Background

Congestive heart failure occurs when the heart becomes less effective in pumping blood around the body. It is often the result of various conditions that leads to impairment of the heart, such as a heart attack, high blood pressure or a damaged valve. An individual suffering from congestive heart failure will experience various symptoms, such as breathlessness, fatigue and swelling of ankles or legs. Due to continual deterioration of the heart, the left ventricle of affected individuals does not empty property. This backlog of blood leads to a build-up of pressure within the atria and nearby veins resulting in fluid retention in the lungs, abdominal organs and legs. Alternatively in some patients, congestive heart failure may result from over activation of the left ventricle. This results in failure of ventricular relaxation, leading to blood retention under backpressure.

The treatment of congestive heart failure often involves multiple facets, from lifestyle changes to pharmacological management. In severe cases, devices such as pacemakers and implantable cardiac defibrillators may be utilised to assist in the proper function of the heart. If a patient is suffering from end-stage heart failure, the only effective long-term treatment option is heart transplantation. Despite advances within the field of cardiac transplantation, the benefits of this procedure are limited to a small proportion of affected patients due to the chronic shortage of donor hearts.

Ventricular assist devices (VADs) were developed as a means of bridging critical patients to cardiac transplantation, essentially prolonging the patient's life until a suitable donor heart becomes available. However, due to the grave prognosis of end-stage heart failure compounded with the likelihood of a long wait to transplantation due to donor shortage, VADs are often utilised for short or long-term support and in some cases destination therapy.

Pulsatile left ventricular assist devices (P-LVADs) have been extensively studied, and the randomised evaluation of mechanical assistance for the treatment of congestive heart failure (REMATCH) has shown that LVAD implantation decreased 1-year mortality by a third (75% to 51%) compared to medical management (Rose et al 2001). This significant improvement in survival was associated with considerable improvements in patient quality of life and functional status. However, it is also important to note that LVAD patients experienced more adverse clinical events compared to medically managed patients. One of the main contributing factors to the high rate of adverse events is device failure and malfunction. Pulsatile devices were developed to physiologically reproduce the natural heartbeat and blood flow, and therefore utilises valves to reproduce pulsatility. However, the use of valves introduces the risk of thromboembolic complications or structural failure.

Implantable P-LVADs are large and heavy, and need to be implanted inside the body with large inflow and outflow grafts adjacent to the dilated heart. A fully implantable compliance chamber is required as well. In order to fit P- LVADs into the abdominal pocket, extensive skin incisions are often required, which results in substantial abdominal wall trauma. This in turn leads to an increased risk of abdominal wall pocket bleeding, recurrent large clot formation and subsequently greater risk of device and pocket infection. The REMATCH trial revealed that sepsis, mechanical difficulties of inflow valve incompetence and pump failure were responsible for 19%, 41% and 22% of LVAD replacements, respectively (Dembitsky et al 2004). In view of this, considerable effort has been directed towards the development of a new generation of LVADs aimed at addressing the shortcomings of pulsatile devices.

Continuous flow LVADs (C-LVAD), have been presented as the alternative to P-LVADs for bridge to transplantation and destination therapy. These LVADs have been touted as next generation systems, and have garnered substantial interest due to its theoretical advantages. One of the major benefits of C-LVADs is the fact that they have less moving parts compared to P-LVADs. This may reduce the incidence of device failure or malfunction that is often observed with P-LVADs due to mechanical wear. In addition, C-LVADs are substantially smaller compared to pulsatile devices; this may confer substantial reductions to the incidence of sepsis and infection.

Despite the purported advantages of continuous flow devices, there are concerns with regards to the long-term use of these new LVADs, such as the potential detrimental effects of non-pulsatile flow, unknown long-term reliability and the biocompatibility of these devices. This horizon scanning report will discuss the current evidence available on C-LVADs, and attempt to elucidate the advantages (if any) of these devices.

## Description of the device

The first scientific article on the application of centrifugal blood pumps for cardiac assist and their potential advantages was published in 1960 (Saxton and Andrews 1960). Over time, various experiments were conducted, leading to the development of continuous flow pumps such as the Biomedicus BioPump and the Medtronic impeller pumps (Thalmann et al 2005). The Biomedicus BioPump has been routinely used clinically for over 20 years to support failing hearts. It was usually utilised in acute and desperate situations, such as support for poscardiotomy shock patients, and was rarely considered for bridging patients to transplantation (Mesana 2004). Non-pulsatile, continuous flow LVADs have recently been utilised for long-term support of patients with end-stage heart failure.

There are two design types for C-LVADs, axial flow and centrifugal pumps. Axial flow devices includes the DeBakey MicroMed, Jarvik 2000, HeartMate II and the

Incor Berlin Heart. Centrifugal pumps include the HeartMate III, CorAide, Medquest and Kriton. Several of these devices are still undergoing the early stages of development and have not been investigated in a clinical setting.

Some examples of current C-LVADs are:

Jarvik 2000
Electrically powered, axial flow pump that provides continuous flow from the left ventricle to the descending thoracic aorta. It can be placed within the left ventricle with no inlet cannula. The blood pump has a simple design, it has a single impeller located within a titanium housing and is rotated by a brushless direct-current motor. All blood contacting surfaces are made of smooth titanium. Power is channelled from an external controller via a percutaneous power cable. The Jarvik 2000 is capable of operating between 8000 rpm to 12000 rpm and can generate flows of up to 6L/min under optimal physiological conditions.

MicroMed DeBakey
The Micromed DeBakey is an electromagnetically actuated, titanium axial flow pump. The pump system consists of a titanium inflow cannula and apical ring, while the housing unit contains the impeller and motor. It is designed to deliver flows of up to 5L/min against 100 mmHg pressure with a speed of 10000rpm. The pump motor cable and flow probe wire exits transcutaneously and connects to the external controller.

HeartMate II
This axial flow pump has an internal rotor with helical blades that curve around the central shaft. As the rotor spins, blood is drawn continuously from the left ventricular apex through the pump and into the ascending aorta. The HeartMate II is capable of achieving flows of 10 L/min (against 100 mmHg) and has an operating range of 6000 to 15000 rpm (Haft et al 2007).

INCOR
The Berlin Heart INCOR is an axial flow pump which utilises an impeller held by magnetic bearings and therefore has no physical contact with other parts of the device. It is capable of achieving flows of 7 L/min (against 150mmHg) at speeds of 10000rpm. The driveline of the device is connected to an external controller and battery pack (Schmid et al 2005).

## Procedure

Implantation of an LVAD is done under general anaesthesia through sternotomy. The inflow cannula of the LVAD is inserted into the failing left ventricle and its outflow cannula into the systemic arterial system (ascending aorta). The LVAD pumps oxygenated blood from the failing left ventricle to the systemic arterial system.

## Clinical need and burden of disease

The health and economic burden of congestive heart failure is expected to increase as the population ages. The Heart Foundation estimates that approximately 1.5% to 2.0% of Australians are affected by congestive heart failure. The incidence and prevalence of heart failure increases with age, from 1% in people aged 50 to 59 years, 10% in people aged 65 years or older and over 50% in people aged 85 years or older (National Heart Foundation 2006).

The Canberra Heart Study revealed that the overall prevalence of clinical heart failure in Australians aged 60 to 86 years was 6.3%. In addition, there is a possibility that nearly 60% of people with left ventricular systolic dysfunction may be in the preclinical stage of heart disease (Abhayaratna et al 2006). This suggests that the incidence of heart failure is understated, and therefore current estimates might be substantially under-representing the national burden of heart failure and left ventricular systolic dysfunction. From 2003 to 2004, heart failure was responsible for 41,425 hospitalisations (0.6% of all hospitalisations) in Australia. In addition, the disease was responsible for 1.7% of all deaths (2279 deaths) in 2004 (Australian Institute of Health and Welfare [AIHW] 2006).

The Australia and New Zealand Organ Donor Registry (ANZOD) noted that as of 1 January 2008, 53 Australians and 6 New Zealanders are on the waiting list for heart transplantation. Due to the constant shortage of donor hearts, patients often have to remain on the transplant list for a long duration of time. LVADs therefore have an important role as a method of bridge to transplantation. However, patients supported with P-LVADs are exposed to significant risks, notably mechanical device failure, which can be life threatening and is an issue that is increasingly important as LVADs are used for longer periods of support. Birks et al (2004) investigated the incidence of device failure in patients treated with the pulsatile TCI HeartMate or Thoratec PVAD and noted that the cumulative probability of major device failure was 6%, 12%, 27% and 64% at 6 months, 1 year, 18 months and 2 years, respectively. This highlights the fact that mechanical failure is not uncommon, and the risk increases rapidly over time. The purported improved reliability of continuous flow LVADs is therefore undoubtedly attractive to patients and clinicians.

## Stage of development

The following table outlines the current stage of development of several continuous flow ventricular assist devices:

**Table 1: C-LVADs currently in clinical trials.**

| Device name | Manufacturer | Stage of development |
|---|---|---|
| DeBakey VAD | MicroMed Cardiovascular Inc. | FDA approved.<br>CE Mark approved. |
| Jarvik 2000 | Jarvik Heart Inc. | CE Mark approved. |
| Flowmaker | | Undergoing pivotal FDA trial for bridge to transplantation. |
| HeartMate II | Thoratec Corporation | FDA approved for bridge to transplantation.<br>CE mark approved. |
| INCOR | Berlin Heart AG | CE mark approved. |
| VentrAssist | Ventracor Limited | TGA approved.<br>CE mark approved.<br>Undergoing FDA trial for bridge to transplantation. |
| Terumo DuraHeart | Terumo Heart Inc. | CE mark approved.<br>Undergoing FDA trial for bridge to transplantation. |
| CorAide | Arrow International | Investigational.<br>CE mark trial underway. |
| HeartWare HVAD | HeartWare Limited | TGA approved. |

**Note:** C-LVADs utilised in Australia are: 1) VentrAssist at the Alfred Hospital in Melbourne and the Prince Charles Hospital in Brisbane; 2) VentrAssist and HeartWare at St. Vincent's Hospital in Sydney; 3) VentrAssist, HeartWare and Jarvik-2000 at the Royal Perth Hospital. At the time of writing, two C-LVADs have been approved by the Therapeutic Goods Administration (Ventrassist, HeartWare HVAD), and are currently undergoing clinical trails.

# Treatment Alternatives

## Existing comparators

The management of patients with end-stage heart failure or acute heart failure is challenging, and often includes a combination of medical therapy (including inotropic support), intra-aortic balloon pumping, and heart transplantation. The key comparator to C-LVADs are P-LVADs, which are utilised quite extensively worldwide for bridge to transplantation in end stage heart failure patients.

The body of evidence currently available on C-LVADs is limited to comparative studies, case series studies and case reports. Due to the emerging nature of these devices, no randomised controlled trials have been conducted to date. A total of 17 comparative studies (Level III intervention evidence) investigating the safety and efficacy of C- LVADs were selected for inclusion in this report. C-LVADs that were utilised within the included studies were: Micromed DeBakey; INCOR; Jarvik 2000; and HeartMate II.

Variation in patient characteristics, clinical management, follow-up durations and the type of devices utilised limits the comparisons that can be made across studies. Please refer to Appendix B for profiles of studies included.

## Safety

A large proportion of the comparative studies retrieved lacked sufficient detail with regards to the safety outcomes of the patient cohort. In particular, incidences of device failure or complications such as thrombosis were not reported in most of the included studies and it is unclear if omission implies that these complications did not occur. The key safety outcomes that were reported are discussed below.

*Infection*

Three of the retrieved studies reported infection outcomes (Table 2). The results were largely variable across these studies and may be due to differences in procedural protocol and the type of LVADs utilised. Baseline patients characteristics were similar in all three studies, with the exception of Schulmann et al (2007) where P-LVAD recipients had significantly higher weight (p=0.016), body mass index (p=0.009) and body surface area (p=0.035).

**Table 2: Comparative studies investigating infection outcomes for patients supported with P-LVADs or C-LVADs.**

| Study details | Infection outcomes |
|---|---|
| Schulman et al (2007)<br><br>Level III-2 intervention study<br><br>Patients<br>**Pulsatile flow:** 65 patients (HeartMate I)<br>**Continuous flow:** 27 patients (HeartMate II/ DeBakey) | **Infection** / **Pulsatile** / **Continuous** / **p-value**<br>Local device: 18/65 (27.7%) / 1/27 (3.7%) / 0.01<br>Driveline: 9/65 (13.8%) / 2/27 (7.4%) / ns<br>Pocket: 10/65 (15.4%) / 0/27 (0%) / 0.031<br>Wound: 10/65 (15.4%) / 0/27 (0%) / 0.031<br>Bacteremia: 17/65 (26.2%) / 7/27 (25.9%) / ns<br>Pump endocarditis: 2/62 (3.2%) / 1/27 (3.7%) / ns<br>Sepsis: 6/62 (9.7%) / 1/26 (3.8%) / ns |
| Siegenthaler et al (2003)<br><br>Level III-2 intervention study | **Infection type** / **Pulsatile flow** / **Continuous flow**<br>Driveline*: 64% (7/11) / 16% (1/6)<br>Pocket: 45% (5/11) / 0%<br>Bloodstream: 27% (3/11) / 0%<br>*=p<0.05 |

*-continued-*

<table>
<tr><th>Study details</th><th>Infection outcomes</th></tr>
<tr><td>Siegenthaler et al (2003)<br>-continued-<br><br><u>Patients</u><br>Pulsatile flow: 11 patients (HeartMate)<br>Continuous flow: 6 patients (Jarvik 2000)</td><td><u>Antibiotic use (p=0.039)</u><br>Pulsatile flow: 55 ± 43 days (52 ± 33% of total support time)<br>Continuous flow: 18 ± 14 days (18 ± 20% of total support time)<br><br><u>Incidence of positive culture (p=0.02)</u><br>Pulsatile flow: 12.0 ± 9.2 per 100 patient days<br>Continuous flow: 1.6 ± 2.6 per 100 patient days<br><br><u>Number of positive cultures (p=0.02)</u><br>Pulsatile flow: 129/380 cultures<br>Continuous flow: 17/50 cultures<br><br><u>Incidence of positive wound culture (p=0.008)</u><br>Pulsatile flow: 4.7 ± 3.6 per 100 patient days<br>Continuous flow: 0.06 ± 0.14 per 100 patient days<br><br><u>Number of positive wound cultures (p=0.008)</u><br>Pulsatile flow: 58/89 cultures<br>Continuous flow: 1/2 cultures<br><br>Note: incidence of positive cultures included the following sites: respiratory, blood, catheter, urine, wound and other cultures.</td></tr>
<tr><td>Patel et al (2008)<br><br>Level III-3 intervention evidence<br><br><u>Patients</u><br>Pulsatile flow: 43 patients (HeartMate I)<br>Continuous flow: 34 patients (HeartMate II)</td><td><table><tr><th></th><th>Pulsatile</th><th>Continuous</th><th>p-value</th></tr><tr><td>Device pocket infection (%)</td><td>7 (16.3)</td><td>1 (2.9)</td><td>0.01</td></tr><tr><td>Driveline infection (%)</td><td>15 (34.9)</td><td>10 (29.4)</td><td>0.63</td></tr><tr><td>Sepsis (%)</td><td>9 (20.9)</td><td>3 (8.8)</td><td>0.20</td></tr></table></td></tr>
</table>

One study noted that patients supported with C-LVAD had significantly lower rates of driveline infections compared to patients who received P- LVAD support (Siegenthaler et al 2003). Schulman et al (2007) reported significantly lower device, pocket and wound infections for continuous flow LVAD patients relative to P-LVAD recipients. In addition, it is interesting to note that continuous flow LVAD recipients had a significantly lower duration of antibiotic use, incidence/number of positive culture overall and incidence/number of positive wound cultures (Siegenthaler et al 2003).

With regards to changes in markers of inflammatory response after LVAD implantation, Loebe et al (2001) noted no significant differences in tumour necrosis factor alpha (TNFα), polynuclear leukocyte elastase (PNM EL) and complement factor 3a (C3a) over a period of three months. However, C-LVAD patients recorded significantly higher interleukin-6 and anaphylatoxin C5a levels compared to P-LVAD patients (63.0 ± 114.7 vs. 23.6 ± 37.6, $p<0.001$ and 1745 ± 1305 vs. 708 ± 352, $p<0.001$, respectively) (Loebe et al 2001). These results suggests that the type of LVAD implanted may have a major influence on the

activation of selected inflammatory subsystems, but the reasons for this remains unclear.

*Bleeding and transfusion*

Patel et al (2008) noted that continuous flow LVAD recipients were less at risk of suffering severe bleeding that required reoperation compared to P-LVAD recipients (2.9% vs. 23.3%; p=0.01). In addition, continuous flow LVAD recipients required significantly less packed red blood cell (7.3 ± 5.1 vs. 9.9 ± 5.6 units, p=0.03), frozen plasma (7.8 ± 5.0 vs. 10.5 ± 6.5 units, p=0.04) and platelet transfusions (2.0 ± 1.4 vs. 5.7 ± 6.4 units, p=0.001) compared to P-LVAD recipients (Patel et al 2008).

Garatti et al (2008) reported similar outcomes to Patel et al (2008). Patients who received the continuous flow LVAD required significantly fewer blood product transfusions (8 ± 2 vs. 14 ± 4 units/patient, $p<0.05$) and platelet transfusions (3 ±1 vs. 6.2 ± 2, $p<0.05$). Conversely, Feller et al (2007) stated that there was no difference between pulsatile and continuous flow LVAD recipients for incidence of major bleeding; however, the authors did not present transfusion outcomes.

*Neurological outcomes*

Patients with end-stage heart failure suffer from low cardiac output, which may lead to inadequate brain perfusion, and eventually brain injury. If LVAD support is utilised, it would be prudent to determine if it provides adequate perfusion to the brain and that neurocognitive function is not compromised.

Potapov et al (2001) investigated the post-operative time courses of protein S-100B (S100B) and neuron specific enolase (NSE) as biochemical markers of brain injury after C-LVAD (DeBakey, n=8) or P-LVAD (Novacor, n=7) implantation. Four hours after cardiopulmonary bypass, mean S100B values increased significantly (6-fold) in both continuous (p=0.006) and pulsatile (p=0.001) groups. However, the elevation of S100B was significantly greater in C-LVAD patients (p=0.031) compared to P-LVAD patients. NSE levels increased 2-fold four hours after cardiopulmonary bypass for both groups (continuous: p=0.01; pulsatile: p=0.019). The extent of NSE elevation was similar between patient groups (Potapov et al 2001). S100B and NSE concentrations returned to baseline values one day post-implantation for C-LVAD recipients. Meanwhile, P-LVAD recipients' S100B and NSE values returned to baseline on day 3 and day 1, respectively. Post-operative mean values for S100B and NSE were significantly elevated for C-LVAD patients relative to P-LVAD patients only on post-operative day 3. Neurologic assessments on post-operative days 3 and 14 did not reveal any neurological deficits within the C-LVAD group. In contrast, two P-LVAD patients had neurologic deficits (patient 1: late awakening; patient 2: cerebral infarction followed by global aphasia) (Potapov et al 2001).

Zimpfer et al (2006) demonstrated that cognitive P300 evoked potentials[1] continuously improved post-implantation compared to pre-operative measurements (Discharge: 399 ± 34, p=0.007; 8-weeks: 403 ± 41, p =0.022; 12-weeks: 394 ± 38; p<0.0001). Comparison between P-LVAD and C-LVAD patients revealed that the course of P300 evoked potential improvement was comparable over the course of follow-up. However, despite significant improvements, P300 peak latencies did not fully normalise at 12-weeks post-implantation compared with controls (p=0.012). Analysis demonstrated that the improvement of P300 evoked potentials was correlated with improvement of cardiac index (R=0.516, p=0.008).

*Right heart dysfunction*

Right heart dysfunction (RHD) has been shown to occur in approximately one third of patients after LVAD implantation. First-generation pulsatile devices in particular have been shown to be causally related to RHD due to the mechanical effects of left ventricular unloading (Dang et al 2006).

The retrospective comparative study by Patel et al (2008) revealed that the incidence of RHD[2] was similar between P-LVAD and C-LVAD (34.9% vs. 41.2%). The proportion of patients requiring right ventricular assist device support was comparable as well (P-LVAD: 8.8% vs. C-LVAD: 14%). Assessment of post-operative inotropic and vasodilator requirements revealed no differences in the total amount of inotropes and vasodilators utilised (Patel et al 2008).

*Vascular reactivity and pulsatility*

Questions remain with regards to the effects of continuous flow produced by C-LVADs on vascular reactivity. Considering the fact that impaired peripheral vasoreactivity is associated with the development of cardiovascular disease (Vita and Keaney 2002, Kaiser et al 2004), it is important to determine if continuous blood flow from the use of C-LVADs reduces vascular reactivity. One comparative study (Amir et al 2006) revealed that after the application and release of a blood pressure cuff on the patient's forearm, flow mediated dilation was significantly less for the C-LVAD group compared to P-LVAD (1.8 ± 3% vs. 15.6 ± 5%, p<0.0001). Almost all P-LVAD recipients had good peripheral vascular reactivity, as indicated by flow mediated dilation >9%, with the exception of one. When supplemental nitroglycerine (an independent vasodilator) was used, nitroglycerin-mediated dilation (NMD) was not statistically different between the two LVAD groups (P-LVAD: 25 ± 8% vs. C-LVAD: 17 ± 11%), although it appeared to be slightly lower for C-LVAD recipients (p=0.09). This implies that continuous blood flow from C-LVADs may impair reactivity of both the endothelial and smooth muscle cell layers.

[1] Measure of neurocognitive function.

[2] Defined as 14 consecutive days of inotropic or vasodilator support, or the need for a right ventricular assist device (Patel et al 2008).

Another key concern associated with the use of C-LVADs is vascular pulsatility. Some researchers have stated that the degree of pulsatility achieved in human subjects under C-LVAD support have not been rigorously assessed with respect to the results achieved by P-LVADs. The concern mainly surrounds the fact that diminished pulsatility with C-LVADs may have significant implications towards long-term organ function and recovery. Haemodynamic waveforms suggest that C-LVAD patients retain a level of vascular pulsatility (although diminished), and even when the C-VLAD is set to high flow rates. Meanwhile, P-LVAD patients have much greater vascular pulsatility, as expected. Travis et al (2007) demonstrated that P-LVAD support augments surplus haemodynamic energy (SHE) and energy-equivalent pressure (EEP) to normal baseline levels, conversely C-LVAD support reduces SHE and EEP. At low support rates, P-LVAD restores SHE levels to within 2.5% of normal baseline[3], while C-LVAD diminished SHE by 93% of normal baseline. At high support rates, P-LVAD increases SHE by 49% over baseline normal levels, while C-LVAD reduced SHE levels by 7% of normal baseline. Vascular impedence readings confirmed positive phases were present for the first few harmonics during C-LVAD, indicating loss of compliance or "stiffening". The results demonstrates that continuous flow from C-LVADs substantially reduces vascular pulsatility from its physiological levels. Prolonged diminished pulsatility may eventually lead to vascular stiffening which in turn increases ventricular workload (Travis et al 2007).

## Effectiveness

Key effectiveness measures include survival, haemodynamic improvement and echocardiographic outcomes. Effectiveness outcomes reported within the included studies are summarised in Table 3.

Most of the studies included had comparable patient characteristics at baseline. It is important to note that all of the included comparative studies had relatively low patient numbers, which in some cases is further exacerbated by substantial loss to follow up. Unless stated otherwise, all results are presented as mean ± standard deviation.

*Survival and post-transplant rejection*

Six of the included studies revealed that recipients of P-LVADs and C-LVADs had comparable survival outcomes (Garatti et al 2008, Zimpfer et al 2006, Feller et al 2007, Radivabcevic et al 2007, Patel et al 2008, Sandner et al 2008) (Table 3). Kaplan-Meier estimates of long-term mortality indicated that recipients of pulsatile or continuous flow LVADs have consistently similar long-term mortality rates up to 5 years post-implantation (Garatti et al 2008). Three studies noted that the proportion of patients surviving to transplantation was similar between both types of LVADs (Feller et al 2007, Radovancevic et al 2007, Klotz et al 2006). Meanwhile, two studies reported similar post-transplantation survival rates (Garatti et al 2008, Klotz et al 2006).

[3] Normal baseline: baseline measurements of patients without heart failure.

Garatti et al (2008) noted that first year post-transplant incidence of rejections that were greater than International Society of Heart and Lung Transplantation (ISHLT) grade IB were similar between P-LVAD and C-LVAD patients. Mean number of rejection per patient was similar as well. In contrast, Klotz et al (2006) observed that C-LVAD rejection rates were significantly higher compared to P-LVAD recipients ($p<0.001$) post-transplantation; these results were for rejections ISHLT grade III or greater.

*Haemodynamic outcomes*

Six of the included studies examined various haemodynamic parameters during device support for patients who received P-LVADs or C-LVADs (Klotz et al 2004, Radovancevic et al 2007, Haft et al 2007, Travis et al 2007, Garcia et al 2007, Patel et al 2008).

Klotz et al (2004) highlighted that patients supported with a P-LVAD achieved significantly higher mean arterial pressure ($p<0.001$), and left ventricular volume unloading ($p<0.001$) compared to those with continuous LVAD support. This was consistent with the observation that P-LVADs had a statistically significant higher pump output compared to C-LVADs ($p<0.001$) throughout the course of this study. Meanwhile, left ventricular pressure unloading was similar between P-LVAD and C-LVAD recipients (Klotz et al 2004).

Garcia et al (2008) highlighted that up to six months post-implantation, both P-LVAD and C-LVAD patients achieved in a significant reduction in pulmonary artery pressure ($p<0.01$), pulmonary capillary pressure ($p<0.01$), and pulmonary vascular resistance ($p<0.01$) compared to baseline measures. In addition to this, both LVADs also significantly increased mean arterial pressure, right arterial pressure, and cardiac output ($p<0.01$ for all). Both LVADs achieved comparable haemodynamic outcomes throughout the course of this study, with the exception of pulmonary vascular resistance, where the reduction which was more pronounced in patients supported with P-LVADs ($p<0.03$) (Garcia et al 2008).

Haft et al (2007) demonstrated that at three months post-implantation, P-LVAD recipients achieved significant improvements in systolic arterial pressure, cardiac index, pulmonary wedge pressure, mean pulmonary artery pressure and central venous pressure ($p<0.05$ for all). In contrast, C- LVAD recipients did not achieve significant improvements in systolic arterial pressure and central venous pressure. However, similar to the P-LVAD group, C-LVAD patients experienced a significant improvement in cardiac index, pulmonary wedge pressure and mean pulmonary artery pressure. C-LVAD patients also experienced a significant improvement in mean arterial pressure and ($p<0.05$) right ventricular stroke work index ($p<0.05$), which was not evident in patients supported with the P-LVAD. Patients who received the P-LVAD exhibited significantly higher systolic ($p<0.05$) and diastolic arterial pressure ($p<0.05$) compared to those supported with C-LVAD at three months follow-up.

**Table 3: Comparative studies investigating effectiveness of C- LVADs relative to P-LVADs.**

| Study details | Effectiveness outcomes |
|---|---|
| Amir et al (2006)<br><br>Level III-2 intervention study<br><br><u>Patients</u><br>**Pulsatile flow:** 10 patients (HeartMate I)<br>**Continuous flow:** 10 patients (Jarvik 2000) | <u>Flow mediated dilation (p<0.0001)</u><br>Pulsatile flow: 15.6 ± 5% [4.4 months post-surgery]<br>Continuous flow: 1.8 ± 3% [3.6 months post-surgery]<br><br><u>Nitroglycerin-mediated dilation (p=0.09)</u><br>Pulsatile flow: 25 ± 8%<br>Continuous flow: 17 ± 11%<br><br><u>Brachial artery flow</u><br>Pulsatile flow: 59.7 to 153.7 cm/s<br>Continuous flow: 17.6 to 82.4 cm/s |
| Feller et al (2007)<br><br>Level III-2 intervention study<br><br><u>Patients</u><br>**Pulsatile flow:** 13 patients (Novacor)<br>**Continuous flow:** 14 patients (Jarvik 2000) | <u>Survival to transplantation (p=n.s.)</u><br>Pulsatile flow: 8/13 (61.5%)<br>Continuous flow: 10/14 (71.4%)<br><br><u>Duration of support (p=0.01)</u><br>Pulsatile flow: 223 ± 162 days<br>Continuous flow: 79 ± 68 days<br><br><u>Cardiopulmonary bypass time (p=0.01)</u><br>Pulsatile flow: 110 ± 49 min<br>Continuous flow: 61 ± 34 min<br><br><u>Mean post-implant ICU stay (p=0.02)</u><br>Pulsatile flow: 14 ± 16 days<br>Continuous flow: 10 ± 16 days<br><br><u>Acute hospital stay</u><br>*Initial (p=n.s.)*<br>Pulsatile flow: 38 ± 14 days<br>Continuous flow: 35 ± 23 days<br>*Total (p=n.s.)*<br>Pulsatile flow: 52 ± 21 days<br>Continuous flow: 40 ± 25 days |

Garcia et al (2008)

Level III-2 intervention evidence

Patients
Pulsatile flow: 15 patients (HeartMate XVE)
Continuous flow: 20 patients (HeartMate II)

Echocardiographic results (mean: 21± 9 days)

| | Before | After | p-value |
|---|---|---|---|
| **Pulsatile flow** | | | |
| End-diastolic diameter (mm) | 70±15 | 59±14 | 0.01 |
| End-systolic diameter (mm) | 63±16 | 51±14 | <0.01 |
| End-diastolic volume ($cc^3$) | 249±141 | 172±117 | <0.01 |
| End-systolic volume ($cc^3$) | 203±120 | 126±99 | 0.02 |
| Ejection fraction (%) | 18±9 | 30±10 | <0.01 |
| **Continuous flow** | | | |
| End-diastolic diameter (mm) | 69±9 | 55±16 | <0.01 |
| End-systolic diameter (mm) | 63±8 | 49±16 | <0.01 |
| End-diastolic volume ($cc^3$) | 241±89 | 146±86 | <0.01 |
| End-systolic volume ($cc^3$) | 193±75 | 109±74 | <0.01 |
| Ejection fraction (%) | 19±10 | 29±13 | 0.01 |

p-values are noted for within-group trends only.
p-values for between-group comparisons were non-significant.

Haemodynamic results

| | Before | 1 mth | 6 mth | p-value |
|---|---|---|---|---|
| **Pulsatile flow** | | | | |
| Mean arterial pressure (mmHg) | 75±16 | 75±10 | 79±17 | <0.01 |
| Right arterial pressure (mmHg) | 14±7 | 15±5 | 6±4 | <0.01 |
| Mean pulmonary artery pressure (mmHg) | 37±9 | 24±7 | 21±10 | <0.01 |
| Capillary wedge pressure (mmHg) | 25±6 | 19±5 | 16±9 | <0.01 |
| Cardiac output (ml/min) | 4.27±1 | 6.4±1 | 5±0.8 | <0.01 |
| Pulmonary vascular resistance (Wood units) | 3.6±2 | 1.1±0.6 | 1.5±0.9 | <0.01 |
| **Continuous flow** | | | | |
| Mean arterial pressure (mmHg) | 76±13 | 78±12 | 81±17 | <0.01 |
| Right arterial pressure (mmHg) | 15±5 | 13±3 | 8±6 | <0.01 |
| Mean pulmonary artery pressure (mmHg) | 36±7 | 25±5 | 24±8 | <0.01 |

| | | | | | |
|---|---|---|---|---|---|
| | Capillary wedge pressure (mmHg) | 24±8 | 18±7 | 12±7 | <0.01 |
| | Cardiac output (ml/min) | 3.8±1 | 5.7±2 | 5.3±1.6 | <0.01 |
| | Pulmonary vascular resistance (Wood units) | 3.2±2 | 1.1±0.5 | 2.2±1.0 | <0.01 |
| | p-values are noted for within-group trends only.<br>p-values for between-group comparisons were non-significant. | | | | |
| Garatti et al (2008)<br><br>Level III-2 intervention evidence<br><br><u>Patients</u><br>**Pulsatile flow**<br>Novacor: 41 patients<br><br>**Continuous flow**<br>DeBakey: 28 patients<br>InCor: 8 patients<br><br>Patient age, haemodynamic characteristics (ejection fraction, cardiac index, pulmonary capillary wedge pressure) and biochemical values (serum blood urea nitrogen, serum creatinine, serum bilirubin) were comparable between groups.<br><br>*Note: Inconsistent p-value statements on incidence of idiopathy dilated cardiomyopathy.* | <u>Duration of support (until transplantation)</u><br>**Pulsatile flow:** 128.3 ± 198.3 days (CI: 52.08-204.52)<br>**Continuous flow:** 119.3 ± 115.4 days (CI: 73.13-165.47)<br><u>Mortality (during VAD support, p=n.s.)</u><br>**Pulsatile flow:** 36.6% (n=15; CI: 22.2-51.78)<br>**Continuous flow:** 33.3% (n=12; CI: 17.64-48.36)<br><br><u>Overall post-transplant mortality (p=n.s.)</u><br>**Pulsatile flow:** 19.2% (CI: 3.92-34.08)<br>**Continuous flow:** 15.8% (CI: 1.33-30.67)<br><br><u>Long-term mortality (Kaplan Meier estimate)</u><br>**Pulsatile flow:** 1 yr: 88.46 ± 6.27%, 3 yr: 88.46 ± 6.27%; 5 yr: 88.46 ± 6.27%<br>**Continuous flow:** 1 yr: 89.47 ± 7.04%, 3 yr: 83.88 ± 8.54%; 5 yr: 83.88 ± 8.54%<br><br><u>Post-transplant rejection</u><br>a) Incidence of rejections greater than International Society of Health and Lung Transplantation grade 1B<br>**Pulsatile flow:** 46% (CI: 26.84-65.16)<br>**Continuous flow:** 36.8% (CI:14.42– 57.58)<br><br>b) Number of rejections/patients<br>**Pulsatile flow:** 0.53 ± 0.83 (CI: 0.21-0.85)<br>**Continuous flow:** 0.38 ± 0.5 (CI: 0.16-0.6) | | | |
| Haft et al (2007)<br><br>Level III-2 intervention evidence<br><br><u>Patients</u><br>Pulsatile flow: 16 patients (HeartMate XVE)<br>Continuous flow: 18 patients | <u>Duration of support (Median) (p=n.s.)</u><br>Pulsatile flow: 5.6 months<br>Continuous flow: 5.1 months<br><br><u>Post-operative hospital stay (p=n.s.)</u><br>Pulsatile flow: 30 days<br>Continuous flow: 26 days | | | | |

(HeartMate II)

Cardiac transplantation
Pulsatile flow: 12/16 (75%)
Continuous flow: 10/18 (56%)

Haemodynamic data (baseline to 3 months)

| | | Pulsatile flow | Continuous flow |
|---|---|---|---|
| **Heart rate (beats/min)** | Baseline | 93 ± 15 | 87± 19 |
| | 3 months | 76 ± 13* (-16 ± 15%) | 80 ± 16 (-2 ± 22%) |
| **Systolic arterial pressure (mmHg)** | | 97 ± 13 | 96 ± 11 |
| | | 116 ±17* (19 ± 20%) | 98 ± 16† (3 ± 20%) |
| **Diastolic arterial pressure (mmHg)** | | 62 ± 9 | 59 ± 8 |
| | | 64 ±10 (4 ± 21%) | 77 ± 9† (34 ± 26%) |
| **Mean arterial pressure (mmHg)** | | 74 ± 9 | 72 ± 7 |
| | | 83 ± 11 (13 ± 20%) | 86 ± 12* (22 ± 22%) |
| **Cardiac index (L/m2/min)** | | 2.2 ± 0.4 | 2.4 ± 0.4 |
| | | 2.9 ±0.7* (38 ± 47%) | 30 ± 0.8* (26 ± 50%) |
| **Pulmonary wedge pressure (mmHg)** | | 27 ± 7 | 23 ± 7 |
| | | 10 ± 5* (-63 ± 20%) | 11 ± 5* (-52 ± 21%) |
| **Mean pulmonary artery pressure (mmHg)** | | 37 ± 8 | 35 ± 9 |
| | | 20 ± 8* (-47 ± 20%) | 20 ± 6* (-41 ± 15%) |
| **Central venous pressure (mmHg)** | | 13 ± 6 | 11 ± 5 |
| | | 7 ± 5* (-41 ± 38%) | 7 ± 3 (-25 ± 42%) |
| **Right ventricular stroke work index (mmHg.L.kg-1)/beat** | | 574 ± 182 | 718 ± 280 |
| | | 483 ± 227 (-8 ± 54%) | 480 ± 143* (-24 ± 35%) |

Numbers in parentheses represent mean ± SD of the percent change from respective baseline preoperatively to 3 months postoperatively.
*p<0.05 compared to baseline
†p<0.05 compared with pulsatile flow LVAD at 3 months

Laboratory data (baseline to 3 months)

| | | Pulsatile flow | Continuous flow |
|---|---|---|---|
| **White blood count (thousands)** | Baseline | 8.7 ± 3.0 | 7.0 ± 1.3 |
| | 3 months | 7.6 ± 2.0 (-11.9 ± 19.7%) | 7.0 ± 2.0 (0.6 ± 31.8%) |
| **Serum sodium (mEq/L)** | | 131 ± 6 | 133 ± 3 |
| | | 141 ± 3* (7.5 ± 4.9%) | 138 ± 2* (3.9 ± 2.8%) |
| **Blood urea nitrogen (mg/dL)** | | 29 ± 15 | 23 ± 10 |

| | | |
|---|---|---|
| | 24 ± 9 (-7.8 ± 42.1%) | 16 ± 4 (-20.8 ± 36.3%) |
| **Serum creatinine (mg/dL)** | 1.4 ± 0.5 | 1.3 ± 0.4 |
| | 1.2 ± 0.4 (-3.4 ± 47.2%) | 1.0 ±0.2 (-18.4 ± 17.7%) |
| **Total bilirubin (mg/dL)** | 2.4 ± 4.4 | 1.0 ± 0.7 |
| | 0.6 ± 0.3 (-47.7 ± 32.1%) | 0.7 ± 0.3 (-0.4 ± 66.4%) |
| **International normalised ratio** | 1.2 ± 0.2 | 1.1 ± 0.1 |
| | 1.0 ± 0.1 (-10.5 ± 12.1%) | 1.7 ± 0.6*† (51.5 ± 48.9%) |
| **Brain natriuretic peptide** | 1725 ± 1289 | 985 ± 866‡ |
| | 204 ± 243* (-81.7 ± 22.7%) | 191 ± 129* (-58.2 ± 67.6%) |
| **Prealbumin (mg/dL)** | 16.6 ± 10.9 | 21.1 ± 7.3 |
| -no postoperative data- | | |
| **Mixed venous oxygen saturation (%)** | 54 ± 9 | 55 ± 8 |
| | 65 ± 10* (20.4 ± 7.6%) | 64 ± 7* (18.1 ± 6.6%) |

Numbers in parentheses represent mean ± SD of the percent change from respective baseline preoperatively to 3 months postoperatively.
*p<0.05 compared to baseline
†p<0.05 compared with pulsatile flow LVAD at 3 months
‡p<0.05 compared to pulsatile flow LVAD at baseline

Echocardiographic data

| | | Pulsatile flow | Continuous flow |
|---|---|---|---|
| **LVEDV (mL)** | Baseline | 357 ± 142 | 362 ± 119 |
| | 3 months | 164 ± 59* (-49 ± 16%) | 242 ± 111*† (-35 ± 20%) |
| **LVESV (mL)** | | 300 ± 128 | 286 ± 111 |
| | | 114 ± 60 * (-59 ± 20%) | 191 ± 110*† (-37 ± 21%) |
| **LVEDD (mm)** | | 74 ± 12 | 74 ± 11 |
| | | 50 ± 9 (-30 ± 11%) | 60 ± 10*† (-18 ± 10%) |
| **LVESD (mm)** | | 68 ± 13 | 66 ± 12 |
| | | 40 ± 11* (-39 ± 15%) | 54 ± 15*† (-19 ± 16%) |
| **LVEF (%)** | | 14 ± 6 | 14 ± 4 |
| | | 27 ± 13* (133 ± 156%) | 18 ± 9† (36 ± 56%) |
| **Sphericity, longitudinal axis/minor axis** | | 1.5 ± 0.1 | 1.5 ± 0.2 |
| | | 1.9 ± 0.3* (30 ± 23%) | 1.7 ± 0.3† (11 ± 16%) |
| **Mitral insufficiency‡** | | 2.7 ± 1.1 | 2.5 ± 0.9 |
| | | 0.6 ± 0.2* (-93 ± 25%) | 1.1 ± 0.9*† (-50 ± 53%) |

| | | | |
|---|---|---|---|
| | **Tricuspid insufficiency‡** | 1.7 ± 1.1 | 1.9 ± 0.8 |
| | | 0.38 ± 0.9* (-65 ± 89%) | 1.0 ± 0.9* (-37 ± 67%) |
| | **Left atrial area (cm2)** | 34.1 ± 8.7 | 33.5 ± 8.4 |
| | | 19.9 ± 6.1* (-37 ± 22%) | 23.9 ± 7.9* (-26 ± 23%) |
| | **Area mitral valve regurgitant jet (MRa)** | 11.5 ± 8.9 | 9.7 ± 6.1 |
| | | 0.4 ± 0.2* (-97 ± 2%) | 2.7 ± 4.1*† (-64 ± 41%) |
| | **Percent mitral valve regurgitant volume (MR%)** | 32.4 ± 20.0 | 27.2 ± 18 |
| | | 0.3 ± 1.2* (-99 ± 2%) | 9.6 ± 12*† (-52 ± 56%) |

Numbers in parentheses represent mean ± SD of the percent change from respective baseline preoperatively to 3 months postoperatively.
*p<0.05 compared to baseline
†p<0.05 compared with pulsatile flow LVAD at 3 months
‡valvular insufficiency score: 0 = none; 1 = mild; 2 = moderate; 3 = severe.

Exercise performance

| | Pulsatile flow | Continuous flow | 95% confidence interval |
|---|---|---|---|
| **Peak Vo2 (mL/kg/min)** | 15.4 ± 4.0 | 15.6 ± 4.7 | (-3.2 to 3.0) |
| **Peak percent predicted (Vo2)** | 46.8 ± 10.2 | 49.1 ± 13.6 | (-6.3 to 11.0) |
| **Exercise time (min:sec)** | 10:25 ± 3:04 | 9:31 ± 3:19 | (-3:35 to 1:02) |
| **METS** | 4.4 ± 1.2 | 4.3 ± 1.4 | (-1.1 to 0.8) |
| **Peak respiratory exchange ratio** | 1.13 ± 0.12 | 1.11 ± 0.12 | (-1.1 to 0.8) |
| **Heart rate at peak exercise (beats/min)** | 131 ± 27 | 124 ± 24 | |
| **Pump flow: preexercise (L/kg/m2)** | 2.4 ± 0.6 | 2.7 ± 0.2 | |
| **Pump flow: peak exercise (L/kg/m2)** | 4.0 ± 0.5* (66.7 ± 7.5%) | 3.4 ± 0.4*† (25.9 ±14.7%) | |

*p<0.05 compared with preexercise pump flow
†p<0.05 compared with the change in pump floe from rest to peak exercise in pulsatile flow group

| | |
|---|---|
| Klotz et al (2006)<br><br>Level III-2 intervention evidence<br><br>Patients | *Pre-transplantation*<br>Pretransplant mortality (p=n.s.)<br>**Pulsatile flow:** 44%<br>**Continuous flow:** 48% |

<table>
<tr>
<td>Pulsatile flow<br>Novacor: 61 patients<br>HeartMate: 19 patients<br><br>Continuous flow<br>DeBakey: 30 patients<br>InCor: 20 patients</td>
<td>Post-transplantation<br><u>Transplantation rate</u><br>Pulsatile flow: 56%<br>Continuous flow: 46% (additional 6% were weaned)<br><br><u>Mechanical support duration (until transplantation)</u><br>Pulsatile flow: 167 ± 96 days<br>Continuous flow: 220 ± 147 days<br><br><u>30-day mortality post-tranplant</u><br>Pulsatile flow: 22.2%<br>Continuous flow: 21.7%<br><br><u>Long-term survival</u><br>Kaplan Meier survival analysis up to 10 years revealed no difference between groups (log rank = 0.07085)<br><br><u>Rejection rate (ISHLT grade III or greater) (p<0.001)</u><br>Pulsatile flow: 33%<br>Continuous flow: 89%</td>
</tr>
<tr>
<td>Klotz et al (2004)<br><br>Level III-2 intervention evidence<br><br><u>Patients</u><br>Pulsatile flow: 21 patients (Novacor/HeartMate VE)<br><br>Continuous flow: 10 patients (DeBakey)</td>
<td><u>Duration of support (p=n.s.)</u><br>Pulsatile flow: 189 ± 71 days<br>Continuous flow: 249 ± 111 days<br><br>
<table>
<tr><th></th><th></th><th>Preoperative</th><th></th></tr>
<tr><th></th><th>Continuous flow</th><th>Pulsatile</th><th>p-value</th></tr>
<tr><td>Haemodynamic</td><td></td><td></td><td></td></tr>
<tr><td>mPA (mmHg)</td><td>40.2 ± 11.0</td><td>33.7 ± 8.0</td><td></td></tr>
<tr><td>PCWP (mmHg)</td><td>30.6 ± 9.5</td><td>23.1 ± 7.6</td><td>0.03</td></tr>
<tr><td>PVR (WU)</td><td>2.7 ± 109</td><td>2.7 ± 1.3</td><td></td></tr>
<tr><td>TPG (mmHg)</td><td>9.6 ± 4.7</td><td>10.3 ± 3.0</td><td></td></tr>
<tr><td>SVR (dyne*s-1*cm-5)</td><td>1244 ± 322</td><td>1251 ± 363</td><td></td></tr>
<tr><td>mAP (mmHg)</td><td>79.8 ± 11.4</td><td>76.7 ± 11.5</td><td></td></tr>
<tr><td>RAP (mmHg)</td><td>6.8 ± 5.9</td><td>7.8 ± 8.1</td><td></td></tr>
<tr><td>CO (L/min)</td><td>4.1 ± 2.0</td><td>4.3 ± 1.4</td><td></td></tr>
<tr><td>PO (L/min)</td><td>-</td><td>-</td><td></td></tr>
<tr><td>LVvu (%)</td><td>-</td><td>-</td><td></td></tr>
<tr><td>Echocardiographic</td><td></td><td></td><td></td></tr>
<tr><td>LVEF (%)</td><td>17 ± 57</td><td>18 ± 13.3</td><td></td></tr>
<tr><td>LVEDD (mm)</td><td>64 ± 10.6</td><td>69 ± 16.3</td><td></td></tr>
<tr><td>LVESD (mm)</td><td>59 ± 2.1</td><td>65 ± 4.6</td><td></td></tr>
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| | | |
|---|---|---|
| FS (%) | 16 ± 12.1 | 19 ± 14.2 |
| LVEDV (ml) | 241 ± 67 | 262 ± 122 |
| LVESV (ml) | 173 ± 48 | 221 ± 36 |

All p-values insignificant unless stated otherwise on table.

| | Postoperative | | |
|---|---|---|---|
| | **Continuous flow** | **Pulsatile** | **p-value** |
| **Haemodynamic** | | | |
| mPA (mmHg) | 18.6 ± 5.1 | 18.3 ± 7.5 | |
| PCWP (mmHg) | 8.9 ± 4.4 | 8.0 ± 7.0 | |
| PVR (WU) | 2.0 ± 1.0 | 2.0 ± 0.9 | |
| TPG (mmHg) | 9.7 ± 4.1 | 10.4 ± 3.7 | |
| SVR (dyne*s-1*cm-5) | 1215 ± 363 | 1579 ± 550 | 0.08 |
| mAP (mmHg) | 77.7 ± 6.2 | 104.6 ± 13.6 | <0.001 |
| RAP (mmHg) | 77.7 ± 6.2 | 2.7 ± 2.2 | |
| CO (L/min) | 5.1 ± 1.0 | 5.6 ± 1.3 | |
| PO (L/min) | 3.6 ± 0.9 | 5.1 ± 1.0 | <0.001 |
| LVvu (%)* | 72.3 ± 17.1 | 90.9 ± 9.3 | <0.001 |
| **Echocardiographic** | | | |
| LVEF (%) | 21.6 ± 12.0 | 21.3 ± 7.5 | |
| LVEDD (mm) | 61 ± 12.7 | 65 ± 9.5 | |
| LVESD (mm) | 53 ± 15.2 | 54 ± 12.2 | |
| FS (%) | 16 ± 7.8 | 18 ± 6.8 | |
| LVEDV (ml) | 199 ± 102 | 222 ± 73 | |
| LVESV (ml) | 149 ± 102 | 152 ± 78 | |

All p-values insignificant unless stated otherwise on table.
CO: cardiac output; FS: fractional shortening;

**Continuous flow LVAD resulted in a time dependant decrease in left ventricular volume unloading between 60 to 120 days post-LVAD implantation ($R^2$=0.699)*

Overall mortality (device support)
3 patients

Post-transplant mortality
4 patients

Patel et al (2008)

Level III-3 intervention evidence

Patients
**Pulsatile flow:** 43 patients (HeartMate I)
**Continuous flow:** 34 patients (HeartMate II)

Duration of support
**Pulsatile flow:** 202.3 ± 258.9 days
**Continuous flow:** 160.5 ± 173.4 days

Cardiopulmonary bypass time (p = 0.04)
**Pulsatile flow:** 96.2 ± 37.5 min
**Continuous flow:** 76.7 ± 34.9 min

Haemodynamic results

| | Preoperative | 1 month | 3 months | 6 months |
|---|---|---|---|---|
| **Pulsatile LVAD** | | | | |
| PCWP (mmHg) | 25.5 ± 7.6 | 10.2 ± 6.6† | 13.4 ± 7.6† | 10.6 ± 3.0† |
| mPAP (mmHg) | 35.9 ± 9.2 | 20.9 ± 7.1† | 24.0 ± 7.8† | 21.5 ± 4.2† |
| CVP (mmHg) | 12.4 ± 5.9 | 9.9 ± 5.7 | 10.8 ± 8.1 | 8.6 ± 4.0 |
| PVRI (dynes/sec*cm-5/m2) | 512 ± 435 | 334 ± 184 | 303 ± 74 | 322 ± 66 |
| Cardiac index (L.min-1.m-2) | 1.9 ± 0.47 | 2.8 ± 0.8† | 2.9 ± 0.8† | 2.7 ± 0.7† |
| RVSWI (g*m/m2) | 8.2 ± 3.9 | 4.8 ± 2.7† | 5.6 ± 2.1 | 5.6 ± 3.1 |
| **Continuous flow LVAD** | | | | |
| PCWP (mmHg) | 25.3 ± 10.5 | 8.6 ± 5.6† | 11.9 ± 4.7† | 11.2 ± 8.6† |
| mPAP (mmHg) | 34.2 ± 12.2 | 19.0 ± 6.8† | 22.7 ± 7.5† | 20.0 ± 9.3† |
| CVP (mmHg) | 12.2 ± 6.5 | 8.8 ± 6.5 | 9.7 ± 4.9 | 9.7 ± 8.2 |
| PVRI (dynes/sec*cm-5/m2) | 433 ± 269 | 290 ± 131† | 345 ± 211 | 276 ± 152 |
| Cardiac index (L.min-1.m-2) | 1.8 ± 0.5 | 3.0 ± 0.5† | 2.8 ± 0.5† | 2.69 ± 0.7† |
| RVSWI (g*m/m2) | 5.7 ± 2.3 | 5.4 ± 2.6 | 5.4 ± 1.9 | 4.2 ± 2.4 |

† p<0.05 compared to preoperative.
CVP: central venous pressure; mPAP: mean pulmonary artery pressure; PCWP: pulmonary capillary wedge pressure; PVRI: pulmonary vascular resistance index; RVSWI: right ventricular stroke work index.

Right heart dysfunction (p=n.s.)
**Pulsatile flow:** 34.9%
**Continuous flow:** 41.2%

Right ventricular assist device implantation (p=n.s.)
**Pulsatile flow:** 8.8%
**Continuous flow:** 14.0%

Renal/hepatic function

| | | | | |
|---|---|---|---|---|
| | **Preoperative** | **1 mth** | **3 mths** | **6 mths** |
| **Pulsatile flow** | | | | |
| Blood urea nitrogen (mg/dL) | 37.0±21.1 | 23.7±21.1 | 18.6±9.5 | 19.2±7.3 |
| Creatinine (mg/dL) | 1.7 ± 0.9 | 1.4 ± 0.9 | 1.2 ± 0.5 | 1.1 ± 0.4 |
| Total bilirubin (mg/dL) | 1.9±1.5 | 2.9±7.21 | 1.9±1.8 | 0.5±0.3 |
| Alanine aminotransferase (IU) | 82.3±96.0 | 30.8±40.8 | 21.1±13.4 | 23.6±17.0 |
| Aspartate aminotransferase (IU) | 72.1±90.6 | 50.3±68.8 | 28.0±16.2 | 33.7±28.6 |
| **Continuous flow** | | | | |
| Blood urea nitrogen (mg/dL) | 42.4±24.4 | 27.1±17.1 | 22.6±15.1 | 25.5±13.4 |
| Creatinine (mg/dL) | 1.7±0.8 | 1.4±0.8 | 1.1±0.5 | 1.3±0.7 |
| Total bilirubin (mg/dL) | 1.5±1.1 | 2.2±3.2 | 1.1±1.1 | 0.8±0.5 |
| Alanine aminotransferase (IU) | 92.1±221.3 | 70.1±165.6 | 38.8±43.00 | 25.6±14.4 |
| Aspartate aminotransferase (IU) | 48.9±63.8 | 101/8±230.5 | 55.4±90.2 | 31.1±20.0 |

<u>30-day mortality (p=n.s.)</u>
**Pulsatile flow:** 27.9% (12/43)
**Continuous flow:** 25.3% (5/33)

<u>Late mortality (p=n.s.)</u>
**Pulsatile flow:** 32.6% (14/43)
**Continuous flow:** 27.3% (9/33)

<u>Kaplan-Meier survival (p=n.s.)</u>
**Pulsatile flow**
1 yr: 50%, 2 yrs: 44%
**Continuous flow**
1 yr: 50%, 2 yrs: 48%

<u>Length of stay (p=n.s.)</u>
**Pulsatile flow:** 63.4 ± 56.8 days
**Continuous flow:** 58.4 ± 37.3 days

| | |
|---|---|
| Radovancevic et al (2007)<br><br>Level III-2 intervention evidence | <u>Blood pressure (p=n.s.)</u><br>*6 months*<br>Pulsatile flow: 79 ± 11 mmHg |

<table>
<tr>
<td>Patients<br>Pulsatile flow: 58 patients (HeartMate I)<br>Continuous flow: 12 patients (Jarvik 2000/HeartMate II)</td>
<td>Continuous flow: 80 ± 14 mmHg<br>12 months<br>Pulsatile flow: 86 ± 12 mmHg<br>Continuous flow: 82 ± 12 mmHg<br><br><u>Use of anti-hypertensive medication at 6 months (p=0.002)</u><br>Pulsatile flow: 25/26 (96%)<br>Continuous flow: 4/9 (44%)<br><br><u>Use of diuretics at 6 months (p=n.s.)</u><br>Pulsatile flow: 12/26 (46%)<br>Continuous flow: 7/9 (78%)<br><br>Note: no difference in medication use between VAD groups at 12 months.<br><br><u>Cardiac transplantation (p=n.s.)</u><br>Pulsatile flow: 28/58 (48%)<br>Continuous flow: 4/12 (33%)<br><br><u>15-month actuarial survival (p=n.s.)</u><br>Pulsatile flow: 74%<br>Continuous flow: 90%</td>
</tr>
<tr>
<td>Sandner et al (2008)<br><br>Level III-2 intervention evidence<br><br><u>Patients</u><br>Pulsatile flow: 29 patients (Novacor)<br>Continuous flow: 63 patients (DeBakey, HeartWare, DuraHeart)</td>
<td><u>Survival</u><br>Survival rate was similar between both VAD groups.<br>6 month Kaplan Meier estimate: 66.4% and 58.7% for pulsatile and continuous, respectively.<br><br><u>Renal function outcomes</u><br>-presented separately under Effectiveness-</td>
</tr>
<tr>
<td>Thohan et al (2005)<br><br>Level III-2 intervention evidence<br><br><u>Patients</u><br>Pulsatile flow: 12 patients (Novacor)</td>
<td><u>Haemodynamic and structural changes</u><br><br>
<table>
<tr><th></th><th>Before</th><th>After</th><th>p-value</th></tr>
<tr><td>Continuous flow</td><td></td><td></td><td></td></tr>
<tr><td>LVEDD (cm)</td><td>7.4</td><td>6.4</td><td>0.022</td></tr>
<tr><td>EDV (ml)</td><td>265.8</td><td>203.2</td><td>0.005</td></tr>
<tr><td>ESV (ml)</td><td>215.4</td><td>160.1</td><td>0.004</td></tr>
</table>
</td>
</tr>
</table>

| | | | | |
|---|---|---|---|---|
| **Continuous flow:** 8 patients (DeBakey) | LV mass (g) | 268.2 | 251.3 | 0.161 |
| | LVEF (%) | 19.4 | 21.9 | 0.197 |
| | RVFAC (%) | 25.6 | 25.1 | 0.459 |
| | LAV (ml) | 102.4 | 76.6 | 0.033 |
| | Mitral E/A ratio | 2.5 | 1.9 | 0.026 |
| | FFA | 0.2 | 0.3 | 0.213 |
| | DT (ms) | 102.9 | 128.6 | 0.094 |
| | TRV (cm/s) | 331.0 | 243.6 | 0.022 |
| | PVAT (ms) | 79.6 | 102.2 | 0.028 |
| | **Pulsatile flow** | | | |
| | LVEDD (cm) | 6.3 | 4.2 | 0.000 |
| | EDV (ml) | 223.2 | 131.2 | 0.000 |
| | ESV (ml) | 175.1 | 74.3 | 0.000 |
| | LV mass (g) | 231.3 | 183.5 | 0.001 |
| | LVEF (%) | 20.9 | 42.5 | 0.000 |
| | RVFAC (%) | 22.5 | 30.0 | 0.007 |
| | LAV (ml) | 121.2 | 72.2 | 0.000 |
| | Mitral E/A ratio | 2.8 | 1.7 | 0.033 |
| | FFA | 0.2 | 0.3 | 0.051 |
| | DT (ms) | 82.0 | 195.5 | 0.000 |
| | TRV (cm/s) | 310.4 | 236.6 | 0.042 |
| | PVAT (ms) | 72.3 | 100.0 | 0.002 |

| | Pulsatile flow | Continuous flow | p-value |
|---|---|---|---|
| LVEDD | -33.3% | -13.7% | 0.04 |
| LVEDV | -41.2% | -23.5% | 0.015 |
| LVESV | -57.6% | -25.6% | 0.01 |
| LV mass | -20.6% | -6.3% | 0.038 |
| LVEF | +103.5% | +12.9% | 0.006 |
| RV fractional area change | -33.3% | -2% | 0.07 |

Significant sustained reduction in LV mass was noted in pulsatile flow patients only.

Prolongation of deceleration time was greater for pulsatile flow compared to continuous flow (138.3% vs. 25.0%).

Cellular changes

Significant reduction of intracradiac TNFα, total collagen and myocyte size for both VAD groups.

| | |
|---|---|
| Travis et al (2007)<br><br>Level III-2 intervention evidence<br><br><u>Patients</u><br>Normal ventricular function: 8 patients<br>Pulsatile flow: 12 patients (HeartMate XVE/Thoratec IVAD)<br>Continuous flow: 10 patients (HeartMate II, DeBakey) | <u>Duration of support</u><br>234 ± 181 days<br><br><u>Haemodynamic results</u><br>Systemic blood flow restored in both pulsatile and continuous flow patients.<br>Haemodynamic waveforms indicate diminished pulsatility for continuous flow VADs despite high flow rates.<br><br><u>Surplus haemodynamic energy (SHE)</u><br>Only pulsatile VADs restore SHE to normal baseline values.<br>Continuous flow decreases SHE considerable.<br>SHE values statistically different between pulsatile and continuous VAD for both low ($p<0.001$) and high flow ($p<0.00001$) rates.<br><br><u>Systemic vascular resistance</u><br>Systemic vascular resistance (impedence magnitude 0Hz) decreased from baseline with pulsatile flow, increased with continuous flow.<br>Both pulsatile and continuous VAD patients had negative phase for initial harmonics (indicating normal vascular compliance) at baseline.<br>Continuous flow support resulted in a positive phase during first few harmonics, indicating loss of vascular compliance. |

Patel et al (2008) stated that both pulsatile and continuous flow LVADs resulted in significant improvements in pulmonary capillary wedge pressure, mean pulmonary artery pressure and cardiac index ($p<0.05$ for all, compared to baseline measurements). Intergroup comparisons revealed that both LVADs had comparable measures of pulmonary capillary wedge pressure, mean pulmonary artery pressure and central venous pressure at 1, 3 and 6-months post-implantation. Patients supported with the P-LVAD achieved significant improvement in ventricular stroke work index 1-month post-implantation ($p<0.05$), but this was not sustained at 3 and 6-months post-implantation. Meanwhile, patients who received the C- LVAD had a significant reduction in pulmonary vascular resistance index at 1-month ($p<0.05$), but this was not evident at later follow-up examinations (Patel et al 2008).

Thohan et al (2005) noted that both types of LVADs successfully improved left atrial volume, mitral E/A, fractional filling of atria, deceleration time, tricuspid regurgitant velocity and pulmonary vein acceleration time ($p<0.05$ for all, compared to baseline measurements). Patients treated with P-LVAD support achieved significantly greater prolongation of deceleration time compared to C-LVAD (138.3% vs. 25.0%, p-value not stated).

The evidence demonstrates that haemodynamic improvements are evident after LVAD implantation. The degree of improvement appears to be comparable between P- LVADs and C-LVADs for most parameters. However, there is some variability in results between studies. However, overall it appears that C-LVADs are capable of achieving similar improvements in haemodynamic indices relative to P-LVADs.

*Echocardiographic structural outcomes*

Garcia et al (2008) stated that the use of pulsatile and continuous flow LVADs resulted in significant improvements in left ventricular end diastolic diameter (LVEDD), left ventricular end diastolic volume (LVEDV), left ventricular end systolic diameter (LVESD) left ventricular end systolic volume (LVESV) and left ventricular ejection fraction (LVEF) compared to baseline measurements (mean time of echocardiographic evaluation: 21 ± 9 days). No significant differences in these parameters were observed between LVAD groups over the course of this study (Garcia et al 2008).

Thohan et al (2005) observed similar outomes, both C-LVAD and P-LVAD recipients achieved significant reduction in LVEDD, LVEDV and LVESV. However, it is interesting to note that only P-LVAD recipients had significant improvements in LV mass, left ventricular ejection fraction (LVEF), right ventricular fractional area change (RVFAC), fractional filling of atria (FFA) and deceleration time (DT) ($p<0.05$ for all). Statistical comparisons between LVAD groups demonstrated that patients treated with the P-LVAD had statistically

greater reductions in LVEDV (p =0.04), LVEDV (p=0.015), LVESV (p=0.001) and LV mass (p=0.038). In addition, P-LVAD patients achieved a significantly greater increase in LVEF compared to C-LVAD patients (p=0.006) (Thohan et al 2005).

Haft et al (2007) recorded significant improvements in LVEDV, LVESV and LVESD for both LVAD types at three months post-implantation. In addition, both LVADs significant decreased mitral valve insufficiency, tricuspid insufficiency and left atrial area ($p<0.05$ for all, compared to baseline measurements). Nevertheless, several significant differences were evident between both LVADs. In contrast to Garcia et al (2008) and Thohan et al (2005), LVEDD only significantly improved for continuous flow patients ($p<0.05$). Conversely, only P-LVAD recipients had a significant increase in LVEF ($p<0.05$) and sphericity ($p<0.05$). Intergroup analysis showed that the decrease in LV size, reduction in degree of mitral insufficiency, and increase in LVEF was significantly greater for P-LVAD patients compared to those treated with continuous flow ($p<0.05$ for all) (Thohan et al 2005).

Overall, two out of three studies which reported structural echocardiographic changes during LVAD support highlighted that P-LVADs appear to have greater beneficial effects towards LV mass/size and LVEF (Thohan et al 2007, Haft et al 2007). This implies that P-LVADs are more capable of inducing reverse cardiac remodelling compared to C-LVADs.

*Organ function parameters*

Three of the retrieved studies investigated organ function parameters during LVAD support (Sandner et al 2008, Patel et al 2008, Radovancevic et al 2007). Sandner et al (2008) stated that both P-LVAD and C-LVAD recipients achieved significant improvements in renal function post-implantation. Paired sample analysis of the C-LVAD group showed that glomerular filtration rate (GFR) increased significantly from implantation to: week 1 ($p=0.001$); week 2 ($p<0.001$); week 4 ($p<0.001$) and week 12 ($p=0.004$). For the P-LVAD group, GFR increased significantly from implantation to: week 1 ($p=0.007$); week 4 ($p=0.007$); and week 12 ($p=0.037$). Although significant improvements were observed from week 1 to week 12, the improvement of GFR from implantation to transplantation (C-LVAD: 145.9 ± 68.8 days; P-LVAD: 196.4 ± 116.4 days) for both continuous and pulsatile LVAD groups was not statistically significant. The authors noted that a trend towards significance appeared to be evident ($p=0.075$ and $p=0.054$, respectively). Meanwhile, creatinine clearance demonstrated improvement up to week 12 for C-LVAD patients only, and a trend towards significance was evident at transplantation ($p=0.066$), no such trend was observed for P-LVAD patients ($p=0.116$). Both LVAD groups had similar acute renal failure rates (C-LVAD: 38.1 %; P- LVAD: 31.0%, $p=0.512$).

Patel et al (2008) (follow-up: 6 months) demonstrated that measures of renal and hepatic function (serum creatinine, total bilirubin, alanine aminotransferase and aspartate aminotransferase) trended towards improvement for C-LVAD recipients, but was not statistically significant. In contrast, significant improvements in serum creatinine, blood urea nitrogen, alanine aminotransferase, and aspartate aminotransferase were evident in P-LVAD recipients (Table 4) (Patel et al 2008).

**Table 4: Organ function outcomes during C-LVAD and P-LVAD support.**

Patel et al (2008)

Level III-3 intervention evidence

Patients
**Pulsatile flow:** 43 patients (HeartMate I)
**Continuous flow:** 34 patients (HeartMate II)

Renal/hepatic function

| | Preoperative | 1 mth | 3 mths | 6 mths |
|---|---|---|---|---|
| **Pulsatile flow** | | | | |
| Blood urea nitrogen (mg/dL) | 37.0±21.1 | 23.7±21.1 | 18.6±9.5 | 19.2±7.3 |
| Creatinine (mg/dL) | 1.7 ± 0.9 | 1.4 ± 0.9 | 1.2 ± 0.5 | 1.1 ± 0.4 |
| Total bilirubin (mg/dL) | 1.9±1.5 | 2.9±7.21 | 1.9±1.8 | 0.5±0.3 |
| Alanine aminotransferase (IU) | 82.3±96.0 | 30.8±40.8 | 21.1±13.4 | 23.6±17.0 |
| Aspartate aminotransferase (IU) | 72.1±90.6 | 50.3±68.8 | 28.0±16.2 | 33.7±28.6 |
| **Continuous flow** | | | | |
| Blood urea nitrogen (mg/dL) | 42.4±24.4 | 27.1±17.1 | 22.6±15.1 | 25.5±13.4 |
| Creatinine (mg/dL) | 1.7±0.8 | 1.4±0.8 | 1.1±0.5 | 1.3±0.7 |
| Total bilirubin (mg/dL) | 1.5±1.1 | 2.2±3.2 | 1.1±1.1 | 0.8±0.5 |
| Alanine aminotransferase (IU) | 92.1±221.3 | 70.1±165.6 | 38.8±43.00 | 25.6±14.4 |
| Aspartate aminotransferase (IU) | 48.9±63.8 | 101/8±230.5 | 55.4±90.2 | 31.1±20.0 |

Radovancevic et al (2007)

Level III-2 intervention evidence

Patients
Pulsatile flow: 58 patients (HeartMate I)
Continuous flow: 12 patients (Jarvik 2000/HeartMate II)

End-organ function parameters

| | Creatinine (mg/dl) | Creatinine clearance (ml/min) | BUN (mg/dl) | Albumin (mg/dl) |
|---|---|---|---|---|
| Reference range | 0.8 – 1.5 | M: 97 – 137<br>F: 88 – 128 | 10 – 26 | 3.5 – 5.0 |
| **Baseline** | | | | |
| C-LVAD | 1.3 ± 0.4 | 74 ± 25 | 25 ± 12 | 3.7 ± 1.4 |
| P-LVAD | 1.6 ± 0.8 | 81 ± 37 | 21 ± 18 | 3.4 ± 0.7 |
| **6 months** | | | | |
| C-LVAD | 1.5 ± 0.9 | 83 ± 40 | 23 ± 7 | 3.7 ± 0.6 |
| P-LVAD | 1.5 ± 1.1 | 91 ± 36 | 24 ± 12 | 3.8 ± 0.5 |
| **9 months** | | | | |
| C-LVAD | 1.3 ± 0.5 | 85 ± 36 | 33 ± 30 | 4.2 ± 0.3 |
| P-LVAD | 1.6 ± 1.1 | 90 ± 48 | 27 ± 15 | 3.8 ± 0.5 |
| **12 months** | | | | |
| C-LVAD | 1.2 ± 0.5 | 100 ± 35 | 26 ± 21 | 4.0 ± 0.4 |
| P-LVAD | 1.6 ± 0.9 | 102 ± 39 | 32 ± 37 | 3.7 ± 0.5 |
| **15 months** | | | | |
| C-LVAD | 1.5 ± 0.8 | 82 ± 34 | 40 ± 34 | 4.1 ± 0.4 |
| P-LVAD | 1.3 ± 0.3 | 104 ± 31 | 18 ± 4 | 4.0 ± 0.4 |
| **p-value** | 0.91 | 0.39 | 0.48 | 0.91 |

-continued below-

| | Total bilirubin (mg/dl) | SGOT (U/liter) | SGPT (U/liter) | LDH (U/liter) |
|---|---|---|---|---|
| Reference range | 0.1 – 1.2 | 5 – 40 | 5 – 50 | 90 – 225 |
| **Baseline** | | | | |
| C-LVAD | 1.8 ± 1.4 | 47 ± 30 | 36 ± 22 | 259 ± 116 |
| P-LVAD | 2.1 ± 1.9 | 54 ± 31 | 46 ± 32 | 249 ± 95 |

| | | | | | |
|---|---|---|---|---|---|
| | **6 months** | | | | |
| | C-LVAD | 0.9 ± 0.6 | 39 ± 15 | 22 ± 12 | 456 ± 331 |
| | P-LVAD | 0.8 ± 0.4 | 43 ± 42 | 38 ± 83 | 351 ± 337 |
| | **9 months** | | | | |
| | C-LVAD | 1.2 ± 0.5 | 38 ± 11 | 18 ± 8 | 540 ± 386 |
| | P-LVAD | 0.9 ± 0.5 | 34 ± 22 | 21 ± 13 | 324 ± 261 |
| | **12 months** | | | | |
| | C-LVAD | 1.0 ± 0.4 | 33 ± 11 | 16 ± 8 | 360 ± 50 |
| | P-LVAD | 1.0 ± 0.8 | 29 ± 7 | 19 ± 11 | 268 ± 145 |
| | **15 months** | | | | |
| | C-LVAD | 1.0 ± 0.7 | 56 ± 80 | 23 ± 25 | 539 ± 272 |
| | P-LVAD | 0.8 ± 0.2 | 28 ± 8 | 23 ± 5 | 302 ± 186 |
| | **p-value** | 0.53 | 0.59 | 0.62 | 0.33 |

BUN: blood urea nitrogen; C-LVAD: continuous flow LVAD; P-LVAD: Pulsatile flow LVAD; LDH: lactic dehydrogenase; SGOT: serum glutamic-oxaloacetic transaminase; SGPT: serum glutamic-pyruvic transaminase.

Sandner et al (2008)

Level III-2 intervention evidence

Patients
Pulsatile flow: 29 patients (Novacor)
Continuous flow: 63 patients (DeBakey, HeartWare, DuraHeart)

Renal function

a) Glomerular filtration rate (Modification of Diet in Renal Disease method, ml/min/1.73m3)

| | Continuous | | Pulsatile | | |
|---|---|---|---|---|---|
| | No. | Mean ± SD | No. | Mean ± SD | p-value |
| Implant | 63 | 59.4 ± 22.4 | 29 | 52.5 ± 20.7 | 0.163 |
| Week 1 | 61 | 76.4 ± 38.6 | 26 | 69.2 ± 34.7 | 0.416 |
| Week 2 | 62 | 80.9 ± 34.7 | 21 | 68.8 ± 34.8 | 0.169 |
| Week 4 | 55 | 84.3 ± 32.9 | 21 | 79.9 ± 38.7 | 0.622 |
| Week 12 | 44 | 75.3 ± 30.2 | 19 | 74.2 ± 27.2 | 0.893 |
| Transplant | 28 | 73.5 ± 22.6 | 15 | 64.1 ± 22.4 | 0.202 |

b) Creatinine clearance (Cockcroft-Gault formula, ml/min)

| | Continuous | | Pulsatile | | |
|---|---|---|---|---|---|
| | No. | Mean ± SD | No. | Mean ± SD | p-value |
| Implant | 63 | 71.6 ± 27.3 | 29 | 63.1 ± 29.8 | 0.183 |
| Week 1 | 61 | 87.5 ± 39.9 | 26 | 81.5 ± 45.5 | 0.540 |
| Week 2 | 62 | 91.6 ± 35.1 | 21 | 81.1 ± 44.4 | 0.274 |
| Week 4 | 55 | 95.6 ± 31.3 | 21 | 92.4 ± 48.7 | 0.782 |
| Week 12 | 44 | 88.1 ± 32.5 | 19 | 89.6 ± 35.9 | 0.873 |
| Transplant | 28 | 86.9 ± 23.9 | 15 | 74.6 ± 26.4 | 0.128 |

Acute renal failure (p=n.s.)
Pulsatile flow: 31%
Continuous flow: 38.1%

Radovancevic et al (2007) did not identify any significant differences in albumin, blood urea nitrogen, creatinine, creatinine clearance, total bilurubin and transaminase (SGOT and SGPT) concentrations between C-LVAD and P-LVAD groups up to 15-months post-implantation. Total bilirubin decreased significantly for both LVAD groups during 6-months of LVAD support (-1.1 ± 0.6 mg/dl; p=0.001) and was maintained throughout. All other measured parameters remained within the reference levels over the course of the study, with the exception of lactic dehydrogenase which was substantially elevated for both groups.

*Exercise performance*

Exercise performance assessed by peak exercise oxygen consumption ($Vo_2$), duration of exercise, and respiratory exchange ratio were comparable between P-

LVAD and C-LVAD groups (Haft et al 2007). Pump flow increased significantly during peak exercise for both LVAD groups compared to pre-exercise measurements. However, the increase in the P-LVAD groups was significantly greater than the increased in flow observed in the C-LVAD group ($p<0.05$) (Table 5).

**Table 5: Exercise performance of C-LVAD and P-LVAD (Haft et al 2007).**

| | Pulsatile flow | Continuous flow | 95% confidence interval |
|---|---|---|---|
| **Peak Vo2 (mL/kg/min)** | 15.4 ± 4.0 | 15.6 ± 4.7 | (-3.2 to 3.0) |
| **Peak percent predicted (Vo2)** | 46.8 ± 10.2 | 49.1 ± 13.6 | (-6.3 to 11.0) |
| **Exercise time (min:sec)** | 10:25 ± 3:04 | 9:31 ± 3:19 | (-3:35 to 1:02) |
| **METS** | 4.4 ± 1.2 | 4.3 ± 1.4 | (-1.1 to 0.8) |
| **Peak respiratory exchange ratio** | 1.13 ± 0.12 | 1.11 ± 0.12 | (-1.1 to 0.8) |
| **Heart rate at peak exercise (beats/min)** | 131 ± 27 | 124 ± 24 | |
| **Pump flow: preexercise (L/kg/m2)** | 2.4 ± 0.6 | 2.7 ± 0.2 | |
| **Pump flow: peak exercise (L/kg/m2)** | 4.0 ± 0.5* (66.7 ± 7.5%) | 3.4 ± 0.4*† (25.9 ±14.7%) | |

*p<0.05 compared with preexercise pump flow
†p<0.05 compared with the change in pump flow from rest to peak exercise in pulsatile flow group

# Potential Cost Impact

## Cost Analysis

No cost effectiveness studies on the use of C-LVADs have been conducted. However, the simpler construction of C-LVADs compared to P-LVADs should translate to lower manufacturing costs. Siegenthaler et al (2003) noted that the lower readmission rates due to infection observed for C-LVAD patients translates to an average cost saving of €12,839 for each re-admission.

# Ethical Considerations

## Informed Consent

End stage cardiac failure patients who require LVAD support must be informed of the risks associated with the procedure. In particular, patients should be made aware of the type of LVAD that will be utilised and the associated risks as well as potential advantages. If a C- LVAD is selected, patients have to be made aware of the fact that these devices have not been subjected to the same level of scrutiny compared to current P-LVADs.

## Access Issues

LVAD implantation is a complex procedure, requiring specific expertise and essential medical equipment. This procedure can only be conducted at specialist hospitals with the required infrastructure and is therefore limited to major metropolitan areas.

# Training and Accreditation

## Training

Training in cardiothoracic surgery may commence following the satisfactory completion of Basic Surgical Training (BST). The program is co-ordinated by the Royal Australasian College of Surgeons Board of Cardiothoracic Surgery which is responsible for the selection, placement and monitoring of all Trainees in Australia and New Zealand. Once BST is completed, an individual may proceed with four years specialist training in cardiothoracic surgery.

Manufacturers of C-LVADs typically provide training to surgeons and clinical support staff in order to ensure proper implantation and setup of the device.

## Clinical Guidelines

According to the guidelines for the prevention, detection and management of people with chronic heart failure in Australia (2006), the recommendations for device-based treatment of symptomatic chronic heart failure are:

**Table 6: Guidelines for the prevention, detection and management of people with chronic heart failure in Australia 2006 (Krum et al 2006).**

| Recommendation | Grade of recommendation |
|---|---|
| Biventricular pacing (cardiac resynchronisation therapy), with or without implantable cardioverter defibrillator, should be considered in patients with CHF who fulfil each of the following criteria:<br>• NYHA symptoms class III–IV on treatment<br>• Dilated heart failure with LVEF ≤ 35%<br>• QRS duration ≥ 120 ms<br>• Sinus rhythm | A |
| Implantable cardioverter defibrillator implantation should be considered in patients with CHF who fulfil any of the following criteria:<br>• Survived cardiac arrest resulting from ventricular fibrillation or ventricular tachycardia not due to a transient or reversible cause<br>• Spontaneous sustained ventricular tachycardia in association with structural coronary heart disease | A |

| | |
|---|---|
| • LVEF ≤ 30% measured at least 1 month after acute myocardial infarction or 3 months after coronary artery revascularisation surgery<br>• Symptomatic CHF (NYHA functional class II–III) and LVEF ≤ 35% | |

NYHA = New York Heart Association. LVEF = left-ventricular ejection fraction.

At the time of writing, no clear national guidelines with specific recommendations on the use of LVADs in end stage heart failure patients were available.

## Limitations of the Assessment

Methodological issues and the relevance or currency of information provided over time are paramount in any assessment carried out in the early life of a technology.

Horizon scanning forms an integral component of health technology assessment; however, it is a specialised and quite distinct activity conducted for an entirely different purpose. The rapid evolution of technological advances can in some cases overtake the speed at which trials or other reviews are conducted. In many cases, by the time a study or review has been completed, the technology may have evolved to a higher level leaving the technology under investigation obsolete and replaced.

A horizon scanning report maintains a predictive or speculative focus, often based on low level evidence, and is aimed at informing policy and decision makers. It is not a definitive assessment of the safety, effectiveness, ethical considerations and cost-effectiveness of a technology.

In the context of a rapidly evolving technology, a horizon scanning report is a 'state of play' assessment that presents a trade-off between the value of early, uncertain information, versus the value of certain, but late information that may be of limited relevance to policy and decision makers.

This report provides an assessment of the current state of development of continuous flow ventricular assist devices, its present and potential use in the Australian public health system, and future implications for the use of this technology.

## Search Strategy used for the Report

The sources utilised in this assessment are listed in Table 7. The medical literature was searched with the search terms outlined in Table 8 to identify relevant studies up to September 2008 in English only. In addition to this, major international health technology assessment databases and clinical trial registers were searched.

**Table 7: Literature sources utilised in assessment**

| Source | Location |
|---|---|
| ***Electronic databases*** | |
| AustHealth | University of Adelaide library |
| Australian Medical Index | University of Adelaide library |
| CINAHL | University of Adelaide library |
| Cochrane Library – including Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, the Cochrane Central Register of Controlled Trials (CENTRAL), the Health Technology Assessment Databese, the NHS Economic Evaluation Database | University of Adelaide library |
| Current Contents | University of Adelaide library |
| Embase | Personal subscription |
| Pre-Medline and Medline | University of Adelaide library |
| PyscINFO | Personal subscription |
| RACS electronic library | Personal subscription |
| ***Internet*** | |
| Blue Cross and Blue Shield Association's Technology Evaluation Center | http://www.bcbs.com/tec/ |
| Canadian Agency for Drugs and Technologies in Health | http://www.cadth.ca |
| Current Controlled Trials metaRegister | http://www.controlled-trials.com/ |
| EuroScan | http://www.euroscan.bham.ac.uk/ |
| Health Technology Assessment International | http://www.htai.org/ |
| International Network for agencies for Health Technology Assessment | http://www.inahta.org |
| Medicines and Healthcare products Regulatory Agency (UK) | http://www.mhra.gov.uk/ |
| US Food and Drug Administration, Center for Devices and | http://www.fda.gov/cdrh/in |

| | |
|---|---|
| Radiological Health | dex.html |
| US Food and Drug Administration, Manufacturer and User Facility Device Experience Database | http://www.fda.gov/cdrh/maude.html |
| UK National Research Register | http://www.nrr.nhs.uk/ |
| Websites of specialty organisations | http://www.health.gov.au/<br>http://www.heartfoundation.org.au |

**Table 8: Search terms utilised**

| Search terms |
|---|
| **MeSH** |
| Heart-assist devices*; heart failure/surgery*; |
| **Text words** |
| Ventricular assist device, continuous flow VAD, axial flow VAD, centrifugal flow VAD |
| **Limits** |
| English, human |

## Availability and Level of Evidence

The medical literature (Table 7) was searched utilising the search terms outlined in Table 8 to identify relevant studies and reviews until September 2008. In addition, major international health assessment databases were searched.

Seventeen comparative studies were retrieved for inclusion in this horizon scanning report. The profiles of the included studies are summarised in Appendix B.

# Sources of Further Information

List of ongoing C-LVAD clinical trials:

Pilot Study of Data Collection During Computerized Tomography (CT) to Determine Accurate Flow Rates for Axial Flow Ventricular Assist Device (VAD) Patients. Estimated completion date: June 2010. C-LVAD: HeartMate II. ClinicalTrials.gov Identifier: NCT00427739.

Evaluation of the VentrAssistTM Left Ventricular Assist Device for the Treatment of Advanced Heart Failure - Destination Therapy. Estimated completion date: June 2012. C-LVAD: VentrAssist. ClinicalTrials.gov Identifier: NCT00490321.

Evaluation of the VentrAssistTM Left Ventricular Assist Device as a Bridge to Cardiac Transplantation - Pivotal Trial. Estimated completion date: June 2010. C-LVAD: VentrAssist.
ClinicalTrials.gov Identifier: NCT00483197.

The HeartMate II LVAS Pivotal Study Protocol, Destination Therapy. Estimated Completion Date: June 2011. C-LVAD: HeartMate II.
ClinicalTrials.gov Identifier: NCT00121485.

The HeartMate II LVAS Pivotal Study Protocol, Bridge to Cardiac Transplantation. Estimated Completion Date: April 2009. C-LVAD: HeartMate II.
ClinicalTrials.gov Identifier: NCT00121472.

# Conclusions

The clinical burden of congestive heart failure continuous to mount worldwide, in Australia and New Zealand, donor heart shortage continues to weigh heavily on the survival of end stage heart failure patients. In order to keep patients alive while waiting for a suitable donor heart, LVADs have been increasingly utilised for long-term support. Pneumatic P-LVADs in particular have been shown to be an effective bridge to transplantation. The REMATCH destination therapy trial demonstrated the significant survival benefits of LVAD support in patients with end stage heart failure; however, this randomised trial also highlighted that patients under LVAD support experience significantly higher rates of complications and adverse events compared to medical therapy. Therefore although P-LVAD support is effective, clinicians are still concerned with the risks of mechanical failure or other complications.

As LVADs begin to play a more prominent role as a bridge to transplantation and destination therapy, researchers have attempted to improve on current designs and to address the shortfalls of current LVADs. A new generation of LVADs that produce continuous flow instead of pulsatile flow has emerged as an alternative to P-LVADs. C-LVADs are substantially smaller and lighter than current P-LVADs and have less moving parts. These characteristics confers some theoretical advantage compared to P-LVADs as less mechanical movement may translate to lower rates of mechanical failure and its smaller size requires less incisions, hence less risk for infections.

The evidence base currently available on C-LVADs is limited to comparative studies and often low quality case series studies. A total of 17 comparative studies (Level III intervention evidence) were retrieved for inclusion in this report.

The evidence retrieved was quite supportive of the capabilities of C-LVADs. Haemodynamic improvements during C-LVAD support were generally

comparable to P-LVADs. However, one study showed that P-LVADs appear to excel in certain haemodynamic parameters, such as mean arterial pressure and ventricular stroke work index. One study demonstrated that C-LVAD support resulted in significant improvements in LVEDD, LVEDV, LVESV, LVESD and LVEF, and the outcomes were comparable to P-LVADs patients. However, some studies with longer follow-up indicated that although C-LVAD support results in significant structural improvements, P-LVADs appear to confer significantly better improvements in LV size, LV mass and LVEF. This implies that reverse ventricular remodelling is more prevalent in patients who receive P-LVAD support. The reason for this is not known and warrants further investigation. Exercise performance appears to be similar for both P-LVAD and C-LVAD patients ($Vo_2$, duration of exercise, respiratory exchange ratio, pump flow), but peak exercise pump flow was significantly greater in P-LVAD supported patients.

When organ function parameters are considered, two studies with follow-up ranging from three to six months reported that measures of renal function (GFR, creatinine clearance) improved significantly post-implantation and was comparable to P-LVAD. In contrast, a third study (follow-up: 15 months) noted that only P-LVAD recipients achieved significant improvements in measures of renal and hepatic function while C-LVAD recipients did not experience significant improvements in these measures. Meanwhile, patient survival was demonstrated to be similar for both types of LVADs in six of the included studies. Long-term Kaplan Meier estimates revealed that patient survival rates remain similar up to 5 years post-implantation.

One of the purported advantages of C-LVAD support was lower infection rates due to the fact that smaller incisions are required during implantation. Two studies supported this view, with significantly lower device, pocket, wound and driveline infections. In addition, antibody use was significantly shorter in duration and the lower rate of positive bacterial culture provides further support that infection rates are lower for C-LVAD recipients compared to P-LVAD recipients. However, one study noted that C-LVAD recipients had significantly higher interleukin-6 and anaphylatoxin C5a levels compared to P-LVAD patients (other inflammatory measures were comparable [TNFα, PNM EL, C3a]), but the reason for this is not known and may be related to the biocompatibility of materials used to construct the C-LVAD pump. The incidence of severe bleeding and need for blood/platelet transfusion was significantly lower for C-LVAD patients.

Biochemical markers of brain injury (S100B, NSE) returned to baseline values within one day post implantation for C-LVAD patients. Neurologic assessments showed that there were no neurological deficits for C-LVAD patients compared to two cases for the P-LVAD group. Examination of cognitive P300 evoked potentials showed that C-LVAD recipients experienced significant improvements post-implantation that were comparable to P-LVAD recipients. This indicates that the use of C-LVAD does not result in neurological injury or impair neurological function.

One of the major questions related to the use of C-LVADs is whether continuous flow has any detrimental effects toward physiological function. One of the included studies highlighted that C-LVAD support appears to impair vascular reactivity. Another study highlighted that vascular pulsatility is markedly reduced during C-LVAD support. These results indicate that long-term C-LVAD support might lead to vascular stiffening and may have long-term implications to health. However, at this point of time high quality long-term clinical data concerning these issues remains scarce.

The overall consensus from the retrieved evidence suggests that C-LVADs are capable of matching the performance of P-LVADs. There are some clear advantages that support the use of C-LVADs as well, such as the lower infection rates and bleeding complications. However, it is important to recognise that all of the studies retrieved had relatively small patient numbers, and the scarcity of long-term data leaves many questions unanswered. The mechanical reliability of C-LVADs was not adequately investigated in the studies retrieved, physiological effects of long-term continuous flow remain ambiguous and issues of pump biocompatibility were not addressed in detail. Randomised-controlled trials are required before the medical community can elucidate the advantages and potential safety issues of C-LVAD support relative to P-LVAD.

# Appendix A: Levels of Evidence

Designation of levels of evidence according to type of research question

| Level | Intervention [§] | Diagnosis [**] | Prognosis | Aetiology [†††] | Screening |
|---|---|---|---|---|---|
| I [*] | A systematic review of level II studies | A systematic review of level II studies | A systematic review of level II studies | A systematic review of level II studies | A systematic review of level II studies |
| II | A randomised controlled trial | A study of test accuracy with: an independent, blinded comparison with a valid reference standard, [§§] among consecutive patients with a defined clinical presentation [††] | A prospective cohort study [***] | A prospective cohort study | A randomised controlled trial |
| III-1 | A pseudorandomised controlled trial (i.e. alternate allocation or some other method) | A study of test accuracy with: an independent, blinded comparison with a valid reference standard, [§§] among non-consecutive patients with a defined clinical presentation[††] | All or none [§§§] | All or none [§§§] | A pseudorandomised controlled trial (i.e. alternate allocation or some other method) |
| III-2 | A comparative study with concurrent controls:<br>Non-randomised, experimental trial [†]<br>Cohort study<br>Case-control study<br>Interrupted time series with a control group | A comparison with reference standard that does not meet the criteria required for Level II and III-1 evidence | Analysis of prognostic factors amongst untreated control patients in a randomised controlled trial | A retrospective cohort study | A comparative study with concurrent controls:<br>Non-randomised, experimental trial<br>Cohort study<br>Case-control study |
| III-3 | A comparative study without concurrent controls:<br>Historical control study<br>Two or more single arm study [‡]<br>Interrupted time series without a parallel control group | Diagnostic case-control study [††] | A retrospective cohort study | A case-control study | A comparative study without concurrent controls:<br>Historical control study<br>Two or more single arm study |
| IV | Case series with either post-test or pre-test/post-test outcomes | Study of diagnostic yield (no reference standard) [‡‡] | Case series, or cohort study of patients at different stages of disease | A cross-sectional study | Case series |

## Tablenotes

* A systematic review will only be assigned a level of evidence as high as the studies it contains, excepting where those studies are of level II evidence.

§ Definitions of these study designs are provided on pages 7-8 *How to use the evidence: assessment and application of scientific evidence* (NHMRC 2000b*)*.

† This also includes controlled before-and-after (pre-test/post-test) studies, as well as indirect comparisons (i.e. utilise A vs. B and B vs. C, to determine A vs. C).

‡ Comparing single arm studies i.e. case series from two studies.

** The dimensions of evidence apply only to studies of diagnostic accuracy. To assess the effectiveness of a diagnostic test there also needs to be a consideration of the impact of the test on patient management and health outcomes. See *MSAC (2004) Guidelines for the assessment of diagnostic technologies*. Available at: www.msac.gov.au .

§§ The validity of the reference standard should be determined in the context of the disease under review. Criteria for determining the validity of the reference standard should be pre-specified. This can include the choice of the reference standard(s) and its timing in relation to the index test. The validity of the reference standard can be determined through quality appraisal of the study. See Whiting P, Rutjes AWS, Reitsma JB, Bossuyt PMM, Kleijnen J. The development of QADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. *BMC Medical Research Methodology*, 2003, 3: 25.

†† Well-designed population based case-control studies (e.g. population based screening studies where test accuracy is assessed on all cases, with a random sample of controls) do capture a population with a representative spectrum of disease and thus fulfil the requirements for a valid assembly of patients. These types of studies should be considered as Level II evidence. However, in some cases the population assembled is not representative of the use of the test in practice. In diagnostic case-control studies a selected sample of patients already known to have the disease are compared with a separate group of normal/healthy people known to be free of the disease. In this situation patients with borderline or mild expressions of the disease, and conditions mimicking the disease are excluded, which can lead to exaggeration of both sensitivity and specificity. This is called spectrum bias because the spectrum of study participants will not be representative of patients seen in practice.

‡‡ Studies of diagnostic yield provide the yield of diseased patients, as determined by an index test, without confirmation of accuracy by a reference standard. These may be the only alternative when there is no reliable reference standard.

*** At study inception the cohort is either non-diseased or all at the same stage of the disease.

§§§ All or none of the people with the risk factor(s) experience the outcome. For example, no smallpox develops in the absence of the specific virus; and clear proof of the causal link has come from the disappearance of small pox after large-scale vaccination.

††† If it is possible and/or ethical to determine a causal relationship using experimental evidence, then the 'Intervention' hierarchy of evidence should be utilised. If it is only possible and/or ethical to determine a causal relationship using observational evidence (i.e. cannot allocate groups to a potential harmful exposure, such as nuclear radiation), then the 'Aetiology' hierarchy of evidence should be utilised.

Note 1: Assessment of comparative harms/safety should occur according to the hierarchy presented for each of the research questions, with the proviso that this assessment occurs within the context of the topic being assessed. Some harms are rare and cannot feasibly be captured within randomised controlled trials; physical harms and psychological harms may need to be addressed by different study designs; harms from diagnostic testing include the likelihood of false positive and false negative results; harms from screening include the likelihood of false alarm and false reassurance results.

Note 2: When a level of evidence is attributed in the text of a document, it should also be framed according to its corresponding research question e.g. level II intervention evidence; level IV diagnostic evidence; level III-2 prognostic evidence etc.

Hierarchies adapted and modified from: NHMRC 1999; Lijmer et al 1999; Phillips et al 2001; Bandolier editorial 1999)

# Appendix B: Profiles of studies

| Study | Location | Study design | Study population | Patient baseline characteristics | Outcomes assessed |
|---|---|---|---|---|---|
| Amir et al (2006) | Texas, United States | Level III-2 intervention study | **Pulsatile flow:** 10 patients (HeartMate I)<br>**Continuous flow:** 10 patients (Jarvik 2000) | **Pulsatile flow**<br>Age: 55±10 years<br>Weight: 96.6±17.9 kg<br>BMI: 30.4±4.9<br><br>**Continuous flow**<br>Age: 51 ± 16 years<br>Weight: 76.7±9.5 kg<br>BMI: 27.3±3.8<br><br>*p<0.05 for weight and BMI between groups | Flow mediated vascular dilation, nitroglycerin mediated dilation. |
| Feller et al (2007) | Maryland, United States | Level III-2 intervention study | Patients<br>**Pulsatile flow:** 13 patients (Novacor)<br><br>**Continuous flow:** 14 patients (Jarvik 2000) | **Pulsatile flow**<br>Age: 52±17.3 years<br>Body surface area: 2.1±0.2 $m^2$<br><br>**Continuous flow**<br>Age: 56±10.3 years<br>Body surface area: 1.9±0.2 $m^2$<br><br>*Baseline characteristics comparable between groups | Perioperative outcomes (CPB time, mean duration of stay), duration of support, inotrope use, postoperative complications. |
| Garcia et al (2008) | Minnesota, United States | Level III-2 intervention evidence | **Pulsatile flow:** 15 patients (HeartMate XVE)<br>**Continuous flow:** 20 patients (HeartMate II) | **Pulsatile flow**<br>Age: 52±12 years<br>Weight: 90±17 kg<br><br>**Continuous flow**<br>Age: 56±14 years<br>Weight: 82±18 kg<br><br>*Baseline characteristics comparable between groups | Echocardiographic outcomes (LVEDD, LVESD etc.), haemodynamic outcomes. |
| Garatti et al (2008) | Milan, Italy | Level III-2 intervention evidence | **Pulsatile flow**<br>Novacor: 41 patients<br><br>**Continuous flow**<br>DeBakey: 28 patients<br>InCor: 8 patients | **Pulsatile flow**<br>Age: 47±12.5 years<br>Body surface area: 1.93±0.16 $m^2$<br>Dilated cardiomypathy: 32 patients (78%)<br><br>**Continuous flow**<br>Age: 48.6±12.4 years<br>Body surface area: 1.77±0.18 $m^2$<br>Dilated cardiomypathy: 21 patients (58.3%)<br><br>*p<0.05 for gender, body surface area, dilated cardiomyopathy. | Mean support duration, Haemodynamic outcomes, mortality/survival, rejection rates. |

| | | | | | |
|---|---|---|---|---|---|
| Haft et al (2007) | California, United States | Level III-2 intervention evidence | **Pulsatile flow:** 16 patients (HeartMate XVE)<br>**Continuous flow:** 18 patients (HeartMate II) | **Pulsatile flow**<br>Age: 51±14 years<br>Body surface area: 2.03±0.20 $m^2$<br><br>**Continuous flow**<br>Age: 52±14 years<br>Body surface area: 2.00±0.32 $m^2$<br><br>*Baseline characteristics comparable between groups | Haemodynamic outcomes, echocardiographic outcomes, exercise performance, laboratory data (serum sodium, bilirubin, blood urea nitrogen, brain natriuetic peptide, prealbumin) |
| Klotz et al (2006) | Muenster, Germany | Level III-2 intervention evidence | **Pulsatile flow**<br>Novacor: 61 patients<br>HeartMate: 19 patients<br><br>**Continuous flow**<br>DeBakey: 30 patients<br>InCor: 20 patients | **Pulsatile flow**<br><u>Novacor</u><br>Age: 45.0±11.9 years<br>BMI: 24.6±3.6<br><u>Heartmate</u><br>Age: 49.4±7.2 years<br>BMI:25.2±4.8<br>**Continuous flow**<br><u>DeBakey</u><br>Age: 43.0±14.6 years<br>BMI: 24.5±3.2<br><u>InCor</u><br>Age: 46.1±11.1 years<br>BMI: 24.9±3.9<br><br>*Baseline characteristics comparable between groups | Mortality/survival, rejection rates. |
| Klotz et al (2004) | Muenster, Germany | Level III-2 intervention evidence | **Pulsatile flow:** 21 patients (Novacor/Heart Mate VE)<br><br>**Continuous flow:** 10 patients (DeBakey) | **Pulsatile flow**<br>Age: 43.5±12.5 years<br><br>**Continuous flow**<br>Age: 33.7±15.0 years<br><br>*Baseline characteristics comparable between groups | Haemodynamic outcomes, Echocardiographic outcomes, mortality/survival. |
| Loebe et al (2001) | Berlin, Germany | Level III-2 intervention evidence | **Pulsatile flow:** 6 patients (Novacor)<br><br>**Continuous flow:** 6 patients (DeBakey) | Overall age: 47±7.7 years<br><br>No other patient characteristics reported | Inflammatory response (TNF, IL-6, PNM EL, C5a, C3a) |
| Patel et al (2008) | Maryland, United States | Level III-2 intervention evidence | <u>Patients</u><br>**Pulsatile flow:** 43 patients (HeartMate I)<br>**Continuous flow:** 34 patients (HeartMate II) | **Pulsatile flow**<br>Age: 48.7±13.2 years<br><br>**Continuous flow**<br>Age: 51.4±14.5 years<br><br>*Baseline characteristics comparable between groups | Operative results (CPB bypass time, haemodynamic outcomes, inotropic requirement, right heart dysfunction, renal and hepatic function, complications, mortality/survival. |

| | | | | | |
|---|---|---|---|---|---|
| Potapov et al (2001) | Berlin, Germany | Level III-2 intervention evidence | Patients<br>**Pulsatile flow:** 7 patients (Novacor)<br>**Continuous flow:** 8 patients (DeBakey) | **Pulsatile flow**<br>Age: 50.4±9.6 years<br>Serum creatinine: 0.96±0.09 mg/dl<br>**Continuous flow**<br>Age: 47.6±12.3 years<br>Serum creatinine: 1.23±0.3 mg/dl<br><br>*p<0.05 for preoperative serum creatinine levels. Other characteristics comparable. | S100B levels, neuron specific enolase levels. |
| Radovancevic et al (2007) | Texas, United States | Level III-2 intervention evidence | **Pulsatile flow:** 58 patients (HeartMate I)<br>**Continuous flow:** 12 patients (Jarvik 2000/HeartMate II) | **Pulsatile flow**<br>Age: 50±14 years<br>Weight: 88±15 kg<br>Haemoglobin: 12.2±1.9 mg/dl<br><br>**Continuous flow**<br>Age: 53±15 years<br>Weight: 81±14 kg<br>Haemoglobin: 10.5±1.7 mg/dl<br><br>*Baseline characteristics comparable between groups (with exception to haemoglobin) | Haemodynamic outcomes, end-organ function (renal and hepatic) |
| Sandner et al (2008) | Berlin, Germany | Level III-2 intervention evidence | **Pulsatile flow:** 29 patients (Novacor)<br>**Continuous flow:** 63 patients (DeBakey, HeartWare, DuraHeart) | **Pulsatile flow**<br>Age: 58.6±7.8 years<br><br>**Continuous flow**<br>Age: 58.6±7.8 years<br><br>*Baseline characteristics comparable between groups | Renal function (creatinine clearance, glomerular filtration rate) |
| Schulman et al (2007) | New York, United States | Level III-2 intervention study | **Pulsatile flow:** 65 patients (HeartMate I)<br>**Continuous flow:** 27 patients (HeartMate II/ DeBakey) | **Pulsatile flow**<br>Age: 51.8±13.3 years<br>Weight: 87±20 kg<br>BMI: 28.6±6.1<br>Body surface area: 2±0.3 $m^2$<br>**Continuous flow**<br>Age: 55.1±12.8 years<br>Weight: 75.2±17.7 kg<br>BMI: 24.9±5.5<br>Body surface area: 1.89±0.25 $m^2$<br><br>*p<0.05 for gender, body surface area, weight and BMI. Other characteristics similar. | Infection rates |
| Siegenthaler et al (2003) | Freiburg, Germany | Level III-2 intervention study | **Pulsatile flow:** 11 patients (HeartMate I)<br>**Continuous flow:** 6 patients (Jarvik 2000) | **Pulsatile flow**<br>Age: 46±13 years<br><br>**Continuous flow**<br>Age: 58±6 years<br><br>*Baseline characteristics comparable between groups | Operative data, infection rates, antibiotic use, bacterial culture, readmission rates |
| Thohan et al (2005) | Texas, Unites States | Level III-2 intervention evidence | **Pulsatile flow:** 12 patients (Novacor) | **Pulsatile flow**<br>Age: 53±14 years | Echocardiographic outcomes, |

| | | | | | |
|---|---|---|---|---|---|
| | | | **Continuous flow:** 8 patients (DeBakey) | **Continuous flow**<br>Age: 50±11 years<br><br>*Baseline characteristics comparable between groups | cellular changes (histologic) |
| Travis et al (2007) | Kentucky, United States | Level III-2 intervention evidence | **Normal ventricular function**: 8 patients<br>**Pulsatile flow:** 12 patients (HeartMate XVE/Thoratec IVAD)<br>**Continuous flow:** 10 patients (HeartMate II, DeBakey) | **Normal ventricular function**<br>Age: 62±16 years<br>Weight: 89±15 kg<br><br>**Pulsatile flow**<br>Age: 56±13 years<br>Weight: 90±21 kg<br><br>**Continuous flow**<br>Age: 51±13 years<br>Weight: 79±21 kg<br><br>*Baseline characteristics comparable between groups | Surplus haemodynamic energy, energy equivalent pressure, LVAD flow rates. |
| Zimpfer et al (2006) | Vienna, Austria | Level III-2 intervention evidence | **Pulsatile flow:** 18 patients (Thoratec, Novacor)<br>**Continuous flow:** 11 patients (DeBakey) | **Pulsatile flow**<br>Age: 50±10 years<br><br>**Continuous flow**<br>Age: 56±15 years<br><br>*Baseline characteristics comparable between groups | P300 evoked potentials |

# Appendix C: HTA internet sites

**AUSTRALIA**

- Centre for Clinical Effectiveness, Monash University
  http://www.med.monash.edu.au/healthservices/cce/evidence/

- Health Economics Unit, Monash University
  http://chpe.buseco.monash.edu.au

**AUSTRIA**

- Institute of Technology Assessment / HTA unit
  http://www.oeaw.ac.at/ita/welcome.htm

**CANADA**

- Agence d'Evaluation des Technologies et des Modes d'Intervention en Santé (AETMIS) http://www.aetmis.gouv.qc.ca/en/

- Alberta Heritage Foundation for Medical Research (AHFMR)
  http://www.ahfmr.ab.ca/publications.html

- Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
  http://www.cadth.ca/index.php/en/

- Canadian Health Economics Research Association (CHERA/ACRES) – Cabot database http://www.mycabot.ca

- Centre for Health Economics and Policy Analysis (CHEPA), McMaster University http://www.chepa.org

- Centre for Health Services and Policy Research (CHSPR), University of British Columbia http://www.chspr.ubc.ca

- Health Utilities Index (HUI) http://www.fhs.mcmaster.ca/hug/index.htm

- Institute for Clinical and Evaluative Studies (ICES) http://www.ices.on.ca

**DENMARK**

- Danish Institute for Health Technology Assessment (DIHTA) http://www.dihta.dk/publikationer/index_uk.asp

- Danish Institute for Health Services Research (DSI) http://www.dsi.dk/engelsk.html

**FINLAND**

- Finnish Office for Health Technology Assessment (FINOHTA) http://finohta.stakes.fi/FI/index.htm

**FRANCE**

- L'Agence Nationale d'Accréditation et d'Evaluation en Santé (ANAES)

  http://www.anaes.fr/

**GERMANY**

- German Institute for Medical Documentation and Information (DIMDI) / HTA

  http://www.dimdi.de/dynamic/en/

**THE NETHERLANDS**

- Health Council of the Netherlands Gezondheidsraad
  http://www.gr.nl/adviezen.php

**NEW ZEALAND**

- New Zealand Health Technology Assessment (NZHTA)
  http://nzhta.chmeds.ac.nz/

**NORWAY**

- Norwegian Centre for Health Technology Assessment (SMM)

  http://www.kunnskapssenteret.no/

**SPAIN**

- Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud "Carlos III" / Health Technology Assessment Agency (AETS)

  http://www.isciii.es/htdocs/investigacion/Agencia_quees.jsp

- Catalan Agency for Health Technology Assessment (CAHTA)
  http://www.aatrm.net/html/en/dir394/index.html

**SWEDEN**

- Swedish Council on Technology Assessment in Health Care (SBU)

  http://www.sbu.se/www/index.asp

- Center for Medical Health Technology Assessment

  http://www.cmt.liu.se/

**SWITZERLAND**

- Swiss Network on Health Technology Assessment (SNHTA)
  http://www.snhta.ch/

**UNITED KINGDOM**

- NHS Quality Improvement Scotland
  http://www.nhshealthquality.org

- National Health Service Health Technology Assessment (UK) / National Coordinating Centre for health Technology Assessment (NCCHTA)
  http://www.hta.nhsweb.nhs.uk/

- University of York NHS Centre for Reviews and Dissemination (NHS CRD)
  http://www.your.ac.uk/inst/crd/

- National Institute for Clinical Excellence (NICE)
  http://www.nice.org.uk/

**UNITED STATES**

- Agency for Healthcare Research and Quality (AHRQ)
  http://www.ahrq.gov/clinic/techix.htm

- Harvard School of Public Health – Cost-Utility Analysis Registry
  http://www.tufts-nemc.org/cearegistry/index.html

- U.S. Blue Cross / Blue Shield Association Technology Evaluation Center (TEC)
  http://www.bcbs.com/tec/index.html

# References


Abhayaratna WP, Smith WT, Becker NG, Marwick TH, Jeffery IM, McGill DA. Prevalence of heart failure and systolic ventricular dysfunction in older Australians: the Canberra Heart Study. *Medical Journal of Australia* 2006 184**(4)**:151-154.

Amir O, Radovancevic B, Delgado RM 3rd, Kar B, Radovancevic R, Henderson M, Cohn WE, Smart FW. Peripheral vascular reactivity in patients with pulsatile vs axial flow left ventricular assist device support. *Journal of Heart and Lung Transplantation* 2006; 25**(4)**:391-394.

ANZOD Registry Report 2008. Australia and New Zealand Organ Donation Registry Adelaide, South Australia.

Australian Institute of Health and Welfare (AIHW). Heart failure. Last updated 2006. http://www.aihw.gov.au/cvd/majordiseases/heartfailure.cfm [Accessed September 2008].

Birks EJ, Tansley PD, Yacoub MH, Bowles CT, Hipkin M, Hardy J, Banner NR, Khaghani A. Incidence and clinical management of life-threatening left ventricular assist device failure. *Journal of Heart and Lung Transplantation* 2004; 23**(8)**: 964-969.

Dang NC, Topkara VK, Mercando M, Kay J, Kruger KH, Aboodi MS, Oz MC, Naka Y. Right heart failure after left ventricular assist device implantation in patients with chronic congestive heart failure. *Journal of Heart and Lung Transplantation* 2006; 25**(1)**:1-6.

Dembitsky WP, Tector AJ, Park S, Moskowitz AJ, Gelijns AC, Ronan NS, Piccione W Jr, Holman WL, Furukawa S, Weinberg AD, Heatley G, Poirier VL, Damme L, Long JW. Left ventricular assist device performance with long-term circulatory support: lessons from the REMATCH trial. *Annals of Thoracic Surgery* 2004; 78**(6)**:2123-9

Feller ED, Sorensen EN, Haddad M, Pierson RN 3rd, Johnson FL, Brown JM, Griffith BP. Clinical outcomes are similar in pulsatile and nonpulsatile left ventricular assist device recipients. *Annals of Thoracic Surgery* 2007 Mar; 83**(3)**:1082-1088.

Garatti A, Bruschi G, Colombo T, Russo C, Lanfranconi M, Milazzo F, Frigerio M, Vitali E. Clinical outcome and bridge to transplant rate of left ventricular assist

device recipient patients: comparison between continuous-flow and pulsatile-flow devices. *European Journal of Cardiothoracic Surgery* 2008; 34**(2)**:275-80.

Garcia S, Kandar F, Boyle A, Colvin-Adams M, Lliao K, Joyce L, John R. Effects of pulsatile- and continuous-flow left ventricular assist devices on left ventricular unloading. *Journal of Heart and Lung Transplantation* 2008; 27**(3)**: 261-267.

Haft J, Armstrong W, Dyke DB, Aaronson KD, Koelling TM, Farrar DJ, Pagani FD. Hemodynamic and exercise performance with pulsatile and continuous-flow left ventricular assist devices. *Circulation* 2007; 116**(11 Suppl)**: I8-I15.

Kaiser DR, Billups K, Mason C, Wetterling R, Lundberg JL, Bank AJ. Impaired brachial artery endothelium-dependent and -independent vasodilation in men with erectile dysfunction and no other clinical cardiovascular disease. Journal of the American College of Cardiology 2004; 43**(2)**:179-184.

Klotz S, Deng MC, Stypmann J, Roetker J, Wilhelm MJ, Hammel D, Scheld HH, Schmid C. Left ventricular pressure and volume unloading during pulsatile versus nonpulsatile left ventricular assist device support. *Annals of Thoracic Surgery* 2004; 77**(1)**:143-149.

Klotz S, Stypmann J, Welp H, Schmid C, Drees G, Rukosujew A, Scheld HH. Does continuous flow left ventricular assist device technology have a positive impact on outcome pretransplant and posttransplant? *Annals of Thoracic Surgery* 2006; 82**(5)**:1774-1778.

Loebe M, Koster A, Sänger S, Potapov EV, Kuppe H, Noon GP, Hetzer R. Inflammatory response after implantation of a left ventricular assist device: comparison between the axial flow MicroMed DeBakey VAD and the pulsatile Novacor device. *American Society for Artificial Internal Organs Journal* 2001; 47**(3)**: 272-274.

Mesana TG. Rotary blood pumps for cardiac assistance: a "must"? *Artificial Organs* 2004; 28**(2)**: 218-225.

National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand (Chronic heart Failure Guidelines Expert Writing Panel). Guidelines for the prevention, detection and management of chronic heart failure in Australia, 2006.

Patel ND, Weiss ES, Schaffer J, Ullrich SL, Rivard DC, Shah AS, Russell SD, Conte JV. Right heart dysfunction after left ventricular assist device implantation: a comparison of the pulsatile HeartMate I and axial-flow HeartMate II devices. *Annals of Thoracic Surgery* 2008; 86**(3)**:832-840.

Potapov EV, Loebe M, Abdul-Khaliq H, Koster A, Stein J, Sodian R, Kopitz M, Hausmann H, Noon GP, DeBakey ME, Hetzer R. Postoperative course of S-100B protein and neuron-specific enolase in patients after implantation of continuous and pulsatile flow LVADs. *Journal of Heart and Lung Transplantation* 2001; 20**(12)**: 1310-1316.

Radovancevic B, Vrtovec B, de Kort E, Radovancevic R, Gregoric ID, Frazier OH. End-organ function in patients on long-term circulatory support with continuous- or pulsatile-flow assist devices. *Journal of Heart and Lung Transplantation* 2007; 26**(8)**: 815-818.

Rose EA, Gelijns AC, Moskowitz AJ, Heitjan DF, Stevenson LW, Dembitsky W, Long JW, Ascheim DD, Tierney AR, Levitan RG, Watson JT, Meier P, Ronan NS, Shapiro PA, Lazar RM, Miller LW, Gupta L, Frazier OH, Desvigne-Nickens P, Oz MC, Poirier VL; Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) Study Group. Long-term mechanical left ventricular assistance for end-stage heart failure. *New England Journal of Medicine* 2001; 345**(20)**: 1435-1443.

Sandner SE, Zimpfer D, Zrunek P, Dunkler D, Schima H, Rajek A, Grimm M, Wolner E, Wieselthaler GM. Renal function after implantation of continuous versus pulsatile flow left ventricular assist devices. *Journal of Heart and Lung Transplantation* 2008; 27**(5)**:469-473.

Saxton GA Jr, Andrews CB. An ideal heart pump with hydrodynamic characteristics analogous to the mammalian heart. *American Society for Artificial Internal Organs* 1960; 10-11**(6)**: 288-291.

Schmid C, Tjan TD, Etz C, Schmidt C, Wenzelburger F, Wilhelm M, Rothenburger M, Drees G, Scheld HH. First clinical experience with the Incor left ventricular assist device. *Journal of Heart and Lung Transplantation* 2005; 24**(9)**:1188-1194.

Schulman AR, Martens TP, Christos PJ, Russo MJ, Comas GM, Cheema FH, Naseem TM, Wang R, Idrissi KA, Bailey SH, Naka Y. Comparisons of infection complications between continuous flow and pulsatile flow left ventricular assist devices *Journal of Thoracic and Cardiovascular Surgery* 2007; 133**(3)**: 841-842.

Siegenthaler MP, Martin J, Pernice K, Doenst T, Sorg S, Trummer G, Friesewinkel O, Beyersdorf F. The Jarvik 2000 is associated with less infections than the HeartMate left ventricular assist device. *European Journal of Cardiothoracic Surgery* 2003; 23**(5)**: 748-754.

Thalmann M, Schima H, Wieselthaler G, Wolner E. Physiology of continuous blood flow in recipients of rotary cardiac assist devices. *Journal of Heart and Lung Transplantation* 2005; 24**(3)**:237-245.

Thohan V, Stetson SJ, Nagueh SF, Rivas-Gotz C, Koerner MM, Lafuente JA, Loebe M, Noon GP, Torre-Amione G. Cellular and hemodynamics responses of failing myocardium to continuous flow mechanical circulatory support using the DeBakey-Noon left ventricular assist device: a comparative analysis with pulsatile-type devices. *Journal of Heart and Lung Transplantation* 2005 May; 24**(5)**:566-575.

Travis AR, Giridharan GA, Pantalos GM, Dowling RD, Prabhu SD, Slaughter MS, Sobieski M, Undar A, Farrar DJ, Koenig SC. Vascular pulsatility in patients with a pulsatile- or continuous-flow ventricular assist device. *Journal of Thoracic and Cardiovascular Surgery* 2007;133**(2)**: 517-524.

Vita JA, Keaney JF Jr. Endothelial function: a barometer for cardiovascular risk? *Circulation* 2002; 106**(6)**:640-642.

Zimpfer D, Wieselthaler G, Czerny M, Fakin R, Haider D, Zrunek P, Roethy W, Schima H, Wolner E, Grimm M. Neurocognitive function in patients with ventricular assist devices: a comparison of pulsatile and continuous blood flow devices. *American Society for Artificial Internal Organs Journal* 2006; 52**(1)**:24-27.