
The use of biventricular assist devices in end stage chronic heart failure

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CERTIFICATE OF ORIGINAL AUTHORSHIP

I certify that the work in this thesis has not previously been submitted for a degree nor has it been submitted as part of requirements for a degree except as fully acknowledged within the text.

I also certify that the thesis has been written by me. Any help that I have received in my research work and the preparation of the thesis itself has been acknowledged. In addition, I certify that all information sources and literature used are indicated in the thesis.

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LIST OF ABBREVIATIONS AND ACRONYMS USED IN THIS THESIS

Abbreviation	Full term
AHA	American Heart Association
AoP	Aortic pressure
AR	Aortic regurgitation
ASAIO	American Society of Artificial Internal Organs
BMI	Body mass index
BiVAD	Biventricular assist device
BiVF	Biventricular failure
BP	Blood pressure
BTB	Bridge to bridge
BTR	Bridge to recovery
BTT	Bridge to transplant
CDAS	Continuous Data Acquisition System
cfBiVAD	Continuous flow biventricular assist device
cfLVAD	Continuous flow left ventricular assist device
cfTAH	Continuous flow total artificial heart
cfVAD	Continuous flow ventricular assist device
CHF	Chronic heart failure
CO	Cardiac output
CVP	Central venous pressure
DCM	Dilated cardiomyopathy
ECMO	Extracorporeal membrane oxygenation
FDA	Food and Drug Administration
HR	Heart rate
HVAD	HeartWare Ventricular Assist Device
IABP	Intra-aortic balloon pump
ICU	Intensive care unit
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
IQR	Interquartile range
IVAD	Intracorporeal ventricular assist device
LA	Left atrium
LAP	Left atrial pressure
LDH	Lactate dehydrogenase

LoS	Length of stay
LVAD	Left ventricular assist device
LV	Left ventricle
LVP	Left ventricular pressure
MAP	Mean arterial pressure
MCL	Mock circulatory loop
MCSD	Mechanical Circulatory Support Device
MPAP	Mean pulmonary arterial pressure
MR	Mitral regurgitation
MVAD	Miniaturized ventricular assist device
NYHA	New York Heart Association
PA	Pulmonary artery
PAP	Pulmonary artery pressure
PVAD	Paracorporeal ventricular assist device
PVC	Poly-vinyl
PVR	Pulmonary vascular resistance
RAP	Right atrial pressure
RNA	Ribonucleic acid
RV	Right ventricle
RVAD	Right ventricular assist device
RVF	Right ventricular failure
RVP	Right ventricular pressure
SD	Standard deviation
SOFA	Sequential Organ Failure Assessment
SPSS	Statistical Software Package for the Social Sciences
SVR	Systemic vascular resistance
TAH	Total Artificial Heart
TET	Transcutaneous energy transfer
TR	Tricuspid regurgitation
UK	United Kingdom
USA	United States of America
VAD	Ventricular Assist Device
VA-ECLS	Veno-arterial extracorporeal life support
VPA-ECLS	Veno-pulmonary arterial extracorporeal life support

ABSTRACT

Patients with severe biventricular failure are often supported with early generation paracorporeal biventricular assist devices (BiVAD). Compared to durable continuous flow left ventricular assist devices (LVAD), these pulsatile BiVAD systems are decades behind in terms of both design and performance. Therefore the aim of this thesis was to assess the use of two continuous flow LVADs (HeartWare HVAD) for biventricular support. Various aspects of this novel BiVAD system were tested. Pump performance and haemodynamic characteristics were tested using an in-vitro model of the human cardiovascular system, clinical short and long term outcomes were retrospectively reviewed in 14 patients (10 over the course of this thesis), and laboratory assessment was undertaken to evaluate the consequences of BiVAD support on the patients cardiac parameters, particularly on the genetic variations of cardiomyocytes in 7 paired samples (implant vs. explant). Our in-vitro simulations revealed that dual LVAD therapy (BiVAD with two LVADs) was an acceptable form of biventricular support. Interestingly, from a haemodynamic viewpoint, post-LVAD induced right ventricular failure was successfully reversed with delayed RVAD support. In addition, our experiments also revealed successful BiVAD support despite the presence of mitral or tricuspid regurgitation. Our clinical investigations depicted acceptable 1 year survival and high transplantation rates. It also demonstrated an innovative methodology of implanting LVAD in both the right ventricle and right atrium for right ventricular support. The laboratory findings resulted in the development of sound methodology and application of investigatory techniques. However, no differences were found between the up/down regulation of genetic markers pre- and post BiVAD support. Further research in the area is warranted. In conclusion, the use of dual LVAD therapy is an acceptable means of providing durable BiVAD support in patients unsuitable for isolated LVAD therapy.

CHAPTER I- INTRODUCTION

1.1 BACKGROUND

Chronic heart failure (CHF) is a complex clinical syndrome that occurs when the heart malfunctions as a pump; failing to either pump enough blood to the lungs or unable to fill enough oxygen rich blood within the ventricles to pump into the systemic circulation, ⁽¹⁾ and is a major health epidemic increasing in prevalence and incidence with age. In addition, it is also one of the major causes of hospitalisations and is often associated with prolonged admissions; contributing to the burden imposed on the health care system. Despite major improvements in the treatment of CHF, some patients continue to experience limiting symptoms requiring mechanical circulatory support or heart transplantation. This subgroup of advanced CHF will be the focus of this research. This thesis presents the evaluation of the Heartware HVAD ventricular assist device (HVAD) in a biventricular setting. This chapter describes the burden of advanced CHF, the use of mechanical circulatory support and the outline of this thesis.

1.2 ADVANCED CHRONIC HEART FAILURE

Similar to CHF, the definition of advanced CHF has been difficult to establish. In the past, patients with a higher risk of mortality, advanced symptoms and a poorer quality of life were defined as having advanced CHF ⁽²⁾. However, these variables are subject to bias and can be difficult to associate with advanced CHF when patients also present with other comorbidities. Currently, the American College of Cardiology/American Heart Association (AHA) defines

advanced CHF as patients with “limiting daily life (New York Heart Association class III or IV) despite previous therapy with angiotensin converting enzyme inhibitors, diuretics, digoxin and more recently beta blockers; requiring inotropic therapy, heart transplantation due to a low cardiac output or left ventricular assist device to sustain life ⁽³⁾. The most defining aspect of advanced CHF patients is their gradual tolerance to agents of proven efficacy ⁽³⁻⁶⁾. This definition of advanced CHF will be used in this research.

1.3 AETIOLOGY

Chronic heart failure has been well established as a disorder that reduces or alters myocardial performance. In general, it diminishes the ventricles ability to efficiently fill or circulate blood ⁽⁷⁾, causing the heart to undergo a vicious cycle of a slow yet progressive decline in myocardial activity ⁽⁷⁻⁹⁾. This cycle is usually initiated with a reduction in cardiac output, which can be caused by; (i) a structural abnormality in the heart, (ii) a condition that can cause pressure overload (e.g. aortic stenosis, chronic hypertension) or volume overload (e.g. mitral regurgitation), or (iii) as a consequence of advanced comorbidities such as coronary artery disease, hypertension, valvular heart disease and diabetes ^(1, 8, 9). When a reduction in cardiac output occurs, the body’s natural feedback regulatory system releases a variety of neurohormones to help increase cardiac output ⁽¹⁾.

The release of neurohormones, particularly the renin-angiotensin aldosterone system results in the promotion of salt and water retention by the kidneys and vasoconstriction throughout the body. This in turn promotes dilation of the chambers, increasing the stress applied to the walls of the myocardium and ultimately results in ventricular dysfunction ^(1, 8). When activated for a short period of time, this mechanism acts to maintain arterial pressure and preserves circulatory homeostasis ⁽¹⁰⁾. However when this mechanism is activated for chronically excess

periods, it promotes a decrease in cardiac function and results in changes to cardiac structure (remodeling), causing hypertrophy and fibrosis ⁽¹⁾. Systolic dysfunction progressively worsens over time. It undergoes a repetitive cycle of ventricular dilation, wall reconfiguration and reduced ejection fraction ⁽⁸⁾ until severe signs and symptoms of CHF manifest i.e. advanced CHF.

1.4 EPIDEMIOLOGY

In conjunction with the aging population and presence of various comorbidities within this cohort, other factors such as improvements in management and survival of CHF patients ^(11, 12), as well as the decreased mortality after myocardial infarction events ⁽¹³⁾, has led to the growing concern that CHF may become the next cardiovascular “epidemic” ⁽¹⁴⁾. Despite the growing concern, there are no national population based studies available to monitor advanced CHF, with few Australian based databases available to track mild to moderate CHF. Although estimates on the prevalence and incidence rates of CHF are available, certain factors such as lack of national epidemiological data ⁽⁷⁾, poor surveillance ⁽¹⁵⁾, and numerous comorbidities present within these CHF cohorts ^(7, 9, 16) can underestimate true values. These limitations are further amplified in advanced CHF cohorts.

1.4.1 Prevalence and Incidence

As aforementioned the prevalence and incidence rate of CHF is often difficult to measure, as the epidemiological data of CHF in Australia is limited compared to other industrialized countries ⁽⁷⁾. To date, most of the management strategies and treatment options have been derived from international large scale CHF cohort studies such as the Framingham study ^(11, 12, 17, 18). Overall, CHF is believed to affect 1% of the general population and has been estimated

to affect 3-5% of people aged 65 and over and 10% of people aged 75 and over in western countries, as shown in Figure 1.1 ⁽¹⁹⁾.

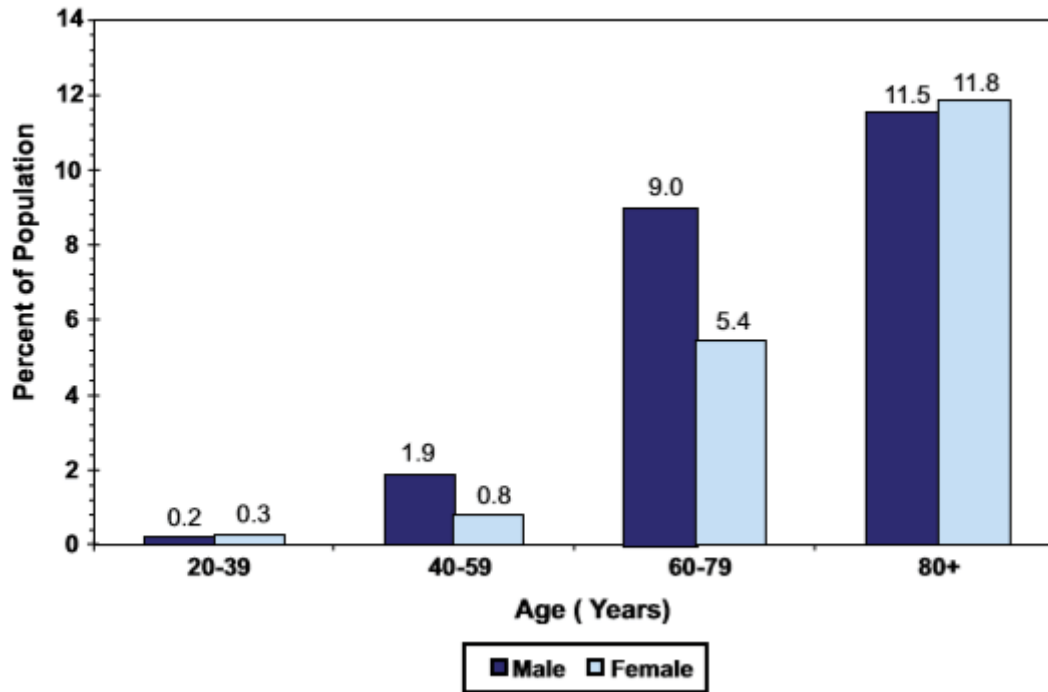


Figure 1.1 Prevalence of CHF across all age groups

While determining the actual prevalence of CHF without a national epidemiological database and an efficient surveillance strategy is difficult ⁽²⁰⁾, rough estimates can be derived by integrating international estimates ⁽¹⁷⁾ with Australian data ⁽²¹⁻²³⁾. Based on these estimates, there are approximately 300,000 Australians living with CHF (1.5-2% of the population) and an average of 30,000 new cases diagnosed each year. No estimates on either prevalence or incidence are currently available on advanced CHF patients. However, according to international data 30% of the diagnosed CHF population progress to develop advanced CHF.

1.4.2 Morbidity

Chronic heart failure is a life limiting and potential lethal condition that significantly contributes to the burden imposed on the health care system. It is a major cause of hospitalisations and is often associated with prolonged admissions. On average, patients can

spend up to 11 to 28 days in hospital before being discharged ^(24, 25). Between 2000 and 2001, 41,000 Australian hospitalizations were attributed to a primary diagnosis of CHF ⁽²⁶⁾. Moreover, according to the NSW Health Information Bureau, 9% of all patients admitted with a primary diagnosis of CHF within NSW hospitals were re-admitted within 28 days ⁽²⁷⁾. Similar trends are also evident in larger international studies in both Europe and the US. Evidence shows that approximately 1/3 of all patients admitted for CHF are re-admitted within 6 months in the United States and 12 months in the United Kingdoms ^(25, 28). Rates of re-admissions increase in patients suffering from advanced CHF ⁽⁴⁾, ranging from 2 to 5 admissions in one year ⁽²⁹⁾. Furthermore, evidence suggests that with each subsequent hospitalization, there is an incremental increase in the patient's risk of death ⁽³⁰⁾. Considering that 57% of all CHF admissions are preventable ⁽³¹⁾, more effort must be made to educate the general public and patients in managing CHF symptoms. Pre-emptive measures such as lifestyle changes, (exercise and dietary changes), and adherence to prescribed medications can improve longevity and patients quality of life ^(1, 8, 16).

1.4.3 Mortality

Aside from the high morbidity rates evident in CHF patients, CHF is also commonly associated with increased mortality ^(1, 30, 32) and a worse prognosis than many common forms of malignancies with the exception of lung cancer, as shown in Figure 1.2 ⁽³³⁾. Although current data suggest improvements in the survival rate of CHF patients during admission and one year following admission ⁽³⁴⁻³⁶⁾, their long-term survival remains poor. Depending on the point of diagnosis (community vs. hospital) and the timing of disease manifestation, the five year survival of CHF can range between 50%-75% ^(14, 17). In fact, when compared to the general population of the same age, the mortality rate was 4 to 8 times greater in CHF patients ⁽³⁷⁾.

Consequently, survival rates of patients with advanced CHF are much worse; ranging from 10-30% at 1 year and approximately 9% at 2 years. Currently, with the exception of breast cancer, CHF has been identified as a main contributor to more life years prematurely lost than the majority of malignancies in women ⁽¹⁷⁾. Based on larger international studies ⁽¹⁷⁾, the true number of CHF related mortality is expected to be 10-fold that of the official figures suggested ⁽³⁸⁾.

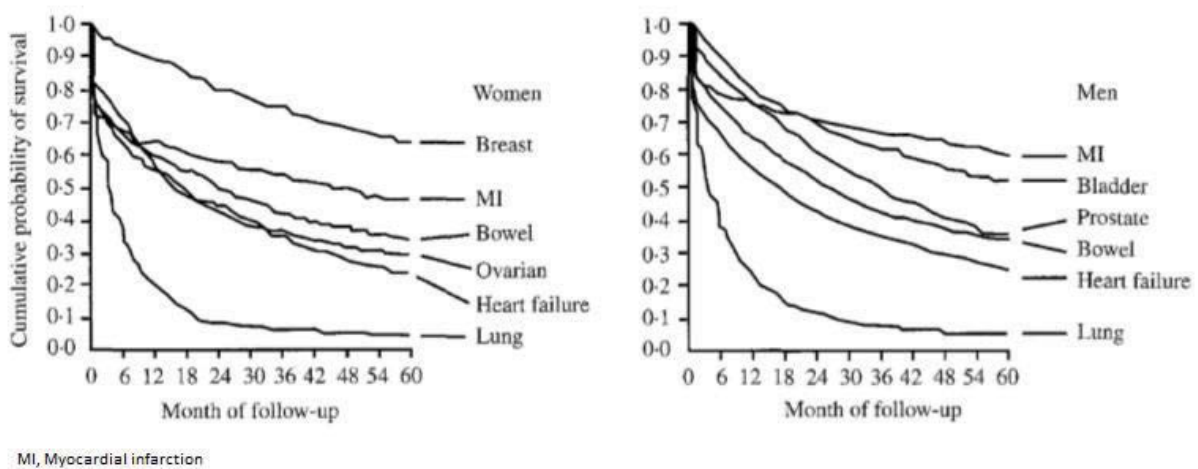


Figure 1.2 Five-year survival rate of CHF vs. most common forms of cancer, adapted from Stewart et al. 2001

1.5 BURDEN AND COST

Chronic heart failure is increasingly recognized as a growing burden on the health care system. In the US alone, CHF related discharges, reported in 2009, accounted for a total of \$4.4 billion of the American health care costs ⁽³¹⁾. Based on international epidemiological data and cost analysis research, CHF consumes approximately 1.5%-2.5% of total healthcare cost ⁽¹⁷⁾. An Australian analysis on the burden of CHF has suggested that CHF contributes to more than \$1 billion of health care cost per annum ⁽³⁸⁾, with CHF related hospitalisation as the greatest contributor. In fact, hospitalisation costs account for 69% of treatment costs in most western countries ⁽¹⁴⁾, making it one of the major factor associated with the burden of CHF. It is

estimated that up to half of all CHF related hospitalisations can be prevented or reduced with appropriate education, and patient compliance to treatment and life-style changes.

To date there are no data available on the burden and cost of advanced CHF on the health care system. However, as advanced CHF is the end-stage clinical course of CHF, its burden and cost on the health care system can be extrapolated from current CHF data. In fact, it may even be greater as advanced CHF patients tend to have higher rates of hospitalisations, more comorbidity, and longer length of stay and often require more drastic expensive medical/surgical procedures.

1.6 MANAGEMENT

The fundamental management goals in advanced CHF involves relieving symptoms, improving patient's quality of life, decreasing hospitalization rates and reducing CHF related mortality ^(1, 8, 16). However, due to the complexity associated with managing advanced CHF, treatment often varies depending on the type (e.g. systolic and diastolic dysfunction), underlying cause (e.g. hypertension, coronary artery disease) and the severity of the disease. In patients with advanced CHF, lifestyle changes and dietary restrictions are recommended ^(1, 8, 16) once heart failure progresses despite traditional pharmacological interventions such as angiotensin converting enzyme-Inhibitors, beta blockers and angiotensin receptor blockers ^(4, 5, 16). In such patients the treatment of choice is to undergo heart transplantation ^(5, 16).

1.7 HEART TRANSPLANTATION

While heart transplantation may be the optimal solution for carefully selected patients with advanced CHF ⁽¹⁶⁾, the decreased availability of donor hearts and increased number of patients on the waiting list has reduced the rate of heart transplantation procedures worldwide ⁽³⁹⁾. Although there has been great success in the performance of such a procedure,

heart transplantations are associated with many disadvantages. While infection, vasculopathy and the manifestation of malignant tumors are potential consequences of heart transplantation, the most serious risk is the possibility of organ rejection ^(16, 39).

In order to prevent organ rejection, patients are dependent on life-long immunosuppressive therapy. Prophylactic measures such as immunosuppressive therapy have side effects that could potentially harm the patient; these include the promotion of diabetes, hypertension, hyperlipidemia and reduced renal function ^(8, 16). The median survival after heart transplantation in Australia is 15 years ⁽⁴⁰⁾. Similar median survival rates were also reported in international registries (11.9 years) ⁽⁴¹⁾, with the highest rate of mortality occurring within the first 6 months post transplantation. As seen in

Figure 1.3, the mortality rate 1 year post transplant remains relatively constant, decreasing from 3-4% per year ⁽³⁹⁾. Despite the concerning post-transplant survival rate, patients with advanced CHF without a heart transplant have an even worse prognosis, quality of life and a higher risk of mortality ^(8, 16). Although it is in the best interest of the patient to receive a new heart, a shortage of donor hearts combined with the long waiting list and stringent criteria of eligibility, can delay if not exclude patients for transplantation. As a result, the use of mechanical assist devices such as ventricular assist devices have increasingly been used as a bridge to transplantation or more recently as destination therapy ⁽⁴²⁻⁴⁴⁾.

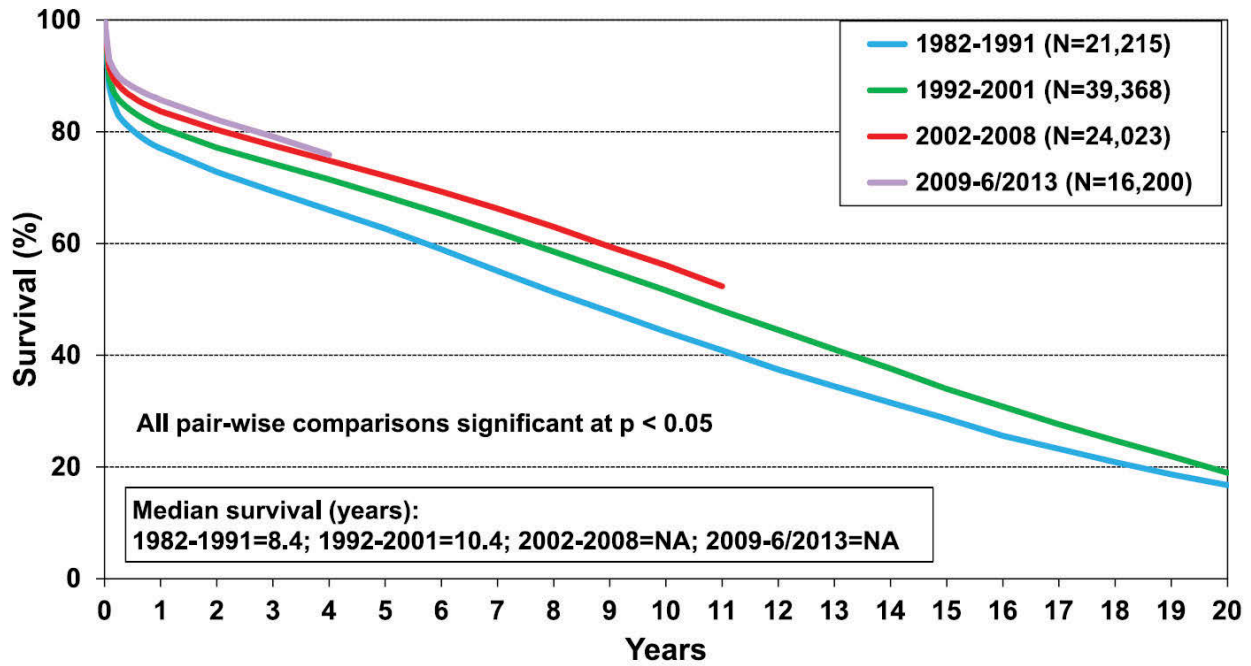


Figure 1.3 Median survival rate post transplantation (adapted from Lund et al ⁽⁴¹⁾)

1.8 VENTRICULAR ASSIST DEVICE

A ventricular assist device (VAD) is a mechanical pump that is surgically implanted into a patient's heart to support the left (LVAD), right (RVAD) or both sides (BiVAD) of the heart in terms of ventricular function and blood flow. The idea of using a mechanical assist device to support patients with cardiopulmonary conditions was first introduced by John Gibbon in 1953 ⁽⁴⁵⁾. In 1963, DeBakey adapted the idea of mechanically supporting the heart and created the first VAD to be implanted into a patient. Although the patient died four days post operation, the feasibility of such an intervention was established. It was not until 1966 that he was able to successfully implant a VAD into a patient with post- cardiectomy shock and demonstrate its potential as a bridge to recovery for 10 days ⁽⁴⁶⁾. Since then, there have been numerous designs of VADs, with marked improvements in patient's survival and quality of life ^(47, 48). An illustration of a second generation VAD is shown in Figure 1.4. While there are many different designs of VADs, all have two things in common. They all consist of an inflow cannula; which is inserted into the native heart, and an outflow cannula; which is often

attached to the aorta or the pulmonary artery depending on LVAD or RVAD support, respectively. As shown in Figure 1.4, blood flows from the left ventricle into the inflow cannula, which then directs the blood to the impeller or artificial valve/chamber. From there, the blood will be pumped through the outflow cannula and into the appropriate circulatory pathway (either systemic or pulmonary circulation). Depending on the VADs operational characteristics, they are classified as first, second or third generation devices ^(49, 50).

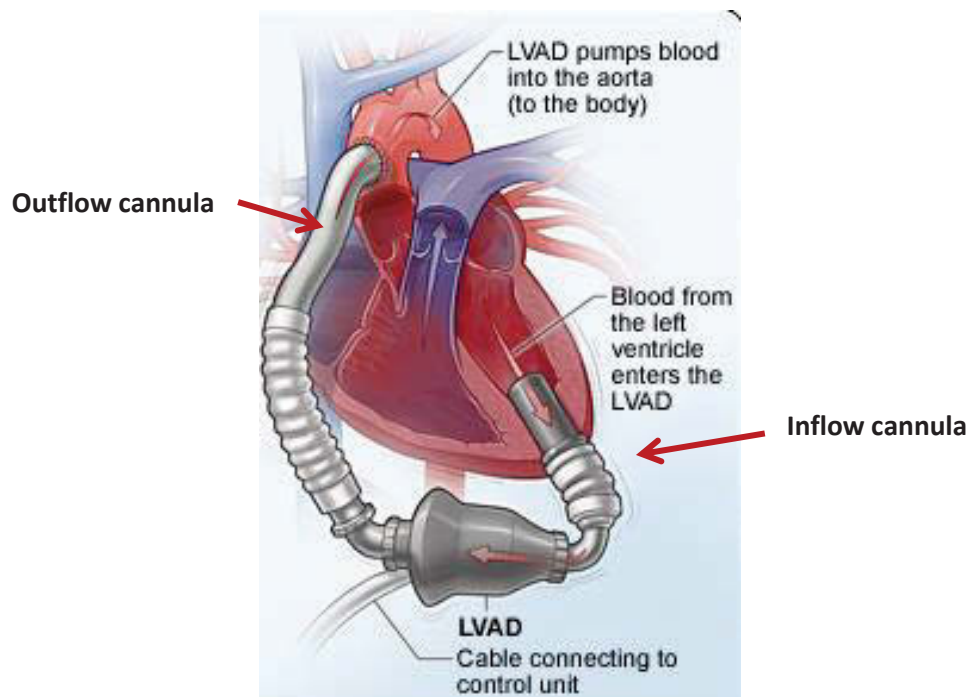


Figure 1.4 Illustration of left ventricular support using the second generation ventricular assist device

1.8.1 First generation devices

First generation devices were large volume displacement pumps that generated pulsatile flow through pneumatic or electronic stimulation ⁽⁴⁹⁾. These devices were the first ventricular assist devices to be introduced in clinical practice and were greatly limited by the size of the device. Only a patient with a body surface area of 1.5m² or greater was eligible for VAD implantation ⁽⁵¹⁾. Although this limitation was eventually overcome with the introduction of smaller, newer version of first generation devices, their efficacy was still limited by the poor durability of the

device. Mechanical failure due to mechanical valve wear, membrane rupture or displacements of small or moving parts created many complications ^(51, 52). First generation devices were associated with severe postoperative bleeding, postoperative infection, thrombus formation and hemolysis ⁽⁵³⁾ and were therefore not recommended for long term support. Their primary function was to act as short or medium-term solutions to support patients for transplant (bridge to transplantation) or even help recover from myocardial infarction (bridge to recovery). Large battery powered driver consoles also limited patient mobility and rehabilitation ^(51, 52). Despite all of these problems, the magnitude of the problem of advanced CHF is highlighted by the far superior 1-year survival with the first generation HeartMate LVAD compared to medical therapy in the REMATCH trial ⁽⁵⁴⁾.

1.8.2 Second generation devices

Second generation devices consist of a single moving rotor and are equipped with smaller driver consoles. Reducing moving or contacting parts reduces wear and tear, resulting in increased device stability and durability, while having a smaller driver console encourages increased patient mobility ^(51, 52). In addition, the smaller size allows them to be implanted into patients with a smaller body surface area. One of the key differences between the first and second generation device is that the latter consists of a rotary centrifuge and axial impeller which produces continuous rather than pulsatile flow ^(51, 52). Although VADs that generate continuous pulseless blood flow have been shown to be physiologically well tolerated ⁽⁵⁵⁾, they have also been associated with an increased risk of thrombogenicity and platelet dysfunction ⁽⁵⁶⁻⁵⁸⁾. These have been associated to the high shear force that is generated near the VADs rotor, bearings and seals ⁽⁵⁶⁻⁵⁸⁾. In a randomized control trial comparing first and second generation devices, second generation devices demonstrated a

much higher 2 year survival of 46% (compared to 11%) and lower device failure rate of 10% (compared to 36%) ⁽⁶⁾. However, no changes to the risk of stroke and overall bleeding were noted between first and second generation devices ⁽⁶⁾. Nonetheless, second generation devices demonstrated improved clinical performance, resulting in a wider acceptance and applicability of VAD interventions in patients with advanced CHF ⁽⁵¹⁾. Although the main complications associated with second generation devices were largely related to anticoagulation (bleeding and thrombosis), evidence shows that through modifications to the devices and improved anticoagulation regimes, many of these complications can be circumvented ^(59, 60).

1.8.3 Third generation devices

Third generation devices are newer devices that have been designed for long term mechanical support ^(51, 52). Similar to their second generation counterparts, third generation devices also generate continuous blood flow via the use of a centrifugal rotor ⁽⁵¹⁾. However, unlike second generation devices, these pumps do not require bearing, eliminating the risk of mechanical failure via wearing ^(51, 52, 59). Instead, third generation devices make use of electromagnetic and hydrodynamic forces to levitate the impeller within the housing and rotate it accordingly ^(51, 52, 61). Moreover, third generation devices are smaller than second generation devices which makes them less surgically invasive. Older generation devices require surgery of both the pericardial and abdominal cavity, whereas certain third generation devices such as the HeartWare HVAD or HeartMate-III can be directly implanted via the pericardial cavity alone ^(62, 63). The exclusion of abdominal surgery has shown improvements in patient survival and outcomes ⁽⁶⁴⁾. However, it is important to recognize that third generation devices are still new to clinical practice and therefore have a limited amount of data available. Nonetheless, these

third generation devices are predicted to provide a support system that has a lower risk of complications and a reduced rate of energy consumption ⁽⁴⁹⁾.

Although there are many first, second and third generation devices available in the market, not all of these VADs are intended for biventricular support. In fact, when compared to LVADs, devices that can act as biventricular support are very few in number (Summarized in Chapter 2). Furthermore, of the few devices available, two of those devices such as the Heartware HVAD (third generation) and the Jarvik 2000 (second generation) were primarily designed for left ventricular support, but have been shown to benefit patients with biventricular failure ^(6, 65).

1.9 INTERAGENCY REGISTRY FOR MECHANICALLY ASSISTED CIRCULATORY SUPPORT

Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) is a collaborative database which collects information on Mechanical Circulatory Support Device (MCSD) implants in the USA ⁽⁶⁶⁾. Data collection commenced in 2006 through to 2014 with more than 15,000 patients' registered ⁽⁶⁷⁾. In order to assess the need for MCSD therapy and the risk associated with its implantation, the INTERMACS established 7 clinical profiles (refer to Table 1.1). This is a more precise categorization of the disease severity in patient with advanced CHF compared to the traditional NYHA.

CHAPTER I – INTRODUCTION

Table 1.1 Interagency Registry for Mechanical Assisted Circulatory Support (INTERMACS) levels

Profile 1	Critical cardiogenic shock	Patient with life-threatening hypotension despite rapidly escalating inotropic support and critical organ hypoperfusion, often confirmed by worsening acidosis and/or lactate levels.
Profile 2	Progressive decline	Patient with declining function despite intravenous inotropic support, which may be manifest by worsening renal function, nutritional depletion, and inability to restore volume balance.
Profile 3	Stable but inotrope- dependent	Patient with stable blood pressure, organ function, nutrition and symptoms on continuous intravenous inotropic support (or a temporary circulatory support device or both), but demonstrating repeated failure to wean from support due to recurrent symptomatic hypotension or renal dysfunction.
Profile 4	Resting symptoms	Patient can be stabilized close to normal volume status but experiences daily symptoms of congestion at rest or during activities of daily living (ADL). Doses of diuretics generally fluctuate at very high levels. More intensive management and surveillance strategies should be considered, which may in some cases reveal poor compliance that would compromise outcomes with any therapy. Some patients may shuttle between Profiles 4 and 5.
Profile 5	Exertion intolerant	Comfortable at rest and with ADL but unable to engage in any other activity, living predominantly within the house. Patients are comfortable at rest without congestive symptoms, but may have underlying refractory elevated volume status, often with renal dysfunction. If underlying nutritional status and organ function are marginal, patient may be more at risk than INTERMACS Profile 4 and require definitive intervention
Profile 6	Exertion limited	Patient without evidence of fluid overload is comfortable at rest, and with ADL and minor activities outside the home but fatigues after the first few minutes of any meaningful activity. Attribution to cardiac limitation requires careful measurement of peak oxygen consumption, in some cases with hemodynamic monitoring to confirm severity of cardiac impairment
Profile 7	Advanced NYHA III	A placeholder for more precise specification in the future, this level includes patients who are without current or recent episodes of unstable fluid balance, living comfortably with meaningful activity limited to mild physical exertion.

1.10 LEFT VENTRICULAR ASSIST DEVICE

In 1994, LVADs were officially approved by the U.S. Food and Drug Administration (FDA) as a treatment option in patients with advanced CHF whom are unresponsive to medical therapy⁽⁶⁸⁾. As discussed above, the technology has rapidly evolved and stimulated a number of clinical trials which showed the use of LVADs as effective tools that can be used to prolong life to heart transplantation (bridge to transplant), reverse unfavorable cardiac remodeling (bridge to recovery), prolong life until a decision is made (bridge to decision) and can be used for the remainder of the patients life (destination therapy)^(54, 69). Older, pulsatile LVAD pumps were proven to deliver superior outcomes compared to medical management, with the pivotal 2001 REMATCH trial demonstrating an increased 1-year survival, 52% versus 25% respectively, a 48% reduction in the risk of death, and improved quality of life for patients with pulsatile flow LVADs^(70, 71). Subsequently, continuous flow LVADs have further improved patient outcomes with actuarial 1-year and 2-year survival rates consistently at 80% and 70% respectively in the seventh INTERMACS annual report⁽⁶⁷⁾.

1.10.1 Effects of LVAD on right ventricular function

Recently, studies have reported an increased rate of right ventricular failure post isolated LVAD implantation of up to 30%⁽⁷²⁻⁷⁴⁾. Similar rates are also seen at St. Vincent's with approximately 1 in 5 patients presenting with right ventricular failure after LVAD implantation. Right ventricular failure has been associated with peri-operative bleeding, blood transfusions, and shifts in the position of the septum which is located between the left and right ventricles of the heart⁽⁷⁵⁻⁷⁷⁾. Although right ventricular failure can be managed in many patients with the use of inotropic agents, prostaglandins and nitric oxide⁽⁷⁵⁾, a subset of patients with persistent right heart failure will require RVAD support⁽⁷²⁾.

The right ventricle is responsible for delivering blood through the lungs and to the left ventricle. The inability to perform such an action can result in inadequate blood delivery to the left ventricle and therefore a decreased delivery of oxygenated blood to the tissue and organs ⁽⁷⁸⁾. While the LVAD can improve left ventricular activity, it does not directly aid the right ventricle to pump blood to the lungs. However, the LVAD can indirectly influence the right ventricle by affecting factors such as venous return, septal motion and pulmonary artery pressure ⁽⁷²⁾. The use of the LVAD has been shown to relieve pulmonary pressure and decrease right ventricular afterload. This is achieved by increasing forward flow to the body, thereby decreasing the right ventricular afterload ⁽⁷⁸⁾. However, the increased cardiac output created by the LVAD has also been related to right ventricular failure. It has been postulated that due to the increased venous return caused by the LVAD, the right ventricle becomes overloaded, causing increased interventricular pressure and promoting ventricular overdistension ⁽⁷⁸⁾.

The use of the LVAD forces the wall of the septum to be shifted towards the left, promoting right ventricular failure by reducing right ventricular compliance and decreasing right ventricular contractility ⁽⁷⁹⁾. However, no sign of right ventricular impairment was evident when this theory was tested in normal hearts with a pulsatile LVAD pump ⁽⁸⁰⁾. Conversely, when the LVAD was implanted into a failing heart, a direct association with the use of the LVAD and right ventricular failure was evident ⁽⁸¹⁾. As such, it has been suggested that LVADs have the potential to promote changes in the right ventricular geometry of CHF patients by increasing right ventricular preload and volumetric work ⁽⁷⁹⁾. Although many studies have shown an association between the use of an LVAD and right ventricular failure, it has not yet been elucidated whether the LVAD is the cause of right ventricular failure or whether it simply unmasks the underlying condition ⁽⁷²⁾. Delayed RVAD implantation following LVAD

implantation is highly associated with increased mortality at 1 year ($45.1 \pm 32.3\%$) ⁽⁷²⁾, with increased survival and improved quality of life achieved with pre-emptive RVAD implantation ⁽⁸²⁾. Therefore, in patients with advanced CHF, early planned BiVAD support may improve patient outcomes and reduce risk of complications.

1.11 BIVENTRICULAR ASSIST DEVICE

Unlike LVADs, which only increases the blood pumped to the systemic circulation, BiVADs simultaneously support both the left and right ventricles, increasing the amount of blood pumped to both the systemic and pulmonary circulation ⁽⁵²⁾. In the past, BiVADs were only used for advanced CHF patients that performed poorly on LVADs alone ⁽⁸³⁻⁸⁵⁾. However, in light of the detrimental consequences of unsuitable LVAD support and potential benefits of novel BiVAD technologies, there has been rapid interest in the development, design and application of BiVAD systems in patients that have evidence of or at high risk of right ventricular failure post LVAD support ^(83, 84). Early BiVAD intervention has been deemed imperative in patients with right ventricular failure as delayed RVAD implantation has been associated with a mortality rate of up to 90% ^(86, 87). Early functional assessment of both ventricles has been suggested to help identify potential cases of right ventricular failure ⁽⁸⁸⁾. Inconsistencies in the literature regarding the cause of right ventricular failure pre- and post LVAD implantation has created a field of uncertainty. With the advent of newer, smaller and more efficient VAD models, the feasibility and applicability of BiVADs as a bridge to transplant, bridge to recovery and as destination therapy has become more established and safer for use. This will be discussed in detail in Chapter 2.

1.12 HeartWare HVAD VENTRICULAR ASSIST DEVICE (HVAD)

The third generation HeartWare Ventricular Assist System (HVAD) (Heartware International Inc, Framingham, MA, US) has been approved by the FDA for left ventricular support in advanced CHF patients for both bridge to transplantation and is under consideration for approval as destination therapy. However, its approval in Australia is primarily for left ventricular support in patients with advanced heart failure requiring bridge to transplantation. Although they have been used to manage patients with severe heart failure without transplantation (destination therapy), destination therapy has not been approved in Australia. As a result, reimbursement for the cost of care for these patients is only linked to acceptance onto a transplant waiting list, meaning that destination therapy is not available in Australian public hospitals ⁽⁸⁹⁾. Its utilization as a BiVAD system remains under investigation and has yet to be approved. Although preliminary data demonstrates great feasibility and applicability of the HVAD as biventricular support ^(48, 90-92), there are challenges involved with its use that needs to be addressed ⁽⁵²⁾. The HVAD was originally designed for left ventricular support ⁽⁶²⁾, therefore its hemodynamic performance and physical characteristics may not necessarily be compatible for right ventricular support ^(48, 72). The left ventricular chamber cavity is much larger than that of the right ventricle. As the HVAD was intended for left ventricular support, the length of the inflow cannula if inserted into the cavity of the right ventricle may cause the HVADs inflow cannula to interact with the opposite interventricular wall of the septum, occluding the blood flow through the right HVAD ⁽⁵²⁾. Thus, testing the performance of the HVAD as a uni and biventricular assist device in an *in-vivo* setting is crucial. Compared with previous options for biventricular mechanical support, dual HVAD therapy offers some advantages. The small and durable frame allow for direct implantation into the

pericardial cavity, reducing surgical invasiveness, procedure time and recovery time. In addition, the portable and light battery/controllers allow for increased patient mobility and enables patient discharge and outpatient care. The controllers also record flow rates, pump speeds and power consumption, easily accessible for monitoring purposes. Finally, the algorithm used is simple and allows for in-depth analysis, which can be used to either alter future pump functions or identify existing markers of potential abnormalities, e.g increased power consumption with relatively maintained flow rates may be indicative of valvular abnormalities.

1.13 STUDY SETTING

St Vincent's Hospital Sydney, is part of St. Vincent's Campus comprising of St. Vincent's Public Hospital, St. Vincent's Private Hospital and St. Vincent's Clinic. It is recognized both nationally and internationally for its heart surgery, particularly for its heart and lung transplant program. They are the leading heart transplant unit in Australia and have been involved with cutting edge research and numerous clinical trials. They are also affiliated with Victor Chang Cardiac Research Institute and the Garvan Institute for Medical Research.

1.13.1 Heart and Lung Transplantation Program

St. Vincent's Heart and Lung Transplant program is the largest and longest running program in Australia, with survival rates that exceed that of international benchmarks. The transplant unit is the only heart and lung transplantation program in NSW and is a major referral center for metropolitan and rural communities as well as South Australia. The program performs approximately 40-45 heart transplantations each year.

1.13.2 Mechanical Circulatory Support Program

The mechanical circulatory support (MCS) program began in 1994 when the 1st generation heartmate IP was first implanted in Australia ⁽⁹³⁾. Figure 1.5 summarizes the mechanical devices used at St. Vincent's Hospital since the beginning of their MCS program and how these devices have changed over time.

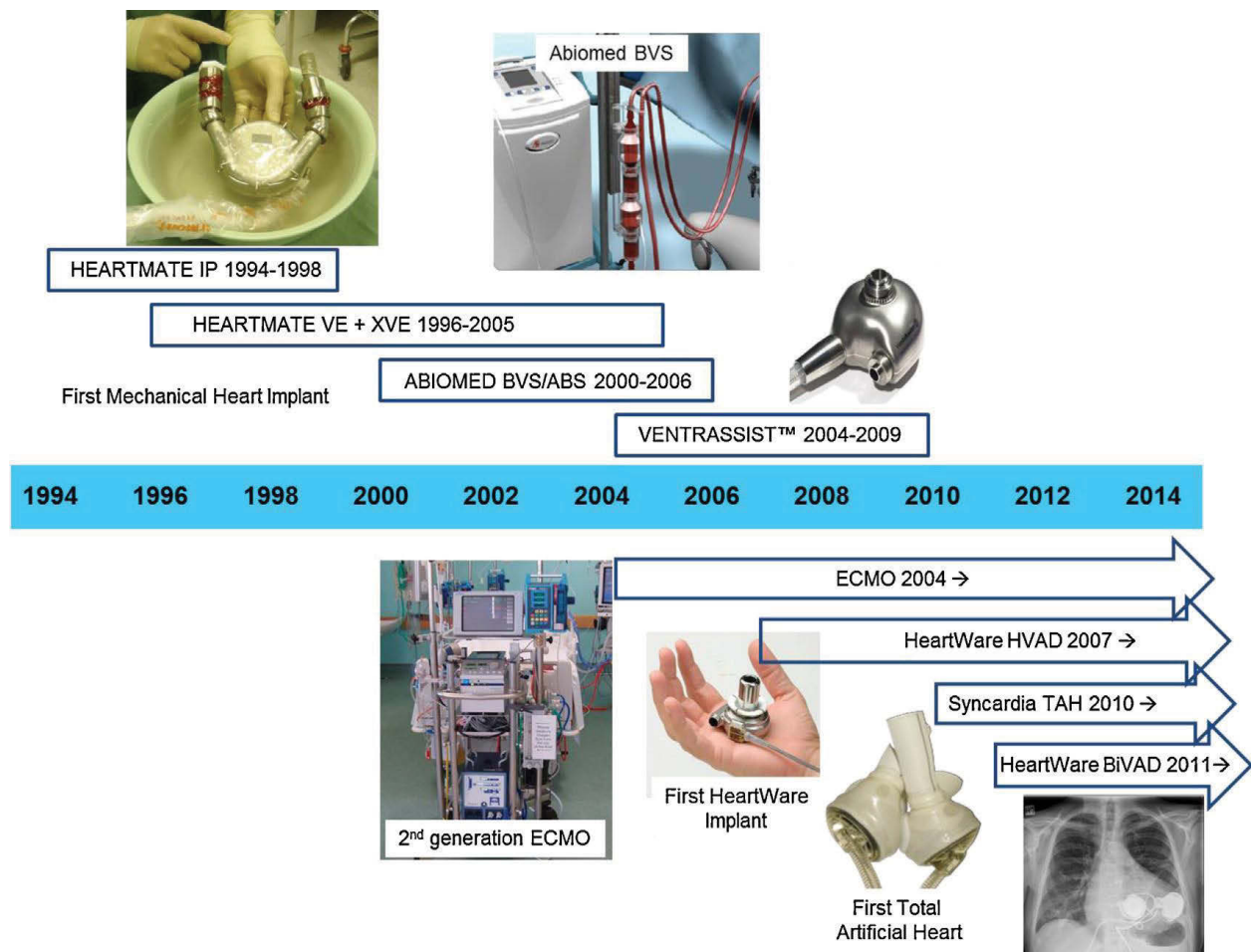


Figure 1.5 Milestones and devices implanted in St Vincent's Hospital since beginning of the mechanical circulatory support program

From 2007 onwards, almost all the devices used for circulatory support were LVADs, with many 1st generation devices being superseded by smaller more durable pumps. This is reflected in Figure 1.6 below. The VENTRASSIST pump and the HVAD pump were the only two LVADs used at St. Vincent's hospital from 2006 onwards, until the VENTRASSIST was

eventually discontinued. Biventricular support was initiated with the dual HVAD therapy in 2012. Prior to this, the Total Artificial Heart (TAH) system was used for patients with biventricular failure. The TAH system replaces the native heart with a mechanical heart, whereas BiVADs supports the native heart. The advantages of the BiVAD aside from mobility and durability is that in the event of device malfunction, patient with the TAH would be at high risk of mortality as the TAH is their primary source of circulation. However, blood circulation can be maintained during mechanical failure with BiVAD as the native heart would still be attached and functional, even if compromised.

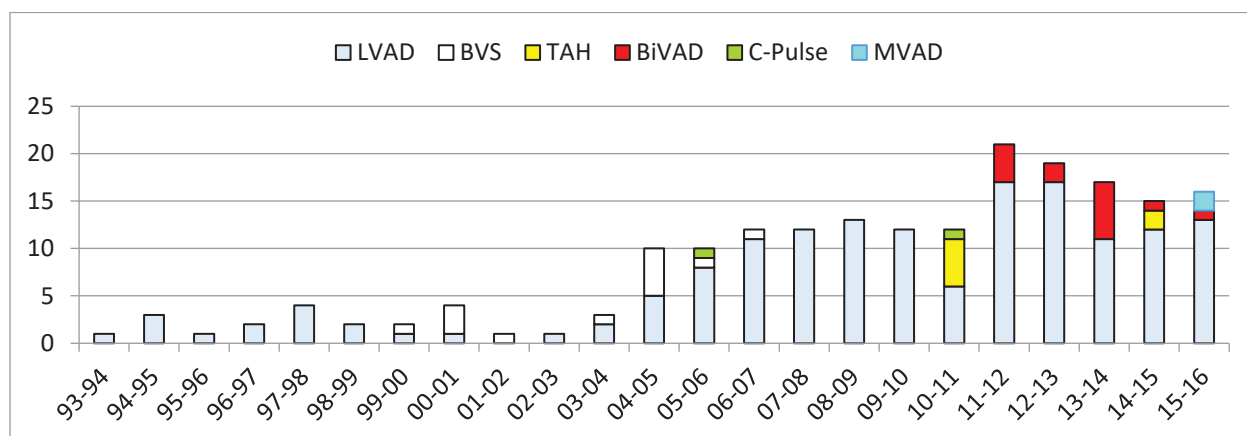


Figure 1.6 The type and number of MCS devices used since the beginning of the MCS program.

Since the commencement of this PhD in 2013, approximately 100 HVADs have been implanted at St. Vincent's Hospital. St. Vincent's hospital receives government funding for 25 VADs each year for patients bridged to transplantation. Of those 100 HVAD patients, 14 are BiVADs which is the main focus of this PhD with slight references to LVAD cohorts in subsequent publications.

1.13.3 Australian vs. international data

Outcomes from the entire HVAD cohort, including patients prior to the commencement of this PhD project (therefore a total approximately 112 patients) were collected and compared

to European databases. Figure 1.7 compares 3-year competing risk outcomes for European⁽⁹⁴⁾ and St Vincent's Hospital populations. As demonstrated, the trends for 'Transplanted or Alive', and 'Death' are very similar for both national and international cohorts. There appears to be a reduced number of 'Alive' (on-pump) patients in the Australian datasets. This can be explained by the higher 'Transplant' population. Therefore, the more patients that are transplanted, the fewer remain alive on-pump. This is explained by the higher rate of transplanted patients compared to the European experience, which includes some destination patients. Destination therapy is limited in Australia as only candidates suitable for 'bridge to transplantation' are currently funded by the government. In the past decade, St. Vincent's has only had three cases of destination therapy; two because patients were no longer suitable for cardiac transplantation and another who was able to financially cover all the costs of the procedure.

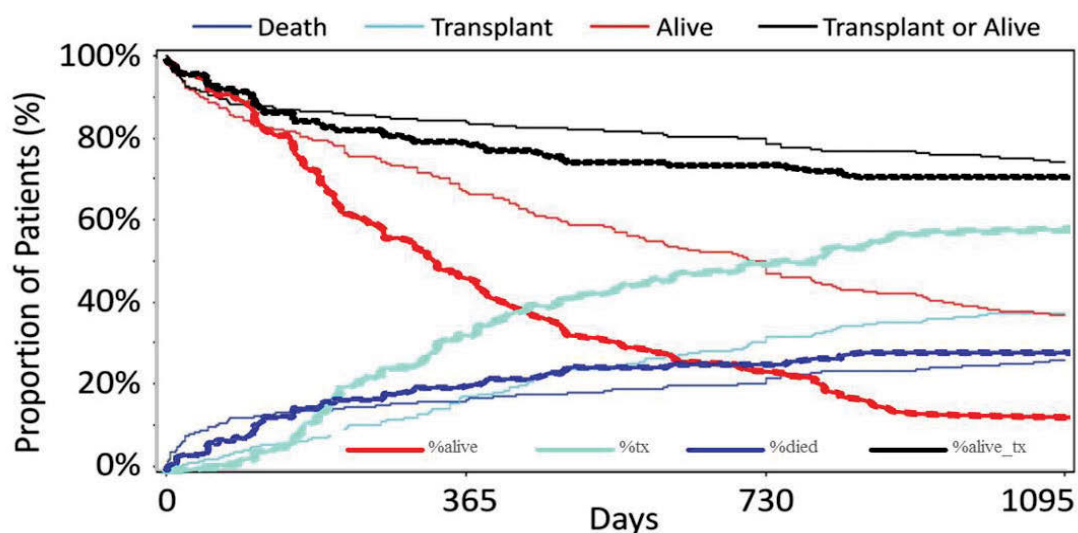


Figure 1.7 Comparison of competing risk outcomes for Europe (solid) vs. Australia (dashed) (Adapted from Schmitto et al⁹⁴)

1.14 SIGNIFICANCE AND INNOVATION

Patients with advanced CHF have a high risk of mortality, poor 1-year prognosis and commonly reduced quality of life. Although, heart transplantation is an acceptable treatment option in these patients, lack of donor heart, a long waiting list and a stringent eligibility criteria can delay if not exclude patients for transplantation. Support with a VAD has shown to improve quality of life and decrease morbidity and mortality. Using the mock-circulatory loop to optimise dual HVAD as BiVAD support may result in the development of the first clinically approved third generation BiVAD device. The potential significance of this innovation is reduced right ventricular failure, a decreased risk of thrombotic and bleeding complications and significantly reduced mechanical failure of device. Decreased adverse events and the needs for hospitalization will potentially lead to an improvement in patients' quality of life, increased patient survival and less demand for heart transplantation.

1.15 STUDY AIMS

This study has five discrete yet interconnected aims. **Firstly**, it seeks to summarise the literature on the outcomes and complications of current BiVADs and dual HVAD support; **secondly**, it describes the process of creating an *in-vitro* model of the human cardiovascular system ('mock-circulatory loop'); **thirdly**, it evaluates and optimises the performance of dual HVAD therapy using the loop on various CHF states, support conditions and valvular pathologies; **fourthly** it assesses the clinical and survival outcomes of patients implanted with dual HVAD and; **lastly** it identifies changes to the up/downregulation of certain genes pre and post dual HVAD support.

1.16 STRUCTURE OF THIS THESIS

This thesis is a series of discrete, yet interrelated studies which addresses the study aims. This thesis is presented in nine chapters. Five of these chapters are presented in the form of peer-reviewed journal articles (three published and 2 currently under review). Each chapter is presented as a stand-alone report in the style of the journal article. To meet journal requirements for manuscript submission, spelling may vary between US English and British English for Chapters 2, 4-7. Chapters 1, 3, 8-11 are written in Australian English.

In **Chapter One**, the significance of the growing burden of advanced CHF has been emphasized. With the aging population and the advancements in cardiovascular treatment, there is a growing number of CHF patients worldwide. Despite major improvements in the treatment of CHF, a quarter of these patients continue to experience life-limiting symptoms requiring mechanical circulatory support or heart transplantation. The rationale, utility and significance of this study was to evaluate the performance of two continuous flow HVAD as biventricular support *in-vitro*. Information gained from this will help reduce complications and improve patient survival on mechanical circulatory support.

Chapter Two provides a detailed review of the various device types and improvements in biventricular devices throughout the years. In addition, it further discusses the shift into using dual VAD continuous flow devices and the clinical outcomes of the third generation HeartWare LVAD in literature. Furthermore, it provides an expert commentary and a five-year review to inform future research on BiVADs. This paper was published in the Journal of Expert Review of Medical Devices in 2015.

Chapter Three presents a critical description and justification of the *in-vitro* human cardiovascular model (mock-circulatory loop). The design and experimental protocol are discussed in detail.

Chapter Four presents the results of the mock circulatory loop experiment which tested the hypothesis that the use of continuous flow BiVAD and RVAD systems may overcome existing limitations of the current treatment of advanced CHF. This paper is published in the Journal of American Society of Artificial Internal Organs.

Chapter Five also presents the results of the mock circulatory loop experiment which observed the consequences of BiVAD support using dual continuous flow devices on valvular pathologies such as aortic, mitral and tricuspid regurgitation. This paper is currently under review in the Journal of American Society of Artificial Internal Organs.

Chapter Six reports the clinical and survival outcomes of 14 patients implanted with dual continuous flow HVAD as bridge to transplant. This paper was published in the Journal of Heart and Lung Transplantation in 2015.

Chapter Seven also reports the clinical and survival outcomes of patients implanted with dual continuous flow HVAD (BiVAD) compared with isolated LVAD support and concomitant veno-pulmonary arterial extracorporeal membrane oxygenation and LVAD. This paper is currently under review in the Journal of Thoracic and Cardiovascular Surgery.

Chapter Eight presents a detailed description and justification of the experimental protocol of the RNA extraction and library sequencing. It also reports the results of the RNA extraction and library sequencing protocol.

Chapter Nine provides a summary of the overall study and highlights the research significance of our results.

References are provided at the end of each chapter. Copies of the data collection form, copies of ethics approval from University of Technology Sydney and St. Vincent's Hospital, Sydney are all provided in the appendix at the end of the thesis.

1.17 REFERENCES

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CHAPTER II- BIVENTRICULAR MECHANICAL SUPPORT DEVICES – CLINICAL PERSPECTIVES

2.1 CHAPTER PREFACE

Publication reference:

Shehab S, Newton PJ, Allida SM, Jansz PC, Hayward CS. Biventricular mechanical support devices- clinical perspectives. Expert Rev Med Devices. 2016.

Chapter 1 provided a summary of advanced chronic heart failure; its aetiology, epidemiology, and the use of mechanical assist devices. Further it provided an outline of this thesis, including the study aims, structure, significance and innovation. This chapter will provide an extensive review of current biventricular assist devices.

This chapter presents an article in its original form, published in the Journal of Expert Review of Medical Devices (2016). This article is provided in its published form as an appendix (Appendix 8).

Background

Cardiac transplantation remains the optimal treatment for end stage heart failure in selected patients. However, the shortage of donor hearts, rigorous eligibility criteria and long waiting lists have increased the demand for alternative treatment strategies such as mechanical circulatory support. While many patients are adequately supported with left ventricular assist devices, frequently there is right heart failure or involvement of the right ventricle, requiring biventricular support.

Aim of this study

This review will summarise the literature on the outcomes and complications from current biventricular support devices and assess the role of dual continuous flow VAD therapy, and the new continuous flow total heart replacement devices.

Summary of results

Pulsatile flow biventricular devices and total artificial hearts approved for temporary biventricular support have limitations including size, high rates of adverse events and restricted mobility which makes them unsuitable for long term support. A number of centres have reported dual continuous flow left ventricular assist devices as a means of supporting the left and right heart.

Implications

A review of existing and upcoming biventricular assist devices (BiVAD) provides valuable insight into the management of patients with or at risk of concomitant right ventricular dysfunction. In addition, it can highlight the strength and weakness of these devices, allowing readers to make an informed decision about device selection.

2.2 INTRODUCTION

Chronic heart failure (CHF) is a progressive syndrome associated with high morbidity and mortality [1-3]. Management strategies vary depending on the stage of disease and severity of symptoms. Early stages of CHF can be managed with a combination of lifestyle modifications, pharmacological therapies and cardiac devices [4]. However, these therapeutic options are often ineffective in patients suffering from advanced CHF. In these cases, cardiac transplantation for those without other contraindications is the preferred treatment option, but is limited by the scarcity of donor hearts, stringent eligibility criteria and long waiting lists [5]. Moreover, critically ill patients have poorer outcomes [6, 7], and many such patients require ‘bridging’ with circulatory support to transplant [8, 9].

While many patients with advanced CHF can be managed with isolated LVADs, up to 30% of patients suffer from concomitant right heart failure, requiring biventricular support [10]. Patients with biventricular failure have higher mortality and greater end organ compromise compared to LVAD recipients, and are generally classified Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACs) status 1 or 2 [11]. The decision to implant BiVADs can be difficult and vary among institutions. The main indications for early biventricular support has been acute circulatory collapse, due to fulminant myocarditis, acute decompensation of dilated cardiomyopathy, massive myocardial infarction, and acute deterioration following toxic cardiomyopathy. In addition to biventricular failure, BiVAD support may be more suitable in the presence of other cardiac pathologies such as infiltrative cardiomyopathy, restrictive cardiomyopathy and other cardiac malignancies that may be contraindicated to isolated LVAD support only.

Most predictors of right ventricular failure assess the performance and structural integrity of the right ventricle. Right ventricular failure has been associated with severe tricuspid regurgitation, an ejection fraction <30%, and RA >50mm [12, 13]. However, as evident from the variety of algorithms proposed to predict right heart failure post-LVAD insertion [14, 15], no single predictive tool has been accepted as the gold standard. Standard haemodynamic measurements such as pulmonary pressures, transpulmonary gradient and right ventricular stroke work index each provide low predictive indices for right ventricular performance [15-17]. Implantation of a sequential RVAD in the setting of right heart failure after LVAD insertion has been associated with mortality rates of greater than 50% in early series [18]. Thus early BiVAD implantation for suitable candidates has been suggested to improve patient survival [19].

Options for biventricular support have previously involved the use of a total artificial heart (TAH) or pulsatile displacement biventricular assist devices. Short term BiVADs continue to use pulsatile flow pumps which remain too large for hospital discharge and are limited by their large driver consoles to adequately restore patients mobility and improve quality of life [20, 21]. Biventricular support with the TAH and pulsatile BiVADs have been associated with lower survival rates than patients with continuous flow LVADs [10]. Recent evidence indicates improved survival rates and outcomes produced with the use of simultaneous short-term RVAD implantation during LVAD implantation [22-24]. The successful selection of patients and high RVAD wean rates have been largely responsible for these favourable outcomes. In patients that were not weaned or were converted into long term support however, mortality remained poor [22, 23]. It is important to note however, that RVAD support was achieved with a third generation, continuous flow device and thus may be more reflective of current

LVAD technology than older generation pulsatile BiVADs or the TAH system. These reports have brought to light a debate whether outcomes for critically ill patients requiring biventricular support may be improved with durable continuous flow devices.

Thus, with the advancement in VAD design and miniaturisation of pumps, the use of two continuous flow LVADs has been suggested for biventricular support [25]. As many case series are only of a limited number of patients, outcomes are heavily affected by patient selection, as well as device type. This review summarises current literature investigating biventricular support device outcomes and complications and discuss the evolution of these devices over the past two decades.

2.3 DEVICE TYPES

Ventricular assist devices can be classified according to their flow profiles (pulsatile vs. continuous), operational characteristics (first, second and third generation), intended length of support (short, intermittent and long), and form of implantation (extra-, para-, and intracorporeal). LVAD have a broad spectrum of devices available and can thus accommodate a wider range of patient profiles, particularly those ineligible for cardiac transplantation in need of long term, or destination, support. BiVAD have fewer options. Most of the BiVAD's approved by the Food and Drug Administration (FDA) consist of first generation, pulsatile flow pumps which contain large and restrictive drivers. Their application is limited to short or intermittent term support and are generally extra- or paracorporeal in nature. Table 2.1 summarises the list of devices capable of providing biventricular support, and Table 2.2 summarizes the clinical outcomes of current devices as reported in the literature.

CHAPTER II – BIVENTRICULAR MECHANICAL SUPPORT DEVICES

Table 2.1 Clinically applied and under development devices providing biventricular support

Device	Type	Drive mechanism	Flow profile	Target therapy	Clinical purpose
<i>Clinically applied</i>					
Abiomed BVS5000 (21)	Extracorporeal	PD, FP	Pulsatile	BTB, BTR, BTT	Short-term
Abiomed AB5000 (22)	Paracorporeal	PD, FP	Pulsatile	BTB, BTR, BTT	Short-term
Thoratec PVAD (23)	Paracorporeal	PD, FV	Pulsatile	BTB, BTR, BTT	Medium-term
Thoratec IVAD (23)	Implantable	PD, FV	Pulsatile	BTR, BTT, DT	Medium-term
Levitronix Centrimag (24)	Extracorporeal	ED, CE	Continuous	BTB, BTR, BTT	Short-term
Berlin Heart Excor (25)	Paracorporeal	PD, FV	Pulsatile	BTR, BTT	Medium-term
Heartware HVAD (26)	Implantable	ED, CE	Continuous	BTT, DT	Long-term
Syncardia TAH (27)	Implantable	PD	Pulsatile	BTT	Long-term
<i>Under development</i>					
Cleveland Clinic cfTAH (28)	Implantable	ED	Continuous	BTT, DT	Long-term
BIVACOR BV Assist (29)	Implantable	ED, CE	Continuous	BTT, DT	Long-term

PVAD, paracorporeal ventricular assist device; **IVAD**, implantable ventricular assist device; **TAH**, total artificial heart; **THI**, Texas Heart Institute; **cfTAH**, continuous flow total artificial heart; **PD**, pneumatically driven; **ED**, electrically driven; **FP**, filled passively; **FV**, vacuum assisted filling; **CE**, centrifugal flow pump; **BTB**, bridge to bridge; **BTR**, bridge to recovery; **BTT**, bridge to transplantation; **DT**, destination therapy

CHAPTER II – BIVENTRICULAR MECHANICAL SUPPORT DEVICES

Table 2.2 Clinical outcomes of current devices

Device	Year	Patient (n)	30 day Mortality	1 Year Mortality	Overall survival	Wean rate	Transplant rate	Discharge rate ^{a8}	DoS (days)	Infection rate	Renal Failure	Liver Failure	Bleeding	Neurological complication
<i>Clinically applied</i>														
Abiomed BVS500														
<i>Kaan et al (30)</i>	1991	2	0%	-	100%	100%	-	-	4.3 (4.9-3.7)	0%	50%	-	100%	0%
<i>Dekkers et al (31)</i>	2001	Group a	11	-	-	23.3%	54.5%	-	-	-	-	-	-	-
		Group b	4			75%	0%	75%						
<i>Morgan et al (32)</i>	2004	22	36.4	-	65.6%	40.9%	13.6%	-	5.1±4.4	12.5% ^{a1}	-	-	25% ^{a1}	37.5% ^{a1}
Abiomed AB5000														
<i>Samuels et al (33)</i>	2005	4	-	-	75%	75%	-	-	-	-	-	-	-	-
Thoratec PVAD														
<i>Farrar et al(34)</i>	1989	21	-	-	-	-	76%	-	-	-	-	-	-	-
<i>Tsukui et al(35)</i>	2005	Group c	29	15%	-	69%	7%	-	-	90% ^{a2}	-	-	34%	52% ^{a2}
		Group d	44					48%		30% ^{a2}				20% ^{a2}
<i>Kirsch et al(36)</i>	2009	62	-	-	63%	5%	58%	50%	42 (2.3-268.0)	71%	32%	15%	26%	29%
<i>Schlensak et al (37)</i>	2011	31	-	-	52%	13%	39%	-	84±72	-	-	-	-	-
<i>Brehm et al(19)</i>	2012	Group e	15	13%	27%	73%	33%	53%	-	137±109	20%	33%	-	40%
		Group f	24	42%	83%	17%	-	42%	-	65±61	46%	38%	-	21%
<i>Creaser et al (38)</i>	2014	24	-	-	83%	-	83%	58%	100±65	11%	-	-	17%	4%
Levitronix Centrimag														
<i>Ranjit et al (39)</i>	2007	12	17%	-	83% ^{a3}	17%	-	-	-	-	-	-	-	-
<i>Shuhaiber et al (40)</i>	2008	14	64%	-	36%	0%	-	-	11 (1-51)	-	-	-	-	-
<i>De Robertis et al (41)</i>	2008	10	10%	-	80%	-	-	-	-	-	-	-	-	-
<i>Haj-Yahia et al (42)</i>	2009	4	0%	0%	100%	0%	-	-	87 (26-105)	0%	0%	0%	25%	0%

CHAPTER II – BIVENTRICULAR MECHANICAL SUPPORT DEVICES

Device		Year	Patient (n)	30 day Mortality	1 Year Mortality	Overall survival	Wean rate	Transplant rate	Discharge rate ^{a8}	DoS (days)	Infection rate	Renal Failure	Liver Failure	Bleeding	Neurological complication
John et al (43)		2011	18	-	-	-	-	-	-	15 (1-60)	11%	0%	0%	11%	6%
Takeda et al (44)	Group g	2014	23	74%	-	50%	-	35%	-	-	26%	74%	-	61%	22%
	Group h		37	30%	-	70%	11%	54%	-	-	16%	46%	-	43%	11%
Berlin Heart Excor															
Rockett et al (45)		2008	4	-	-	50%	0%	50%	-	-	-	-	-	-	-
Potapov et al (46)		2010	69	33%	-	67%	-	-	-	-	22% ^{a1}	-	-	-	-
Moreno et al (47)		2011	4	0%	-	100%	0%	100%	-	94 (3-264)	-	-	-	0%	-
Morales et al (48)		2011	31	-	-	36%	0%	97%	-	-	-	-	-	-	-
Fan et al (49)		2011	15	21%	73%	47%	7%	33%	-	-	40%	27%	-	27%	27%
Schweiger et al (50)		2013	4	25%	-	50%	-	50%	-	218.8 (4-525)	50%	25%	-	25%	25%
Heartware HVAD															
Stepanenko et al (51)		2011	10	10%	30%	70%	-	10%	-	-	10%	-	-	30%	-
Krabatsch et al (20)		2011	17	18%	47%	47%	12% ^{a4}	6%	59%	39	6%	-	-	35%	-
Syncardia TAH															
Copeland et al (52)		2012	101	23% ^{a5}	77%	68%	-	68 %	-	87±94.8	63%	-	-	43%	15.8%
Demonion et al (53)		2013	27	-	-	44%	-	44%	-	254	44%	-	-	41%	15%
Torregrossa et al (54)		2014	47	-	-	74%		72%	85%	554(365-1374)	27% ^{a6} -53% ^{a7}	26%	-		19%

PVAD, paracorporeal ventricular assist device; **IVAD**, implantable ventricular assist device; **TAH**, total artificial heart; **THI**, Texas Heart Institute; **cfTAH**, continuous flow total artificial heart; **DoS**, duration of support; **Group a**, postcardiotomy patients; **Group b**, BiVAD bridge to transplant patients; **Group c**, implanted between 1990-1999; **Group d**, implanted between 2000-2003; **Group e**, acute heart failure; **Group f**, chronic heart failure; **Group g**, unplanned right ventricular support (unable to wean); **Group h**, planned biventricular support; ^{a1}, outcomes based on cause of death; ^{a2}, outcomes based on actuary freedom; ^{a3}, survival based on direct transplant or bridge to another device; ^{a4}, RVAD weaned only; ^{a5}, 14 day mortality only; ^{a6}, driveline related infection; ^{a7}, systemic infection requiring antibiotics, ^{a8}, refers to discharge while on mechanical support

2.3.1 Extracorporeal biventricular support devices

Extracorporeal BiVADs were among the first devices to be approved by the FDA as a bridge to transplant (BTT) or bridge to recovery (BTR). The Abiomed BVS5000 was one of the first dual chambered ventricular assist systems capable of providing complete uni- and biventricular support. It was originally approved by the FDA in 1992 as a short term support system for BTT. However, its applicability in a “bridge to bridge” (BTB) and BTR have also been documented [20, 60]. Its widespread use, particularly for the treatment of acute cardiogenic shock was attributed to its simplicity, low cost and the limited commercial availability of other BiVAD systems [48]. Consistent with its role as a last resort device in cardiogenic shock, the survival rate is poor [36, 37], and as most experience was accrued prior to the initiation of INTERMACS in 2005 [61], survival rates remains elusive. While it has been shown to support patients for short periods, long term support is associated with a high incidence of multiple organ failure (40%) [20, 62] and excessive bleeding [20, 63, 64]. The BVS5000 has been superseded by more compact and reliable paracorporeal and extracorporeal devices.

In contrast to the BVS5000, the Levitronix CentriMag (Figure 2.1) provides continuous blood flow. It is a third generation, extracorporeal, centrifugal blood pump that also provides short term support in a left, right and biventricular failure setting. It is FDA approved to support patients as bridge to decision device, and in Europe, its support has been approved for up to 30 days [65], with survival rates of up to 75-80%. In comparison to other first generation pulsatile BiVADs, the CentriMag impeller is magnetically levitated, without the need for mechanical bearings. This eliminates friction and wearing during operation, thereby improving durability and decreasing the risk of haematological damage [66]. Its applicability in the treatment of primary graft failure has safely demonstrated positive outcomes [67].

While high survival rates at 30 days and 1 year have been reported (pre-and post-explant, respectively) [44, 46], evidence also suggests a high mortality rate of patients supported with the CentriMag for right ventricular support after LVAD implantation [45]. As described by Takeda and colleagues, patients who required late unplanned right ventricular support after LVAD had much higher in-hospital mortality (74%) compared to those with initial planned BiVAD support (24%) [49]. Although the CentriMag is widely used, the large driver console (6.6 kg) and the requirement for prophylactic pump exchange every 28 days [63] means that patients are unable to be discharged from hospital. Major complications associated with the CentriMag include bleeding, infection, respiratory failure, liver dysfunction, haemolysis and neurological dysfunction [45, 68, 69].



Figure 2.1 The Levitronix Cetrimag ventricular assist system. (A) bearingless magnetic motor. (B) Single use disposable pump head. (Courtesy of Thoratec Corporation)

2.3.2 Paracorporeal biventricular support devices

The Thoratec PVAD (Figure 2.2) is a first generation, pulsatile flow pump approved for both uni- and biventricular support. Although initially approved in 1995 for BTT, indication for use was broadened to include postcardiotomy support in 1998 and has since demonstrated

applicability as a BTR and BTB circumstances. The PVAD initially required a large driver console (Dual Drive Console), however the TLC-II portable pneumatic driver has since been introduced to improve patient mobility. Since then there have been a number of small case series demonstrating the feasibility of home discharge [43, 71].



Figure 2.2 The Thoratec PVAD ventricular assist system. (A) PVAD pump. (B) Dual Driver Console. (C) TLC-II portable driver console with battery (Courtesy of Thoratec Corporation)

In terms of adverse events, Tsukui et al reported reduced rates of driveline infection, bloodstream infection and neurological events in patients implanted after the year 2000 who remained supported with the Dual Drive Console [40]. Improvements to management, better patient selection or adjustments to surgical procedure could explain these outcomes. However, the rates of infection, bleeding, renal failure and neurological events are still widely reported in other studies [21, 41], as shown in Table 1. Despite the adverse events, overall survival remains greater than 50%, indicating effective post-operative management. In a comparison between BiVAD and LVAD support, no significant differences in survival between LVAD and BiVAD (45% vs. 63%, respectively) were observed ($p=0.18$) [41].

After successful introduction of the Thoratec PVAD, the new Abiomed AB5000, gained FDA approval in 2003 for BTT, BTR and BTB circumstances. The AB5000 is a portable adaptation

of the BVS5000, designed specifically to improve patient mobility through the use of a smaller driver console [73]. Similar to its predecessor, it is a first generation, pneumatically actuated pump that generates pulsatile blood flow. A major difference is the paracorporeal implantation and in its ability to provide intermediate term support [27] in patients with body surface area of 1.3m² or greater. Moreover, the drivelines are compatible with the older extracorporeal model, and it is able to replace the BVS5000 without the need for repeat operation [38]. However, despite slight improvements in patient mobility and the length of support, adverse events such as device related thrombus formation and mechanical failure remain a major impediment for its continued use [20]. To date, the literature for AB5000 is limited to short case series insufficient to draw conclusions from in terms of survival and wean rates.

The more contemporary Berlin Heart EXCOR (Figure 2.3) is a first generation pulsatile, paracorporeal, paediatric specific VAD. It was the first device capable of providing complete left, right and biventricular support in patients as small as infants to adult sized adolescents [53]. However, similar to the earlier models, its large driver console (93kg) and the high rates of thromboembolic events remained significant limitations. It was FDA approved in 2008 for investigational purposes and has since been approved for compassionate use only after conventional treatment modalities have failed. Although preliminary studies have demonstrated great potential in the applicability of the Berlin Heart EXCOR [50, 74], small BiVAD sample size and reporting method make it difficult to determine the outcomes contributed by biventricular support.



Figure 2.3 Berlin Heart EXCOR ventricular assist device system. (A) Berlin Heart EXCOR pump. (B) Stationary driving unit Ikus. (C) EXCOR mobile driving system

Some evidence suggests that higher mortality rates are associated with increased age, temperature and overall total of the Sequential Organ Failure Assessment (SOFA) score [51, 55, 75]. Contrary to these findings, the initial North American multicentre study, consisting of 73 patients (42 LVAD, 31 BiVAD), reported that younger age and BiVAD implantation were associated with higher rates of mortality [53]. The mortality in patients with BiVAD was 36% (11/31) compared to 12% of LVAD (5/42). This increase in the mortality rate was evident in all three age groups assessed (<1 year, between 1-5 years and >5 years old, respectively) [53]. However, one of the biggest limitations of the study is the exclusion of patients with adverse events such as stroke, thromboembolism, device malfunction and infection. These must be considered when assessing the limitations and advantages of the device, especially when complications such as bleeding [51, 55], neurological complications [76], thromboembolism, and multiple splenic infarctions due to septic embolization [77] are still reported in the literature.

In terms of technical advancements, the EXCOR comes in many different sizes (10, 15, 20, 35, 50, 60 and 80 mL). Despite a bioactive coating on all blood contacting surfaces of the device, a high rate of thrombus formation is still reported. While this remains an issue, new surgical techniques proposed by Bigdeli et al [78], have demonstrated reduced intra- and postoperative complications such as bleeding, and may allow intensification of anticoagulation in selected patients. While adult pumps are capable of being supported with a mobile driving system (9kg), biventricular support can only be maintained for a maximum of five hours prior to recharging and patients are often restricted to hospitals and other specialist facilities [79].

The Medos HIA VAD is very similar to the Berlin Heart EXCOR system as it shares many features. Aside from also being a first generation, pulsatile flow, paracorporeal device capable of providing uni and biventricular support in both adults and paediatric populations, it also comes in a wide variety of pump size ranging from 10-80ml. Unlike the EXCOR however, the RVAD of the Medos device produces 10% lower stroke volume, reducing the risk of pulmonary edema [80]. While promising, studies remain limited to a handful of case reports and small single centre experiences, whose BiVAD samples are too small to derive meaningful survival and outcomes data [81, 82].

The Medos HIA VAD and the Berlin Heart EXCOR system remain the only two devices capable of providing intermittent to long-term mechanical support in children and neonates. Although previous studies have demonstrated successful support of young adolescence with the off-label of the HeartMate VAD [83] and the Thoratec PVAD [84], support remains limited to patients with a large body surface area and those not contraindicated from adult pump

support. A series of pediatric specific pulsatile and continuous flow devices are currently under development [80].

2.3.3 Implantable biventricular support devices

The intracorporeal Thoratec IVAD (Figure 2.4) was the first implantable BiVAD to be introduced, approved in 2004 for intermediate and long term support as BTR and BTT. Similar to the PVAD, the Thoratec IVAD is also pneumatically actuated; generating pulsatile blood flow with the same valves and polyurethane pump. While it maintains most of the features of its predecessor, there are major differences between the two models. In comparison to the polyurethane used in the PVAD, the IVAD utilises titanium alloy housing for improved external surface biocompatibility [28]. Its smaller weight and size was designed to improve patient mobility and reduce the risk of infection [85]. When compared to 4400 patients implanted with the PVAD, the IVAD has only been used in 560 patients. These differences in numbers may be explained by the ease of pump exchange in the case of device malfunction or adverse events with the PVAD, and the limitations that the IVAD does not allow visualisation of thrombus formation in the pump and remains too large to be implanted in children and small women. At present there is little information on the biventricular outcomes of the Thoratec IVAD. While there are studies published as conference abstracts, these studies do not provide detailed information on outcomes of the device but rather as a combined outcome of both the PVAD and IVAD [86].



Figure 2.4 The Thoratec IVAD titanium alloy pump and driveline (Courtesy of Thoratec Corporation)

2.3.4 Total artificial heart

The total artificial heart (TAH) (Figure 2.5) is a permanent orthotropic pneumatic pulsatile system that enables biventricular support. Unlike pulsatile BiVAD devices, the TAH completely replaces the native heart. The SynCardia 70cc TAH (CardioWest) is the first FDA approved completely implantable organ and has been implanted in approximately 1400 patients worldwide [32]. Survival to transplantation and the 1-year survival were initially reported to be 26% and 50%, respectively [87], but more recent experience with better patient selection and post-operative management has resulted in improved outcomes (transplantation and 1-year survival data (68% and 77% respectively) [57]. With the exception of infection, all other complications associated with the SynCardia were similar to those of other pneumatic BiVAD devices. As evident from more recent outcomes, infection remains the biggest adverse event, with 53% suffering from systemic infection (25/47) and 27% from driveline infections (13/47) [59] in long term patients (median support time of 554 days). With a minimum support of at

least one year, 72% were successfully transplanted, 24% died on support and 2% remained on support. It is clear that the Syncardia-TAH represents a significant improvement on previous options for severe biventricular failure and allows long-term hospital discharge. With the introduction of a smaller 'Freedom' driver, patients are significantly more mobile, with improved quality of life. The noise associated with the 4 metallic valves and pneumatic driver, while initially confronting, is actually tolerated very well by patients and carers. Until recently, the Syncardia-TAH system has been limited to patients with a body surface area greater than 1.7m². However, with the introduction of the smaller 50cc model, which is currently undergoing an Investigational Device Exemption clinical trial, patients with a much smaller surface such as adolescents and smaller women can now be supported.



Figure 2.5 The CardioWest Syncardia Total Artificial Heart. (A) Syncardia pumps. (B) C2 driver caddy (C) Freedom driver. (Courtesy: SynCardia Systems, Inc)

The most recent option for total heart replacement is the Carmat device, a pulsatile pump with pericardial tissue valves. At present most of the information available is reported in the form of conference abstracts and published in-vitro or animal trials. There are currently only 3 patients implanted with the Carmat TAH with no formal human publications in the

literature. While it is hypothesised that the tissue valves will result in less blood trauma compared to the Syncardia device, ongoing anticoagulation is required, due to the large exposure to foreign surfaces. The initial analysis of the second patient implanted demonstrated effective 9 month support prior to complications associated with reduced cardiac output caused by irregularities with the steering of the pumps motor. These findings will help improve future performance and patient outcomes. Additional outcome data is awaited.

2.4 DUAL VAD CONTINUOUS FLOW DEVICES

The use of continuous flow LVAD therapy has become a standard treatment option for patients suffering from advanced heart failure with preserved right ventricular function. Despite initial concerns due to lack of significant arterial pulsation, continuous flow LVADs are tolerated well physiologically [89, 90]. Unlike pulsatile BiVADs and the TAH, these LVADs are smaller, lighter, and do not require valves. These features have improved the durability and longevity of the device, as well as significantly restoring patient mobility. It is with these improvements in mind that current effort has been directed into implementing these LVADs within a biventricular setting. There are numerous cases of hybrid application of a LVAD combined with a temporary BiVAD device; however, the use of dual LVADs for both left and right ventricular support remains novel with only small case series or reports documenting outcomes.

The Jarvik 2000 is a second generation, axial flow LVAD and was the first device to attempt biventricular support using dual LVAD pumps [91]. Initial implants directed the outflow conduit to the descending aorta, which made removal during subsequent heart transplantation difficult. A similar case of biventricular replacement with the HeartMate II

LVAD has also been reported [92]. Despite stabilising haemodynamic parameters, the patient died from neurological complications. The study demonstrated the feasibility of dual VAD therapy with the HeartMate II LVAD but recommended further testing prior to larger scale human trials.

The third generation HeartWare LVAD (HVAD) (Figure 2.6), being smaller has also been used for biventricular support. An initial study of 17 patients with the HVAD, biventricular support was successful and with good long term support [25]. The 30 day survival was reported at 82% [25], an incremental improvement on the 70% survival rate of pulsatile BiVADs [93]. To date, long term outcomes remain limited. While the 6 month survival rate has been reported to reach 50%, these outcomes were derived from initial experiences and may be improved with increased experience, better patient selection and management. Discharge while on support has been reported in 10/17 patients (59%) with a mean length of stay of 39 days [25]. Three patients died on support and one patient required reoperation to relocate the RVAD from the right ventricle to the right atrium due to interaction with the interventricular septum [25].



Figure 2.6 HeartWare HVAD ventricular assist system. (A) HVAD pump. (B) HVAD battery powered portable carrycase driver. (Courtesy of HeartWare Inc)

While preliminary outcomes are favourable, there are still a number of challenges that must be overcome before dual VAD therapy can become part of clinical practice. Given that the HVAD was originally designed for left ventricular support [25], its haemodynamic performance and physical characteristics are not necessarily compatible for right ventricular support. Various recommendations to modify pump function have been suggested including increasing the resistance of the outflow graft through banding/restricting of the outflow cannula to a smaller diameter [95, 96], or running the RVAD at lower speed [97]. However, there is little data available that can help establish the degree of banding necessary and how this may vary between person to person [95, 98].

Secondly, inserting the HVAD into the free wall of the right ventricle may cause the HVADs inflow cannula to interact with the opposite interventricular wall of the septum, occluding the blood flow through the right HVAD. This may be avoided by reducing the inflow cannula's insertion length [25, 96, 98] by adding spacers between the HVAD and the wall of the right

ventricle [95, 98]. Finally, interaction between the inflow cannula and the opposite interventricular wall of the septum can potentially occur after right ventricular remodelling. As the right ventricle becomes smaller in size after RVAD implantation, an appropriately positioned cannula at implant may start to abut the septum at end-systole. Repetitive intermittent occlusion by the inlet cannula hitting the septum results in an increase in the risk of ingested clot and RVAD thrombus. At this point, once that the RV has remodelled, it has been suggested the RVAD can be decommissioned with the driveline severed and the pump left in situ [99], eliminating the need for invasive reoperation. To circumvent this, some investigators have placed the HVAD to the right atrial free wall [100], however little data is available on the long term outcomes of this approach. While preliminary data demonstrates feasibility and applicability of the HVAD as biventricular support [22, 25, 95, 96, 99, 101, 102], more data is required before such an intervention can be considered for approval. A formal outcome registry of BiVAD therapy has been suggested.

2.5 OUTCOMES

The rapid evolution of mechanical assist circulatory support (MCS) devices has significantly contributed to the way patients with advanced CHF are managed. With improved durability, interim mechanical support of a patient with advanced CHF before transplant has become standard of care for those unlikely to survive while waiting. Survival rates in patients ineligible for transplant supported with LVADs have demonstrated to be superior compared to medical therapy alone [103], with the benefit further enhanced with the introduction of continuous flow devices [104]. While randomised controlled trials for BiVAD recipients have not been conducted, based on the Fifth INTERMAC's Annual Report (Figure 2.7), continuous flow BiVAD's (cfBiVADs) have also been shown to be superior to pulsatile BiVADs [105]. In terms

of BiVAD support, outcomes have long since depended on careful patient and device selection. It is likely that some of the difference in outcomes with BiVAD patients is due to the significantly greater comorbidity as demonstrated in the very early postoperative mortality. After the first 3 months, the rate of mortality in cfBiVADs appears less than isolated continuous flow LVADs (cfLVADs) (Figure 2.7).

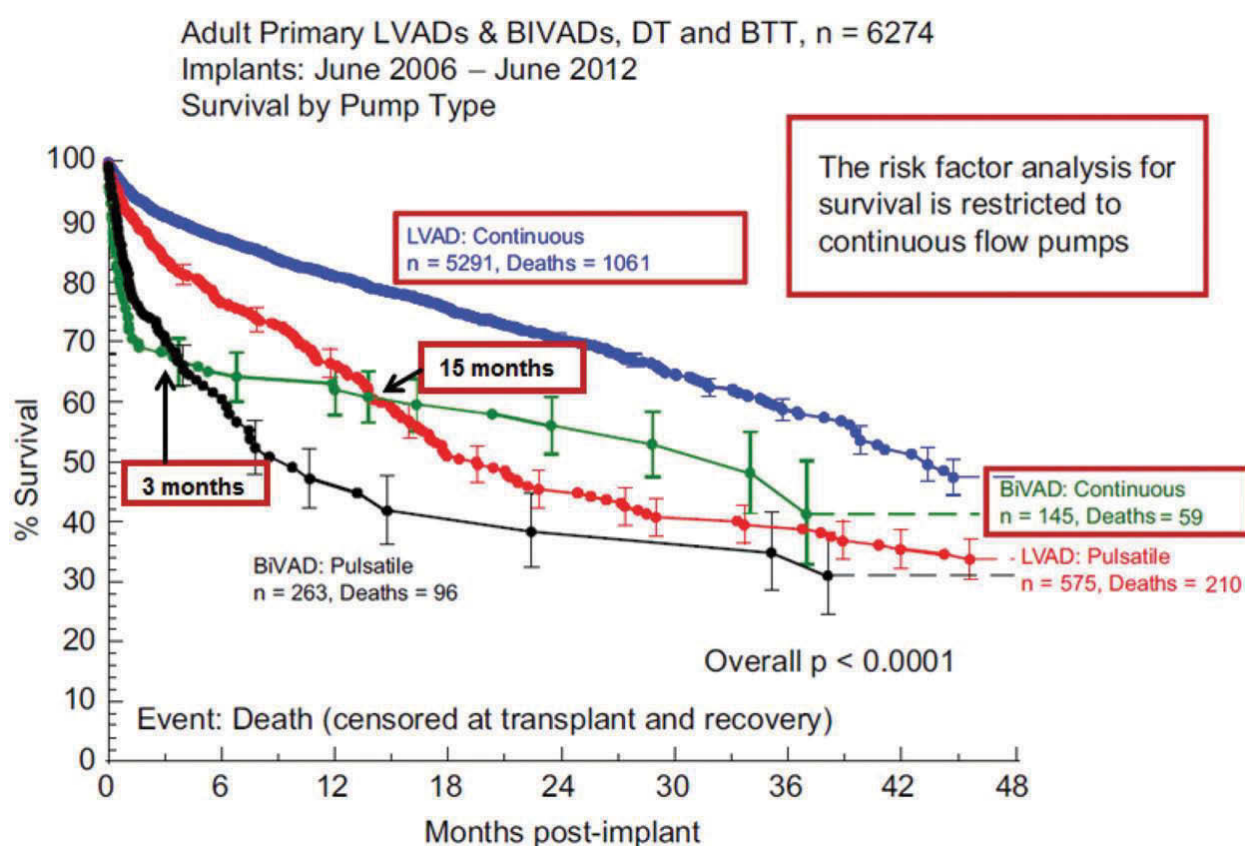


Figure 2.7 Adult left ventricular assist devices (LVADs) and biventricular assist devices (BiVADs) are shown stratified by continuous flow vs pulsatile flow pumps. Adapted and modified with permission from Kirklin et al (2013)

The main adverse events reported with BiVAD support include infection, bleeding, thrombus related complication, neurological complications and mechanical failure. These complications differ between paediatric and adult populations and are largely influenced by the type of device used. The use of adult pumps in paediatric patients has been associated with intracranial haemorrhage and systolic hypertension as a consequence of large stroke volumes

caused by device mismatch. In addition, the mandatory attachment of four adult sized pumps into a limited pericardial space has been associated with increased rate of infection and elevated rate of adverse events due to excessive surgical procedure [106]. While the Berlin Heart EXCOR and the Medos HIA VAD are able to overcome many of the limitations imposed by adult pumps, these devices are associated with increased rates of neurological complications resulting in death [50, 74]. Although increasing experience has resulted in significant improvements, neurological complications and infection remain the greatest complications in paediatric patients. With the increasing number of devices available; each which have different configurations and contraindications, direct comparisons are difficult to make. Nonetheless, it is evident that a similar shift towards smaller, durable and more mobile continuous flow BiVADs are necessary for further improving outcomes in these critically ill patients.

2.6 EXPERT COMMENTARY

Over the last twenty years there have been massive gains in terms of acute and long term management with severe biventricular heart failure. These patients are, by definition, the sickest chronic cardiac patients, and their heart failure is often associated with other significant organ dysfunction. Furthermore the chronicity and severity of advanced heart failure, results in a state of physiological frailty, previously termed cachexia, which has been shown to have marked survival implications, independent of whichever therapy is required – routine cardiac surgery, transplant or mechanical support. It is into this milieu that biventricular support is applied, and the high mortality and complication rates need to be seen in this context.

The emphasis for whichever device is used is initially adequate haemodynamic support. Beyond that, immediate surgical invasiveness, short and long term complications, and finally durability and quality of life considerations. These latter issues are only applicable due to the success of earlier devices to navigate patients through life-threatening illness.

Application of dual cLVAD therapy remains novel, with clinical outcomes expected to improve with better patient selection and accumulated experience. With the continuing miniaturisation of pump designs, less invasive, more durable and cost-effective pumps become available for dual cLVAD therapy in these critically ill patients. Newer smaller pumps, such as the HeartWare Miniaturized Ventricular Assist Device (MVAD) may offer a further option of dual cfVAD support, with smaller device burden. Should dual cfVAD therapy become established, it would be expected that the controller and battery packs be incorporated into a single unit.

Size is an important consideration for biventricular support. Not only does it dictate whether the heart needs to be completely excised (as with dual HeartMate II pumps), it is likely to contribute to the risk of infection. Current devices require external pneumatic or electric drivelines offering a portal for introduction of infection into the mediastinum. Notwithstanding this, even the short-lived Lion Heart experience, which was completely implantable without a driveline due to transcutaneous power induction, was associated with a significant infection risk, suggesting the volume (or surface area) of material within the chest itself is a major risk factor for late sepsis. Future efforts to develop transcutaneous energy transfer (TET) technology need to acknowledge the importance of this, with emphasis on the minimisation of device size. A further advantage of the smaller continuous flow pumps in this

light, is the fact they can be implanted without median sternotomy, reducing the risk of infection related complications.

Aside from the miniaturisation of ventricular pump, there has also been a push for the miniaturisation of driver consoles. With the increasing emphasis on patient's quality of life and hospital discharge, a number of driver consoles have been reduced in size to restore patient mobility over the last 5 years. Combination driver for left and right sided cfBiVAD should be part of their development. A significant advantage of the cfTAH devices is the requirement for only one controller, and the simplicity and decreased size associated with that.

Thrombosis remains one of the biggest issues in biventricular support. Due to the position of the right sided support, RVADs are at a significantly increased risk of venous thrombus ingestion. This is exacerbated by the fact that many of these patients have implantable defibrillators or pacemakers, with associated lead thrombus commonly detected at transplantation, even in non-VAD patients. The reality of right sided thrombus needs to be addressed in ongoing development, should these pumps be considered for long term support. An advantage of the newer LVADs and cfTAH devices is the option for intermittent pump speed modulation which may provide washout to areas of stasis and within the pump. This hypothesis remains to be tested clinically, and is currently in trial in current generation LVADs (MVAD and HeartMate-III).

2.7 5- YEAR REVIEW

The three major issues for the field of biventricular mechanical support are device durability, adverse events and miniaturisation with improved quality of life. Just as continuous flow

LVADs have completely supplanted pulsatile LVADs due to improved device durability, it is likely that continuous flow TAH will supplant current pulsatile devices over time. Although still within the early stages of the development process, two CFTAH models have been proposed for future application. While the dual LVADs discussed above function independently, the CFTAH devices incorporate flow balancing algorithms between the left and right sides. The Cleveland Clinic has produced a CFTAH with a single motor and one rotary assembly maintained by a hydrodynamic bearing [33]. In-vivo testing has demonstrated excellent, haemodynamic status, end-organ function and pump performance. In a recent study, a calf implanted with CFTAH achieved a steady state blood flow and pressure for 90 days [107]. During this, the calf did not show any signs of haemolysis or thrombosis, with good end-organ and vasomotor function. However, this is the first study in which the Cleveland CFTAH support was observed in an animal model.

A second device under development and testing is the BiVACOR BV Assist (Figure 2.8), a third generation device, able to provide complete circulatory support for patients with advanced heart failure. There have been nine short-term pre-clinical studies successfully performed in 2007 as a “proof of concept”. Both in-vitro and in-vivo testing confirm that the device was able to balance left and right outflow to prevent atrial collapse in response to simulated changes in posture and extreme changes in systemic and pulmonary resistance [108, 109]. The first chronic implant was completed without complication in 2014 [110]. The BiVACOR rotary device is smaller than previous BiVADs as both the LVAD and the RVAD impellers have a common rotating hub. With these promising devices becoming available for human use within the next five years, their superior features such as their smaller size, improved mobility,

superior durability and continuous flow design may supersede existing devices; potentially allowing long term support, and perhaps even be considered for destination therapy.



Figure 2.8 The BiVACOR BV Assist ventricular assist system (Image © Texas Heart Institute, www.texasheart.org)

The adverse event profile of biventricular support, in common with isolated LVAD therapy, includes pump thrombus / embolic events, bleeding and infection. Improvements in pump design to minimise pump related thrombosis will likely come through software modulation to provide pump washout and possibly contribute to decrease gastrointestinal bleeding due to controlled arterial pulsatility. Miniaturisation will allow decreased operative risks, and improved patient mobility. Infection remains a significant long term obstacle to success, and enthusiasm for completely implantable systems needs to be balanced with an awareness of the risk of infection associated with large surface area of implanted devices.

Improved battery design will further decrease the imposition of having to carry power source (either internally or externally). Improved characterisation of suitable patients and evidence

of reversal of the frailty phenotype, often associated with the biventricular heart failure patients, will allow improved patient survival and outcomes. It is likely that a durable chronic heart replacement device will be developed, but at present does not seem likely within a 5 year timeframe.

Key issues

- Pulsatile displacement biventricular assist devices and the total artificial heart have successfully supported patient for BTB, BTR and BTT circumstances.
- Primarily due to differences in patient cohorts, clinical outcomes in BiVAD or TAH patients remain inferior compared to isolate LVAD patients.
- Use of chronic dual continuous flow VADs is feasible and may provide similar outcomes compared to TAH with increasing experience
- Miniaturisation of both pump devices and controllers has allowed discharge and improved quality of life in selected patients
- Ongoing issues of infection and pump thrombus / embolic events limit durability beyond bridge to transplant patients, destination therapy is not currently realistic
- Pump size impacts both surgical morbidity, but may also be an important consideration in risk of late infection. This needs to be incorporated into development of transcutaneous energy transfer technologies.
- Application of continuous flow technology into total heart replacement holds some promise, and further developments are awaited.

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CHAPTER III- METHODOLOGY OF THE 'MOCK CIRCULATORY LOOP'

3.1 BACKGROUND

3.1.1 Mock circulatory loop

The in-vitro testing of ventricular assist devices (VADs) is conducted in a mock circulatory loop (MCL) ⁽¹⁻⁴⁾. A MCL is a mechanical representations of the human cardiovascular system capable of simulating the various physio/pathological haemodynamic parameters of the heart ⁽¹⁾. To date, a number of MCL's with varying complexities have been used to test different performance aspects of commercially available and prototype VAD's ⁽⁵⁻¹¹⁾. Simple MCL designs can be developed relatively quickly and involve a single non-pulsatile circuit. More accurate loops include a pulsatile source. Their ability to replicate the natural heartbeat makes them ideal for testing the durability of prosthetic valves ^(12, 13). Their utility in the assessment of haemodynamic, haemolysis and hydrodynamic factors of prosthetic vessels and VADs has also been reported ⁽¹⁴⁻¹⁶⁾.

As the human body is a pulsatile system, early non-pulsatile MCL designs may not accurately assess the performance of VADs ⁽¹⁷⁾. These early designs were largely conducted to determine the durability and longevity of VADs as many devices at the time were only intended for short term-bridge to transplantation. To overcome this limitation, subsequent studies developed pulsatile MCL's that more accurately represent the systemic circulation ⁽¹⁸⁻²¹⁾. Further

modifications to these MCL's have demonstrated improvements in their operation by including features such as vascular resistance and vessel compliance ^(12, 22, 23). Despite these adjustments, many early MCL designs reproduce the systemic circulation alone ⁽²⁴⁾, making them unsuitable to test either right ventricular assist devices (RVADs) and biventricular assist devices (BiVADs).

Twenty years ago, RVAD and BiVAD technologies were almost non-existent with the earliest forms of dual mechanical biventricular support entirely dependent on the Total Artificial Heart system (TAH). However, as the significance of right ventricular failure post isolated LVAD support were repeatedly brought to light, improved models for VAD designs and thus by association MCL designs capable of testing these models were becoming increasingly available. Such MCL models were more elaborate than simple designs and were capable of capturing different features of the human cardiovascular system ⁽¹⁻⁴⁾. Right and biventricular support were assessed by including both the systemic and pulmonary circulatory pathways into the loop ^(17, 25). Depending on the design and purpose of these complex MCL, natural auto-regulatory feedback mechanisms such as the Frank-Starling response and the baroreceptor reflex could also be replicated ^(17, 23, 26). To produce valid simulations accurately depicting physiological flows and pressures, many previous models incorporated atrial compliance, peripheral resistance and characteristic resistance, otherwise known as the three-elemental Windkessel-model ⁽²⁴⁾. However, evidence suggests that better waveform can be attained by applying a 4th (fluid inertia) and 5th (venous compliance) element to the circuit ⁽²⁷⁻²⁹⁾. While fluid inertia is increasingly recognised as a contributing factor to better flow and aortic waveform production, the difference it makes when compared to the traditional three-elemental Windkessel-model is minimum ⁽²⁷⁾. The integration of venous

compliance however, has resulted in market improvements to ventricular outflow waveforms^(27, 28). Although the 5-elemental Windkessel model has been predicted to produce the most accurate results, the 3- and 4-element models are easier to physically construct and have been shown to provide reliable flow and waveform data similar to the native heart⁽²⁷⁾.

Future modifications will strive to further enhance flow and pressure waveform production and produce a compact model capable of representing the full mechanisms of the human cardiovascular system. These advancements often require sophisticated in-vitro models coupled with computational fluid dynamic (CFD) simulations. Computational fluid dynamics are programs that use applied physics, mathematics and computational analysis to visualize flow dynamics of gases and liquids, as well as their interaction with the surrounding objects (piping, ventricles, etc). They can provide a reference point to many aspects of the in-vitro model including flow, pressure, velocity, temperature and density of the moving fluid. However, it is important to note that these CFD simulations are only used as a referencing point for MCL development and cannot supplement the in-vitro process. In-vitro simulation is necessary for identifying associations, trends and causality in a physical model. With the rapid development of newer, smaller and novel VADs, in-vitro testing prior to expensive animal and human trials have become even more paramount. The significance of these in-vitro tests lie in the accurate measurements of device performance, such as pressure and blood flow readings. This can identify optimum values for many of the device characteristics, and can therefore be incorporated during *in-vivo* tests.

The growing awareness of the consequences of delayed/concomitant right ventricular failure (RVF) following isolated LVAD support has resulted in rapid interest in the area of continuous flow BiVAD/RVAD design and development in recent years. Although LVAD technology has

been vigorously tested, the haemodynamic consequences of continuous flow BiVAD and RVAD devices remains largely unexplored. Thus a new MCL was developed to produce physiologically accurate haemodynamic flow and pressure waveforms capable of mimicking the entire human cardiovascular system and testing various VAD configurations, such as isolated LVAD, RVAD and BiVAD support.

3.2 MOCK LOOP DESIGN

The 4-elemental MCL in this study incorporated the systemic and the pulmonary circulation, systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), VAD implantation sites, valves, left and right heart functions, aortic, pulmonary and venous compliance, physiological viscosity, and the resistance of blood vessels. A diagrammatic illustration of the MCL is shown in Figure 3.1 with the physical model depicted in Figure 3.2.

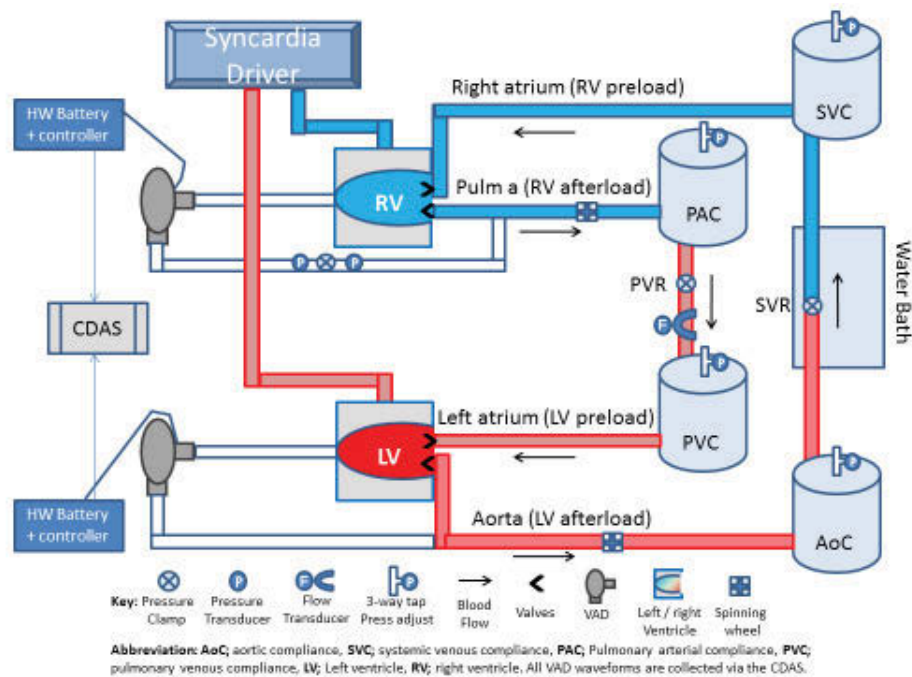
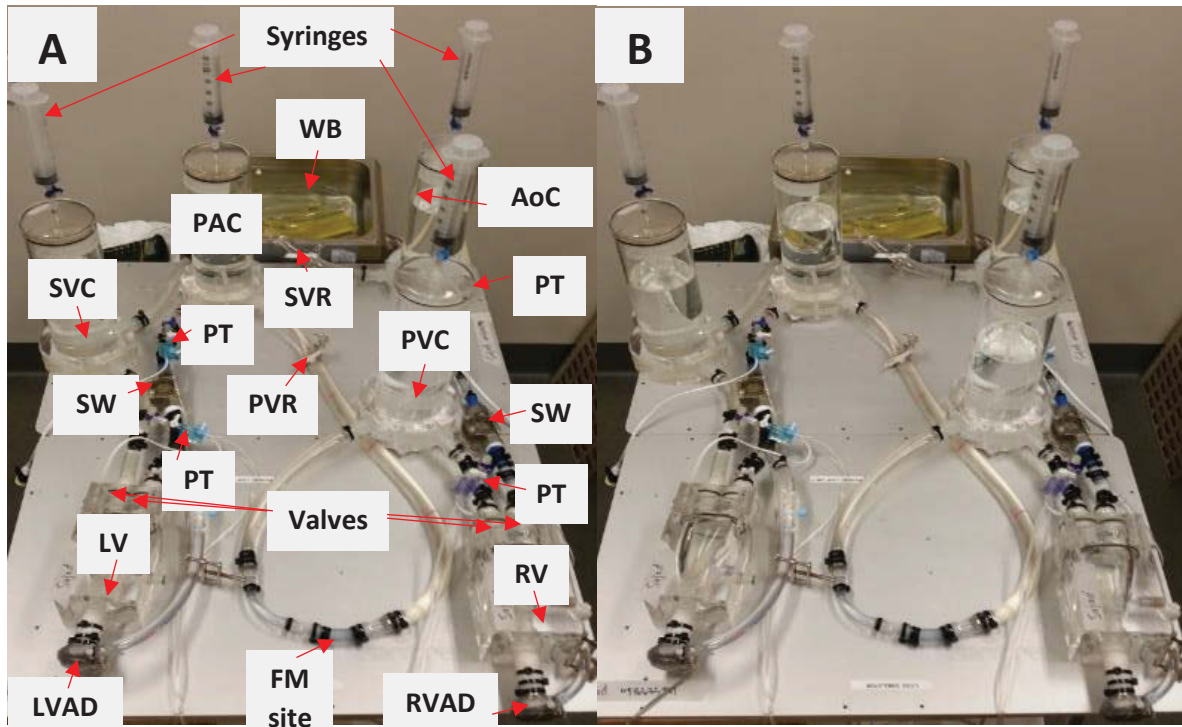


Figure 3.1 Diagrammatic illustration of the current MCL design



LVAD, left ventricular assist device; **RVAD**, right ventricular assist device; **LV**, left ventricle; **RV**, right ventricle; **PT**, pressure transducers; **PVR**, pulmonary vascular resistance; **SVR**, systemic vascular resistance; **FM site**, flowmeter site (where flow probe is connected); **SW**, spinning wheel; **AoC**, aortic compliance; **SVC**, systemic venous compliance; **PAC**, pulmonary arterial compliance; **PVC**, pulmonary venous compliance

Figure 3.2 Physical model of the MCL. For clarity, two identical images were reproduced where figure A on the left is labelled while figure B on the right is not

3.2.1 Artificial heart

The left and right ventricles were constructed using a truncated-ellipsoidal shaped deformable silicone diaphragm (77mm x 49mm) encased inside a transparent sealed air chamber. The ventricles measured 170 mm in length and 95 mm in width at the base. HeartWare HVADs (HeartWare, Framingham MA) were attached to the apex of each ventricle, which directed flow to their respective systemic or pulmonary pathways via mechanical bi-leaflet valves (On-X, On-X Life Technologies Inc.'s Heart Valve Product Group, Austin TX). The On-X mechanical valves were identical in shape and size measuring at a diameter of 27mm. All valves are detachable and can be replaced by an identical valve with only one-leaflet (other leaflet removed) during simulated severe pathological valvular regurgitation conditions. An

illustration of the artificial ventricles as well as the On-X mechanical bi-leaflet valves are shown in Figure 3.3.

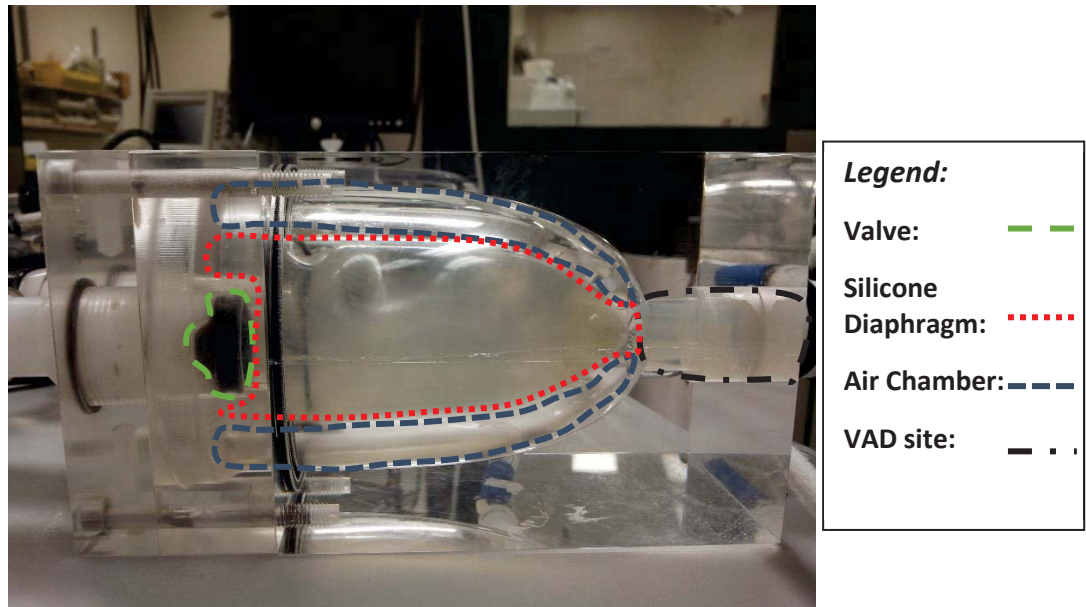


Figure 3.3 Close up of the artificial left ventricle depicting the location of the On-X bi-leaflet valve, silicone diaphragm, air chamber where air is compressed/decompressed the SynCardia Companion driver and VAD implantation site found at the apex of the ventricle directing flow away from the heart and into the circulation

3.2.2 Contractility

Ventricular contraction and pressures were generated by the 70cc SynCardia Companion Driver system (SynCardia Systems, Inc. Tucson AZ) as has been previously described.⁽³⁰⁾ The SynCardia Companion driver provides pulsatile flow by pneumatic compression of the silicon ventricles with ejection both through the aortic valve and through the pump in pump systole. Systolic ratio and pneumatic driving pressures were varied for both ventricles to simulate physio/pathological ventricular function. The pneumatic driving pressure for left and right ventricles were reduced to minimum performance, valued at 120 and 40mmHg respectively. Heart rate was maintained at 90 beats per minute and systolic ejection ratio at 40%. These low range pneumatic driving pressures and systolic ejection ratios were used to generate haemodynamic parameters to model the impaired ventricular contractility with short ejection

duration (280msec) and low cardiac output seen in advanced heart failure patients. However, pneumatic driving pressure, heart rate and systolic ejection ratio are able to be altered depending on the desired hemodynamic conditions tested. Suction settings (set to 0mmHg) were not altered throughout the study. Heart rate, ventricular contraction and cardiac output were all actively recorded using the SynCardia Companion driver.

3.2.3 Compliance

Four identical hermetically sealed cylinder shaped chambers (10cm diameter x 32cm height), commonly referred to as windkessel chambers, were used to simulate the pulmonary artery compliance, left atrium/pulmonary venous compliance, aortic compliance, and the right atrium/systemic venous compliance. The method of simulating compliance by using airtight tanks containing a certain volume of trapped air above the fluid has been previously validated ⁽³¹⁻³³⁾. However, for any adjustments to be made to previous models, cessation of MCL activity was required to calibrate new setting. In the current MCL, slight modifications were made to allow for changes in compliance to be made during experimentation similar to the designs proposed by Litwak et al ⁽³¹⁾ (Figure 3.4). To do this, air valves were incorporated on top of each windkessel chamber to help regulate pressure/volume levels. These valves were attached to an air filled syringe that was able to adjust the amount of air present within the sealed chamber and hence compliance. Compliance values were then calculated using validated formula which takes into consideration the relationship between air pressure and volume, and fluid pressure and volume ⁽³⁴⁾.

$$C = \frac{dV_{fluid}}{dP_{fluid}} = \frac{V_{air}}{P_{air}} = \frac{V_{tank} - A_{tank}h_{fluid}}{P_{fluid} - \rho gh_{fluid}}$$

Legend: **C** is compliance of the tank, **V** is the volume of air in the tank, **P_{air}** is the absolute pressure of air in the tank, **V_{tank}** is the volume of the tank, **A_{tank}** is the cross sectional area of the tanks, **P_{fluid}** is the absolute pressure of fluid in the tank, **h_{fluid}** is the height of fluid in the tank, **ρ** is the density of the fluid, and **g** is acceleration due to gravity ⁽³¹⁾.

Figure 3.4 Formula for measuring compliance (adopted from Liu et al ⁽³¹⁾)

3.2.4 Blood volume and viscosity

To accurately simulate a representation of the human cardiovascular system, factors such as blood volume and blood viscosity must be carefully controlled to ensure all segments of the loop consist of physiologically accurate haemodynamic volumes and parameters. For referencing material, values from the literature of previous MCL models were used to determine the amount of fluid, viscosity and dimensions of pipe lengths and diameters for the current MCL. A 40% glycerol solution (60% sterilised water and 40% glycerol) was used to simulated natural blood viscosity ⁽³⁵⁾, while the total volume of fluid within the MCL was approximately five litres and was maintained at 37 degrees by in-line water bath to simulate the viscosity of blood with a haematocrit of 34%. If required, the viscosity could be varied by altering circulating temperature, with a higher temperature resulting in lower viscosity ⁽³⁶⁾.

3.2.5 Blood flow

Blood flow is normally measured in litres per minute (L/min) and always flows from an area of high pressure (P1) to low pressure (P2). Blood flow (Q) in the vessels are commonly calculated by determining the difference in pressure of a vessel by the resistance of that vessel (R) and can described by the following equation; $Q = P1 - P2 / R$. However, in the heart, blood flow is often measured by the amount of blood pumped per minute, which is also

known as the cardiac output (CO). The CO can be calculated by multiplying the heart rate by the stroke volume. The CO is often used to determine the functionality of a patient heart. A healthy adult at rest can have a CO of approximately 5 L/min while a patient suffering from heart failure would have lower CO of around 2-3 L/min ⁽¹⁷⁾.

However, flow throughout the MCL was measured using three different simultaneous flow recordings during each experiment. These include LVAD, RVAD, and independent systemic flow values. Both LVAD and RVAD parameters were recorded using proprietary software (continuous digital acquisition system) while systemic flow was measured using a TS410 transit-time tubing flow meter (Transonic System Inc. Ithaca NY) positioned between the PA and LA chamber, after the PVR clamp (Figure 3.1). The flow probe was attached directly to clear PVC tubing and was recorded using LabChart 7 software (ADInstruments Pty Ltd, Bella Vista). There have been some reports suggesting the use of two flow meters to measure the systemic and pulmonary circulations independently as slight variations between the two have been noted immediately after a change in heart function. However, as the MCL is a closed loop system, the flow values between the systemic and pulmonary circulation should stabilise briefly after changes are made yielding an equal flow through the MCL. As a mandatory waiting period was enforced for all experiments, a second flow meter was not necessary and had negligible consequences on the results obtained.

3.2.6 Resistance

To measure resistance, the length and cross sectional area of the clear PVC tubing (15.9mm x 2.4mm) used to connect the major components of the MCL together were determined and carefully compared to the literature. These tubes provide similar venous and systemic flow resistance as those seen in the cardiovascular system. However, as systemic and pulmonary

vascular resistances vary greatly between conditions, additional resistance was added using tuning clamps to replicate SVR and PVR. By strategically positioning these clamps within the MCL, we can discretise the MCL into different segment to represent various compartments of the cardiovascular system. The following formula were used to calculate SVR and PVR within the MCL.

Equation 1: $SVR = 80 \times (MAP - RAP) / CO$

Equation 2: $PVR = 80 \times (MPAP - LAP) / CO$

3.2.7 Blood pressure

Blood pressure (BP) is the measure of blood in the arteries as it is pumped around the body by the heart. To measure the BP, both the systolic and diastolic pressures are recorded and often reported alongside one another, e.g. the resting BP of a healthy person should be approximately 120/80 mmHg. The larger number represents the systolic pressure which refers to the pressure in the arteries as blood leaves the heart during each beat. The second represents the diastolic pressure which indicates the pressure of the heart as it relaxes and prepares for the next beat. The BP can change from minute to minute depending on changes to activity, posture, stress or sleep and is increasingly recognised as an important endpoint in the evaluation of MCLs and humans. There are four different pressures that are assessed in our experiments. These include mean arterial pressure (MAP), pulmonary artery pressure (PAP), left atrial pressure (LAP) and right atrial pressure (RAP). All pressures are continuously recorded using S5-Collect software (GE Healthcare, Finland).which directly records and converts data from the anaesthetic monitor (Datex-Ohmeda, Inc) onto the laptop via a RS323 adaptor.

Mean arterial pressure

The MAP is the average pressure over one cycle taken from the aorta. It is calculated using the formula $[(2 \times \text{diastolic pressure}) + \text{systolic pressure}/3]$. Low MAP values are often a strong indication of poor blood perfusion throughout the body and into the vital organs. Conversely prolonged elevated MAP values are associated with over working of the cardiac muscles which may in time promote advanced heart failure.

Pulmonary artery pressure

The PAP is a measure of blood pressure that is found within the pulmonary artery. The mean PAP (MPAP) is typically within the range of 9-18 in healthy humans and can be calculated using the same formula described for MAP, e.g. $\text{MPAP} = [(2 \times \text{diastolic PA}) + \text{systolic PA}/3]$. Elevated MPAP levels are suggested of pulmonary hypertension and other clinical abnormalities.

Left atrial pressure

Left atrial pressure or commonly known as pulmonary wedge pressure is a measure of the estimated pressure within the left atrium of the heart. It is commonly measured by wedging a pulmonary catheter with an inflated balloon into a small pulmonary artery branch and ranges between 6-12mmHg in healthy humans. It is vital for diagnostic purposes as elevated values are commonly associated with acute pulmonary edema, left ventricular failure and mitral stenosis.

Right atrial pressure

Right atrial pressure or central venous pressure (CVP) is the blood pressure in the venae cavae located near the right atrium of the heart. Although the two terms are not identical, CVP is a good approximation of the RAP. Both are strong indicators of the functional capacity of the

right ventricle to pump blood out of the heart and of the amount of blood returning into the right side of the heart. Normal haemodynamic values range between 0-6 mmHg, where elevated measurements are features of right ventricular failure and potential abnormalities with the tricuspid valve.

3.2.8 Frank Starling Law

The Frank Starling Law is a natural phenomenon describing the mechanisms involved in the process of increased ventricular contractility in response to increased venous return. Simply put, the law states that as the heart is exposed to increased preload (increased blood flow into the heart), the heart increases its ability to eject blood out of the heart. This mechanism is especially important during exercise and situations where the 'fight or flight' response is triggered due to external stimuli. Unlike the human heart, the artificial ventricles in the current MCL are bound by strict dimensions which limit the degree of expansion in response to increased preload. However, this limitation has been overcome to a certain extent by the SynCardia Companion driver which incorporates a limited Frank-Starling like response with some pre-load sensitivity ⁽³⁷⁾. This is achieved by deliberately setting LVP and RVP pressure as to allow for optimum, yet not complete, filling of the ventricles. The purposely under-filled ventricles provide a cushion effect of 10-20 ml to allow for augmentation of venous return and to prevent pulmonary edema from occurring ⁽³⁸⁾.

3.2.9 Setting up the MCL

Prior to experimentation, the MCL and all its components were carefully examined for leakage in the tubes or mould formation. If leaks were present, tightening of the site with a 200mm x 4.8 mm cable tie (Cooper Tools Pty. Ltd) was often sufficient to prevent further leakage. However, if three-way valves or other connectors become damaged, then replacement of

parts are essential. Through trial and error, limitation of leakage was achieved by opening the valves to atmospheric pressure after experiments to relieve the internal pressure within the MCL. If fungal growth occurred, disassembling the MCL and thorough physical cleaning was undertaken. In some instances, replacing tubing is also necessary for ensuring complete sterilisation. To prevent future fungal outbreaks, an anti-fungicide (Sodium Azide, NaN_3 0.02% concentration) is injected into every fresh batch of 40% glycerol solution.

After the loop had been thoroughly examined, the SynCardia Companion driver and the pressure transducers were attached. The SynCardia Companion driver was attached to the left and right ventricle using the pneumatic tubing provided and remained off. The dextrose drips were attached to the pressure transducers and were 'flushed'. The term 'flushed' refers to the process of washing out the dextrose solution on one side of the valve to release any air particles that were present. Air particles can dampen the signal received from the MCL to the pressure transducers. After all the air particles were removed, the pressure transducers were then attached to the MCL via a three-way valve which can be used to open and close flow between the MCL and the pressure transducers. Once attached, it was necessary to 'zero' the pressure transducers to establish a standard baseline value equivalent to atmospheric pressure. The term 'zero' refers to the process of establishing a zero pressure reference value that can be used to measure against all other intravascular pressures. The zeroing process begins by opening the three-way valve to atmospheric pressure while blocking flow from the MCL. Once the transducers are exposed to the atmosphere, the 'zero' button on the anaesthetic monitor was pressed to automatically calibrate our zero pressure reference value. After all the pressure transducers were successfully 'zeroed', the three-way valves were then rotated to obstruct exposure to the atmosphere and re-connect the flow from the MCL

to the transducer. Once the MCL was set up, acquisition software (S5 collect, CDAS, and LabChart 7) was initialized.

3.3 EXPERIMENTAL PROTOCOL

Following the design and development of the physical MCL, a series of experiments were designed to first validate the MCL and then test scenarios of clinical significance prior to animal and clinical trials.

3.3.1 Pre-validation tests

Prior to the validation of the MCL, a total of twelve brief experiments were designed to test various aspects of the loop. These tests were used to determine the total volume, compliance, resistance, and parameters such as HR, left and right ventricular pressures and systolic ratio of subsequent experimental protocols. The first set of ten tests were used to determine trends and changes in the MCL in response to various LAP values (between 10-30mmHg) during different settings of HR, systolic ratio and LVAD pump speeds. All baseline parameters for experiments 1 to 10 are shown in Table 3.1.

Table 3.1 Baseline SynCardia and HVAD pump parameters for each experiment

Experiments	HR (min)	LVP (mmHg)	RV (mmHg)	RVAD speed (RMP)	LVAD speed (RPM)	Sys (%)
Exp1: HR 80	80	100	40	2000	2600	40
Exp2: HR 100	100	100	40	2200	2600	40
Exp3: HR 120	120	100	40	2200	2600	40
Exp4: Sys 50%	80	100	40	2000	2600	50
Exp5: Sys 60%	80	100	40	2000	2600	60
Exp6: LVAD 2200	80	100	40	1800	2200	40
Exp7: LVAD 2400	80	100	40	1800	2400	40
Exp8: LVAD 2800	80	100	40	2400	2800	40
Exp9: LVAD 3000	80	100	40	2600	3000	40
Exp10: LVAD 3200	80	100	40	3000	3200	40

LVAD, left ventricular assist device; **HR**, heart rate; **LVP**, left ventricular pressure; **RVP**, right ventricular pressure; **RPM**, rounds pre minute; **Sys**, systole (%).

All experiments followed the same methodology. E.g. For experiment 1 (HR80 setting), baseline parameters were established and maintained for 5 minutes. After the first five minutes, the LA pressure was increased by increments of 5mmHg from 10mmHg to 30mmHg every five minutes by inserting air into the LA chamber. No other variables were changed. Once LA 30mmHg was recorded air was removed from the same chamber at increments of 5mmHg from 30mmHg to 10mmHg and then increased again to 15mmHg where baseline values were observed. After baseline was re-established, the HR was increased from 80 (experiment 1) to 100 (experiment 2) and the same methodology described above was repeated for the new HR100 setting. The methodology for these experiments are summarized in Figure 3.5.

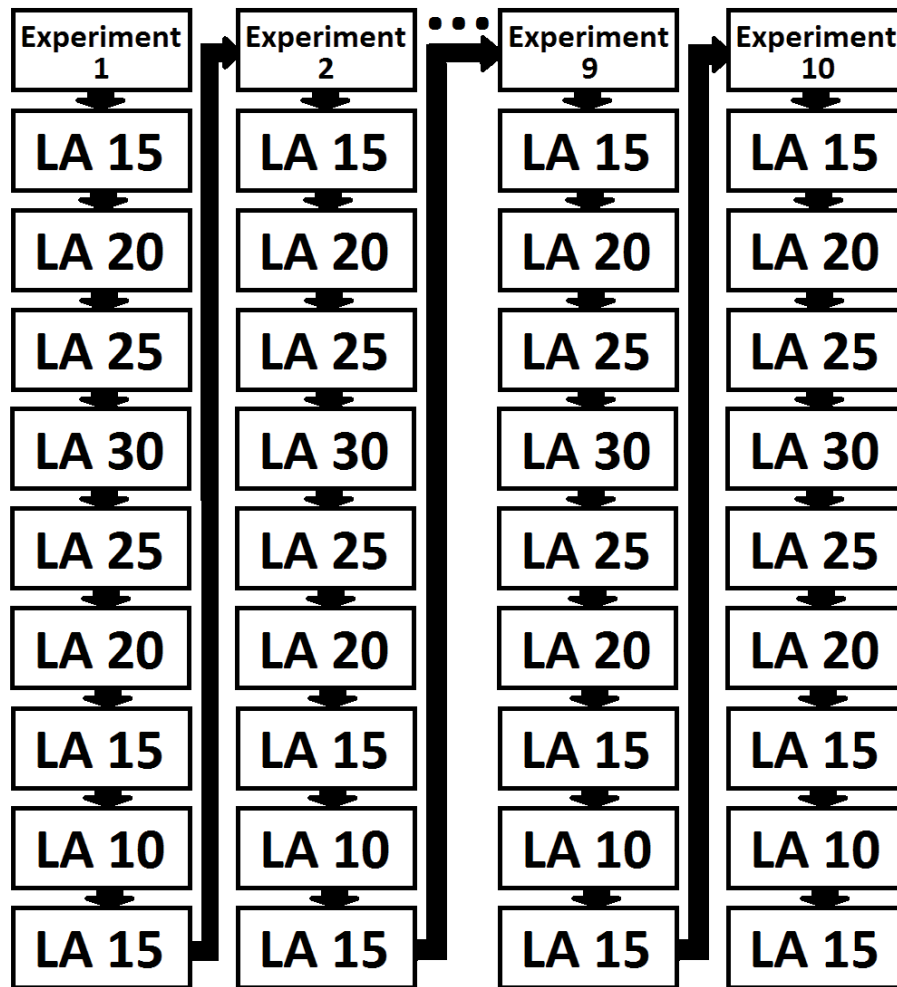


Figure 3.5 Methodology for experiments 1 to 10. Only the first and last two experiments are shown for simplicity. The same methods apply for experiments 3 to 8

The last two experiments (experiments 11 and 12) have five components each and were designed to test the impact of various left and right ventricular pressures controlled by the SynCardia Companion driver on baseline pressures and flows. For these experiments, similar baseline pressures and device settings were selected and maintained for 5 minutes. Following which LVP pressures were increased at increments of 40mmHg from 120mmHg (min) to 280mmHg (max) every 3 minutes. The experimental protocol for this component of the MCL experiments is shown in Figure 3.6 below (experiment 11). All other variables were unchanged. Changes to the pressure and flows in the system can thus be directly associated with the changes made to the LVP contractility. Following the completion of each experiment

(once LVP pressure reaches 280mmHg), the MCL is reset to starting baseline values before changing one variable such as HR (80-120, experiments 11 (i), (ii), (iii)) or systolic ratio (40-60, experiments 11 (iv) and (v)) (refer to Figure 3.6). To assess changes attributed by RVP fluctuations, the experiment was repeated for the right side (experiment 12). For RVP experiment, all pressures and device settings were identical to LVP setting. The only exception was that instead of increasing LVP at increments of 40mmHg, we would now increase RVP in increments of 30mmHg from 40mmHg (min) to 150mmHg (max). The LVP was unchanged during all RVP experiments and remain constant at 160mmHg.

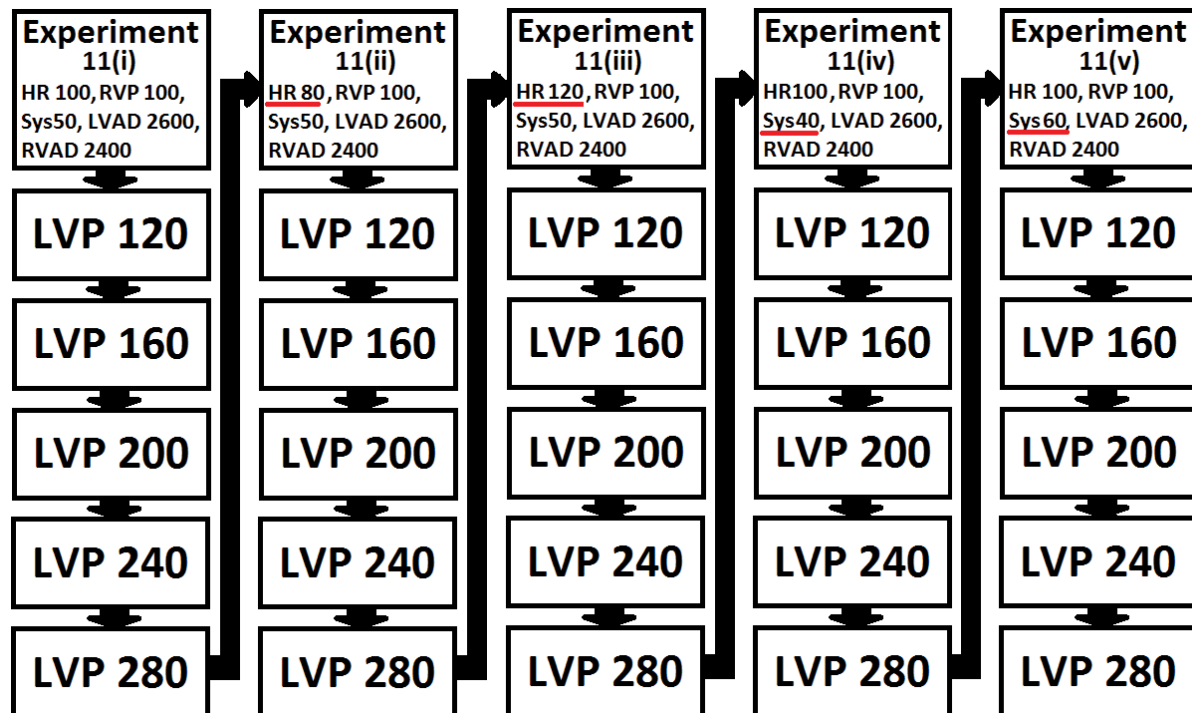


Figure 3.6 Summary of experimental methodology for testing the SynCardia pneumatic driver

3.3.2 Validating the MCL

As the MCL is required to accurately simulate similar haemodynamic parameters to those of the natural cardiovascular system, validation of the MCL was necessary prior to experimental testing with VADs. To do so, normal cardiac haemodynamic parameters illustrated in Table

3.2 below were simulated. By demonstrating the MCL's ability to reproduce normal healthy cardiac parameters, we can be confident in the outcomes produced during our experiments.

Following normal parameters four different experiments were designed according to the literature to illustrate its ability to simulate common clinical haemodynamic conditions without VAD support. These conditions include patients with borderline heart failure (HF), left ventricular failure (LVF), biventricular failure (BiVF) and severe biventricular failure (severe-BiVF). The haemodynamic parameters and driver setting are summarized in Table 3.2.

As our ventricles were designed with dimensions similar to clinical heart failure settings, LVP and RVP were increased to maximum performance (280 and 150, respectively) to simulate less severe decompensated cardiac settings to reflect early stages of heart failure (HF). In addition, SVR and PVR clamps were not as restrictive and systolic ratio was increased to 60%. For all other experiments, both the LVP and RVP were set to minimum performance values of 120mmHg and 40mmHg respectively, while systolic ratio was set to 40%. The SVR and PVR were adjusted according to the condition tested. The MCL was validated through the successful simulation of these conditions without any VAD support.

Table 3.2 Baseline haemodynamic pressures, flows and SynCardia parameters for four physio/pathological conditions simulated without VAD support

Experiments	AoP (mmHg)	LAP (mmHg)	RAP (mmHg)	PAP (mmHg)	Flow (L/min)	LVP (mmHg)	RVP (mmHg)	HR (min)	Sys (%)
Normal	120/80	9	6	30/11	4.36	280	150	90	60
Healthy Heart									
Borderline	100/60	15	10	30/15	4.4	280	150	90	60
BiVF									
LVF	90/60	25	10	60/30	2.7	100	40	90	40
BiVF	90/60	25	25	50/30	2.3	100	40	90	40
Severe BiVF	90/60	30	25	60/30	1.8	100	40	90	40

BiVF, biventricular failure; **LVF**, left ventricular failure; **AoP**, aortic pressure; **LAP**, left atrial pressure; **RAP**, right atrial pressure; **PAP**, pulmonary artery pressure; **LVP**, left ventricular pressure; **RVP**, right ventricular pressure; **HR**, heart rate; **Sys**, systolic ratio (%).

3.3.3 Experiments involving VADs

For experiments involving VADs, the MCL was run in steady state and real time flow waveforms and pressures were monitored using an Aespire anaesthesia machine (Datex-Ohmeda, Inc.). Four cardiac conditions were simulated with and without the HVAD operating (Table 3.3). These include (1) biventricular failure; (2) biventricular failure with isolated continuous flow LVAD support; (3) biventricular failure supported with LVAD receiving delayed RVAD support; and (4) biventricular failure with initial concomitant LVAD and RVAD support providing BiVAD support.

For the first experiment, biventricular failure was simulated and recorded (Condition 1). Both HVADs (LVAD and RVAD) were then turned on and SVR and PVR adjusted to accommodate the changing flows. This demonstrated the effects of initial BiVAD support (Condition 4). The two VADs were then turned off and SVR and PVR reversed to simulate biventricular failure again (Condition 1). Once recorded, only the LVAD was turned on to represent biventricular failure support with isolated LVAD support (Condition 2). Again, slight modifications were

made to SVR and PVR. After all measurements were recorded, the RVAD was then turned on to simulate the hemodynamic consequences of delayed RVAD support following LVAD (Condition 3). As before, SVR and PVR alterations were required to balance pressures. All conditions were recorded for a period of 5 minutes while in steady state.

CHAPTER III- METHODOLOGY OF THE 'MOCK CIRCULATORY LOOP'

Table 3.3 Simulated biventricular failure reversed with optimum initial BiVAD and delayed RVAD support

Condition(s)	HR (min)	Ao (mmHg)	MAP (mmHg)	LAP (mmHg)	MPAP (mmHg)	RAP (mmHg)	SVR dyn. sec.cm ⁻⁵	PVR dyn. sec.cm ⁻⁵	LVP (mmHg)	RVP (mmHg)	Flow (CO) (L/min)	LVAD flow (L/min)	LVAD speed (RPM)	RVAD flow (L/min)	RVAD speed (RPM)
HVAD Off															
Biventricular failure pre-VAD	90	90/60	70 (0.26)	25 (0.5)	37 (0.7)	25 (0.32)	1565 (56.8)	406 (13.6)	120	40	2.3 (0.10)	-	-	-	-
HVAD turned on															
BiVF with isolated LVAD	90	111/78	89 (1.1)	8 (0.13)	15 (0.25)	17 (0.33)	1694 (47.6)	157 (9.1)	120	40	3.5 (0.08)	3.8 (0.5)	2600 (20.6)	-	-
BiVF + LVAD + delayed RVAD	90	115/72	86 (1.4)	8 (0.38)	18 (0.60)	3 (0.28)	1509 (36.0)	194 (2.8)	120	40	4.4 (0.16)	4.5 (0.66)	2600 (22.7)	4.5 (0.59)	2200 (9.0)
BiVF + BiVAD	90	100/71	81 (1.6)	8 (0.29)	13 (0.71)	4 (0.19)	1311 (27.9)	85 (8.9)	120	40	4.7 (1.1)	4.9 (1.8)	2600 (22.8)	4.4 (0.65)	2200 (8.8)

HR, heart rate; **Ao**, aortic pressure; **MAP**, mean arterial pressure; **LA**, left atrium; **mean PA**, mean pulmonary artery; **RA**, right atrium; **SVR**, systemic vascular resistance; **PVR**, pulmonary vascular resistance; **LVP**, LV pressure (pneumatic generated); **RVP**, RV pressure (pneumatic generated); **CO**, cardiac output; **LVAD**, left ventricular assist device; **RVAD**, right ventricular assist device; **VAD**, ventricular assist device; **BiVAD**, biventricular assist devices; **BiVF**, bi-ventricular failure. (LVAD flow and RVAD flow were recorded directly from HVAD controlled. Mock loop flow measured using transonic flowmeter). Data shown as mean (SD).

3.3.4 Hypertension experiments

Hypertension is clinically defined as abnormally elevated blood pressure. Simulating high pressures in the MCL can be achieved by simply increasing the overall pressure of the MCL by increasing the amount of air present. However, just adding air into the MCL may not accurately reflect certain cardiac conditions. To determine the most appropriate means of increasing pressures without deviating from physiological waveform morphologies, three different experiments were designed.

Experiment 1

The first experiment looked at the influences of increasing LVP pressure from 120 to 280mmHg at increments of 20mmHg, similar to the pre-validation experiments seen with the SynCardia Companion driver (Figure 3.6). Baseline parameters are shown in Table 3.4 and maintained for 5 minutes. The LVP pressure was then increased from 120 to 140mmHg and flow and pressure parameters were recorded. Once max LVP pressures of 280mmHg were achieved, new parameters were recorded the second experiment was commenced. This experiment demonstrated how opening of the aortic valve (previously closed) could be achieved with LVP pressure greater than or equal to 240mmHg. The greater the LVP pressure the greater the opening of the aortic valve due to increased ventricular contractility.

Experiment 2

For the second experiment, it was important to determine the consequences of decreasing MAP pressure from the new 92mmHg back to baseline 80mmHg. All pressures and settings were unchanged from the last setting of experiment 1 as shown in Table 3.2 (LVP 280). The MAP was decreased in two intervals of 6mmHg by reducing the SVR slightly. This method demonstrated how pressures can be changed without altering air levels or LVP/RVP

pneumatic pressures. Once MAP 80mmHg was restored and recorded. The SVR was returned back to normal and the original baseline setting were re-established (LVP120).

Experiment 3

The third experiment investigated the consequences of manually increasing MAP in increments of 10 mmHg from 80 to 120 mmHg. This was achieved by increasing air pressure into the aortic compliance chamber. Baseline parameters are the same as those seen in LVP 120 settings (Table 3.4). As expected, increasing air pressure in the MCL increased the pressure within all segments of the MCL, including LA, RA and PA. This may not be ideal in testing clinical conditions.

These experiments demonstrated how pressures in the MCL are primary influenced by variations to LVP/RVP pneumatic pressures, differences to SVR/PVR levels and changes made to air levels within the chamber. Although changing air pressure is not recommended during experimentation, it is vital for setting up condition and ensuring physiological compliance levels. During experiments, either pneumatic pressures, or SVR/PVR levels can be changed to redirect pressure gradients within the MCL without introducing external stimuli. Depending on what is being tested, one method may be more suitable than the other. For many LVAD speed variation experiments, slight alterations to the SVR and PVR are suitable adjustment that can be found clinically. In humans, SVR and PVR values naturally adapt or can be influenced with medications.

Table 3.4 Baseline, minimum and maximum pressure and VAD settings for all three pressure variation experiments

Conditions	MAP mmHg	LA mmHg	RA mmHg	MPAP mmHg	RVAD speed	LVAD speed	AV	LVP mmHg	RVP mmHg
Baseline									
(experiment 1 – LVP 120)	80	11	0	39	2400	2600	C	120	40
Experiment 1 - LVP 280	92	7	2	36	2400	2600	O	280	40
Experiment 2 – SVR ↓, MAP 86)	86	3	5	36	2400	2600	O	280	40
Experiment 2 – SVR ↓, MAP 80)	80	2	14	38	2400	2600	O	280	40
Experiment 3 – MAP 80 (air variation)	80	10	0	39	2400	2600	C	120	40
Experiment 3 – MAP 120 (air variation)	120	49	36	83	2400	2600	C	120	40

MAP, mean arterial pressure; **LA**, left atrium; **MPAP**, mean pulmonary artery pressure; **RA**, right atrium; **SVR**, systemic vascular resistance; **LVP**, LV pressure (pneumatic generated); **RVP**, RV pressure (pneumatic generated); **LVAD**, left ventricular assist device, **RVAD**, right ventricular assist device, **AV**, aortic valve; **C**, closed; **O**, open

3.3.5 Valvular regurgitation experiments

Although continuous flow VAD technology has been well integrated into clinical practice, the use of continuous flow BiVAD remains experimental with no current FDA and TGA approved devices available in the market. As the off-label use of dual LVAD therapy for BiVAD support using the HeartWare HVAD has shown promising outcomes in previous MCL and clinical experiences, we decided to investigate the effects of continuous flow BiVAD support in the setting of valvular abnormalities such as aortic, mitral and tricuspid regurgitation (AR, MR, and TR respectively).

As such, four different conditions were designed for testing with the MCL including intact valves, AR, MR and TR. To mimic severe AR, MR and TR states, the functional On-X mechanical

bi-leaflet valve was removed and replaced with an identical duplicate with only one leaflet (the other leaflet was manually removed). To observe hemodynamic consequences of continuous flow BiVAD support within these simulated conditions, two different experimental protocols were designed. All experiments were conducted in series to ensure there were no variations in terms of pressure, compliance, resistance and flow between each test. Once all settings were recorded the LVAD pump speeds were changed and the effects observed. A mandatory waiting period of 2-3 minutes were allocated following each change made to the MCL to allow the system to stabilise before the effects on flow rate and aortic (Ao), RA and PA pressures were recorded. The methodology for valvular experiments is summarized in Figure 3.7.

For comparability, all experiments started with a simulated state of no VAD support (LAP25, RAP25, MAP 80). All baseline parameters were maintained for five minutes before the LVAD pump was turned on and protocol 1 of the experiments commenced. In Protocol 1 conditions were assessed across a range of pump speeds (2200-4000) and configurations (isolated LVAD vs. dual BiVAD support). For intact valves, AR, MR and TR conditions, LVAD speed varied and RVAD speed was constant at 2400rpm. Initial LVAD and RVAD pump speeds of 2600rpm and 2400rpm respectively were selected on the bases of their most common clinical setting for left or right ventricular support. For protocol 1, at the completion of recording baseline values, the LVAD pump speed was reduced to a minimum 2200rpm at decrements of 200. It was then returned to 2600rpm where it increased to 3200 rpm at increments 200 again. From 3200rpm it increased to 3600rpm and then a maximum pump speed of 4000rpm. To demonstrate the difference between BiVAD and isolated LVAD support, the RVAD was turned on and the right ventricular outflow graft opened. The same methodology described for isolated LVAD was

repeated for the BiVAD configuration. The system was observed carefully for any variation between flows pre- and post RVAD support and the initial baseline parameters were restored, priming the MCL for Protocol 2.

In Protocol 2, LV filling pressure was actively varied at a fixed pump speed. The LA pressure was increased from 10mmHg to 15mmHg and the process previously described in protocol 1 was repeated (e.g. changing pump speed from baseline to minimum and maximum capacity). The same was completed for LA pressures of 20mmHg and 25mmHg. The incremental increase of 5mmHg from 10 to 25mmHg at the end of each protocol 1 experiment was achieved by slight modifications to the SVR and PVR. Contractility, HR, viscosity, haematocrit, LV and RV pressures were not altered.

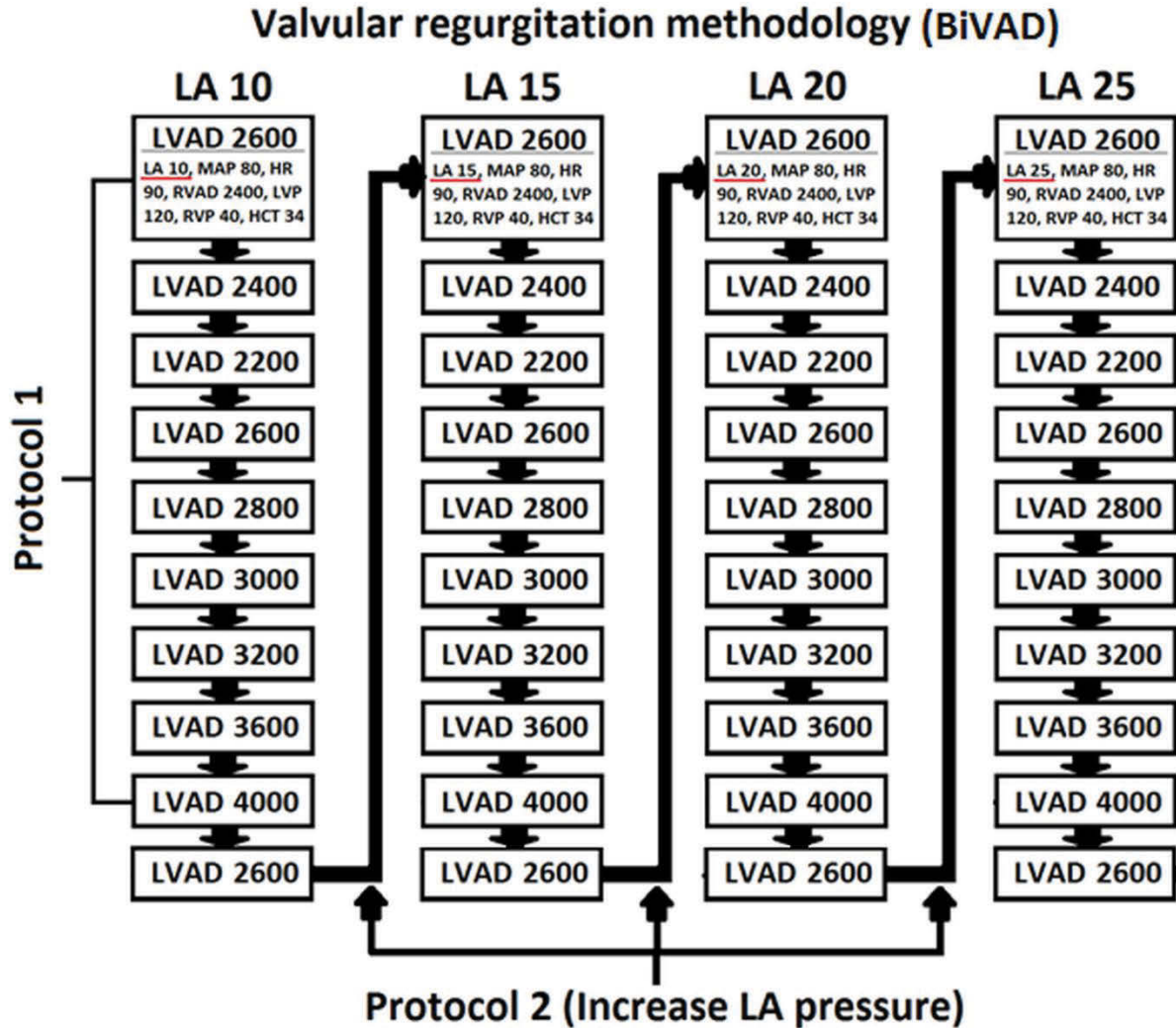


Figure 3.7 Methodology for valvular regurgitation experiments

3.4 DATA ACQUISITION AND ANALYSIS

Flow and pressure waveforms were recorded using Labchart 7 (ADInstruments Pty Ltd, Bella Vista) and Datex-Ohmeda S/5™ Collect software (GE Healthcare, Finland), respectively. LVAD and RVAD pump parameters were recorded directly from pump controllers onto a laptop using proprietary software (continuous digital acquisition system) sampled at 50Hz. All data was analysed using statistical Matlab software (The MathWorks, Inc. Natick MA). All waveforms were smoothed with a low pass filter using Savitzky-Golay method and were averaged over four cycles. This study was observational. As the pressures and flows were all

measured in steady state at the same pump speeds and pneumatic ventricular rate no statistical tests are available.

3.5 SIGNIFICANCE OF *IN-VITRO* STUDIES

Although there are a number of encouraging VADs currently in development, these devices must first undergo a series of stringent testing phases before being implemented into clinical practice ⁽³⁹⁾. These tests often include in-vitro proof of concept, in-vivo proof of principle, and clinical validation ⁽⁴⁾. Although in-vivo experimentation, such as human and animal trials are considered the gold standard, these can be quite expensive to perform and can carry a great risk to the patient if the device has not previously been tested in the laboratory ⁽⁴⁾. Therefore in-vitro experimentation is an important segment of the validation process, as it provides a chance to safely evaluate the performance of the device, and assess its ability to achieve its intended function before it is inserted into a living organism ⁽⁴⁾. Moreover, in-vitro testing of a device can aid to identify faults or areas of improvements of the device, saving a considerable amount of time and expense prior to in vivo trials ⁽⁴⁾.

3.6 CONCLUSION

This chapter has provided a description of the ongoing evolution of MCL designs and outlined the features available with current MCL model. In addition, all parameters measured during experimentation such as pressures, flows and intrinsic feedback mechanisms such as the Frank Starling response were explained and their clinical significance highlighted. Finally, a description of experimental designs was explained with an emphasis on how each experiment was conducted. The following chapters will present the results of the *in-vitro* model.

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CHAPTER IV- RIGHT VENTRICULAR FAILURE POST LVAD IMPLANTATION CORRECTED WITH BIVENTRICULAR SUPPORT: AN IN-VITRO MODEL

4.1 CHAPTER PREFACE

Publication reference:

Shehab S, Allida SM, Newton PJ, Robson D, Davidson PM, Jansz PC, Hayward CS. Right ventricular failure post LVAD implantation corrected with biventricular support: an in-vitro model. ASAIO. 2016.

Chapter III provided a detailed description and justification of the experimental methods of this in-vitro model. This chapter presents the results of the performance of the Heartware ventricular assist device as biventricular support.

This chapter presents an article in its original form, published in the Journal of American Society of Artificial Internal Organs (2016). This article is provided in its published form as an appendix (Appendix 8).

Background

Right ventricular failure post LVAD implantation is associated with high mortality. Management remains limited to pharmacological therapy and temporary mechanical support. Delayed RVAD support post LVAD implantation is associated with poor outcomes. With the advent of miniaturised, durable, continuous flow ventricular assist device systems, chronic RVAD and BiVAD support has been used with some successes.

Aim of this study

The purpose of this study was to assess combined BiVAD and LVAD with delayed RVAD support within a 4-elemental MCL simulating the human cardiovascular system. Our hypothesis was that delayed continuous flow RVAD (RVAD) would produce similar hemodynamic and flow parameters to those of initial BiVAD support. Using the MCL, baseline biventricular heart failure with elevated right and left filling pressures with low cardiac output was simulated.

Summary of results

The addition of LVAD within a biventricular configuration improved cardiac output somewhat, but was associated with persistent right heart failure with elevated right sided filling pressures. The addition of an RVAD significantly improved LVAD outputs and returned filling pressures to normal throughout the circulation.

Implications

Delayed RVAD support with the HVAD system successfully restored hemodynamic parameters. If translatable into clinical practice, the HVAD system may provide much needed support to patients that develop right ventricular failure post-LVAD implantation without the significant risk to mortality and morbidity.

4.2 INTRODUCTION

Lack of donor heart availability and improved short term outcomes of durable LVAD have resulted in a rapid rise in long term mechanical circulatory support. Although LVADs are well-established form of practice, long term effects on the right ventricle remain controversial ⁽¹⁾. The development of right ventricular failure (RVF) following LVAD implantation has been associated with mortality rates of up to 40% ⁽²⁾. Although inotropic therapy, nitric oxide and prostaglandins can often restore function, management for periods greater than 14 days without recovery is associated with worse clinical outcomes ⁽²⁾. Thus, in patients at high risk or with symptomatic RVF, early biventricular assist device (BiVAD) support has been suggested ⁽³⁾. Biventricular support with existing paracorporeal BiVADs and the total artificial heart systems have, however, been associated with lower survival rates than isolated LVAD systems ⁽⁴⁾. These findings may be one of the main reasons why many institutions opt to provide isolated LVAD and use only temporary extra/paracorporeal support ⁽⁵⁻⁸⁾. There is a common misconception that the BiVADs themselves are responsible for the decreased survival rates of BiVAD patients. However, patients requiring BiVAD support are more critically unstable than those capable of being managed with isolated LVADs ^(3, 4). While RVF may be reversed in some instances, patients with persistent RVF will require bridging with a durable RVAD ^(6, 7).

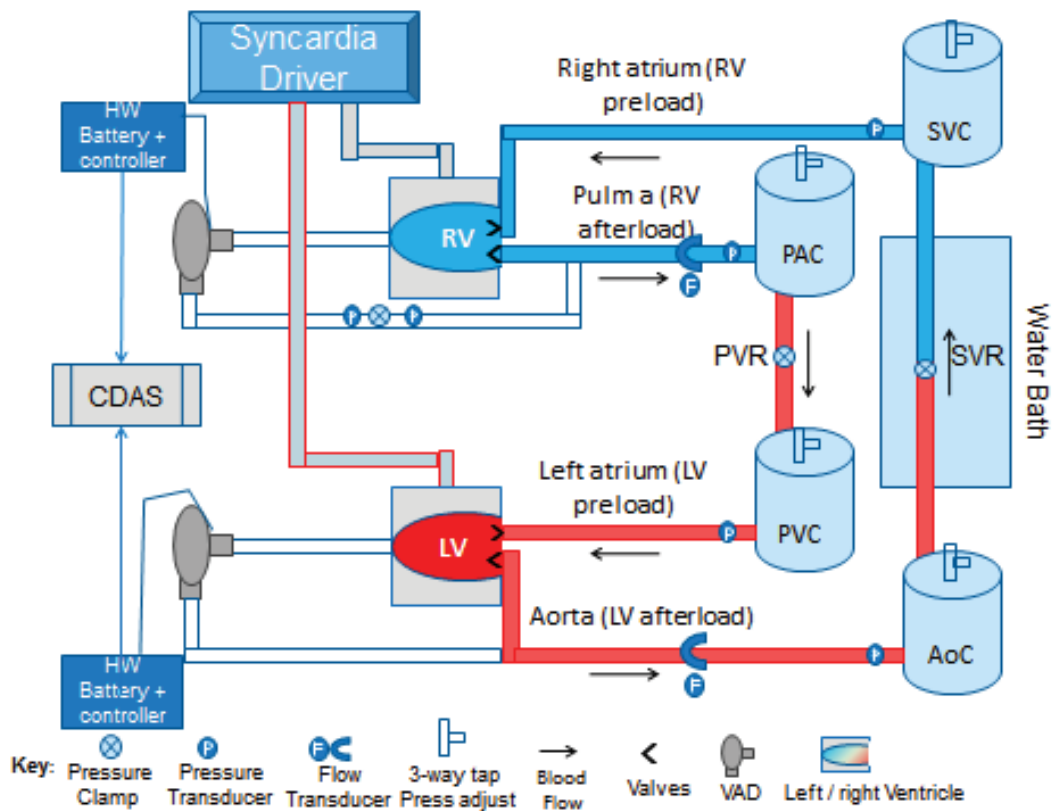
Due to the advantages of miniaturised third generation devices, current focus has shifted to providing biventricular support with continuous flow devices. While right ventricular (RV) support using the HeartWare HVAD is not currently FDA approved, the use of dual HeartWare HVAD in a BiVAD configuration has been successfully demonstrated ⁽⁹⁻¹¹⁾. Anecdotal experience suggests delayed RVAD implantation support for persistent right heart failure

after LVAD is not as well tolerated as planned BiVAD implantation, although this has not been formally tested. We hypothesized that delayed continuous flow RVAD (RVAD) support would produce hemodynamic and flow parameters similar to patients receiving initial BiVAD support. Therefore, the aim of this study was to assess the hemodynamic performance of isolated LVAD, BiVAD and isolated LVAD with delayed RVAD in a model of biventricular failure within a 4-elemental MCL.

4.3 METHODS

4.3.1 Mock Circulatory loop design

The MCL in this study incorporated the systemic and the pulmonary circulation, systemic vascular resistance (SVR), pulmonary vascular resistance (PVR), VAD implantation sites, valves, left and right heart functions, aortic, pulmonary and venous compliance, physiological viscosity, and the resistance of blood vessels. An illustration of the MCL is shown in Figure 4.1. The left and right ventricles were constructed using a truncated-ellipsoid shaped deformable silicone diaphragm (77mm x 49mm) encased inside a transparent sealed air chamber; measuring 170 mm in length and 95 mm in width at the base. HeartWare HVADs (HeartWare, Framingham MA) were attached to the apex of each ventricle, which directed flow to their respective systemic or pulmonary pathways (Figure 4.1) via mechanical bi-leaflet valves (On-X, On-X Life Technologies Inc. Heart Valve Product Group, Austin TX).



AoC, aortic compliance; SVC, systemic venous compliance; PAC, pulmonary arterial compliance; PVC, pulmonary venous compliance; LV, left ventricle; RV, right ventricle; CDAS, continuous data acquisition system

Figure 4.1 Mock loop diagram

4.3.2 Contractility

Ventricular contraction and pressures were generated by the 70cc SynCardia companion driver system (SynCardia Systems, Inc. Tucson AZ) as has been previously described ⁽¹²⁾. The SynCardia driver provides pulsatile flow by pneumatic compression of the silicon ventricles with ejection both through the aortic valve and through the pump in pump systole. Systolic ratio and pneumatic driving pressures were varied for each ventricles to simulate pathological ventricular function. The pneumatic driving pressure for left and right ventricles were reduced to minimum performance, valued at 100 and 40mmHg respectively. Heart rate was maintained at 90 beats per minutes and systolic ejection ratio at 40%. These low range pneumatic driving pressures and systolic ejection ratios were used to generate

hemodynamics to model the impaired ventricular contractility with short ejection duration (270msec) and low cardiac output seen in advanced heart failure patients. Suction settings were not altered throughout the study.

4.3.3 Circulation model

Four identical hermetically sealed cylinder shaped chambers (100m diameter x 320m height), commonly referred to as Windkessel chambers, were used to simulate the pulmonary artery compliance, left atrium/pulmonary venous compliance, aortic compliance, and the right atrium/systemic venous compliance. Each chamber contained a certain level of fluid and air. Compliance was calculated using validated formula which takes into consideration the relationship between air pressure and volume, and fluid pressure and volume ⁽¹³⁾. On top of each chamber, valves were placed to help regulate pressure/volume. These valves were attached to an air filled syringe that was able to adjust the amount of air present within the sealed chamber. While the Windkessel configuration does not account for fluid inertia, ^(13, 14) these changes are very small. By allowing the system to stabilize prior to data collection, any changes due to inertia were minimized.

The major components of the MCL were connected via clear PVC tygon tubing (15.9mm x 2.4mm) which provided venous and systemic flow resistance. Additional resistance was added using tuning clamps to replicate the SVR and PVR. Flow was measured using TS410 transit-time tubing flow meter (Transonic System Inc. Ithaca NY) between the PA and LA chamber, after the PVR clamp (Figure 4.1). The total volume of fluid (40% glycerol solution) within the MCL was approximately five litres and maintained at 37 degrees by in-line water bath to simulate the viscosity of blood with a hematocrit of 34%.

4.3.4 Experimental method

The MCL was run in steady state and real time flow waveforms and pressures were monitored using an Aespire anaesthesia machine (Datex-Ohmeda, Inc.). Four cardiac conditions were simulated with and without the HVAD operating (Table 4.1). These include (1) biventricular failure; (2) biventricular failure with isolated continuous flow LVAD (LVAD) support; (3) biventricular failure supported with LVAD receiving delayed RVAD support; and (4) biventricular failure with initial concomitant LVAD and RVAD support providing BiVAD support. Each experiment was run on four separate occasions. Prior to the introduction or changes to pump speed, a waiting period of 2-3 minutes was incorporated to allow the system to achieve steady state. For the first experiment, biventricular failure was simulated and recorded (Condition 1). Both HVADs (LVAD and RVAD) were then turned on and SVR and PVR adjusted to accommodate the changing flows. This demonstrated the effects of initial BiVAD support (Condition 4). The two VADs were then turned off and SVR and PVR reversed to simulate biventricular failure again. Once recorded, only the LVAD was turned on to represent biventricular failure support with isolated LVAD support (Condition 2). Again, slight modifications were made to SVR and PVR. After all measurements were recorded, the RVAD was then turned on to simulate the hemodynamic consequences of delayed RVAD support following LVAD (Condition 3). As before, SVR and PVR alterations were required to balance pressures. Data shown is the average of both the pressure and flow values across the four runs (mean $\pm$ SD). The 'aortic' and 'pulmonary' valves were monitored throughout all experiments at 2 minute intervals before and after any changes and during transitional changes between experimental states e.g. VAD vs. no VAD support. The valves did not open

during any of the experiments. Pump speed remained constant for all experiments with an LVAD of 2600rpm and RVAD of 2200rpm.

4.3.5 Data acquisition

Flow and pressure waveforms were recorded using Labchart 7 (ADInstruments Pty Ltd, Bella Vista) and Datex-Ohmeda S/5TM Collect software (GE Healthcare, Finland), respectively. LVAD and RVAD pump parameters were recorded directly from pump controllers onto laptop using proprietary software (continuous digital acquisition system) sampled at 50Hz. All data was analysed using statistical Matlab software (The MathWorks, Inc. Natick MA). All waveforms were smoothed with a low pass filter using Savitzky-Golay method and were averaged over four cycles. This study was observational. As the pressures and flows were all measured in steady state at the same pump speeds and pneumatic ventricular rate no statistical tests are available.

4.4 RESULTS

The MCL produced physiological equivalent hemodynamic waveform magnitudes and morphology for each condition targeted for simulation. (Table 4.1, Figure 4.2,). As expected, higher calculated SVR and PVR values were observed in baseline biventricular failure compared to VAD supported conditions. Initial BiVAD support was closest to achieving normal ranges but remained within expected values for VAD supported patients. It can be seen that the elevated left and right sided filling pressures (25mmHg each respectively) were normalized under BiVAD support. While isolated LVAD improved cardiac output (from 2.3 to 3.5L/min), the addition of RVAD markedly increased LVAD pump flow as well as overall circuit flow. RVAD and LVAD flow rates were well matched, despite not actively adjusting speed to

achieve this. The mechanical ‘aortic’ and ‘pulmonary’ valves were monitored throughout and remained closed during all studies.

CHAPTER IV – IN-VITRO MODEL OF BIVENTRICULAR SUPPORT

Table 4.1 Biventricular heart failure with and without ventricular assist device support- mock loop and clinical hemodynamics

Condition	HR (beat/sec)	Ao (mmHg)	MAP (mmHg)	LA (mmHg)	Mean PA (mmHg)	RA (mmHg)	SVR dyn. sec.cm ⁻⁵	PVR dyn. sec.cm ⁻⁵	LVP (mmHg)	RVP (mmHg)	Flow (CO) (L/min)	LVAD flow (L/min)	LVAD speed (RPM)	RVAD flow (L/min)	RVAD speed (RPM)
A. Mock Circulatory Loop- VAD off (n= 4 runs)															
Heart failure pre-VAD	90	90/60	70 (0.26)	25 (0.5)	37 (0.7)	25 (0.32)	1565 (56.8)	406 (13.6)	-	-	2.3 (0.10)	-	-	-	-
Mock Circulatory Loop- VAD on (n= 4 runs)															
BiVF with isolated LVAD	90	111/78	89 (1.1)	8 (0.13)	15 (0.25)	17 (0.33)	1694 (47.6)	157 (9.1)	120	40	3.5 (0.08)	3.8 (0.5)	2600 (20.6)	-	-
BiVF + LVAD + delayed RVAD	90	115/72	86 (1.4)	8 (0.38)	18 (0.60)	3 (0.28)	1509 (36.0)	194 (2.8)	120	40	4.4 (0.16)	4.5 (0.66)	2600 (22.7)	4.5 (0.59)	2200 (9.0)
BiVF + BiVAD	90	100/71	81 (1.6)	8 (0.29)	13 (0.71)	4 (0.19)	1311 (27.9)	85 (8.9)	120	40	4.7 (1.1)	4.9 (1.8)	2600 (22.8)	4.4 (0.65)	2200 (8.8)
B. Hemodynamics in patients with biventricular failure, requiring mechanical support (n= 36 patients)															
Heart failure Pre-VAD (n=36)	87 (17)		77 (11)	27 (5)	40 (8)	16 (6)	1485 (560)	290 (173)	-	-	3.7 (1.1)	-	-	-	-
LVAD + VPA ECMO (acute n=22)	93 (14)	-	78 (10)	15 (6)	26 (7)	10 (5)	1189 (445)	189 (102)	-	-	4.9 (1.0)	5.3 (0.7)	2700 (218)	-	-
Post-BiVAD (chronic) (n=14)	76 (14)	-	77 (16)	13 (6)	22 (7)	12 (5)	994 (343)	125 (54)	-	-	5.6 (1.2)	5.2 (0.8)	2694 (192)	5.2 (0.7)	2543 (255)

HR, heart rate; Ao, aortic pressure; MAP, mean arterial pressure; LA, left atrium; mean PA, mean pulmonary artery; RA, right atrium; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance; LVP, LV pressure (pneumatic generated); RVP, RV pressure (pneumatic generated); CO, cardiac output; LVAD, LV assist device, RVAD, RV assist device, VAD, ventricular assist device; VPA ECMO, veno-pulmonary artery extra-corporeal membrane oxygenation; BiVAD, biventricular assist devices; BiVF, bi-ventricular failure. LVAD flow and RVAD flow were recorded directly from HVAD controlled. Mock loop flow measured using transonic flowmeter.

Figure 4.2 shows pressure and flow waveforms for all experimental conditions with and without HVAD support. The Syncardia ejection period, which is approximated as a square wave ejection pulse has been added to the waveforms. It can be seen that the aortic pressure and the VAD flow rise in a linear fashion during the pneumatic compression of the silicon ventricles. The atrial pressure also increases somewhat as further flow is impeded entering the ventricle and then rapidly decreases upon cessation of pneumatic support, as the silicon ventricle returns to its neutral non-compressed form. Biventricular supported with simultaneous RVAD and LVAD support resulted in restoration of hemodynamic parameters to normal and best overall flow (4.7 L/min). Biventricular failure supported with isolated LVAD resulted in improved overall flows compared to biventricular failure without VADs (3.5 ± 0.1 vs. 2.3 ± 0.1 L/min, respectively), however there remained persistently elevated right atrial pressure with low pulmonary pressures and left atrial pressures with right heart failure. Delayed RVAD support then reduced right atrial pressures from 17 mmHg to 3 mmHg and increased systemic flow from 3.5 ± 0.1 to 4.4 ± 0.2 L/min. When RVAD was introduced after completion of isolated LVAD, the hemodynamic outcome was similar to that obtained with combined initial BiVAD. Slight variations between delayed compared to initial BiVAD may be explained by the increased clamping of the SVR and PVR during delayed RVAD support. Nonetheless, in both cases of initial and delayed biventricular support, pathological states were reversed and normal physiological filling pressures and flow restored.

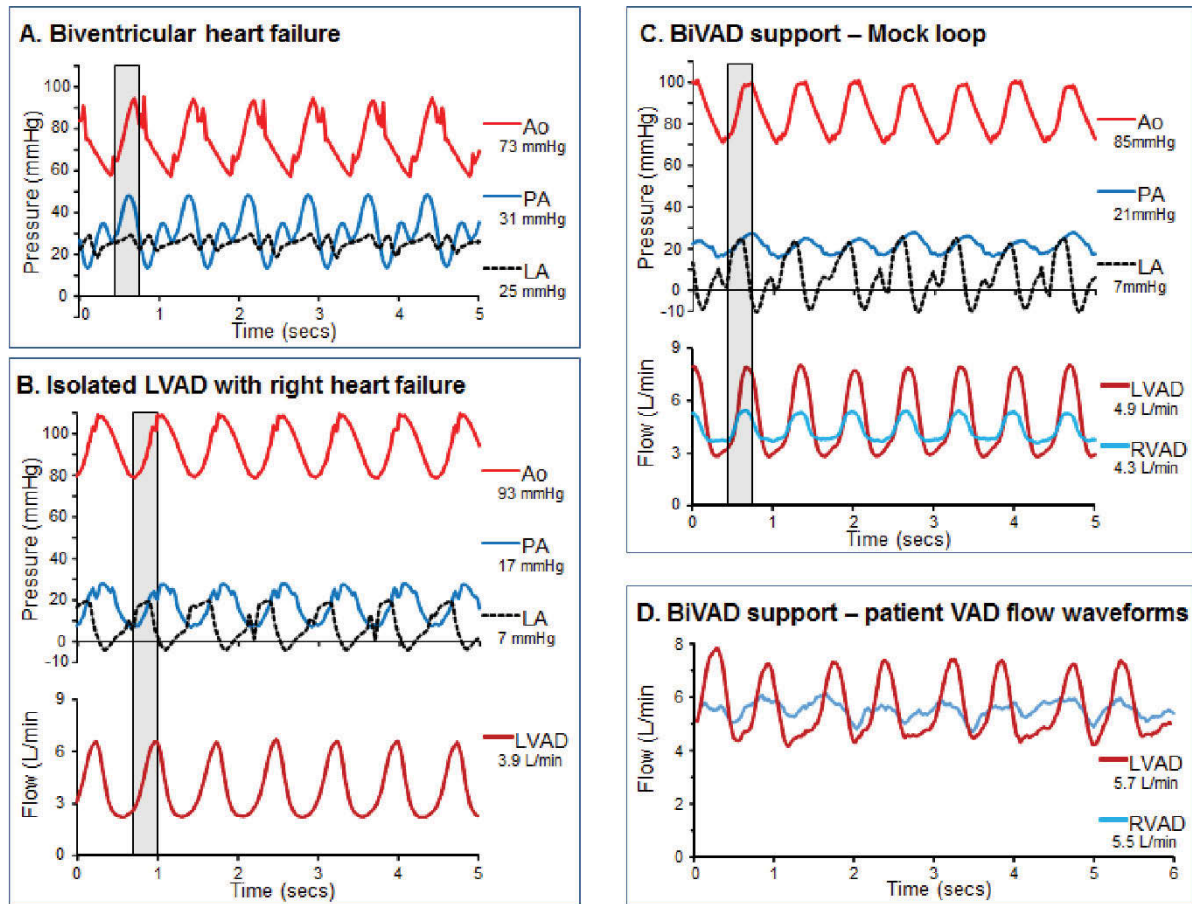


Figure 4.2 Baseline physiological and pathological cardiac pressures without VAD support for the four three physiological states created: A) biventricular failure; B) biventricular failure with isolated LVAD support; C) biventricular failure with BiVAD support, D) demonstrates the LVAD and RVAD flow waveforms in a clinical patient, and confirms the close similarity of the waveforms to those generated by the MCL.

In Table 4.1B it can be seen that the pressures generated by the MCL (both supported and unsupported) are similar to a population of patients with biventricular failure who go on to have biventricular support. In the clinical population the RVAD pump speed was slightly higher than used in the current MCL. In Figure 4.2D, LVAD and RVAD flow waveforms from a patient with chronic BiVAD support is demonstrated. It can be seen that the low RVAD flow pulsatility shown in the MCL matches closely with the waveforms in clinical patients. In vivo, there is significant respiratory inflow variation, which is not modelled in the current MCL. The shape of the LVAD waveform is also similar to that generated by the Syncardia driver.

4.5 DISCUSSION

In this study, we developed a MCL to investigate the impact of BiVAD vs. delayed RVAD support in the setting of biventricular failure. We generated haemodynamically realistic biventricular failure with low cardiac output and elevated filling pressures at rest as well as right heart failure with isolated LVAD, both of which were reversed by dual HVAD support. The stability of this MCL allows for assessment of the impact of changes in flow or other conditions on the pump function, flow waveforms and hemodynamic parameters. We have also shown the pressure and flow waveforms generated in this MCL are very similar to those seen clinically.

The reported incidence rate of right ventricular failure post isolated LVAD implantation varies with most reports approximately 30%, ^(3, 15) with higher rates noted with paracorporeal LVAD systems compared to LVAD ⁽¹⁵⁻¹⁷⁾. Clinical manifestation of RVF following LVAD support is associated with high mortality and morbidity ⁽¹⁷⁻¹⁹⁾. Improvements to patient survival with planned biventricular support is suggested ⁽³⁾ yet remains limited by the challenges associated with identifying RVF pre-LVAD implantation ^(20, 21). While right ventricular recovery may occur, many patients continue to suffer with RVF managed with medical therapy and short term surgical alternatives such as IABP which are associated with increased mortality. One of the biggest barriers to initiating early BiVAD support or delayed RVAD implantation is the higher mortality associated with BiVAD or delayed RVAD support compared to patients who only require isolated LVAD configurations ^(4, 7). These findings however, relate largely to pulsatile BiVADs with few short-term BiVADs assessed. Dual HVAD therapy is a novel and promising approach for patients with biventricular failure requiring long-term BiVAD support. It is less surgically invasive, more durable and does not require subsequent explantation following

right ventricular remodelling ⁽²²⁾. We have shown that the hemodynamics of persistent right heart failure with isolated LVAD are reversed with an RVAD. Portable controllers enable hospital discharge and improved patient quality of life by allowing patients to return to their daily activities. The small pump also allows for different implant configurations (atrial or ventricular RVAD implantation) ⁽¹¹⁾.

With the advent of more durable, long-term, miniaturized implantable continuous flow LVAD, RVAD and BiVAD systems, ^(23, 24) clinical application of a second VAD may overcome the current limitations of delayed RVAD support following LVAD implantation. Our clinical experience is that sequential, delayed durable RVAD in patients with severe RV failure with isolated LVAD is associated with increased short term mortality ⁽¹¹⁾. This has also been shown in a larger clinical study of planned (temporary) compared to unplanned RVAD support ⁽⁷⁾. Whether costs and length of stay and other clinical outcomes are enhanced by planned BiVAD implantation is not answered in the case cohort studies, and population differences make comparisons difficult.

Our findings demonstrate the expected haemodynamic improvements seen with the use of delayed RVAD support in the setting of isolated LVAD with persistently deranged hemodynamics consistent with RV failure. Isolated LVAD resulted in persistent elevated right atrial pressures, with only slight flow improvements to those of baseline biventricular failure. Delayed RVAD support restored normal hemodynamic parameters and significantly increased flows LVAD and circuit flow. Higher flow waveforms were achieved with initial biventricular support (Figure 2), which was influenced by the level of SVR and PVR clamping. Both clamps were slightly more restrictive in the delayed RVAD experiment as two sets of alterations to

the SVR and PVR were made. Although restrictions to RVAD flow via narrowing of the outflow cannula are recommended by some investigators to avoid overflowing the pulmonary arteries and preventing pulmonary oedema, ^(10, 11) the level of restriction varies between patients and remains at the discretion of the surgeon. ⁽¹¹⁾ From Table 4.1, it can be seen that both SVR and PVR were within expected values. The SVR and PVR seen in baseline biventricular failure are reflective of real patients with biventricular failure and are associated with elevated left atrial (LAP) and right atrial pressures (RAP) combined with reduced cardiac output and mean arterial pressure (MAP). While, the SVR values obtained from the MCL for all VAD configurations were slightly higher than those observed in the clinical cohort, these values are within expected physiological ranges seen in VAD patients. Elevated MAP, LAP and reduced flows are often associated with high SVR ⁽¹⁴⁾. Therefore, the slight improvements observed in the clinical cohort compared to the MCL may be attributed to the medications used to lower SVR to increase overall perfusion, thus compromising MAP ⁽¹⁴⁾. Furthermore, as the MCL is a stable system, the degree of variation between experiments is kept to a minimum, as reflected by the small standard deviations of our data. In terms of clinical outcomes, the standard deviations are quite large, which is expected from a heterogeneous cohort. Aside from the severity of baseline heart failure, patient outcomes may be further confounded by various comorbidities, medications and dietary/fluid restrictions. Despite these slight discrepancies, the MCL fundamentally reflects the overall trends seen in the clinical cohort. MAP, LAP and circuit flows are increased with BiVAD support while RAP and pulmonary artery pressure are reduced.

Both combined BiVAD and LVAD with subsequent delayed RVAD achieved physiological hemodynamic conditions (Figure 2). Isolated LVAD use results in increased venous return. This

has been shown to overload the right ventricle, causing increased interventricular pressure and promoting ventricular overdistension ⁽¹⁾. In the setting of right heart failure, the significantly lower pressure in the left ventricular cavity caused by LVADs results in the interventricular septum shifting towards the left. Its inability to remain neutral further impairs right ventricular function and thus reduces cardiac output. The importance of ventricular interaction with the achievement of a 'neutral' septal position ⁽¹⁷⁾ is well recognised, and often used in determining appropriate continuous flow pump speeds. As both the right ventricular and left ventricular chambers were encased in the current MCL, there was no detrimental impact of increased flow on contractility efficiency as may be seen in acute RVF. Notwithstanding this, the current MCL did manifest impaired outputs in the unsupported, failing RV as well as elevated right atrial pressures in the setting of isolated LVAD support, as is seen clinically. Future studies should focus on assessing a cardiac chamber which allows for visualization of left and right ventricular septal shifts in response to pump changes and pathological conditions.

Despite successfully demonstrating restored hemodynamic with delayed RVAD support similar to those seen with initial BiVAD support, it is important to recognize that all outcomes achieved are limited to clinical observations from a purely hemodynamic viewpoint. The MCL is not intended to circumvent in vivo trials, but rather to act as testing platforms to assess the feasibility of the intervention and derive an idea of expected outcomes. The impact of return to theatre for placement of a second VAD, rather than both being placed in the same operation, needs to be further considered. Furthermore, patients who undergo delayed RVAD placement are by definition failing isolated LVAD and are a higher risk population, with likely

incipient organ dysfunction. Assessment of ventricular remodelling, genetic phenotype or activation of regulatory proteins cannot be determined with the MCL.

4.6 LIMITATIONS

The left and right ventricles were identical in dimension, which is an inaccurate depiction of the natural geometry of the heart. However, we found that this did not affect cardiac output as flows for the left and right ventricles were able to be achieved using different pneumatic driving pressures with the Syncardia controller. The pressures recorded in the MCL are comparable to those of the natural cardiovascular system and are adequate for testing cardiac devices. Both HVADs were implanted into the apex of the left and right silicon ventricles. While this remains a valid approach, RVAD placement has been achieved in the body of the ventricle, as well as in the right atrium ⁽¹¹⁾.

While pneumatic drivers such as Syncardia can provide physiologically appropriate systolic pressure, the characteristics of both the driver and of the silicon mock ventricle do not mirror diastolic properties including ventricular compliance. Furthermore while the Syncardia driver does not demonstrate time varying elastance, and is afterload insensitive (within operating limits), outputs do vary in an apparent Starling-like behavior due to some pre-load sensitivity ⁽¹²⁾. Also, while the performance characteristics of the Syncardia pneumatic drive on the silicon ventricles are likely to be different to clinical Syncardia pumps but as discussed above despite this limitation, the pressures and waveforms are very close to those seen clinically. As the current MCL houses the RV and LV separately, the impact of ventricular interdependence is not able to be modelled. While the MCL is unable to assess interventricular interaction between the various pathological states, it is able to successfully simulate decreased RV

contractility (observed during experimentation), simulate LV collapse during excessive pump speeds, and control LV and RV filling with the Syncardia driver, all of which have been associated with VAD induced shifts to the interventricular septum ^(1, 25). Despite all of these limitations, the current MCL successfully models the hemodynamics of BiVF, right heart failure with isolated LVAD acute correction with acute right heart support (LVAD + VPA ECLS) and in the setting of chronic BiVAD support.

The use of mechanical valves may also impair the accurate reproduction of physiological waveforms. As shown in this study, mechanical valves produce pressure spikes and oscillations attributed by the water hammer effect during valve leaflet closure. However, these disruptions to waveform morphology were minimized using a low-pass filter and pressure and flow waveforms are similar to those reported in patients with mechanical valves ⁽²⁶⁾. A significant difference to in vivo circulation, is the lack of ventriculo-vascular coupling through arterial baroreceptor modulation of vascular tone and sympathetic outflow. Longer term changes of ventricular remodelling are not able to be simulated by the MCL. Despite these limitations, the MCL presented here has demonstrated to be an effective tool for in-vitro assessment of mechanical assist devices, developing experimental protocols and training personnel on the maintenance and operation of mechanical assist devices.

4.7 CONCLUSION

Through the use of a 4-elemental windkessel model, we have reproduced the clinical syndrome of biventricular failure, with RVF post isolated LVAD, and shown reversal with initial and delayed BiVAD with normalized output and decreased filling pressures. These hemodynamic findings are consistent with the clinical benefit seen in patients and warrant

further evaluation. Future MCLs incorporating ventricular interdependence and vascular feedback may further enhance these physical models. With their reduced invasiveness and complication profiles, durable RVADs may be suitable options for patients previously contraindicated for current paracorporeal systems.

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CHAPTER V- EFFECTS OF BIVENTRICULAR SUPPORT ON VALVULAR PATHOLOGIES: AN IN-VITRO MODEL

5.1 CHAPTER PREFACE

Publication reference:

Shehab S, Allida SM, Newton PJ, Robson D, Davidson PM, Jansz PC, Hayward CS. Effects of biventricular support on valvular pathologies: an in-vitro model. ASAIO. 2017.

Chapter IV provided the results of the mock-circulatory loop experiment. This chapter presents the results of a sub- experiment of an in-vitro model to test the effects of the Heartware ventricular assist device as biventricular support on aortic, mitral and tricuspid regurgitation.

This chapter presents an article in its original form, submitted to the Journal of American Society of Artificial Internal Organs.

Background

Aortic (AR), mitral (MR) and tricuspid regurgitation (TR) after continuous flow left ventricular assist device (LVAD) are common and may increase with prolonged LVAD support.

Aim of this study

The aim of this study was to simulate severe AR, MR and TR within a 4-elemental pulsatile mock circulatory loop (MCL) and observe their impact on isolated left ventricular assist device (LVAD) and biventricular assist device (BiVAD) with HeartWare HVAD. Simulation of AR, MR

and TR were achieved via the removal of one leaflet from bi-leaflet mechanical valve from the appropriate valves of the left or right ventricles. The impact of alteration of pump speed (LVAD 2200-4000rpm, RVAD 2400rpm) and altered LVAD preload (10-25mmHg) was assessed.

Summary of results

Isolated LVAD support provided sufficient output in the setting of severe mitral or tricuspid regurgitation compared to control, and flows were further enhanced with BiVAD support. In severe aortic regurgitation there was minimal benefit of BiVAD support over isolated LVAD, and loop flows remained low. High LVAD flows and power combined with low RVAD flows and dampened aortic pressures are good indicators of AR.

Implications

The 4-elemental MCL successfully simulated several control and abnormal valvular conditions using various pump speeds. Current findings are consistent with conservative management of mitral and tricuspid regurgitation in the setting of mechanical support, but emphasise the importance of the correction of aortic regurgitation.

5.2 INTRODUCTION

Due to a lack of donor hearts and long waiting lists, management of advanced heart failure in transplant waitlists has increasingly become reliant on the use of continuous flow left ventricular assist devices (LVAD). Although LVAD therapy has been well established, a growing proportion of patients develop concomitant right ventricular dysfunction either pre- or post LVAD implantation and may require biventricular assist device (BiVAD) therapy. There is increasing interest and experience in the use of smaller pumps such as the HeartWare HVAD for continuous flow BiVAD ⁽¹⁻³⁾. While promising, there are many uncertainties surrounding the use of dual LVAD therapy for biventricular support (one HVAD pump for left ventricular support and another for right ventricular support), particularly on the effects of pump performance and hemodynamic alterations of long-term BiVAD support in the presence of concomitant valvular disorders such as aortic, mitral and tricuspid regurgitation.

Current data regarding the hemodynamic effects of long-term BiVAD support in the presence of valvular disorders remains largely unexplored with few studies reporting on pulsatile BiVADs ⁽⁴⁻⁶⁾. With several models of miniaturised, implantable continuous flow BiVAD and RVAD devices currently under development and testing ^(7,8), understanding the hemodynamic consequences of both isolated LVAD and BiVAD under these pathological conditions is essential. While assessment of hemodynamic characteristics can be performed in-vivo, they can be difficult to achieve as many factors including patient heterogeneity and challenges associated with measuring accurate hemodynamic parameters can mask direct associations. Thus, the aim of this study was to assess the impact of pump speed and of differences in preload during isolated LVAD as well as with BiVAD support in a pulsatile in-vitro mock-

circulatory loop (MCL) in the presence of valvular regurgitation including aortic (AR), mitral (MR) and tricuspid regurgitation (TR).

5.3 METHODS

5.3.1 Experimental model

The pneumatic pulsatile mock circulatory loop (MCL) using dual HeartWare HVAD pumps (HeartWare Inc Framingham, MA) in this study has been previously described ⁽⁹⁾. In brief, real time flow and pressure waveforms were captured using TS410 transit-time tubing flow meter (Transonic System, Inc. NY) and an Aespire anaesthesia machine (Datex-Ohmeda, Inc. Madison, WI), respectively. Four different conditions were tested with the MCL, including intact valves, AR, MR, and TR. Baseline variables for all conditions include heart rate (HR) 90, pneumatic left and right ventricular driving pressures of 120 and 40 mmHg respectively, and maintained mean arterial pressure (MAP) of 70mmHg. All experiments were conducted with a 40% glycerol solution (60% water), which was kept at a set temperature of 37 degrees Celsius by passing the systemic circulation tubing through a water bath to maintain viscosity analogous to human blood (haematocrit of 34%) ⁽¹⁰⁾. Pulsatility was provided using the pneumatic SynCardia Companion 2 DriverTM with a heart rate of 90/min, LV pneumatic driving pressure 120mmHg, RV pneumatic driving pressure 40mmHg, ejection duration 280msec, suction set to 0mmHg for LV and RV. These settings were not altered during the series of experiments. Baseline left atrial pressure (LA) varied (10, 15, 20 and 25mmHg) depending on the Protocol 2 experiment tested. Flows (Flowmeter, RVAD and LVAD) and other hemodynamic pressure such as pulmonary artery (PA) and mean pulmonary artery pressure (MPAP) were not directly controlled, and their initial flows/pressures were dependent on

starting right atrial (RA), LA and MAP pressures. Mechanical bi-leaflet valves (27mm On-X Life Technologies Inc. Heart Valve Product Group, Austin, TX) were used for all experiments. The MCL was initially configured to test various hemodynamic flow and pressure waveforms with all valves attached under different LVAD pump speeds (ranging from 2200-4000rpm). To mimic AR, MR and TR, one leaflet was deliberately removed to reliably generate stable, severe regurgitation. To observe hemodynamic consequences of isolated LVAD and continuous flow BiVAD support within these simulated conditions, two different experimental protocols were designed. Protocol 1 examined the impact of pump speed, and Protocol 2 examined the impact of varying preload.

In Protocol 1, all conditions were assessed across a range of LVAD pump speeds (2200-4000rpm) and configurations (isolated LVAD vs. dual BiVAD support, RVAD pump speed set at 2400rpm). In Protocol 2, recordings were repeated with starting LA pressures of 10, 15, 20 and 25mmHg with LVAD pump speed 2600rpm and RVAD 2400rpm. The results were then compared between conditions and waveforms analysed to determine (i) whether increased pump speed within a continuous flow BiVAD configuration compensated for regurgitant flow, and (ii) whether there was a difference between isolated LVAD support compared to BiVAD support across different valvular pathologies.

5.3.2 Experimental procedure

All experiments began from a simulated state of no VAD support. The outflow graft of the LVAD and RVAD pumps were occluded and the MCL was entirely run by the SynCardia Companion 2 Driver™. Initial baseline hemodynamics (LA 25mmHg, MAP 70mmHg, and RA 25mmHg) were established and maintained for 5 minutes. Once recorded, the LVAD outflow

graft was opened and the LVAD turned on. The SVR and PVR were adjusted until a similar MAP parameters were achieved as seen in patients with isolated LVAD (MAP 85mmHg-100mmHg). We used the control experiment (intact valves) as a reference point and discovered that a MAP of 88mmHg produced physiological flows and pressures (LAP, RAP and MPAP). To remain consistent, a MAP of 88mmHg was reproduced for AR, MR and TR experiments. No other changes were made and the new baseline parameters for isolated LVAD were recorded. At the completion of recording the new baseline values (LVAD 2600), the LVAD pump speed was reduced to a minimum 2200rpm by decrements of 200. It was then returned to 2600rpm where it increased to 3200 rpm by increments of 200 again. From 3200rpm pump speed was increased to 3600rpm and then to a maximum speed of 4000rpm. To minimize the effect of inertia, a waiting period of 2 minutes was allocated following changes to pump speed to allow the system to stabilise before the effects on flow rate and MAP, LA, RA and PA pressures were recorded. Upon completion, the LVAD pump speed was returned to 2600 rpm and the baseline restored. To demonstrate the difference between BiVAD and isolated LVAD, the RVAD was turned on and the outflow graft opened. The SVR and PVR were then adjusted until a MAP of 93mmHg was achieved. A MAP of 93mmHg for BiVAD support was selected based on the same rationale described for isolated LVAD (MAP 88mmHg). Baseline parameters at new pump speeds (LVAD 2600, RVAD 2400) were recorded for 5 minutes before increasing LVAD pumps speeds from 2200-4000rpm as previously described, while the RVAD remained constant at 2400rpm. Once completed, baseline parameters were restored, priming the MCL for Protocol 2. No other variables were changed.

In Protocol 2, LV filling pressure was actively varied at a fixed pump speed. The LA pressure was increased from 10mmHg to 15mmHg and the process previously described in Protocol 1 was repeated. The same was completed for LA pressures of 20mmHg and 25mmHg. The incremental increase of 5mmHg from 10 to 25mmHg at the end of each Protocol 1 experiment was achieved by slight modifications to the SVR and PVR. Contractility, HR, viscosity, haematocrit, LV and RV pressures were not altered. All four valves remained attached to the ventricles during LVAD control. The same test was repeated with one leaflet of the aortic, mitral or tricuspid valve removed during different stages to mimic their respective pathological states.

5.3.3 Data acquisition

Flow and pressure waveforms were recorded using LabChart 7 (ADInstruments Pty Ltd, Bella Vista) and Datex-Ohmeda S/5TM Collect software (GE Healthcare, Finland), respectively. LVAD and RVAD pump parameters were recorded directly from pump controllers onto laptop using proprietary software (continuous digital acquisition system) sampled at 50Hz. All data were analysed using statistical Matlab software (The MathWorks, Inc. Natick MA). All waveforms were smoothed with a low pass filter using Sovitzky-Golay method and were averaged over four cardiac cycles.

5.4 RESULTS

5.4.1 Effect of pump speed on regurgitant flow

Figure 5.1 illustrates the effect of pump speed on flow and pressure during various control and abnormal valvular conditions such as AR, MR and TR. For the LVAD control with intact valves, increased LVAD pump speed resulted in increased MAP and RA pressures and reduced

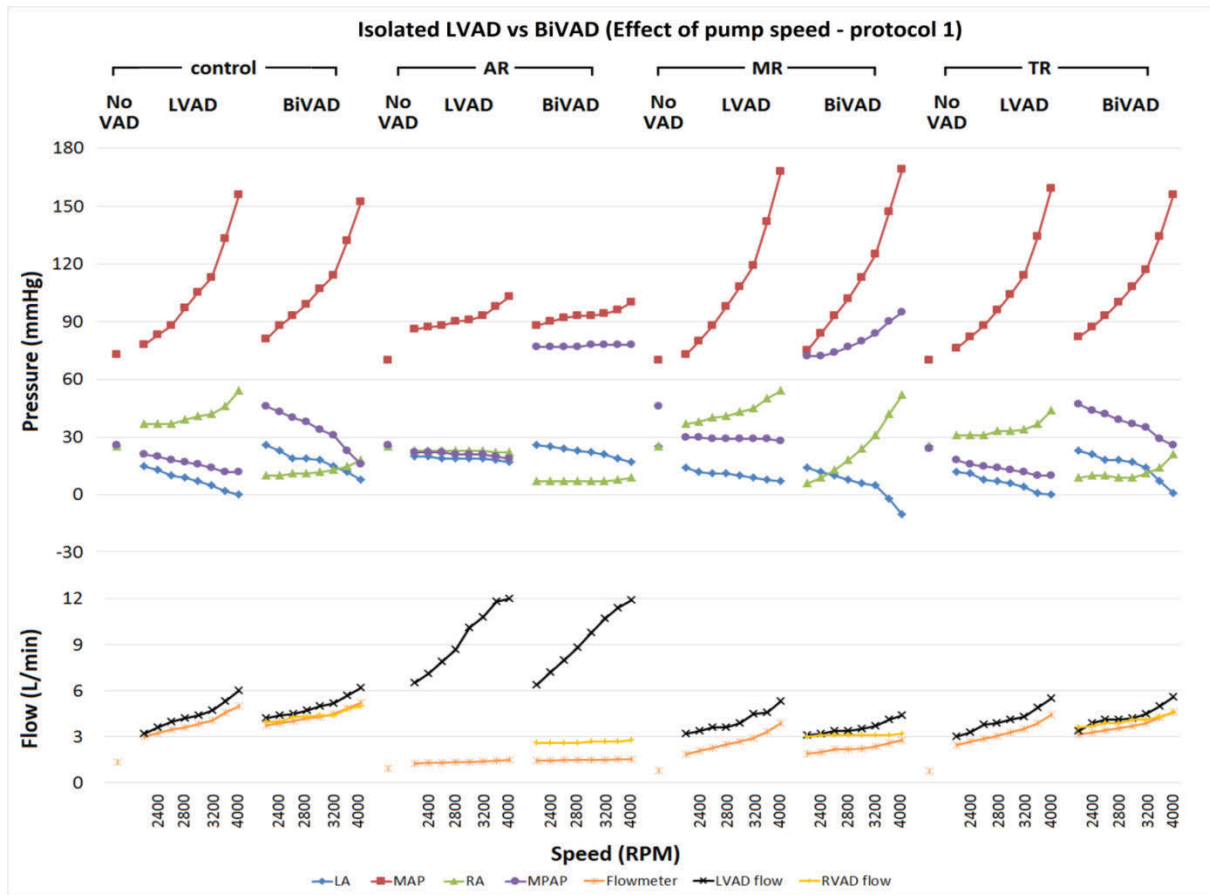
LA and MPAP pressures. Flow values for flowmeter, LVAD and RVAD also increased with increased pump speed.

Similar trends were seen with TR as with LVAD control. BiVAD support appears to effectively compensate for regurgitant flow through the tricuspid valve during tricuspid regurgitation. Equally, MR yielded similar trends to those seen in LVAD control with the exception of maintained elevated MPAP and slightly reduced overall flows (Flowmeter, LVAD and RVAD). BiVAD support resulted in increased MPAP and RA with increasing LVAD pump speeds. For AR, the pressures and flow parameters were very different to the rest of the conditions tested. In comparison to LVAD control, TR and MR, increased LVAD speed had little effect on MAP and RA pressures due to the high rate of re-circulation through the aortic valve. MPAP was higher during BiVAD support and was maintained despite LVAD speed changes. Finally, flows measured with the flow meter and RVAD were much lower compared to controls, while LVAD flows measured much higher. Low flows indicate poor overall circulation and high rate of regurgitation into the left ventricle, suggestive of a closed loop.

5.4.2 No VAD vs. LVAD vs. BiVAD support

Figure 5.1 also illustrates the various flow and pressure trends between the differing support configurations tested such as no VAD support, isolated LVAD support and BiVAD support. Baseline configuration, without any VAD support, simulated severe biventricular failure (MAP 70mmHg, LA 25mmHg, and RA 25mmHg). Compared to unsupported experiments, isolated LVAD effectively increased MAP and flow parameters while reducing LA and MPAP in the LVAD control and TR. For AR, MPAP was slightly increased and only marginally increased with increasing pump speeds. Furthermore, AR resulted in reduced LA, RA and MPAP pressures

and circulatory flow despite increased pump speeds. With the exception of elevated RA pressures, Isolated LVAD support during MR yielded similar trends as its respective LVAD control group. However, once the experiment commenced, LA pressures decreased rapidly while circulatory flows remained low. Although the shift from no VAD to isolated LVAD effectively reduces LA pressure and increases circulatory flow under all conditions except AR, it also increase RA pressures, which increases with increased pump speed. BiVAD support appears to effectively reduce RA pressures, increase LA, MPAP and circulatory flow parameters. LVAD pumps speeds of 2400rpm to 2800rpm appear to effectively compensate for MR and TR conditions. BiVAD support was not sufficient to restore hemodynamic to baseline during severe AR.



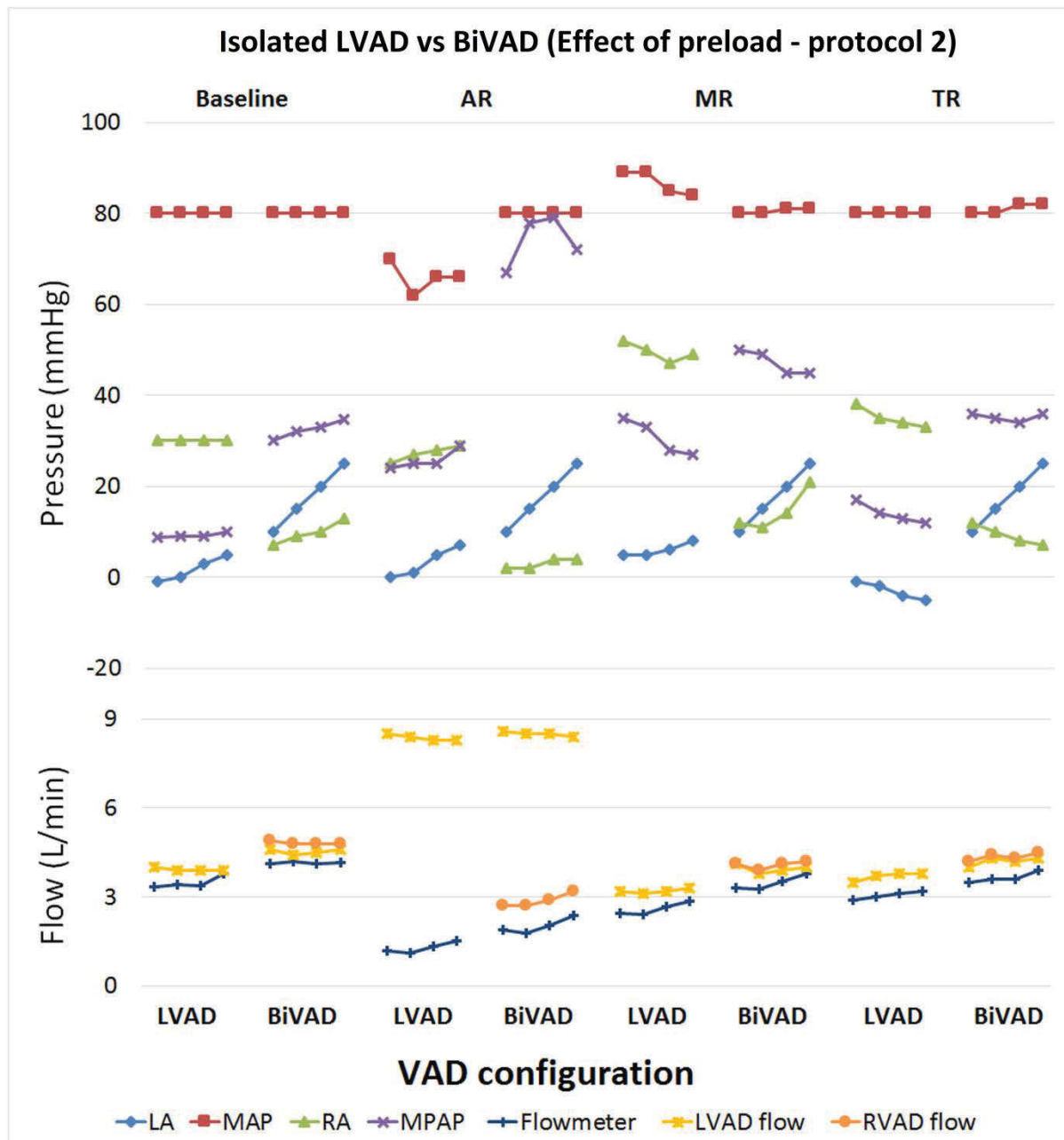
AR, aortic regurgitation; MR, mitral regurgitation; TR, tricuspid regurgitation; LA, left atrium; MAP, mean arterial pressure; RA, right atrium; MPAP, mean pulmonary arterial pressure; rpm, rounds per minute; Starting pressures (LA15 and MAP80), (RVAD pump speeds remained unchanged at 2400rpm for LVAD control, AR and MR, and LVAD pump speeds remained unchanged at 2600rpm for RVAD control and TR)

Figure 5.1 Effect of pump speed on flow and pressure during various control and abnormal valvular conditions and illustrates BiVAD vs. isolated LVAD support for each condition tested.

5.4.3 Impact of varying LA pressure

Figure 5.2 illustrates the effects of isolated LVAD vs. BiVAD support for various control and abnormal valvular conditions such as AR, MR and TR for the four main LA pressures of 10, 15, 20 and 25mmHg. LVAD and RVAD speeds were 2600 and 2400 respectively for LVAD control, AR, MR and TR. BiVAD support resulted in higher flows (Flowmeter, LVAD and RVAD) and lower RA pressures. Isolated LVAD support resulted in reduced MPAP and LA pressures. Flows for all conditions were higher for the BiVAD configuration compared to isolated LVAD support.

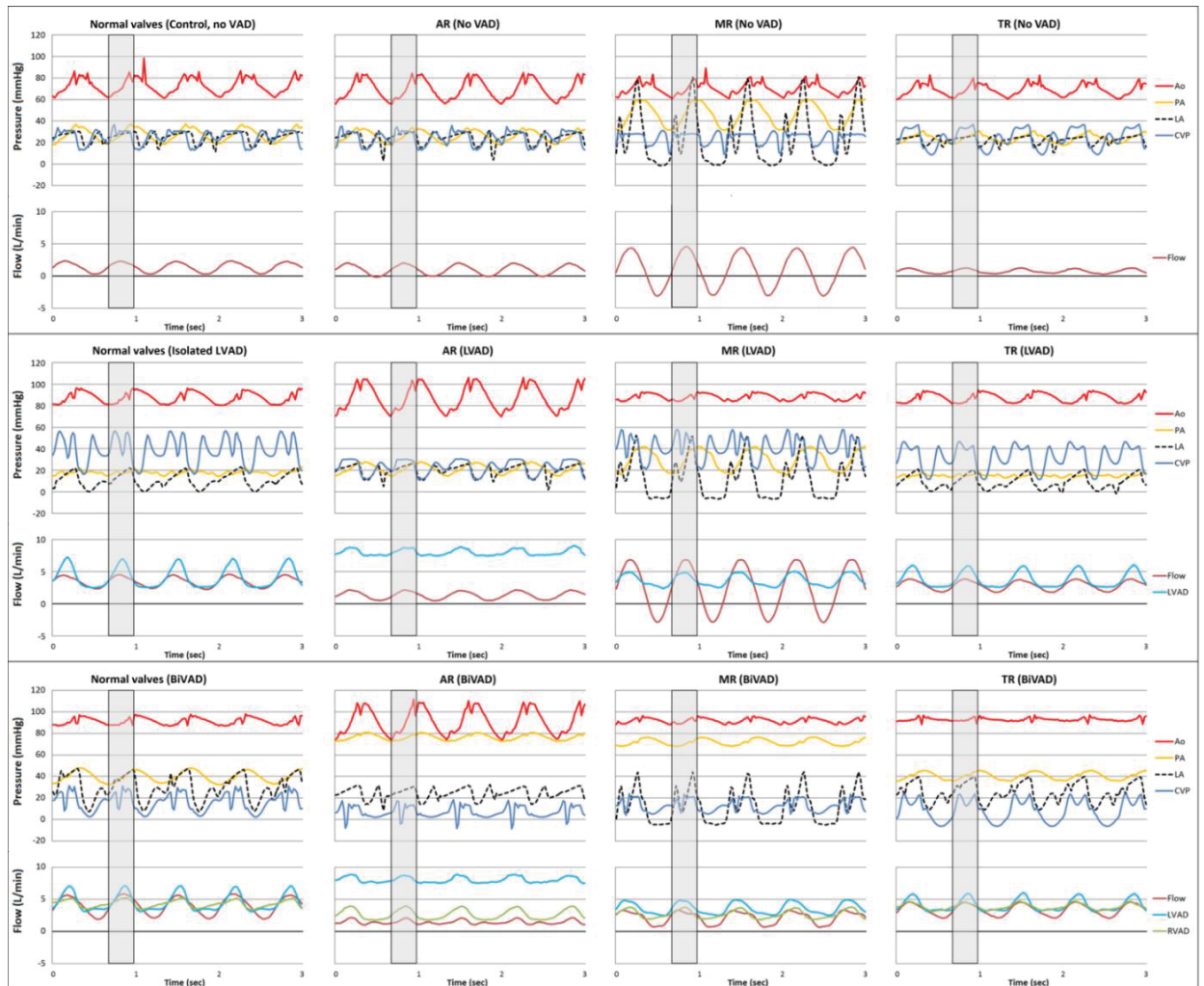
During AR, MAP and MPAP dropped significantly during isolated LVAD support while RA increased. During MR, RA was higher in isolated LVAD support compared to BiVAD support, while MPAP, PA and LA pressures were lower. When compared to baseline, isolated LVAD during TR resulted in decreasing hemodynamic parameters. While BiVAD support demonstrated similar MAP, LA and MPAP to that of baseline, RA pressures continued to decrease. For all experiments, increasing LA pressure from 10-25mmHg at increments of 5mmHg had little effect on all flow parameters (Flowmeter, RVAD flow and LVAD flow).



AR, aortic regurgitation; MR, mitral regurgitation; TR, tricuspid regurgitation; LA, left atrium; MAP, mean arterial pressure; RA, right atrium; MPAP, mean pulmonary arterial pressure; (LVAD and RVAD pump speeds were 2600 and 2400 respectively for LVAD control, AR and MR, and 2600 and 2600 respectively for RVAD control and TR)

Figure 5.2 Isolated LVAD vs. dual BiVAD support for various control and abnormal valvular conditions during the four main LA pressures of 10, 15, 20 and 25mmHg. Pressure and flow waveforms in the setting of biventricular support.

Figure 5.3 shows pressure and flow waveforms for all experimental conditions and configurations. The waveforms produced were equivalent to physiological waveform magnitudes and morphologies for control and pathological valvular disorders. The ejection period (280ms) created by the SynCardia Companion 2 Driver™ has been visualised as a square wave ejection pulse and placed during the second cycle. Based on LVAD control waveforms, it can be seen that aortic pressure and VAD flows rise in a linear fashion during pneumatic compression of the artificial ventricles. The LA and PA pressures also increase during the ventricular ejection period and then rapidly decrease upon ventricular expansion and opening of the mitral valve. Biventricular support resulted in improved flow and pressure waveforms compared to isolated LVAD and no VAD configurations. Elevated RA pressures were evident for all isolated LVAD experiments compared to no VAD and BiVAD configurations. Typical ‘V-waves’ were observed in both the LA pressure of MR and the RA pressure of TR, as would be seen clinically. The most notable difference was AR, with its reduced RVAD and flowmeter flow values (even negative diastolic flow recorded across the flowmeter) and high LVAD flow values. Moreover, aortic (Ao), MAP and RA were lower than controls and PA was much higher.



AR, aortic regurgitation; **MR**, mitral regurgitation; **TR**, tricuspid regurgitation; **Ao**, aortic pressure; **LA**, left atrium; **MAP**, mean arterial pressure; **RA**, right atrium; **MPAP**, mean pulmonary arterial pressure

Figure 5.3 Pressure and flow waveforms for no VAD, isolated LVAD and BiVAD support configurations on a 4-elemental MCL.

5.5 DISCUSSION

Valvular pathologies are a common phenomenon in patients suffering from advanced heart failure and are often present in patients considered for VAD support. Although concomitant surgical intervention via valve replacement or repair is often considered to stabilize patient hemodynamic parameters, concomitant repair/replacement is associated with an increased risk of mortality in LVAD cohorts ⁽¹¹⁾. There remains controversy on whether correction of

significant tricuspid or mitral regurgitation is required at VAD implant ⁽¹²⁻¹⁶⁾, although it is acknowledged that correction of AR is mandatory ^(17, 18). Whereas MR and TR tend to decrease post VAD implant ⁽¹⁹⁾, AR may progress ⁽²⁰⁾. The consequences of valvular regurgitation on the effects of continuous flow BiVAD systems remain largely unexplored. This study assesses for the first time the impact of pump speed and LV filling pressures in the setting of biventricular support for all three common pathological valvular conditions (AR, MR and TR). The off-label use of the HeartWare HVAD for biventricular support is not FDA approved and is currently only approved for isolated LVAD support.

5.5.1 Aortic regurgitation

Aortic regurgitation occurs frequently in patients supported with continuous flow VADs, regardless of the presence of pre-existing aortic valve abnormalities. Factors which may contribute to AR include high pump speeds ^(20, 21), increased aortic root diameter or circumference ⁽²⁰⁻²²⁾ and a lack of aortic valve opening as a consequence commissural fusion and the deterioration of leaflet tissue ⁽²³⁾. In the presence of AR, re-circulation results in ineffective forward systemic flow, increased left ventricular diastolic pressure and decreased efficacy of VAD performance. Evidence indicates that continuous flow LVAD implantation leads to worsening clinical outcomes in patients with pre-existing aortic regurgitation ^(20, 24) and for that reason valve replacement or repair is recommended in the setting of pre-existing AR.

To compensate for the regurgitant flow, increasing pump speeds have been suggested ⁽²³⁾. However, little is understood regarding suitable speed profiles that can provide effective forward flow without increased risk to patient's health, and their efficacy during the various

stages of AR (mild, moderate and severe). Using a 5-elemental MCL, Gregory et al demonstrated improved systemic flow with increased LVAD speed during mild and moderate AR events ⁽²⁵⁾. However, severe AR showed minimum improvement with increased pump speeds. While our findings also demonstrated minimum improvements to systemic flow during AR, higher pump speeds in the state of severe AR did gradually decrease LV filling pressures (Figure 5.1). We have also shown that there was no impact of BiVAD support on systemic flows in the setting of AR (Figure 5.1).

Although BiVAD support was unable to compensate for severe AR, it did produce higher flow waveforms compared to isolated LVAD configurations and restored RA pressures to physiological boundaries (Figure 5.2). As AR worsens over time, identifying early signs of AR is essential. Not only can re-circulation cause haemolysis, reduced output as a consequence of untreated AR could result in multiple organ failure and death ⁽²⁶⁾. Based on our findings, high LVAD flows and power consumption (data not shown), combined with simultaneous low RVAD flows and dampened aortic pressure with dirotic notches on waveforms are indicators of AR, which may be able to be confirmed with echocardiography (Figure 5.3). Complimentary to LVAD studies ⁽²⁰⁾, concomitant repair or replacement should be considered in patients undergoing BiVAD support with or at risk of developing severe AR.

5.5.2 Mitral regurgitation

Whereas aortic regurgitation is usually degenerative, the etiology of mitral regurgitation may be due to coaptation failure due to papillary muscle dysfunction, in the setting of inferior myocardial infarction; coaptation defect due to annular dilatation; degenerative myomatous disease or post-inflammatory / rheumatic scarring. Of these, in patients with advanced heart

failure requiring VAD support, MR is most commonly a result of left ventricular enlargement and/or increased ventricular sphericity with annular dilation with resultant coaptation defect⁽²⁷⁾. Mitral valve repair or replacement has been suggested to stabilise differential blood flow and thus promote aortic valve opening⁽¹²⁾. In addition, it has been predicted to reduce right ventricular afterload, thereby lowering the risk of right ventricular dysfunction. Reduced mean pulmonary artery pressure (MPAP) and pulmonary venous resistance (PVR) have been demonstrated with concomitant mitral valve repair compared to LVAD therapy alone⁽¹²⁾. However, the additional dissection and incisions in the heart, bicaval cannulation, and prolonged cardiopulmonary bypass time accompanying concomitant surgical intervention is associated with poor long term outcomes⁽²⁸⁾. In addition, the use of mechanical and prosthetic valves has also been associated with increased risk of mortality compared to patients undergoing LVAD support without concomitant mitral valve repair⁽²⁹⁾.

Evidence suggests a significant reduction of moderate to severe MR with LVADs. However, unbalanced left ventricular filling pressures are associated with potential risk of residual MR despite LVAD support. Low pump speeds may not provide enough support to compensate for the regurgitant flow, especially during left ventricular recovery where restored native ventricular function increases regurgitant force into the atrium and pulmonary veins. Alternatively, high pump speeds may overcompensate and promote a left shift in the interventricular septum, increasing the risk of ventricular suction and promoting right ventricular dysfunction⁽³⁰⁾. Our findings show that, in the setting of maintained RV flow, mitral regurgitation does not adversely affect LVAD pump performance in a mock loop setting and supports conservative management of severe MR with mechanical support. Increasing pump

speeds resulted in predictable trends of increased flows (RVAD, LVAD and Flowmeter), as well as MAP, LA and RA pressures. Unlike LVAD control, MPAP remained mostly steady, which can be attributed to the severity of the mitral regurgitation (Figure 5.1). LVAD speeds of 2600 and 2800 provide enough improvement to flow to compensate regurgitation while maintaining MAP and LA pressures within normal physiological ranges. However, isolated support resulted in elevated RA pressures, which increased with increasing LVAD pump speed and are also noted in control and TR experiments. This can be explained by the ventricular design and pneumatic output parameters. As the right ventricle was designed to mimic severe right ventricular dysfunction and set to minimum right ventricular performance (40mmHg with the pneumatic driver), their output was rather low and was unable to compensate for the increased flow facilitated by the LVAD. The low output combined with the severity of MR and the fact that the entire circulation was being driven by the LVAD could also explain why MPAP values were lower than RA values during MR. However, the risk of right ventricular dysfunction is also reduced with BiVAD support as when compared to LVAD, BiVAD provided improved flows (RVAD, LVAD and flowmeter) as well as reduced RA pressures (Figure 5.1). During MR, LVAD pump speeds greater than 2800rpm also resulted in high RA pressures with BiVADs. This can be addressed by increasing the RVAD pump speed. In the following experiments, RVAD pump speeds remained constant (2400rpm). Increasing RVAD speeds would further increase circulatory flows, reduce RA pressures and increase LAP and MPAP.

Typical ‘V-waves’ were observed with LA waveform analysis (Figure 5.3). Aside from slightly lower flows and steady elevated MPAP, no other hemodynamic indicators can be used to suspect MR. While concomitant repair or replacement is suggested for isolated LVAD support,

BiVAD appears to sufficiently compensate for regurgitant flows and reduces risk of right ventricular dysfunction. Nonetheless, the need for concomitant mitral valve repair depends on patient selection and intended outcomes. Patients treated as a bridge to transplantation often perform well without surgical correction. However, valvular repair may be recommended in patients bridged to recovery. These findings are mostly reflective of patients supported with LVAD support and remain limited to case reports, abstract papers and only a handful of small single centre experiences. As per our findings, the effects of BiVAD support may provide alternatives to concomitant mitral valve repair, particularly where right ventricular afterload and PVR require attention.

5.5.3 Tricuspid regurgitation

Tricuspid regurgitation (TR) is common in patients with advanced heart failure with an incidence rate of 30-64% ⁽³¹⁾. Although it is often a sign of structural abnormality, TR typically manifests secondary to right ventricular enlargement or long standing pulmonary hypertension ⁽¹⁵⁾. Structural alterations to the tricuspid valve have also been observed in patients using pacemakers and implantable defibrillators. The changes may be caused by the leads passing through the valve which have been known to stent and/or adhere to the valve causing regurgitation ⁽³²⁾. Findings extrapolated from LVAD studies have reported conflicting recommendations. Some studies have demonstrated reduced right ventricular dysfunction and improved outcomes in patients undergoing concomitant tricuspid repair or replacement ^(4, 15). Conversely, others have associated concomitant repair with increased post-operative complications ^(33, 34) and have demonstrated no differences between patients receiving concomitant repair and those on LVAD only ⁽³⁰⁾. Although surgical intervention may be

appropriate in patient receiving long term LVAD support, this may not be necessary for patients requiring BiVAD. There are currently no recommendations for the management of TR in patients supported with continuous flow BIVAD therapy. Potapov et al compared the short term outcomes of concomitant LVAD support and tricuspid repair (n=7) vs. BiVAD and total artificial heart support (n=18) ⁽⁴⁾. The study concluded no differences in the short-term outcomes between the two groups. This may indicate that BiVAD support effectively provide right ventricular unloading, despite increased right ventricular preload and blood flow caused by LVAD support.

Our findings demonstrate improved flow and pressure waveforms with BiVAD support when compared to isolated LVAD support (Figure 5.1). The reduced RA and higher flow values are positive indicators of improved flow and reduced risk of developing right ventricular dysfunction. Moreover, increased LVAD speeds resulted in decreased MPAP and LA with relatively maintained RA until LVAD pumps speeds of 3600rpm. High MPAP pressures with RVAD support is normal but may result in pulmonary edema in patients. LVAD pump speeds between 2600 and 3000 appear to sufficiently compensate for regurgitant flow, while maintaining low RA and MPAP pressures to prevent long-term pulmonary and right ventricular complications. Except for the typical ‘V-waves’ seen in RA waveforms and general dampening of MAP pressures (Figure 5.3), all other waveforms appear to have normal waveform morphologies and amplitudes. Although BiVAD appears to be an effective alternative to concomitant surgical intervention and isolated LVAD support, further in-vivo studies are required to assess the effects of BiVAD outside a pure hemodynamic setting.

5.6 LIMITATIONS

Despite successful replication of control and abnormal valvular states similar to those seen in real patients, it is important to recognise that all outcomes achieved are limited to clinical observations from a purely hemodynamic viewpoint. These in-vitro models act as a testing platform to identify limitations and allow for exploration of hemodynamic conditions prior to in-vivo trials. Systemic flow values were lower than LVAD/RVAD flows. Although 40% glycerol solution is analogous to human blood, it lacks the electrical conductivity present in human blood, yielding slightly lower flow values. The addition of saline or 1% corn starch has been recommended to increase the ultrasound scattering particle ⁽³⁵⁾.

In addition, as an entire leaflet of the On-X mechanical bi-leaflet valve was removed, only severe regurgitation conditions could be simulated. Nonetheless, these findings remain reflective of patients with advanced heart failure suffering from severe aortic, mitral and/or tricuspid regurgitation. A further limitation is the fixed ventricular size in the mock loop setting. While the RV dimension may change in response to loading conditions, the current loop is unable to account for volume shifts and is only valid for pressure measurements. Similarly, as the two ventricles are separate in the mock loop model, ventricular interaction cannot be simulated.

Finally, the use of mechanical valves may create slight variations to waveform morphologies as a consequence of oscillations during mechanical valve closure when compared to patients without mechanical valves. However, waveform oscillations can be reduced by running a low pass filter. Despite these limitations, the MCL presented here has demonstrated to be a useful

tool for in-vitro assessment of mechanical assist devices and simulating accurate physiological and abnormal valvular waveform morphology.

5.7 CONCLUSION

Using a 4-elemental windkessel model, numerous control and abnormal valvular condition were replicated using various pump speeds (2200-4000) and VAD configurations (isolated LVAD vs. BiVAD) using the HeartWare HVAD. Dual BiVAD support provided improved flows for LVAD, RVAD, flowmeter and reduced RA pressure for all conditions when compared to isolated LVAD control. In addition, BiVAD proved capable of compensating for severe regurgitation during MR and TR states but remained ineffective during AR. High LVAD flows and power combined with low flows and dampened aortic pressure and MAP are strong indicators of severe AR during isolated or biventricular support.

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CHAPTER VI- LONG-TERM BIVENTRICULAR HEARTWARE VENTRICULAR ASSIST DEVICE SUPPORT- CASE SERIES OF RIGHT ATRIAL AND RIGHT VENTRICULAR IMPLANTATION OUTCOMES

6.1 CHAPTER PREFACE

Publication reference:

Shehab S, Macdonald PS, Keogh AM, Kotlyar E, Jabbour, A, Robson D, Newton PJ, Rao S, Wang L, Allida SM, Connellan M, Granger E, Dhital K, Spratt P, Janssz PC, Hayward CS.

Chronic biventricular HVAD support- Case series of right atrial and right ventricular implantation outcomes. J Heart Lung Trans. 2015.

Chapter 5 presented the results of the effect of the HVAD on valvular disorders in advanced CHF. This chapter presents the implantation outcomes of the Heartware ventricular assist device (HVAD) as biventricular support.

This chapter presents an article in its original form, published in the Journal of Heart and Lung Transplantation (2015). This article is provided in its published form as an appendix (Appendix 8).

Background

There is limited information on outcomes using the HeartWare ventricular assist device (HVAD) as a biventricular assist device, especially with respect to site of right VAD implantation.

Aim of this study

This study will report our experience with the HVAD as a biventricular device in patients who were considered to be unsuitable for isolated LVAD support and to compare right ventricular and right atrial RVAD implantation. Outcomes in 13 dilated cardiomyopathy patients with severe biventricular failure who underwent dual HVAD implantation as bridge to transplant between August 2011 and October 2014 were reviewed.

Summary of results

Ten of 13 patients were INTERMACS Level 1, with the remainder Level 2. Mean age was 45 ± 11 years; BMI 26 ± 4 kg/m². Seven patients were on temporary mechanical support pre-operatively (ECLS n=5, IABP n=2). The median hospital length of stay was 53 (interquartile range (IQR) 33-70) days with a median ICU length of stay of 14 (IQR 8-36) days. The median support on device was 269 (IQR 93-426) days. The right HVAD was implanted in the right ventricular free wall in six, and in the right atrial free wall in seven. Five patients were successfully transplanted and overall survival for the entire cohort was 54%. RVAD pump thrombosis occurred in 3/6 RV pumps and 1/7 RA pumps. No LVAD pump thrombosis was observed. Bleeding was higher in RV implanted group (3/6 vs 0/7). Six patients died during follow up (4/7 in the RA group vs. 2/6 in the RV). In total, three patients died from multi-organ failure; two from sepsis and one from intracerebral haemorrhage.

Implications

Critically unwell patients who require biventricular support can be successfully bridged to transplant using two HVADs. Right atrial implantation may allow right heart support with lower pump thrombosis and bleeding complications, although this was at the expense of a higher mortality in this cohort.

6.2 INTRODUCTION

Due to superior outcomes with continuous flow left ventricular assist devices (cfLVADs) compared to pulsatile pumps, they have become the therapy of choice for chronic support in advanced heart failure ¹. There is limited data on chronic continuous flow biventricular assist device support. Established options for biventricular support include total artificial heart replacement or long term pulsatile paracorporeal VADs and rely on large drivers which limit full patient mobility ^{2,3}. Widespread use of dual cfLVADs is limited due to logistic issues with separate controllers, reimbursement issues for the second pump and poor reported long term prognosis compared with those on isolated left ventricular support⁴. Early reports have shown the feasibility of dual HVAD implantation for biventricular support ⁵⁻⁷. The aim of this case series was to report our experience with the HVAD as a biventricular device in patients who were considered to be unsuitable for isolated LVAD support and to compare right ventricular and right atrial RVAD implantation.

6.3 METHODS

6.3.1 Study population/Patients

From August 2011 through October 2014, 13 dilated cardiomyopathy patients (10 male) underwent implantation of two HeartWare HVAD pumps at St Vincent's Hospital, Sydney for biventricular support. Approval for collection of data reported in this audit was obtained from the St Vincent's and Mater Health Human Research Ethics Committee. All patients had advanced heart failure (INTERMACS Score 1-2). Six patients were implanted from inotropes and temporary mechanical support pre-operatively (ECLS n=4, IABP n=2) and the remaining seven patients required inotropic support alone.

6.3.2 Biventricular implantation decision

The decision to implant dual HVAD was based on a combination of hemodynamic parameters (right ventricular stroke work index, mean pulmonary arterial pressure, transpulmonary gradient) and echocardiographic markers (degree of RV dilatation, RV systolic impairment, estimated pulmonary arterial systolic pressure and severity of tricuspid regurgitation) of right ventricular dysfunction. The dominant reason for considering biventricular support was the severity of right ventricular impairment and dilatation pre-LVAD. Two patients underwent delayed RVAD implant (at one week post LVAD) due to inability to wean from temporary mechanical RV support used in association with the initial LVAD procedure.

The RVAD was implanted in the right ventricular free wall in the first six consecutive patients (RV group) and in the right atrial free wall in the subsequent seven consecutive patients (RA group). All patients were implanted as bridge to transplantation (BTT) and were followed up until heart transplantation, death on mechanical support or until last observed (February 2015). Eleven patients underwent planned biventricular implant and two underwent delayed right ventricular implant within two weeks after isolated LVAD implantation, due to intractable right heart failure (patient 4 and 13). Pre-operative demographics for all patients are shown in Table 6.1.

CHAPTER VI – CHRONIC BIVENTRICULAR HVAD SUPPORT

Table 6.1 Pre-operative data

Pt	Sex	Age	BMI kg/m ²	INTERMACS	Etiology	Previous Procedures	Creatinine (umol/L)	eGFR (mL/min BSAc)*	Bilirubin (umol/L)	RA/PAW P ratio	TR grade	RAP	RVSWI	LVEF (%)	LVEDD (mm)
RV (n=6)															
1	M	37	28.6	2	DCM	ICD	130	60	100	0.58	3	15	0.91	25%	83
2	M	33	29.4	1	DCM	None	60	126	25	0.68	1	27	0.26	20%	85
3	M	33	22	1	CCTGA	IABP, ICD	111	75	32	0.77	2	23	1.09	15%	74
4	F	36	19.4	1	DCM	TVA + ASD repair, V-PA ECLS, LVAD	135	43	22	NA	NA	NA	NA	25%	42
5	M	51	29.1	1	DCM	CVVHD, ICD	137	51	18	0.60	3	18	0.44	25%	76
6	M	31	23.5	1	DCM	IABP, ICD	202	37	35	0.24	1	7	0.41	20%	83
RA (n=7)															
7	M	49	24.6	1	DCM	ICD	91	85	41	0.73	2	19	0.20	20%	64
8	M	64	28.6	2	DCM	ICD	108	62	17	1	4	21	0.24	35%	61
9	M	55	24.6	2	DCM	ICD	109	65	39	0.54	2	15	0.82	40%	75
10	M	44	34.6	1	DCM	VA ECLS, ICD	82	100	35	NA	NA	NA	NA	15%	80
11	M	62	26.8	1	DCM	VA ECLS, ICD	109	62	50	NA	NA	NA	NA	39%	80
12	F	40	22.1	1	GCM	VA ECLS	91	68	14	NA	NA	NA	NA	akinet ic	NA
13	F	54	22.9	1	DCM	V-PA ECLS, LVAD	124	42	29	NA	NA	NA	NA	40%	54
Mean (SD)		45 (11)	26 (4)	10 L1, 3 L2		5 VA ECLS, 2 IABP (46%)	115 (34)	67 (25)	35 (22)	0.66 (.21)	2 (1.3)	18 (6)	0.55 (0.34)	27 (10)	71 (13)

CHAPTER VI – CHRONIC BIVENTRICULAR HVAD SUPPORT

RV, right ventricle; **RA**, right atrial; **BMI**, body mass index; **DCM**, dilated cardiomyopathy; **CCTGA**, congenitally corrected transposition of the greater arteries; **IDCM**, idiopathic dilated cardiomyopathy; **GCM**, giant cell myocarditis; **VA**, veno-arterial; **ECLS**, extracorporeal life support; **V-PA**, veno-pulmonary arterial; **IABP**, intra-aortic balloon pump; **ICD**, implantable cardioverter defibrillator; **RA/PAWP ratio**, ratio of right atrial pressure to pulmonary artery wedge pressure; **TR**, tricuspid regurgitation; **RAP**, right atrial pressure; **RVSWI**, right ventricular stroke work index; **LVEF**, left ventricular ejection fraction; **LVEDD**, left ventricular end-diastolic diameter; **LVAD**, left ventricular assist device; **NA**, not available, right ventricular parameters not applicable in patients on ECLS.

6.3.3 Implantation procedure

In all 13 patients, the left HVAD was implanted into the apex of the left ventricle, with the outflow graft attached to the ascending aorta. The right HVAD was implanted at two different sites. The first six consecutive patients received an implant in the free wall of the right ventricle opposite the interventricular septum (RV group). In the course of looking after these patients, it was recognised that following RV remodelling, RV thrombosis was occurring at a higher than expected rate. A decision was made to change the implantation technique in the future and the next seven consecutive patients underwent right atrial implantation (RA group). For HVAD implantation into the RV, four layers of Teflon felt were cut into donut shapes and placed between the sewing ring and right ventricle to allow for a 7mm reduction in the intra-ventricular protrusion distance of the inflow cannula, similar to that described by Krabatsch et al⁶. For right atrial HVAD implantation no spacers were used, however the inflow cannula was maximally retracted with only 5mm of the inflow cannula protruding beyond the sewing ring into the right atrium. The sewing ring was however ‘over-tightened’ beyond that allowed for by the supplied torque wrench. After coring of the right ventricular free wall, any trabeculae in the immediate vicinity of the planned inflow cannula were resected. No atrial trabecular resection was needed, however pacing wires coursing through the right atrium were sutured to the atrial free wall out of the way of the inflow cannula in those patients receiving an atrial RVAD. No pacemakers or pacemaker wires were removed and the tricuspid valve was not operated on in any of the patients. The RVAD outflow graft for all patients was attached to the main pulmonary artery, which was restricted according to the patient’s pulmonary vascular resistance. The outflow graft was narrowed to a diameter of 5-7mm over a distance of 35cm⁸ for all patients except one, who had near systolic pulmonary artery pressures prior to implantation.

6.3.4 Anticoagulation

Post-operative anticoagulation with intravenous heparin began 8 to 12 h after surgery, and only after blood loss from drain tubes reached less than 50mL/h, to derive an activated partial thromboplastin time between 50 and 75 seconds. Oral anticoagulation began following the removal of mediastinal or chest drain tubes. A combination of aspirin (100mg), clopidogrel (75mg) and warfarin (INR 2-2.5) were used until 2014. All RV implanted patients were therefore treated with dual antiplatelet therapy as well as Warfarin, however the second antiplatelet agent had to be stopped in 3 RV implanted RV patients due to bleeding. From 2014 to present, the postoperative antithrombotic regimen included aspirin (100mg) and warfarin (INR 2-3) only. To detect clinically significant haemolysis due to the use of two HVAD pumps, free haemoglobin, bilirubin, haptoglobin and lactate dehydrogenase (LDH) blood levels were analysed on a daily basis during ICU stay and then on a monthly basis for outpatient visits.

6.3.5 Post-operative management

All patients received routine postoperative care for VAD support. This included prophylactic broad spectrum antibiotics for the first three days post-implantation and close monitoring and correction of coagulation profiles. Within a week of restoring patient's hemodynamic profile, echocardiography was performed to determine structural improvements and pump performances.

6.4 STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 10.00 for Windows (SPSS, Inc. Chicago, IL). Results are presented as mean (SD) for normally distributed data, and median (interquartile range) for non-normally distributed data. Fisher's exact test was used to assess

association between post-operative outcomes/adverse events and implantation technique (RV vs. RA).

6.5 RESULTS

6.5.1 Patient characteristics

Between August 2011 and October 2014, 13 patients (10 men) underwent biventricular implantation of two HeartWare HVAD. Eleven patients had dilated cardiomyopathy (DCM), one end-stage congenitally corrected transposition of great arteries and one end-stage giant cell myocarditis. Patient age ranged from 31 to 64 years (mean 45.3 ± 11.3 years) and body mass index from 22 to 39.4 kg/m² (mean 26.7 ± 4.7 kg/m²). Ten patients (77%) were Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) class I and 3 patients (23%) were INTERMACS class II before biventricular assist device (BiVAD) implantation. Three patients were on VA ECLS support prior to LVAD and the two patients who underwent delayed RVAD placement were supported post LVAD with venous-pulmonary artery (V-PA) ECLS. With the exception of patients 4 and 13 (supported on V-PA ECLS for right heart failure post LVAD), all patients had clinically elevated right atrial pressures (RAP). In addition, Patients 4 and 12 were retrieved on VA ECLS to our institution, and as a result, it was not possible to obtain some pre-operative cardiac measurements.

6.5.2 Right and Left Pump flows

The mean pump speeds for the right HVAD were 2531 ± 259 rpm and 2746 ± 190 rpm for the left HVAD. There were no differences in the pump speed settings for RV compared to RA support. Estimated pump flows were 5.1 ± 1.0 L/min on the right and 5.4 ± 0.9 L/min on the left. There was no significant difference in flow on the right HVAD according to right atrial vs right ventricular implantation. The concordance in flow between the RVAD and LVAD was very

close in 10 out of the 13 patients. In one patient with moderately severe pulmonary regurgitation RVAD flow was significantly greater than LVAD (6.6 vs 4.4 L/min), one patient had significant aortic regurgitation (RVAD 3.8 vs LVAD 6.5 L/min), and in one patient with recurrent pericardial effusions and mediastinal sepsis there was no apparent valvular abnormality (RVAD 4.0 vs LVAD 6.0 L/min) – difference unexplained. In the other 10 patients the RVAD and LVAD flows corresponded well ($r^2=0.77$, $p<0.001$, mean difference 0.17 ± 0.46 L/min).

6.5.3 Post-operative outcomes

We report outcomes from a cumulative BiVAD support duration across all patients of 3807 days. The median duration of support was 269 (IQR 93 to 426) days, 329 (IQR 187 to 543) days for RV group and 132 (IQR 78 to 391) days for the RA group. All post-operative outcomes were censored at the time of transplantation. Perioperative (30 day) and one-year survival were 100% and 62% respectively. At 30 days, serum creatinine improved from $115 \pm 34 \mu\text{mol/L}$ to $79 \pm 24 \mu\text{mol/L}$, while eGFR improved from $67 \pm 25 \text{ mL/min (BSAc)}$ to $95 \pm 28 \text{ mL/min (BSAc)}$. Discharge post BiVAD implant was successfully achieved in 69% of patients and overall survival at 2 years was 54%. Six patients (4/7 in the RA group vs. 2/6 in the RV group) died during VAD support (46%) typically early in the BiVAD support period, after a median 78 (IQR 61 to 122) days; three from multiple organ failure, two from sepsis (unrelated to driveline) and one from intracerebral haemorrhage. Five patients (38%) were successfully bridged to transplantation after a median of 513 (IQR 269 to 594) days of support and two patients remain supported at 356 and 426 days post implantation. No significant difference were observed using Fishers exact test. Post-operative outcomes are reported in Table 6.2.

Table 6.2 Post-operative outcomes and adverse events

Variables	Number of patients (%)		
	All patients (n=13)	RV group (n=6)	RA group (n=7)
Post-operative outcomes			
LoS, days [IQR]	53 [33-70]	41 [28-73]	60 [37-70]
ICU LoS, days [IQR]	14 [8-36]	8 [8-43]	15 [12-27]
Duration of support, days [IQR]	269 [93-420]	329 [187-543]	132 [77-391]
TR grade	1.5 ± 1.3	1.6 ± 1.5	1.4 ± 1.2
Survived to discharge	9 (69)	5/6 (83%)	4/7 (57%)
Transplanted	5 (38)	4/6 (67%)	1/7 (14%)
Ongoing support	2 (15)	0 (0)	2/7 (29%)
Died on support	6 (46)	2/6 (33%)	4/7 (57%)
Adverse events			
Death	6 (46%)	2/6 (33%)	4/7 (57%)
LVAD thrombosis	0 (0%)	0 (0)	0 (0)
RVAD thrombosis	4 (31%)	3/6 (50%)	1/7 (14%)
Bleeding	3 (23%)	3/6 (50%)	0 (0)
Infection			
<i>Driveline</i>	1 (8%)	1/6 (17%)	0 (0)
<i>Sternal wound</i>	2 (15%)	2/6 (33%)	0 (0)
<i>Blood culture >0</i>	5 (38%)	2/6 (33%)	3/7 (43%)
Renal dysfunction	4 (38%)	2/6 (33%)	2/7 (29%)
Neurological	2 (15%)	1/6 (17%)	1/7 (14%)
Respiratory dysfunction	3 (23%)	2/6 (33%)	1/7 (14%)

RV, right ventricular; **RA**, right atrial; **Los**, length of stay; **ICU**, intensive care unit; **IQR**, interquartile range; **LVAD**, left ventricular assist device; **RVAD**, right ventricular assist device. Fisher's exact test showed no significant difference between RV and RA groups in terms of postoperative outcomes and adverse events. Data showing for median and [interquartile range] or represent (percentages) where appropriate.

6.5.4 Adverse events

Adverse events during VAD support have been provided in Table 6.2 and were classified according to the INTERMACS definitions. As expected for this patient population, the rates of infection, renal failure and thrombus formation were elevated. Seven patients (54%) suffered from infective complications. One (8%) developed a driveline infection, two (15%) sternal wound sepsis and five (38%) returned positive blood cultures (in the absence of a driveline infection). Of these patients, three suffered from multiple infectious complications. Acute renal failure requiring haemodialysis occurred in four patients, of which three patients (2 in RV and 1 in RA group) successfully recovered. The one patient whose renal function did not recover during the immediate postoperative period died. RVAD thrombosis was mainly observed in the RV group (3/6) at an average of 13 months (range 8-20months). It was treated with thrombolysis and was recurrent in one patient. One patient in the RA group suffered RVAD thrombosis, which was able to be treated successfully with thrombolysis at 18 months. One patient (patient 1) experienced multiple right ventricular thrombotic events. The high rate of pump thrombosis with RV implantation is thought to be related to reverse remodelling of the right ventricle with chronic support. In Patient 1, the RV dimension normalized with the inflow cannula abutting the septum with expiration (confirmed on echocardiography), resulting in repetitive suction seen on review of the RVAD flow waveforms (Figure 6.1). There were only relatively minor changes in the LVAD flow waveform. No thrombus events occurred in the LVADs. Bleeding rates were more frequent in the RV implanted group (3/6) compared to the RA implanted group (0/7). Low rates of respiratory failure, and neurological complications were also reported (Table 6.2). Fisher's exact test showed no significant differences between the two groups for any variables.

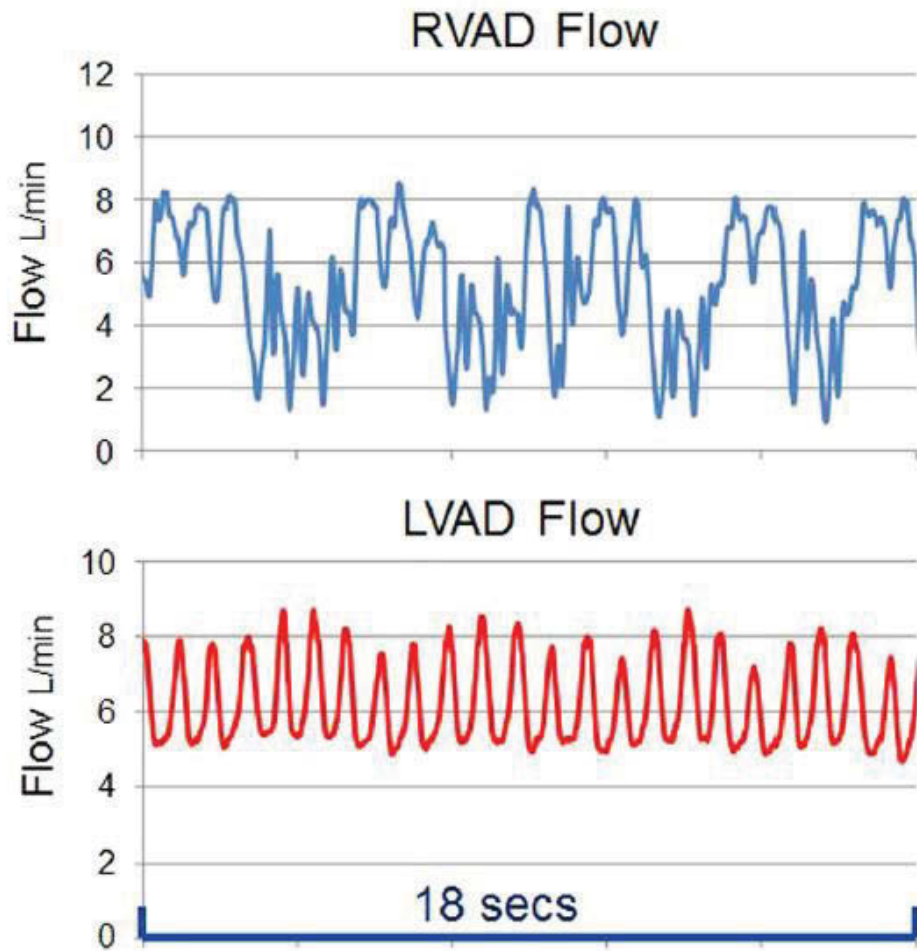


Figure 6.1 Flow waveforms demonstrating recurrent suction events according to respiratory cycle. With expiration, the decreased venous return to the right heart is associated with abutment of the right ventricular assist device (RVAD) onto the ventricular septum and results in suction, with sudden drop in RVAD flow. Only minor changes in flow are seen in the simultaneous LVAD flow waveform.

6.6 DISCUSSION

Continuous flow LVAD therapy is the standard treatment option for patients with advanced heart failure with preserved right ventricular function. However, in patients with significant concomitant right ventricular dysfunction, options include the use of a total artificial heart (TAH) or short term pulsatile displacement biventricular assist devices. Due to the barriers associated with large pulsatile flow pumps and driver consoles used in short term BiVADs, the use of two continuous flow LVADs for biventricular support has been suggested. The use of dual HVAD as a means of biventricular support is still in its infancy with limited experience reported ^{5-7,9}. This is the largest reported series of right atrial support, and provides a comparison with right ventricular implantation in a contemporaneous cohort.

6.6.1 Implantation site

The impact of right ventricular placement with a higher rate of pump thrombosis than is seen with LVADs is highlighted by the current series. A case report of pump decommissioning due to RV remodelling and pump thrombosis has been reported previously ¹⁰, and the current study suggests a solution to this problem, with right atrial placement of the right sided HVAD. A likely cause for the high rate of thrombosis include microtrauma from repetitive suction events abutting the septum as described above, as well as the possibility of ingestion of small emboli from distant venous sites. Pacemaker / defibrillator leads were not removed in the current cohort, although that has also been suggested as a possible source thrombus. The fact that one of the RA implant patients also suffered pump thrombus is consistent with ingestion from a distant source. Three of these patients right sided VAD thrombosis, were successfully treated with thrombolysis. In one patient, where thrombolysis was contraindicated, the pump driveline was cut and left in place. There was no retrograde flow,

as the pump had thrombosed and the patient was successfully transplanted 6 months later. The selection of right atrial implantation in our series was largely based on the high rates of RVAD thrombosis observed early in our experience, and was the site of choice for the last seven consecutive patients supported with dual HVAD therapy. All RV implanted patients were initially treated with dual antiplatelet therapy as well as Warfarin, but the second antiplatelet agent was withdrawn due to bleeding in three. It is unlikely therefore that more intensive anticoagulation would have been successful in this group, due to the bleeding risks. Right atrial implantation also reduces the risk of occlusion from interactions with different chambers of the heart. It also eliminates the need for additional surgical correction in the presence of severe tricuspid regurgitation and potentially increases right ventricular cardiac output in such patients. Additionally, the RA site enables implantation in smaller patients without risk of suffering from VAD positional changes following sternum closure. As shown in Table 6.2, length of stay and adverse events were similar in both groups. Although the main difference noted was the reduced rate of post-operative bleeding and right pump thrombosis in the RA group, there was a non-significant trend to higher mortality in the RA group. Further studies with larger cohorts are required to clarify the risk benefit ratio.

6.6.2 BiVAD outcomes

The present study reports our experience with dual VAD support using dual HVADs as a bridge to transplantation. Our findings show similar 1 year survival rates (62%) with outcomes reported in another study by Krabatsch and colleagues using the same device (47%) ⁶ and similar rates to that of published registry data for pulsatile and continuous flow BiVADs (46% and 63% respectively) ⁴. Our institutional 1 and 2 year alive / transplanted outcomes for isolated BTT LVAD are 78% and 72% respectively. Of the entire cohort, six patients died during

support (2 in RV group and 4 in RA group). All patients that died (except patient 8) were INTERMACS 1 status and were supported with either ECLS or IABP support prior to BiVAD implant. The use of ECLS prior to VAD implantation has been associated with high rates of morbidity and mortality ¹¹ and has been identified as a predictor of right ventricular failure post LVAD insertion ¹². It has been associated with exacerbating respiratory complications, ¹³ increasing the risk of bleeding and infection, and contributing to inflammatory and/or metabolic complications prior to VAD implantation ¹¹. However, the use of ECLS or any short term mechanical support before LVAD can also just be a marker of sicker patients, indicating a higher degree of initial hemodynamic instability, since, of those who were not implanted from short term MCS, only one died. Five of the six deaths occurred without hospital discharge suggesting very late stage implantation without recovery of organ recovery or rehabilitation. All but one of those who were able to be discharged did well with good clinical status. Nonetheless, the results of this case series suggest that BiVAD placement is still not sufficient to overcome multi-organ failure complicated by cardiogenic shock with predictable outcomes.

Pre-operative prediction of BiVAD support remains challenging despite much research in the area ^{14,15}. Many standard haemodynamic measurements such as pulmonary pressures, transpulmonary gradient and right ventricular stroke work index each provide low predictive indices for right ventricular performance ¹⁵⁻¹⁷. Delayed RVAD implantation has also been associated with high mortality rates ¹⁸. Our results were consistent with this as both patients (patients 4 and 13), who were supported with an LVAD and V-PA ECLS for 6-10 days prior to RVAD implantation, were among the earliest deaths (at postoperative day 60 and 59

respectively). In addition, these patients tended to have worse clinical course among our cohort and remained in the acute hospital setting for the duration of support.

While our initial experience demonstrated acceptable outcomes, better results may be expected with accumulated experience. Compared to existing BiVADs, dual HVAD therapy is less surgically invasive and promotes both increased mobility and hospital discharge. Although many pulsatile BiVADs have now introduced portable drivers,^{19,20} their driver consoles remain a significant impediment for full mobility. Aside from clinical outcomes, once discharged, the HVAD patients were able to mobilize fully post-implantation, allowing patients to resume their daily routine, with 2 patients returning to fulltime work while waiting for transplant and able to undertake vigorous activities such as cycling. Although preliminary data demonstrates feasibility and applicability of the HVAD as a means of biventricular support,^{5-7,9,21-23} more data is required before such an intervention can be considered for widespread use, and use of HVAD to support the right heart remains off-label. Our institutional experience with the SynCardia total artificial heart (SynCardia Systems, Inc Tucson, AZ) includes 7 patients in the last 5 years. Survival for those patients is similar to the BiVAD cohort (57% alive or transplanted at 1 year). Each of the females, and 1 small stature male would not have qualified for TAH implantation on the basis of size. The remaining patients were implanted with HVADs due to greater institutional experience with HVAD therapy.

6.7 LIMITATIONS

While lower pumps thrombosis and bleeding complications may have been observed with RA support, they did not demonstrate to be statistically different from right ventricular support.

One explanation for these lower complications rates in bleeding and thrombosis may be due to the higher mortality rates of our RA cohort.

Through Fisher's exact test, the null hypotheses of equal rates of postoperative outcomes or adverse events across the two techniques cannot be rejected for any given variable. Although no statistical significance is achieved, the confidence intervals of the odds ratios can be very large indicating that large sample size would be needed to reveal differences in the event rates. In addition, the consecutive nature of the study cohorts, may have resulted in a time bias, due to the above learnings and increased experience with patient selection. Additional limitations such as changes to the anti-coagulation strategy between the two groups and initial experience with right atrial implantation and refinement of patient selection may have further confounded any comparison between the groups.

6.8 CONCLUSION

Our experience supports the use of dual HVAD pumps for biventricular support in critically ill patients not suitable for isolated left ventricular support. The use of right atrial implantation may be an acceptable alternative for patients with unsuitable right ventricular dimensions or severe tricuspid regurgitation. Although reduced rates of thrombotic events were achieved with right atrial support, larger cohorts are required to ensure long term outcomes. As such, outcomes remain guarded in light of the complexity of the patient population.

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CHAPTER VII- OUTCOMES OF VENO-PULMONARY ARTERIAL EXTRACORPOREAL LIFE SUPPORT AS TEMPORARY RIGHT VENTRICULAR SUPPORT POST LEFT VENTRICULAR IMPLANTATION

7.1 CHAPTER PREFACE

Publication reference:

Shehab S, Rao S, Macdonald PS, Keogh AM, Kotlyar E, Jabbour, A, Robson D, Allida SM, Newton PJ, Connellan M, Spratt P, Jansz PC, Hayward CS. Outcomes of veno-pulmonary arterial extracorporeal life support as temporary right ventricular support post left ventricular assist implantation. American Journal of Cardiovascular and Thoracic Surgery

Chapter 6 presented the outcomes of a case series of right atrial and right ventricular implantation of the HVAD as biventricular support in 13 patients. This chapter presents the outcomes of using veno-pulmonary arterial extracorporeal life support (VPA-ECLS) as temporary right ventricular support post LVAD implantation.

This chapter presents an article in its original form, submitted and undergoing peer-review in the American Journal of Cardiovascular and Thoracic Surgery.

Background

Patients with biventricular failure represent a high risk group for isolated LVAD implantation. The decision to provide short vs. long-term biventricular support remains uncertain.

Aim of this study

We report our experience with perioperative veno-pulmonary arterial extracorporeal life support (VPA-ECLS) as temporary short-term right ventricular (RV) support in patients with biventricular failure undergoing HeartWare left ventricular assist device (LVAD) implantation and compared these outcomes to isolated LVAD support and long-term biventricular assist device (BiVAD) support. A total of 112 consecutive patients were studied, 75 with isolated Heartware LVAD, 23 with concomitant LVAD and VPA-ECLS and 14 with initial BiVAD support.

Summary of results

Seventeen patients in the VPA-ECLS cohort (17/23) were on short term mechanical support prior to VAD support. Eight (8/23) were on veno-arterial ECLS (VA-ECLS), seven (7/23) were on intra-aortic balloon pump (IABP) and two (2/23) were on both before implantation. Preoperative mean right atrial (RAP) and pulmonary artery pressures (PAP) for all patients were 13.6 ± 4.8 and 39 ± 8.0 mmHg, respectively. Initial concomitant VPA-ECLS and LVAD implantation was initiated in 21 patients (21/23). In two (2/23), VPA-ECLS was initiated for post-operative RV failure within a week. VPA-ECLS could be weaned and successfully removed at a mean of 7 ± 5 days in all but one patient. Thirty-day, six-month and one-year survival for VPA ECLS was 82.6% (19/23), 70.0% (16/23), and 61.0% (14/23), respectively. Comparative survivals for isolated LVAD, and BiVADs were 100% (75/75), 89.3% (67/75), 84% (63/75) and, 100% (14/14), 64.3% (9/14), 64.3% (9/14), respectively.

Implications

In patients who may otherwise require chronic biventricular support, planned VPA-ECLS provides acceptable perioperative RV support and allows time for the RV to adapt to the increasing cardiac output and preload.

7.2 INTRODUCTION

Implantation of continuous flow left ventricular assist devices (LVADs) have significantly improved survival rates for patients with end-stage heart failure awaiting heart transplantation ^(1, 2). Despite improvements, 20-30% of LVAD patients develop concomitant right heart failure requiring right ventricular support ⁽³⁾. Right ventricular failure post LVAD implantation is associated with poor clinical outcomes and high rates of mortality. While some patients may improve with pharmacological therapies such as prostaglandins, nitric oxide and inotropic agents ⁽⁴⁾, others require mechanical circulatory support ⁽⁵⁾ which include intra-aortic balloon pumps (IABP), right ventricular assist devices (RVAD), and extra corporeal life support (ECLS). Ideally, patients at risk of concomitant right ventricular failure should be supported with early biventricular assist device (BiVAD) support as delayed RVAD following LVAD implantation with current devices has led to poor outcomes ^(6, 7).

Due to the better outcomes with isolated LVAD, many institutions decide to use BiVAD support as the last option and in many instances utilise long-term LVAD with a temporary RVAD system. Short term-RVAD support has been successfully performed with various VAD models yielding similar results ^(7, 8) but repeat surgery for explantation and the limitations associated with paracorporeal systems increase the risk of mortality from temporary RVADs ⁽⁹⁾. The veno-pulmonary arterial (VPA) ECLS is a modified version of a cardiopulmonary bypass circuit routinely used in cardiac surgery. The use of VPA-ECLS is a well- established technique ⁽¹⁰⁾ with many advantages including its non-invasiveness (avoids re-do sternotomy incision) ⁽¹¹⁾ and ability to provide both cardiac and pulmonary support for patients at the bedside ⁽¹²⁾. Recent advances in cannulation techniques have resulted in an improved risk-benefit profile and broadened potential applications of VPA-ECLS ⁽¹³⁾, making it a feasible alternative to

traditional temporary paracorporeal RVADs. These improvements may allow for restored right ventricular function and thus prevent the need for long term BiVAD support. However, there is little information concerning long term clinical outcomes in patients receiving temporary VPA-ECLS in combination with LVADs ⁽⁵⁾. The aim of this study is to report our experience with VPA-ECLS as temporary right ventricular support in patients undergoing LVAD implantation and compare the outcome of this approach to that of isolated LVAD only and to an initial surgical strategy of BiVAD support.

7.3 METHODS

7.3.1 Study population

We reviewed all patients undergoing implantation of mechanical circulatory support at a single quaternary Heart Transplant Centre between 2007 and 2016. All patients were implanted as bridge-to-transplantation strategy, and were followed up until heart transplantation, death on mechanical support or until last observed (August 2016). The data collection in this study was approved by the local Human Research Ethics Committee. All patients had advanced heart failure classified according to the Interagency Registry for Mechanically Assisted Circulatory Support score (INTERMACS Score 1-3).

7.3.2 Criteria for various configurations

The implant strategy for BiVAD support was based on a combination of hemodynamic parameters [right ventricular stroke work index (RVSWI) <0.50, right atrial pressure (RAP) ≥15mmHg, RA/PAWP ratio >0.63, mean pulmonary arterial pressure (MAP) <60mmHg, transpulmonary gradient >12mmHg] and echocardiographic markers [right ventricular (RV) dilatation score (≥3), RV systolic impairment score (≥3) and severity of tricuspid regurgitation (TR) grade (>3)]. Echocardiographic derivatives were calculated using previously described

methodology ⁽¹⁴⁾. In brief, numeric codes were assigned for various valvular and ventricular abnormalities ranging from 0 (normal or trivial) to 5 (severe regurgitation or impairment). In patients with minimum right ventricular impairment (RV impairment score ≤ 3) and high probability of weaning of RVAD post implantation (TR grade ≤ 3 , RV dilatation score ≤ 3 , RAP < 15 , RVSWI (≤ 0.50), RA/PAWP < 0.63), concomitant LVAD and short-term VPA-ECLS were utilised. Isolated LVAD was used in the absence of clinical signs of right ventricular dysfunction. Eleven (11/14) BiVAD patients and eighteen (18/23) VPA-ECLS patients met both the echocardiographic and haemodynamic criteria for RVAD support. The remainder were elected based on clinical signs of RV failure in accordance to either echocardiographic or haemodynamic parameters only. Ultimately, the final decision between the short and long-term BiVADs was at the discretion of the treating heart failure team and determined according to the patient's holistic clinical status.

7.3.3 Implantation procedure

As previously described ⁽¹⁵⁾, VPA-ECLS with the Maquet Rotaflow centrifugal pump was instituted using femoral venous cannulation withdrawing blood to pump. Outflow from the Maquet Rotaflow was then attached to an 8 mm Dacron graft tunnelled through the precordium and sutured end to side to the proximal pulmonary arterial (PA) trunk. This enables separation from ECLS to be conducted in the intensive care unit (ICU) without returning to theatre. As the ECLS circuit has an integrated oxygenator (Maquet PLS-I Oxygenator, Rastatt, Germany), it was used for all cases. The left HVAD was implanted via sternotomy into the apex of the left ventricle, with the outflow graft attached to the ascending aorta in all 112 patients. The right HVAD implantation procedure for our BiVAD cohort was in either an RA and or an RV configuration, and has been previously described ⁽¹⁶⁾.

7.3.4 Anticoagulation

Post-operative anticoagulation with intravenous heparin began 8 to 12 h after surgery, and only after blood loss from drain tubes reached less than 50mL/h, to derive an activated partial thromboplastin time between 50 and 75 seconds. Oral anticoagulation in combination with aspirin anti-platelet therapy began following the removal of mediastinal or chest drain tubes. To detect clinically significant haemolysis, free haemoglobin, bilirubin, haptoglobin and lactate dehydrogenase (LDH) blood levels were analysed daily during ICU stay and then on a monthly basis for outpatient visits.

7.3.5 Post-operative management

All patients received a standardised protocol for postoperative care for VAD support. This included prophylactic broad spectrum antibiotics for the first three days' post-implantation and close monitoring and correction of coagulation profiles. Within a week of restoring patient's hemodynamic profile, echocardiography was performed to determine structural improvements and pump settings.

7.3.6 RVAD Weaning and explantation process

RVAD removal was considered once patients showed improvements in their right ventricular parameters (RAP <15mmHg, MAP > 60mmHg, RA/PAWP <0.63, RV dilatation <2, RV impairment <2, and TR grade ≤2). The removal was performed after gradual reduction of the RVAD flow to 2L/min at 0.5L/day increments. Standard doses of inotropic agents were then initiated and patients were carefully monitored over the next 48 hours. Excess portions of the 8mm Dacron graft were removed before it was heavily ligated, clamped and oversewn. The graft was retracted back into the chest and the skin incision closed. The prosthesis can be

removed during subsequent cardiac transplantation. The procedure can be performed at the bedside without re-operation.

7.3.7 Outcomes

Post-operative outcomes measured in this study include length of stay, ICU length of stay, survival at 30 days and 1 year and duration of support. Post-operative clinical outcomes such as eGFR and adverse events such as infection and bleeding were also measured. All post-operative outcomes were censored at the time of transplantation.

7.4 STATISTICAL ANALYSIS

Statistical analysis was performed using SPSS version 11.5 for Windows (SPSS, Inc. Chicago, IL). Results are presented as mean (SD) for continuous data and percentages for categorical data. Non-parametric Mann Whitney U test was used to analyse both continuous and categorical data. Paired samples t-test was used to assess associations between pre- and post-operative outcomes and adverse events. A p-value of less than 0.05 was considered statistically significant. Time to death and time to transplantation were analysed as competing outcomes. Adjusted p-values were obtained by cox regression analysis.

7.5 RESULTS

7.5.1 Patient characteristics

Between April 2007 and August 2016, 112 patients (90 male) underwent implantation of the HeartWare HVAD for isolated left ventricular support (n=75), concomitant LVAD and short-term VPA-ECLS (n=23) and initial BiVAD support (n=14). Patient age ranged from 12 to 76 years (mean 51±14 years) and body mass index from 16 to 43 kg/m² (mean 26±5 kg/m²). All patients were on intravenous inotropes therapy at the time of implantation; while thirty-five were on IABP and twenty-one patients were on veno-arterial extracorporeal life support (VA-

ECLS) support prior to LVAD. Four patients (two in the VPA-ECLS and two in the BiVAD group) received delayed right ventricular support 3-10 days' post LVAD support.

As illustrated in Table 7.1, there were statistical significant differences observed in INTERMACS class between the VPA-ECLS and LVAD cohort ($p=0.002$) and BiVAD and LVAD cohort ($p=0.002$). All patients had clinically elevated right atrial pressure (RAP), mean pulmonary artery pressure (MPAP), pulmonary artery wedge pressure (PAWP) and reduced cardiac output and cardiac index values. BiVAD patients had significantly higher RA pressure than the VPA-ECLS ($p=0.018$) and LVAD ($p=0.033$) cohort. This is also observed in the RA/PAWP ratio of the BiVAD and LVAD ($p=0.021$) group compared to VPA-ECLS. BiVAD patients had greater RV impairment compared to LVAD patients ($p=0.034$), while RV dilatation was significantly different between all groups. Compared to isolated LVAD, patients in the VPA-ECLS and BiVAD cohort had marked hepatic congestion demonstrated by their bilirubin levels 39.4 ± 29.6 ($\mu\text{mol/L}$) and 35.1 ± 25.3 ($\mu\text{mol/L}$); $p=0.03$, respectively. Adjusted cox regression analysis showed age at implant, gender, liver dysfunction (albumin and bilirubin) and poor pre-operative RV dilatation and high TR grade to be significantly associated with increased risk of mortality between interventions. No other clinical characteristics were significantly different between the three groups.

Table 7.1 Preoperative outcomes

	Total (n= 112)	Isolated LVAD (n= 75)	LVAD + VPA-ECMO (n= 23)	BiVAD (n= 14)	Unadjusted p-value	Adjusted Cox Regression, p-value ¹
Age, mean (SD)	51 (14)	53 (13)	51 (16)	47 (11)	NS	0.036
Sex, M (%)	90 (80%)	60 (80%)	19 (83%)	11 (79%)	NS	0.002
BMI (kg/m²), mean (SD)	26 (6)	26 (5)	28 (6)	27 (5)	NS	-
BSA	1.9 (0.2)	1.9 (0.2)	1.9 (0.3)	2.0 (0.2)	NS	-
INTERMACS, n (%)					+0.002 #0.002	NS
Class 1	33 (29%)	14 (19%)	11 (48%)	8 (57%)	NS	NS
Class 2	69 (62%)	51 (68%)	12 (52%)	6 (43%)	NS	NS
Class 3	10 (9%)	10 (13%)	-	-	-	-
Aetiology, %						
Dilated cardiomyopathy	77 (69%)	53 (71%)	12 (52%)	12 (85.7%)	NS	-
Ischaemic cardiomyopathy	24 (21%)	15 (20%)	9 (39)	0 (0%)	NS	-
Hypertrophic cardiomyopathy	6 (5%)	4 (5%)	2 (9%)	0 (0%)	NS	-
Valvular heart disease	2 (2%)	2 (3%)	0 (0%)	0 (0%)	NS	-
CCTGA	2 (2%)	1 (1%)	0 (0%)	1 (7%)	NS	-

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Giant cell myocarditis	1 (1%)	0 (0%)	0 (0%)	1 (7%)	NS	-
Previous procedures, %						
VA-ECLS	20 (18%)	7 (9.0%)	10 (43%)	4 (29%)	NS	NS
IABP	35 (32%)	24 (32%)	9 (39%)	2 (14%)	NS	NS
Ventilator	17 (15%)	7 (9%)	8 (38%)	3 (21%)	NS	-
CVVHD	4 (4%)	3 (4%)	0 (0%)	1 (7%)	NS	-
Urea (μmol/L), mean (SD)	10.4 (5.2)	10.2 (5.1)	11.3 (6.2)	10.1 (4.2)	NS	-
Creatinine (μmol/L), mean (SD)	112.9 (38.0)	110.7 (39.4)	121.8 (36.9)	107.8 (33.9)	NS	-
eGFR (μmol/L), mean (SD)	53.8 (15.0)	53.3 (16.2)	48.3 (14.6)	60.8 (14.7)	NS	NS
Albumin (μmol/L), mean (SD)	34.8 (5.9)	35.5 (6.2)	33.1 (5.6)	34.6 (5.4)	NS	0.029
Bilirubin (μmol/L), mean (SD)	30.2 (24.0)	25.2 (19.6)	39.4 (29.6)	35.1 (25.3)	+#0.03	0.036
ALT (nmol/L), mean (SD)	96.5 (213.6)	92 (174.6)	139.3 (337.5)	48 (69.7)	NS	-
AST (mmol/L), mean (SD)	69.3 (126.7)	67.2 (120.1)	93.1 (174.0)	40.1 (23.8)	NS	-
GGT (mmol/L), mean (SD)	152.0 (123.6)	151.4 (135.1)	121.7 (74.6)	179.2 (125.7)	NS	-
Haemoglobin (g/L), mean (SD)	113.9 (21)	115.5 (20)	106.8 (16)	114.3 (29)	NS	-

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Platelets (g/L), mean (SD)	217.0 (105)	230.8 (110)	174.6 (85)	222.5 (98)	NS	-
RV dilatation score (SD)	0.98 (1.3)	0.7 (1.1)	1.1 (1.1)	2.5 (1.9)	*0.043 +0.001 #0.023	0.011
RV impairment score (SD)	1.0 (1.5)	0.7 (1.2)	1.2 (1.4)	2.1 (2.1)	+0.034	NS
TR grade (SD)	1.9 (1.5)	1.7 (1.5)	1.7 (1.6)	2.8 (1.6)	*0.045 +0.017	0.050
RAP (SD)	14.7 (6.7)	14.3 (6.7)	13.6 (4.8)	18.7 (6.0)	*0.018 +#0.033	NS
MPAP (SD)	39.0 (7.9)	38.9 (7.9)	38.7 (8.0)	40.2 (8.5)	NS	NS
MPCWP (SD)	26.8 (6.2)	26.8 (6.2)	27.1 (5.6)	27.4 (5.0)	NS	-
RA/PAWP ratio (SD)	0.55 (0.22)	0.53 (0.23)	0.51 (0.18)	0.69 (0.22)	+0.021	NS
Cardiac Index (SD)	1.8 (0.48)	1.7 (0.4)	1.87 (0.55)	1.9 (0.6)	NS	-
RVSWI (SD)	0.56 (0.29)	0.59 (0.30)	0.52 (0.24)	0.52 (0.30)	NS	-
LVEF, % (SD)	22.4 (8.0)	21.6 (7.3)	21.7 (8.4)	26.1 (9.3)	NS	-
LVEDD (mm), mean (SD)	72.3 (11.3)	71.1 (10.5)	77.0 (12.2)	71 (12.9)	NS	-

BMI, body mass index; **BSA**, body surface area; **CCTGA**, congenitally corrected transposition of the greater arteries; **VA-ECLS**, veno-arterial extracorporeal life support; **IABP**, intra-aortic balloon pump; **CVVHD**, continuous veno venous haemodialysis; **RV**, right ventricle; **TR grade**, tricuspid regurgitation grade; **RAP**, right atrial pressure; **MPAP**, mean pulmonary artery pressure; **MPCWP**, mean pulmonary wedge pressure, **RA/PAWP**, right atrial/pulmonary artery wedge pressure; **RVSWI**, right ventricular stroke work index; **LVEF**, left ventricular ejection fraction; **LVEDD**, left ventricular end-diastolic diameter; **NS**, not significant; **NA**, not applicable; * means there is a statistically significant difference between VPA and BiVAD cohort of a given variable, + means there is a statistically significant difference between LVAD and BiVAD cohort of a given variable, and # means there is a statistically significant difference between LVAD and VPA cohort of a given variable. ¹ Due to missing data, statistics were carried out on 13/14 BiVAD, 22/23 VPA-ECLS, and 57/75 isolated LVAD patients.

7.5.2 Post-operative outcomes

We report outcomes from a cumulative VPA-ECLS support duration across twenty-three patients of 6962 days with a mean duration of support of 302.7 (211.0) days. Cumulative support duration of the entire cohort (n=112) was 42,919 days. Total one year survival was 78%, with the highest survival achieved with isolated LVAD (84%), followed by VPA-ECLS (65%) and BiVAD (64%). Patients requiring right ventricular support experienced higher mortality regardless of configuration. Perioperative (30 day) survival was significantly reduced in the VPA-ECLS (87%) group when compared to LVAD (100%) and BiVAD groups (100%) ($p=0.002$). A total of 34 patients (LVAD= 17, BiVAD = 7, and VPA-ECLS = 10) died during VAD support (30%; $p=0.035$) typically early in the support period. Fifteen patients (44%) died from neurological complications (13 CVA and 2 TIA), eleven (32%) from multiple organ failure, six (18%) from sepsis (unrelated to driveline), one (3%) from cancer and another 3% from accidental damage to driveline. A total of sixty-three patients (56%) were successfully bridged to transplantation after a mean 418 (292) days of support and fifteen patients remain supported after a mean 586 (515) days post implantation.

At 30 days, eGFR increased from 46 ± 11 mL/min (BSAc) to 71 ± 24 mL/min (BSAc). There were significant differences observed in the 30-day bilirubin levels of those in the BiVAD and VPA-ECLS groups (47.1 ± 15.9 $\mu\text{mol/L}$) and 21.8 ± 11.0 ($\mu\text{mol/L}$); $p=0.005$) respectively. Tricuspid Regurgitation (TR) grade was also significantly different between the three groups (BiVAD; $p=0.001$, LVAD; $p=0.005$ and VPA-ECLS; $p=0.005$) at 30-days. Longer ICU length of stay was observed in patients on BiVAD support and VPA-ECLS compared to those supported with isolated LVAD ($p=0.009$). Hospital discharge post LVAD, BiVAD and VPA-ECLS implant was successfully achieved in 91%, 71% and 86% of patients, respectively.

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Table 7.2 Post-operative outcomes, clinical outcomes and adverse events

	Total (n= 112)	Isolated LVAD (n= 75)	LVAD + VPA-ECMO (n= 23)	BiVAD (n= 14)	p-value
Post-operative outcomes					
LoS, days (mean)	37.6 (21.7)	33.9 (20.2)	46.3 (25.6)	41.5 (21.2)	NS
ICU LoS, days (mean)	12.7 (12.3)	9.0 (7.9)	20.6 (12.1)	19.8 (20.8)	⁺⁺ 0.009
Duration of support, days (mean)	393.0 (336.4)	421.4 (364.7)	302.7 (211.0)	312.6 (261.5)	NS
TR grade (mean)	0.8 (1.2)	0.8 (1.3)	0.3 (0.7)	1.6 (1.3)	*0.000, ⁺ 0.004 [#] 0.005
Thirty-day survival (%)	109 (97%)	75 (100%)	20 (87%)	14 (100%)	[#] 0.002
Survived to discharge (%)	96 (86%)	68 (91%)	19 (83%)	10 (71%)	NS
One-year survival (%)	87 (78%)	63 (84%)	15 (65%)	9 (64%)	NS
Transplanted (%)	63 (56%)	46 (61%)	11 (48%)	7 (50%)	NS
Died on support (%)	34 (30%)	17 (23%)	10 (43%)	7 (50%)	⁺⁺ 0.035,

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Ongoing support (%)	15 (13%)	13 (17%)	2 (9%)	0 (0%)	NS
Clinical outcomes (30 days)					
Urea (μmol/L), mean (SD)	7.3 (4.2)	6.9 (3.5)	8.0 (4.2)	7.9 (4.1)	NS
Creatinine (μmol/L), mean (SD)	88.7 (47.7)	85.8 (33.0)	89.5 (37.1)	97.1 (82.8)	NS
eGFR (μmol/L), mean (SD)	66.2 (18.8)	65.5 (15.9)	62.1 (20.6)	69.2 (23.4)	NS
Albumin (μmol/L), mean (SD)	35.9 (4.7)	36.9 (4.6)	34.4 (5.5)	33.6 (3.5)	NS
Bilirubin (μmol/L), mean (SD)	22.9 (49.9)	15.4 (11.0)	21.8 (11.0)	47.1 (15.9)	⁺⁺ 0.005
ALT (nmol/L), mean (SD)	25.7 (21.5)	25.6 (23.0)	23.1 (14.9)	27.6 (20.7)	NS
AST (mmol/L), mean (SD)	31.3 (33.6)	29.0 (19.3)	28.4 (14.2)	40.5 (65.0)	NS
GGT (mmol/L), mean (SD)	156.7 (119.6)	154.0 (131.6)	172.2 (122.2)	155.5 (73.1)	NS
Adverse events					
LVAD thrombosis	6 (5%)	4 (5%)	2 (9%)	0 (0%)	⁺⁺ 0.026
RVAD thrombosis	-	-	-	4(29%)	NA

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Bleeding	26 (23%)	14 (19%)	9 (39%)	3 (21%)	NS
Infection	49 (44%)	25 (33%)	15 (65%)	9 (64%)	+ [#] 0.030
○ Driveline	14 (13%)	9 (12%)	4 (17%)	1 (7%)	NS
Sternal wound	9 (8%)	4 (5%)	3 (13%)	2 (14%)	NS
○ Blood culture >0	37 (33%)	20 (27%)	11 (48%)	6 (43%)	NS
Renal dysfunction	16 (14%)	8 (27%)	4 (17%)	4 (29%)	NS
Neurological	19 (17%)	14 (19%)	3 (13%)	2 (14%)	NS
Respiratory dysfunction	15 (13%)	7 (1%)	5 (22%)	3 (21%)	+ [#] 0.015

LoS, length of stay; **ICU**, Intensive Care Unit; **LVAD**, left ventricular assist device; **RVAD**, right ventricular assist device; **TR**, tricuspid regurgitation; **NS**, not significant; **NA**, not applicable; * means there is a statistically significant difference between VPA and BiVAD cohort of a given variable, + means there is a statistically significant difference between LVAD and BiVAD cohort of a given variable, and # means there is a statistically significant difference between LVAD and VPA cohort of a given variable.

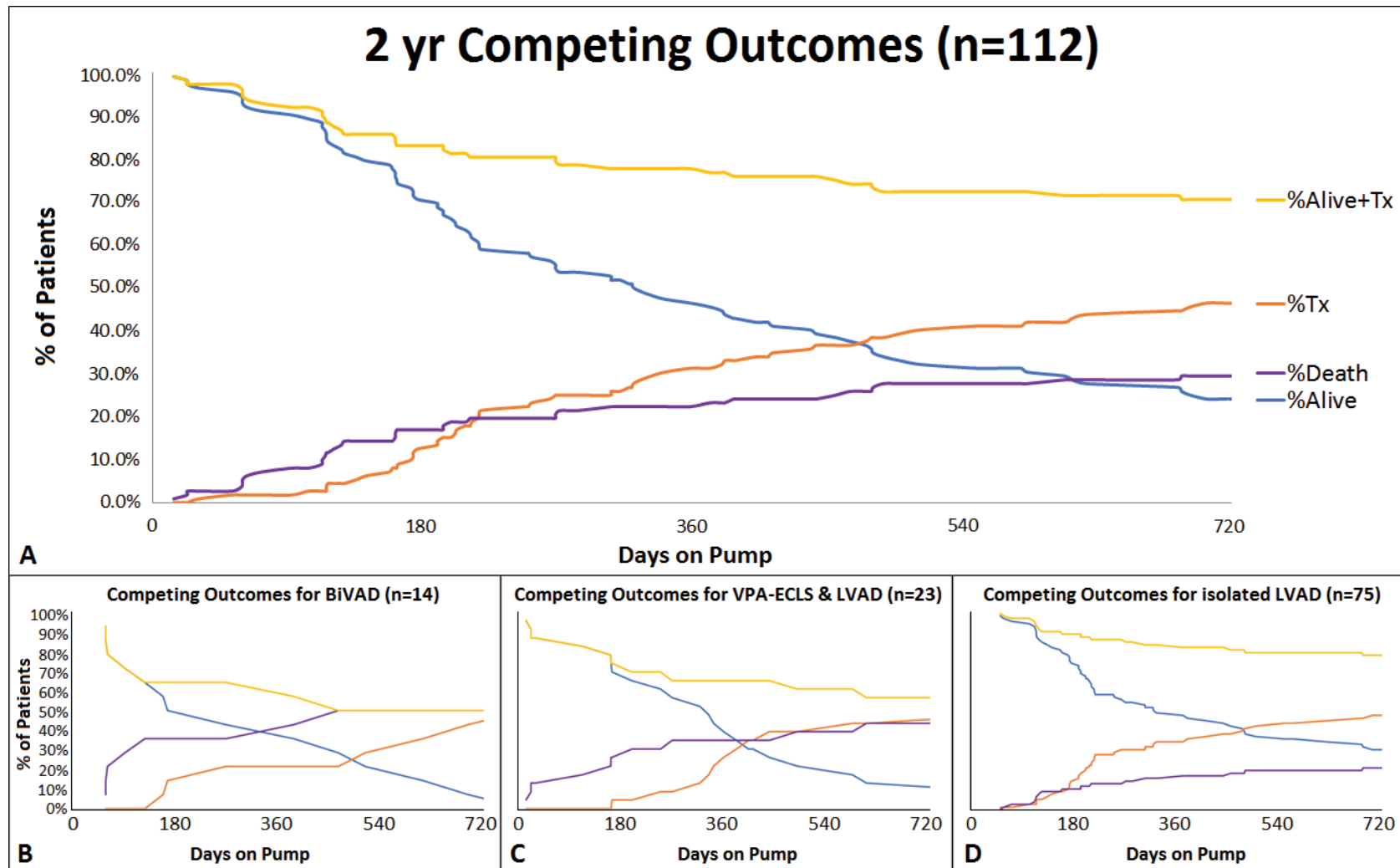


Figure 7.1 Two year competing outcomes for the entire cohort (Figure 1A) as well as for the three different interventions; BiVADs (Figure 1B), VPA-ECLS (Figure 1C), and isolated LVAD (Figure 1D).

7.5.3 Adverse events

Adverse events during VAD support have been provided in Table 7.2 and were classified according to the INTERMACS definitions. A total of forty-nine patients (44%) suffered from infectious complications. Nine (8%) developed sternal wound sepsis, fourteen (13%) driveline infection, and thirty-seven (33%) returned positive blood cultures (in the absence of a driveline infection). Of these patients, twenty suffered from multiple infectious complications. Infection rates were significantly higher in the BiVAD and VPA-ECLS groups compared to isolated LVAD ($p=0.03$). Acute renal failure requiring haemodialysis occurred in nineteen patients (17%), of which fifteen patients (5 in LVAD group, 7 in VPA group and 3 in BiVAD group) successfully recovered. Four patients in the VPA-ECLS cohort developed immediate post-operative acute renal failure which were all successfully resolved within a week. Although neurological complications were more frequently observed in the LVAD group (19%; CVA 13% and TIA 5%) compared to the VPA-ECLS (13%; all CVA) and BiVAD group (14%; CVA 7% and TIA 7%), the analysis showed no significant difference among them. In contrast, the elevated rates of respiratory dysfunction in the BiVAD and VPA-ECLS group was found to be statistically significant (22% and 21%; $p=0.015$, respectively) compared to isolated LVAD group. Bleeding rates were more common in the isolated LVAD and VPA-ECLS cohort compared to BiVAD but this was not a significant difference. All adverse events reported were events during index hospitalisation and from subsequent readmissions.

7.6 DISCUSSION

The study summarises overall experience with patients suffering from cardiac failure requiring mechanical circulatory support using the HeartWare HVAD. Three different configurations have been adapted over the last decade including isolated LVAD support, planned concomitant LVAD and temporary VPA-ECLS support and long-term BiVAD support using dual HVADs. Our results with isolated LVADs offer adequate one-year survival (84%) and transplantation rates (61%) similar to those reported by other groups using the same device ^(17, 18) and to that of published registry data ⁽¹⁹⁾. Although initial BiVAD support also resulted in acceptable outcomes, early mortality remains an area in which major improvements can be made. Nearly half of all patients requiring short or long term RV support are INTERMACS Level 1 at implant and in this cohort, advanced heart failure is often associated with other significant multi-organ dysfunction ⁽⁹⁾. Furthermore, the chronicity and severity of advanced heart failure, results in a state of physiological frailty which has been shown to have marked survival implications, independent of whichever therapy is required – routine cardiac surgery, transplant or mechanical support.

Our VPA-ECLS cohort is reflective of patients at risk of developing right ventricular failure post-LVAD implantation. Their pre-operative demographics consisted of similarities found in both isolated LVAD and long-term BiVAD cohorts. Bilirubin and RVSWI were closely matched with the BiVAD cohort while other markers such as RAP, RA/PAWP, and LVEF were more comparable to the isolated LVAD cohort. Echocardiographic markers used as part of the BiVAD selection criteria such as RV dilatation (≥ 2), RV impairment (≥ 2), and TR grade (≥ 3) were lower than what was required for long-term initial BiVAD support but higher than isolated LVAD. Due to the higher survival and significantly lower complication rates of LVAD patients

compared to BiVAD patients in the literature, temporary VPA-ECLS was elected as the median between the two interventions.

Various configurations of VPA-ECLS have been previously reported. Right atrial to pulmonary artery bypass is well accepted but requires re-operation to remove the cannula, increasing the risk of infection and surgical related bleeding. The same limitations apply to existing paracorporeal RVAD and BiVAD systems ⁽²⁰⁻²²⁾. However, our institutional configuration of femoral venous cannulation for inflow and pulmonary arterial trunk for outflow enables removal of VPA-ECLS without re-operation, eliminating additional risk of infection, bleeding or device contamination. A similar procedure was reported by Saeed et al ⁽²³⁾ on 21 patients using the Levitronix Centrimag as the temporary RVAD. The inflow cannula was inserted percutaneously into the right atrium through the right femoral vein while the outflow graft was connected to the main pulmonary artery. Eleven patients were successfully weaned off RVAD support, two were weaned to transplantation and eight died during RVAD support. The 1 year survival rate was similar between our cohort (65%) and those reported by Saeed et al (52%) ⁽²³⁾. The lower survival rates may have been associated with the high number of patients (n=12, 57%) requiring an oxygenator at the time of RVAD support. In our study all patient were standardly supported with an oxygenator (Maquet PLS-I Oxygenator, Rastatt, Germany) which can be helpful in the event of hypoxia, severe lung edema or in patients on ECLS support prior to VAD support ⁽²⁴⁾ as presented in our current study. The large number of ECLS support prior to VAD support in our study is depictive of the severity of our patient's clinical condition. Our post-operative outcomes have shown similar duration of support, transplantation and discharge rates of VPA-ECLS patients to those implanted with initial BiVAD and isolated LVAD. ICU length of stay between BiVAD and VPA-ECLS cohorts were comparable, while it was found

to be significantly higher in VPA-ECLS cohort compared to isolated LVAD ($p=0.009$). There are several reasons for the elevated ICU and hospital length of stay observed in this cohort. Firstly, patients requiring right ventricular support (BiVAD or VPA-ECLS) are initially sicker than isolated LVAD patients, reflected by the greater number of INTERMACS class 1 patients in VPA-ECLS and BiVAD cohorts than isolated LVAD patients. The degree of INTERMACS class has been associated with greater risk of mortality and morbidity (19). Secondly, the novelty of our BiVAD and VPA-ECLS strategies are associated with a learning curve which can improve outcomes with increased experience and better patient selection. This can be seen in the current VPA-ECLS cohort, where all patients implanted post 2013 have a significantly lower ICU length of stay 15.4 ± 9.6 days compared to 20.6 ± 12.1 of the entire cohort.

In terms of adverse events, bleeding, neurological complications and acute renal failure in VPA-ECLS patients yielded similar outcomes seen in both isolated LVAD and initial BiVAD support. However, a large proportion of VPA-ECLS acute renal failure cases (4/7) occurred in the immediate post-operative period (0-2days), whereas no immediate post-operative acute renal failure was observed with either initial BiVAD and isolated LVAD support. Acute renal failure following mechanical support is a marker of poor outcome, with mortality greatest within the first 30 and 180 days ⁽²⁵⁾. Nonetheless, none of the patients that died within the first 30 days developed acute renal failure. All cases of acute renal failure were quickly resolved and outcomes were similar to those without acute renal failure. The treatment of renal failure post VAD support remains controversial ^(26, 27) and a large cohort would be required to elucidate these findings. Although the incidence of acute renal failure was highest in the VPA-ECLS cohort, it was not statistically significant and outcomes were comparable to both BiVAD and LVAD groups and to those without post-operative renal failure.

The occurrence of respiratory failure was similar to BiVAD patients but higher compared to isolated LVAD patients ($p=0.015$). These results may be explained by the fact that more VPA-ECLS patients had a ventilator or other mechanical device (IABP and ECLS) prior to VAD support. Similarly, elevated infection rates were observed in both the BiVAD and VPA-ECLS cohorts compared to isolated LVAD, but no significant difference was observed between the types of infection. The elevated infection rates observed in the BiVAD group may be due to the use of two pumps, and therefore two different potential sources of infection. Conversely, the separate incision site (entry and exit site) required for VPA-ECLS implantation may explain the increased rates of infection observed in the VPA-ECLS cohort. Infection can also occur in the VPA-ECLS during RVAD removal, whereby the graft is cut and retracted into the mediastinum. There was only one incidence of mediastinitis in the VPA-ECLS cohort which was successfully treated. There were no infection related deaths in isolated LVAD, but four in BiVAD and one in VPA-ECLS. Aside from increased risk of infection, retracting the 8mm graft into the patient chest also increases the risk of pulmonary embolism. Monitoring patients via computer tomography (CT) has been recommended during follow up. Although we did not follow up with CT scans, none of our patients presented with episodes of pulmonary embolism or bleeding complications associated with retained outflow grafts. The feasibility of leaving the outflow tract has been previously validated ⁽²⁸⁾.

The VPA-ECLS cohort also experienced a much higher mortality rate compared to the isolated LVAD cohort. This may be attributed to the higher proportion of sicker patients as evident by their INTERMACs class and their need for pre-operative mechanical support with ECLS and/or IABP. Pre-operative mechanical support has been independently associated with higher mortality and morbidity when implemented prior to VAD support ⁽²⁹⁾. As shown in Figure 7.1,

the highest rate of mortality occurred within the first six months post implantation. Of the entire VPA-ECLS cohort, ten patients died during support, of which only one death occurred while on concomitant VPA-ECLS support at 23 days due to failure to be weaned from device. The rest of the nine deaths occurred post VPA-ECLS explantation and re-stabilisation to an isolated LVAD. All other patients were successfully weaned from VPA-ECLS after a mean of 7 ± 5 days of support. Although one-year survival rate of 65% seems low when compared to isolated LVAD (84%), our VPA-ECLS survival rate are higher than currently existing VA-ECLS published reports ^(13, 30) and existing registry databases ⁽³¹⁾.

Despite controversy surrounding the efficacy of ECLS, recent improvements in design, technique and patient selection has resulted in its increased frequency of use. Existing evidence indicates increasing survival rates with ECLS over the last few decades from 38% (1990-2000) to 46% (2011) ⁽³¹⁾. While our initial experience demonstrated acceptable outcomes, better results may be expected with accumulated experience. These improvements are clearly demonstrated in our VPA-ECLS cohort as all patients supported after the year 2014 have either been transplanted or remained alive to date (mean duration of support of 336 ± 75 days).

Clearly patient selection and early recognition of predictive markers of RVF have played an integral role in improving clinical outcomes. Previous studies have revealed a number of pre-operative markers of RVF post-VAD implantation including INTERMACS score, pre-VAD mechanical support such as ECLS or IABP, albumin or bilirubin values, age, body surface area (BSA) and hemodynamic such as RA, MPAP, RA/PAWP and RVSWI parameters ^(4, 32, 33). Although device intervention was selected based on these haemodynamic and

echocardiographic markers, the final decision was left at the discretion of the attending cardiologist and cardiac surgeon.

7.7 LIMITATIONS

This study was conducted in a single centre and therefore was limited in the number of enrolled patients. The small BiVAD and VPA-ECLS sample size is likely underpowered to detect significant differences between groups and thus limits the study's ability to delineate characteristics that may aid in determining the type of intervention suitable for patients. The consecutive nature of the study cohorts may have resulted in a time bias, due to the above learnings and increased experience with patient selection.

7.8 CONCLUSION

In patients who may otherwise require biventricular support, planned concomitant VPA-ECLS provides acceptable perioperative RV support and may allow time for the RV to adapt to the increasing cardiac output and preload. Rekindled interest in ECLS therapy has direct implication for patient care, resource usage and clinical training.

7.9 REFERENCES

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CHAPTER VIII- LONG NON-CODING VARIATION PRE- AND POST BIVAD SUPPORT

8.1 CHAPTER PREFACE

Chapter 8 has described the protocol at St. Vincent's Hospital, Darlinghurst, and the Victor Chang Cardiac Research Institute (VCCRI) that allows our translational research team to collect and analyses human cardiac tissue that can be used for biological research. To date we have procured approximately 150 samples from a total of 60 patients. However, for the purpose of this thesis only patients with biventricular support that have both implant and explant samples will be reported (7 out of 14 patients, n=27 samples). Results from isolated LVAD patients have been previously reported ⁽¹⁾. This chapter will first discuss the process for collection and the storage process before proceeding to the analysis and testing of the tissue samples.

8.2 INTRODUCTION

Chronic heart failure is often defined as the progressive decline of cardiac function typically associated with chronic stress dependent pathological hemodynamic and neurohormonal signals which eventually result in a maladaptive remodeling response ⁽²⁾. At a molecular level, various genetic transcription markers involving contractile proteins, inflammation, calcium handling and adrenergic signal mechanisms ⁽³⁾ have been associated with heart failure which

has led to immense interest in transcriptional profiling. Transcriptional profiling of new genetic markers can aid identify biomarkers for better diagnostic accuracy and assess the impact of therapeutic interventions such as pharmaceutical agents and cardiac devices ^(4, 5). Previous studies have placed heavy emphasis on coding and small non-coding ribonucleic acids (RNA) molecules (mRNA and microRNA, respectively), limiting most studies by their use of conventional microarray or polymerase chain reaction based assays. However, mRNA and microRNA (miRNA) account for approximately 1% of the total 90% transcribed species present in the mammalian genome ⁽⁶⁾. Recent in-depth analysis and identification of other non-coding RNA classes have been made possible by the advancements to deep sequencing and other analysis technologies. One of the most promising classes of non-coding RNA are the long non-coding RNA (lncRNA) molecules. These lncRNA molecules are defined by their size and are typically equal to or greater than 200 nucleotides. They have shown to be functional and have been associated with specific physiological and pathological processes involving transcription mechanisms ⁽⁷⁻⁹⁾. Furthermore, some evidence indicates that they are expressed in cell-type and context specific manner ^(10, 11). Considering their potential functionality, lncRNA was investigated for any variation pre-and post BiVAD support.

Ventricular assist devices (VADs) have been successfully integrated into the clinical management of patients with advanced heart failure. Their efficacy in prolonging patients life to transplantation, permitting patient discharge, and improved quality of life have resulted in vast interest and investment in the area. While VADs can restore and stabilize patient hemodynamic parameters, their effect on the cellular level remains unknown. Many studies have reported cases of myocardial recovery and restored cardiac function after VAD support ^(12, 13). However, it is uncertain whether reversal of pathological myocardial remodeling is a

consequence of restored gene regulation of cardiac tissue or as a result of improved unloading and reduced pressure imposed on the cardiac muscle from VAD support. Perhaps a combination of both methods is at play. Therefore, understanding the genetic and cellular consequences of VAD support can further enhance our understanding, improve patient management and the future VAD models. The aim of this chapter is to describe the strategies and methods used in collecting, storing and analyzing cardiac tissue samples and assess whether there are changes in the gene regulation of cardiac markers pre- and post VAD support in our cohort.

8.3 METHODS

8.3.1 Informed consent

The current study has been approved by St. Vincent's Hospital research governance body and the human research ethics committee (HREC10/SVH/100) (Appendix 1). The study focusses on patients with advanced heart failure demonstrating clinical signs and symptoms of biventricular failure as defined by our institution. Consent was obtained during listing for heart transplantation by a member of the patient clinical team (Appendix 5). It was made clear that in the event of mechanical support, the left and right ventricular tissues would be collected during VAD implantation and during subsequent cardiac transplantation. An amendment to the consent form was made in 2014 where consent was also requested for right atrial tissue to be added to the list of tissues tested. All patients were informed on how their tissue samples would be collected and stored. They were also informed of the potential risk associated with the study, particularly related to the potential loss of confidentiality if data was accidentally disclosed. All patient included into the current study are over the age of 18 years. A total of 7 patients are included, summing to a total of 27 samples tested.

8.3.2 Tissue Collection

The collection of some tissues (3 left and 3 right ventricular tissues) precedes the current thesis. The process however remains the same with minor changes made in how the tissues were stored following collection (refer to 1.3.3 Tissue storage). The collection protocol was designed to optimize the quality of the samples obtained. During collection, great efforts were made to ensure (i) that samples are collected immediately after the tissues leave the body, (ii) samples are kept cold right after collection, and (iii) minimum time was lost from the point of collection to the moment it was stored.

The collection process is triggered with a notification from a transplant coordinator. Transplant coordinators often provided a notice of around 2-24 hours in advance of a potential or planned cardiac transplant or VAD implantation. The appointed research student is then responsible for confirming the procedure, preparing a work space to receive the heart/tissue, organizing a portable ice bucket with dry ice inside, and introducing themselves to the staff prior to the commencement of the surgery to ensure no disruptions are caused by confusion due to their unexplained presence. Once the heart/tissue is removed, a small sample (weighting between 500mg to 700mg) is collected and stored within a 2ml Eppendorf tube containing a solution of RNALater™ (Qiagen, CA). RNALater is a preservative that inhibits DNA and RNA degradation and has been recommended by the collaborating genetic specialist at the VCCRI for enhancing the quality of our tissue samples. The tubes are then immediately placed inside the ice bucket containing dry ice and transported to the designated, secure laboratory for storage in a -80 freezer. For samples prior to the current thesis, the same methodology was used with the exception of RNA Later. Instead, after storing tissue inside an empty 2 ml Eppendorf tube, samples were immediately placed in dry ice and stored in liquid

nitrogen. The later approach remains a valid and commonly practiced methodology for tissue storage.

8.3.3 Tissue storage

All samples were stored inside a -80 freezer. All samples (Eppendorf tubes) were labelled with a date, an identifiable patient marker (e.g. specific number), and the type of tissue collected, e.g. case #1, left ventricular implant, 01/07/2014. Tissue samples were coded before storage (A1 to A5, B1 to B5, etc) and placed alphabetically. The tissue type (left or right ventricular tissue), tube location, storage box position and status (un/processed) of all samples were digitally recorded on a secure, password protected database at the VCCRI and was restricted to the research student and the collaborating generic scientist. All the information stored here was de-identified and was limited to the results obtained from tissue analysis. All samples prior to the thesis were stored inside large tanks containing liquid nitrogen. These samples have since been relocated to the -80 freezer alongside newer samples collected. To ensure samples remained frozen, they were transported in dry ice for no longer than 8 minutes before reaching the -80 freezer.

8.3.4 Patient confidentiality

To maintain patient confidentiality, all samples (Eppendorf tubes) were coded with numbers (1-84) that were unique to each patient, there tissue type and dated, (e.g. #10, LVI, 10/10/2015). Any information that could possible reveal the patients identify was removed, e.g. patient name, initials, and medical record numbers. All patient details were stored on-site at St. Vincent's Hospital and alongside their unique sample codes. Only the research student and the primary supervisor had access to the database.

8.3.5 RNA extraction and integrity

Total RNA was successfully extracted from the tissue sample using miRNeasy Mini Kit protocol (Appendix 2). To put briefly, the process involved rupturing the cells to release the intracellular material. This was achieved by shredding a small sample of the tissue (40mg) in the presence of Trizol (Life Technologies, NY) using a homogenizer. Trizol inhibits DNA and RNA degradation and can aid maintain the integrity of our samples despite being in room temperature for up to 3 hours or indefinitely if stored in the -80 freezer. The RNA material is then isolated from the rest of the intracellular matrix via a series of laboratory procedures described in the miRNeasy Mini Kit (Appendix 2).

The quality and integrity of our isolated RNA samples were then determined by using the Agilent RNA 6000 Nano Kit (Agilent Technologies, CA). The procedure is designed to separate the nucleic acid fragments according to their size before being analyzed by the Agilent 2100 bioanalyzer (Agilent Technologies, CA). The entire protocol is presented in Appendix 3. The RNA integrity number (RIN) is a scaled value ranging from 1 to 10. A low RIN score is associated with high RNA degradation and thus poor overall quality, while a high RIN score means a pure sample with maintained genetic structure. The majority of our samples resulted in RIN scores greater than 7. However, three samples yielded RIN scores as low as 5.1, 5.3 and 5.7. Due to our limited sample cohort, we decided to lower our threshold and accept all samples with a RIN score of 5 or greater.

8.3.6 Library preparation and sequencing

All RNA libraries were prepared using Ion Ampliseq RNA Library Kits containing standard panels (Life Technologies) in accordance with the manufacturers' recommendations (**Error! Reference source not found.**) and summaries in Figure 8.1. These panels contain primer pairs

that are designed to amplify at least one splice junction from 20812 RNA transcripts. In brief, 10 ng of total RNA was reverse transcribed to synthesize complementary deoxyribonucleic acids (cDNA). The target sequences were then amplified and digested using FuPa reagent from the Ion Ampliseq library Kit (Life Technologies). Ampliseq adaptors were then ligated to the re-constructed cDNA and purified using Dynabead Magnetic Beads. The Dynabead Magnetic Beads were used to isolate and discard excess primer sequences and other high molecular weight DNA molecules from the solution. The remaining sample was then amplified again before commencing a final purification process with the Dynabead Magnetic Beads. The library was then quantitatively measured using Qubit 2.0 fluorometer and assessed on an Agilent high sensitivity RNA chips. For consistency, all library sequence procedures were carried out by the same operator.

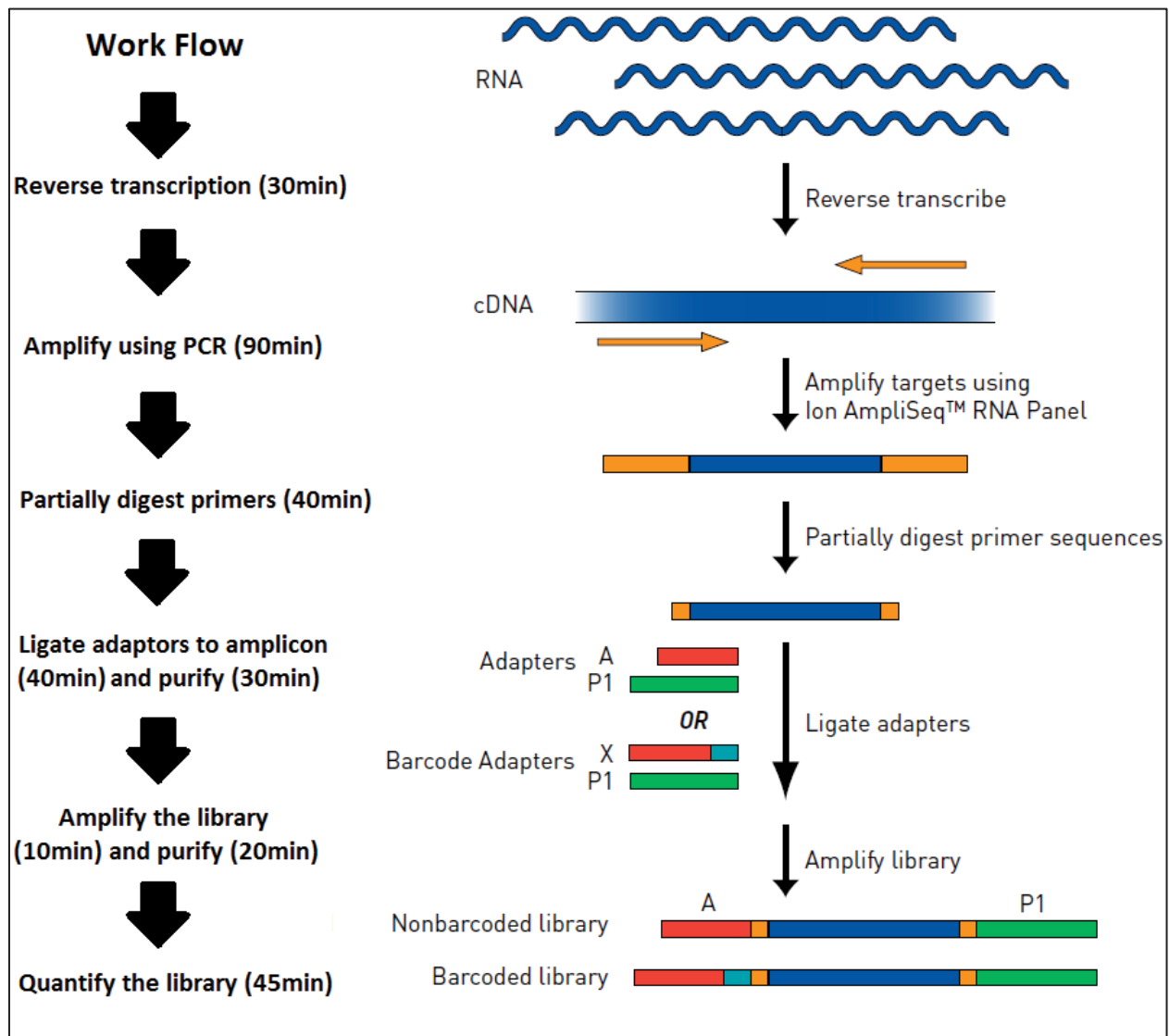


Figure 8.1 Diagrammatic representation of the Library preparation and sequencing

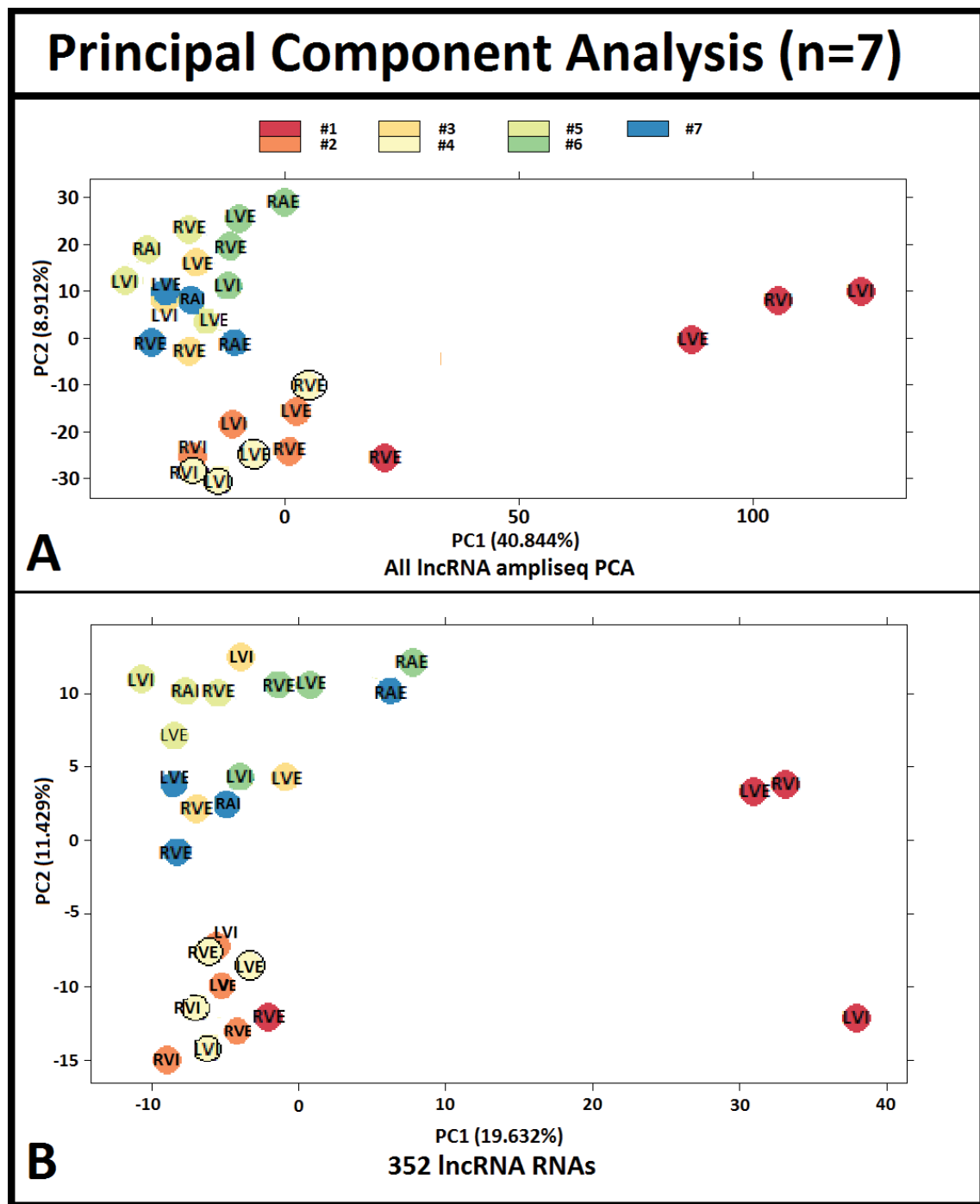
8.3.7 Statistical analysis

Gene counts were generated using the Ion torrent software suite and were imported into the R software. The expression of each gene on the cardiac panel was normalised to the total reads that aligned to all transcripts. Differential expression analysis was conducted using statistical software edgeR.

8.4 RESULTS

8.4.1 Principal component analysis

The principal component analysis (Figure 8.2) revealed no significant differences between implant and explant tissue in our cohort. A batch effect is evident between the two separate libraries performed. Patients 1,2 and 4 were analyzed first (Batch A) and are located at the lower end of the graph, while patients 3, 5, 6 and 7 were analyzed in the second batch (Batch B) and are closely located to one another at the top-left section of the graph. Although no distinct differences were observed between the two groups, there were slight variations on an individual level. Most patients exhibited unique variations between the positions of implant and explant tissue. The greatest variation was demonstrated in patient 1. The poor RIN score in patient 1's LVI, RVI and LVE samples may be associated with significant RNA degradation. To support this assumption, we can compare patient 1's results to their RVE sample. Patient 1's RVE yielded similar RIN scores (yet still lower than 7 RIN) to those of patient 2 and 4 and therefore could explain its proximity to the other samples assessed in batch A. Similar trends are seen in both analysis (All RNA molecules vs. only the top 352 lncRNA molecules).

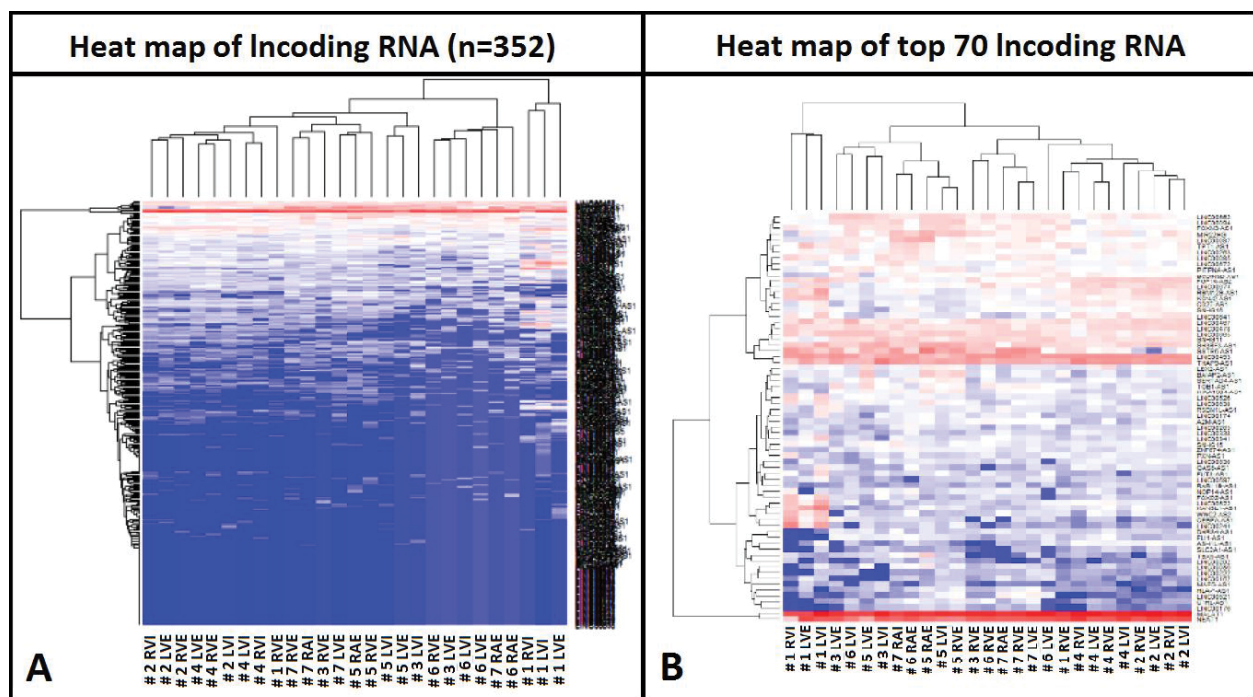


LVE, left ventricular explant; LVI, left ventricular implant; RVE, right ventricular explant; RVI, right ventricular implant; RAE, right atrial explant; RAI, right atrial implant.

Figure 8.2 Principal component analysis identifying variation between implant and explant tissue samples for all RNA molecules (Figure 1.2A) and 352 of the most common IncRNA molecules detected.

8.4.2 Expression signature and Heat Maps

The expression heat map and clustering dendrogram of a subset of the lncRNA are summarized in Figure 8.3. Figure 8.3A reports on all the lncRNA that was detected in the library while Figure 3B illustrates the top 70 expressed lncRNA markers in the entire library. Based on the results obtained, no distinct variation between implant and explant tissues were evident. Similar results were attained from analyzing the top 10 and top 5 expressed lncRNA marker.



LVE, left ventricular explant; LVI, left ventricular implant; RVE, right ventricular explant; RVI, right ventricular implant; RAE, right atrial explant; RAI, right atrial implant.

Figure 8.3 Heat Map and unsupervised hierarchical clustering of lncRNA expression profiles derived from the microarray data of cohort of human cardiac tissue. Figure 3A depicts the total (352) long non-coding RNA markers detected, while Figure 3B reports on the top 70 long non-coding RNA markers expressed.

8.5 DISCUSSION

The present study used targeted next generation sequencing to provide a quantitative analysis of lncRNAs in patients with advanced heart failure pre- and post BiVAD support. In contrast to the vast knowledge surrounding coding RNAs and small non-coding RNAs, very little is known about the cardiovascular function of lncRNAs. In fact, the significance of lncRNAs were largely attributed by the recent discovery of Braveheart, a cardiac specific lncRNA marker in mice ⁽¹⁴⁾. Braveheart has been identified as a vital component necessary for the activation of key cardiovascular gene networks and functions upstream of mesoderm posterior 1, a master regulator of a common multipotent cardiovascular progenitor ^(9, 14). In addition to the many genetic factors that govern the cardiac development, lncRNA may represent an additional layer of regulation in humans. Given that these lncRNAs appear to contribute to the regulation of cardiac networks, these transcripts may also be expected to contribute to cardiac pathologies.

Validated laboratory protocols were followed and ensured best practice was taken when collecting and extracting samples. The results obtained are reflective of real life patients on BiVAD support at a metropolitan hospital. A total of 7 patients were included in the analysis. Three hundred and fifty-two lncRNA markers were identified from a total of 20812 RNA coding genes. We correlated our findings with other studies and identified many similarities ^(7, 8). However, unlike Yang et al ⁽⁷⁾, our results demonstrated no difference between implant and explant tissue. BiVAD support had no detectable effects on the up or down regulation of our lncRNA markers. While a large sample may have yielded different results, our cohort was similar in size to those reported by Yang et al ⁽⁷⁾. Some evidence suggests the lncRNA may be expressed differently depending on the patients underlying condition ^(6-8, 13). Therefore, a

patient with dilated cardiomyopathy would be expected to express different lncRNA signatures when compared to a patient with ischemic heart disease. This may explain why there were no genetic differences pre- and post BiVAD support. Of the seven patients included in this study three had dilated cardiomyopathy, two had ischemic heart disease, one had hypertrophic cardiomyopathy and another with transposition of the greater arteries. A larger and homogenous sample may yield different results. Conversely, some studies support our findings and have also demonstrated a lack of genetic variation pre- and post VAD support⁽¹⁵⁾. The remodeling process is associated with the reduced cardiac workload and therefore less stress on the cardiac muscles. Further research is warranted to elucidate whether there is a difference pre- and post BiVAD support

8.6 LIMITATIONS

The number of samples included were small, and were collected from a heterogeneous cohort in terms of demographics (sex, age, race, etc.) and aetiology (dilated cardiomyopathy, ischemic heart disease, etc.). In addition, sequencing technologies and data analysis methodologies are constantly evolving. The Ampliseq sequencer allows for in-depth analysis despite non-optimum RIN scores in some of our samples. Due to its relatively new entry into the commercial markets, there are very few studies available which utilize the same technology, making direct comparison difficult. In addition, the ampliseq panel does not capture all lncRNA. They are designed to amplify 4000 lncRNA molecules. While we were able to demonstrate evidence of expression, we were only able to capture a small portion lncRNA molecules. Additional lncRNA can be captured using hi depth unbiased RNA-sequencing approaches.

8.7 CONCLUSION

A systematic collection and extraction protocol has been developed which can be used for future tissue research. There were no significant differences noted between lncRNA markers pre- and post BiVAD support in patients with advanced heart failure. A larger, homogenous cohort is required to validate our findings. The following chapter (Chapter 9) will conclude the thesis by providing a brief summary of the individual chapters, as well as recommendations for future research.

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CHAPTER IX- CONCLUSION

9.1 INTRODUCTION

The previous chapters have reported a series of experiences described in Chapters 2-8 with the off-label use of the HeartWare HVAD as continuous flow biventricular assist devices (BiVADs) in patients with advanced heart failure (CHF). This thesis has focused on three main areas of interest, including in-vitro experimentation involving a mock circulatory loop (MCL), clinical findings in real patients supported with BiVADs, and laboratory tissue analysis to determine genetic changes pre- and post BiVAD support. This thesis has provided thorough assessment of the HVAD system and the clinical consequences they have on patients, as well as their performance in a simulated model of the human cardiovascular system. The findings provide insight into the outcomes of dual LVAD therapy with the HVAD in Australia and can provide useful information to help shape future guidelines, including patient/device selection, management, and methods of implantation. In this chapter, the thesis is concluded by summarising the conclusions drawn from previous chapters and identifying the potential areas of improvement in future research.

9.2 THE OVERALL DOCTORAL STUDY

The aim of this thesis was to improve the understanding of the effects of using two continuous flow ventricular assist devices for biventricular support in patients with advanced heart failure. Specifically as part of this doctoral study; i) a mock circulatory loop capable of

accurately simulating various healthy and pathological haemodynamic conditions was developed, ii) reported on the clinical outcomes of patients receiving BiVAD support with the HVAD system , and iii) assessed the genetic variations between left ventricular, right ventricular and right atrial tissue pre- and post VAD support. By combining clinical and academic research, it is possible to accelerate the transition and translation of our research findings into the community and other health services.

9.3 CHAPTER TWO – LITERATURE REVIEW OF BiVADs

The literature review of BiVAD devices summarised all existing FDA approved devices used for biventricular support. This review identified both the strengths and limitations of each device and highlighted key clinical outcomes previously reported in the literature. This review also defined all adverse events according to the INTERMACs definitions, allowing for comparability between studies. Furthermore, the benefits of continuous flow BiVAD were demonstrated by incorporating dual HVAD therapy and comparing them to pulsatile BiVAD systems. The advantages of a more durable, mobile, and miniaturised BiVAD system were emphasised with an in-depth expert commentary. Finally, recommendations for future BiVAD and battery designs were provided with insight into upcoming developments within the next five years.

Recommendation 1:

- There is a need for deeper understanding on the performance of continuous flow BiVADs in patients with advanced heart failure.
- Enhancing the knowledge of clinician's and other health professionals on continuous flow BiVAD will help shape future guidelines in terms of patient/device selection and encourage further research in the area.

- Randomised clinical trials are needed to compare pulsatile and continuous flow BiVAD systems.

9.4 CHAPTER THREE – MOCK CIRCULATORY LOOP DESIGN AND VALIDATION

Chapter three provided a brief literature review on the evolution of MCL designs. It highlighted the novel adaptations made to the MCL such as incorporating the pulmonary circulation, using a validated total artificial heart driver (SynCardia Companion 2) to provide pulsatile flow, addition of air valves on top of the Windkessel chambers to regulate pressure/fluid levels, and the use of two silicon based transparent ventricles designed with similar dimension to patients with CHF. It rationalised the MCL design used in this thesis and justified the use of a 4-elemental MCL. In addition, all parameters measured during experimentation such as pressures, flows and intrinsic feedback mechanisms such as the Frank Starling response were explained and their clinical significance highlighted. The MCL setup and pre-validation experiments were clearly reported. Pre-validation experiments were primarily designed to determine the functionality of the MCL and were used to gauge the consequences of manipulating various variables such as heart rate, systolic ejection ration, LVAD/RVAD pump speeds and left and right ventricular pressures and thus ventricular contractility. The MCL was validated by successfully replicating five controlled conditions including normal healthy heart, borderline heart failure, left ventricular failure, biventricular failure and severe biventricular failure without VAD support. Following validation, various experimental conditions using VADs were simulated and their results published. This MCL is capable of accurate replicating of various haemodynamic conditions of the human cardiovascular system. It is a vital tool for teaching purposes as well as future development and testing of cardiovascular devices.

Recommendation 2:

- Instead of two independent ventricles, the artificial heart should contain both ventricles in one unit separated by the interventricular septum. This would more accurately depict the natural cardiac anatomy as well as allow for visualisation of septal shifts during various pump speeds and abnormal valvular condition.
- Artificial bovine valves should be considered to reduce waveform disruption caused by the water hammer effect during opening and closing of the valves.
- Develop a clear division between the various components of the mock circulatory loop. This would allow for various components to be added, removed or replaced and enable testing of different or newer designs without the need to develop a whole new system.
- Design an easier way to add/remove the cardiac pumps tested without having to shut the MCL down. Similarly, there should be a simpler way of adding or removing the cardiac valves. This would not only save time, but also prevent changes to internal conditions such as pressure and flows.

9.5 CHAPTER FOUR – ASSESSMENT OF RIGHT VENTRICULAR FAILURE CORRECTED WITH BIVENTRICULAR SUPPORT USING MOCK CIRCULATORY LOOP

Chapter four described the design, methodology, and experimental outcomes of four experiments including borderline heart failure, left ventricular failure, initial biventricular failure and delayed biventricular failure. These experiments were designed to demonstrate that delayed RVAD support can restore hemodynamic parameters from failing to normal conditions, and overcome right heart failure, commonly seen in isolated LVADs. The in-vitro experiment was validated by comparing them to the general population of patients with

biventricular failure that have received subsequent BiVAD support at St. Vincent's Hospital. If translatable into clinical practice, the HVAD system may provide much needed support to patients that develop right ventricular failure post-LVAD implantation without the significant risk to mortality and morbidity currently associated with pulsatile BiVAD systems. However, it is important to recognize that all outcomes are limited to clinical observations from a hemodynamic viewpoint. In addition, patients who undergo delayed RVAD placement are by definition failing on isolated LVAD and are a higher risk population, with likely incipient organ dysfunction. Therefore, the impact of return to theatre for placement of a second VAD, rather than both being placed in the same operation, needs to be further considered and thorough in-vivo assessment required.

Recommendation 3:

- In-vivo trials are required to further investigate the outcomes of delayed RVAD support with the HVAD system beyond a hemodynamic viewpoint.
- A controlled study should be conducted to investigate the difference between planned BiVAD and delayed BiVAD for third generation continuous flow pumps.

9.6 CHAPTER FIVE – EFFECTS OF VALVULAR REGURGITATION DURING BIVAD SUPPORT ASSESSED USING MOCK CIRCULATORY LOOP

Chapter five described the in-vitro outcomes of simulated severe aortic (AR), mitral (MR) and tricuspid (TR) regurgitation in the presence of continuous flow BiVAD support. Initial no VAD configuration was established before isolated LVAD and BiVAD configurations were assessed. Patients with valve defects are often recommended valve repair/replacement prior to VAD support. However, these additional surgical interventions may provide an unnecessary risk in an already vulnerable population. Dual BiVAD support provided improved flows for LVAD,

RVAD, flowmeter and reduced RA pressure for all conditions when compared to isolated LVAD control. In addition, BiVAD proved capable of compensating for severe regurgitation during MR and TR states but remained ineffective during AR. All AR conditions generated high LVAD flows and power output. These factors combined with low flow and dampened aortic pressure and MAP may provide useful non-invasive markers of severe AR during isolated or biventricular support.

Recommendation 4:

- Further in-vitro assessment could be undertaken to determine the outcomes of other valvular conditions such as mild and moderate regurgitation.
- In-vivo trials are required to investigate the outcomes of continuous flow BiVAD in the presence of various valvular abnormalities.
- Improved quantification of the degree of systemic and pulmonary vascular resistance to enhance the physiological representation of the mock loop

9.7 CHAPTER SIX – LONG TERM RIGHT ATRIAL AND RIGHT VENTRICULAR BIVAD OUTCOMES

Chapter six reports on the St. Vincent's experience with the HVAD as a biventricular assist device. A total of thirteen patients were reviewed (six with right ventricular support and seven with right atrial support). All patients received the same post-operative management. Clinical outcomes were similar and the implantation procedures for ventricular and atrial support were clearly described. There are a few case reports and single centre experiences that previously reported on the HVADs applicability as a right ventricular system. However, the utilisation of the HVAD as a right atrial device remains unexplored. Right atrial support was investigated following a series of thrombotic events in patients with right ventricular support.

A likely cause for the high rate of thrombosis include microtrauma from repetitive suction events abutting the septum, as well as the possibility of ingestion of small emboli from distant venous sites. Although spacers are used to reduce the length of the inflow cannula, obstruction is still possible following ventricular recovery and remodelling, which reduces the dimensions of the right ventricle and draws the inflow cannula closer to the interventricular septum. Right atrial support eliminates the possibility of interventricular obstruction. Furthermore, in the event of tricuspid regurgitation, surgical intervention such as valvular repair or replacement is often recommended in patients with right ventricular support, increasing the risk of morbidity and mortality. However, there may be no need for surgical intervention of the tricuspid valve during right atrial support. The use of right atrial implantation may be an acceptable alternative for patients with unsuitable right ventricular dimensions or severe tricuspid regurgitation. Our experience supports the use of dual HVAD pumps for biventricular support in critically ill patients not suitable for isolated left ventricular support.

Recommendation 5:

- A larger sample size is required to identify differences between right ventricular and right atrial implantation. A single-blinded randomized control trial would be most suitable to determine any clinical difference between the two interventions in terms of adverse events, hospitalization and mortality.
- Future cardiac devices should consider their designs more carefully and allow for multi-site implantation. This would enable them to support both the right ventricle and the right atrium depending on what's most suitable for the patients.

9.8 CHAPTER SEVEN – SHORT TERM BIVAD WITH VPA-ECLS

Chapter seven describes the cumulative St. Vincent’s experience with the HVAD system. A total of 112 patients were enrolled and three different configurations reviewed (75 patients with isolated LVAD, 23 patients with VPA-ECLS and concomitant LVAD, and 14 patients with initial continuous flow BiVAD). The VPA-ECLS was investigated as an alternative to initial long term BiVAD support primarily due to the higher survival and significantly lower complication rates of LVAD patients compared to BiVAD patients in both the literature as well as our previous experience. Post-operative management and anti-coagulation regimens were similar in all three groups. Type of support configuration was largely dependent on hemodynamic (RAP, RVSWI, RA/PAWP) and echocardiographic markers (degree of right ventricular impairment and dilatation). Outcomes were similar between VPA-ECLS and initial BiVAD cohorts. Although VPA-ECLS yielded the lowest survival rates of the three cohorts, they still produced higher outcomes compared to currently existing ECLS related studies. Better results may be achieved with accumulated experience and larger sample size. Finally, in patients who may otherwise require chronic biventricular support, planned VPA-ECLS provides acceptable perioperative RV support and may allow time for the RV to adapt to the increasing cardiac output and preload.

Recommendation 6:

- A large sample size is required to delineate differences between the VPA-ECLS and initial BiVAD group. A randomized trial would be most suitable to determine any clinical difference between the two interventions in terms of adverse events, hospitalization and mortality. The similar outcome in our experience provides equipoise in the design and conduct of such a trial.

- Both VPA-ECLS and initial BiVAD support patients with biventricular failure but differ in their period of support (short vs. long, respectively). To produce the most optimum outcomes for our patients, better distinction between the two is required. Further research is needed to determine the criteria needed to provide temporary RVAD instead of long term BiVAD.

9.9 CHAPTER EIGHT – GENE REGULATION PRE- AND POST BiVAD SUPPORT

Chapter eight described laboratory findings on the genetic variation pre- and post BiVAD support. This chapter provides a clear description of the various methods undertaken including, tissue collection, RNA extraction and library sequencing. Due to the high volume of research surrounding coding genes, long non-coding RNA was investigated. The methodological approach was systematic in its execution and was repeated multiple times for reproducibility and reliability. Although no variation was identified in long non-coding genes between the implant and explant samples, slight individual differences within each patient were observed. A larger sample size may provide a more conclusive result. While many coding genes were previously reported in the literature, our small sample size limits the findings produced. Nonetheless, we demonstrated methodological reproducibility and designed a systematic approach to collecting and analysing future RNA research.

Recommendations 7:

- A larger sample size is required to determine whether a difference exists between the genetic markers present pre- and post BiVAD support.
- Much research is published on the discovery of new coding and non-coding genetic markers. Due to these rapid discoveries, certain findings are later discovered to be

duplicates of other studies or even classified incorrectly to today's registry databases.

As such, an update of current classifications of coding and non-coding RNA would elucidate much of the confusion regarding what markers are long non-coding and which are coding.

- A gold standard protocol highlighting the various methodologies including tissue collection, extraction and analysis should be developed and followed by future studies to enable comparability.

9.10 SIGNIFICANCE OF RESEARCH

Despite expansion of ventricular assist technology with over 25,000 devices implanted globally to date, understanding of biventricular support with durable continuous flow devices remains limited. The in-vitro findings presented here demonstrate successful haemodynamic support provided by dual continuous flow dual LVADs in a field previously dominated by older generation pulsatile devices – despite the HVAD being test not being designed for right sided support. We have validated the MCL and contributed to international experience, attempting to answer some important clinical questions including delayed right ventricular support post LVAD implantation, considerations in the selection of right sided support implantation site (right atrial versus right ventricular) and the impact of continuous flow BiVAD in the presence of valvular abnormalities. This makes the MCL a valuable teaching tool and a proven means of conducting future in-vitro simulations. This model will allow the rapid and effective testing of new VAD models by comparing them to our current experimental database encompassing over 120 different simulations. More importantly, we have been able to learn much from the current model and have taken the necessary steps to overcoming the limitations. An anatomically correct heart is currently under development, containing both ventricles within

the same unit and allowing for interventricular septal interaction and observation. Improvements to waveform recording and analysis are also being undertaken.

This thesis has demonstrated successful long term biventricular support in both right ventricular and right atrial configurations. Right atrial support is now considered to be preferable in most patients requiring dual ventricular support. Decisions are often complicated by concomitant valvular abnormalities or other implantable mechanical devices. Right atrial HVAD placement also eliminates the need for concomitant surgical tricuspid valve intervention and thus may reduce costs. In our series, right atrial support resulted in lower thrombotic events than right ventricular support. Thrombosis is a frequent complication associated with pulsatile BiVAD systems and can be life threatening if not treated immediately. Increased experience and better post-operative anticoagulation regime may further reduce our thrombotic events. While our samples were too small to determine direct associations, our findings will encourage additional research into the benefits of right atrial support.

Chapter seven also demonstrated successful short term VPA-ECLS support for patients with borderline right ventricular dysfunction. The benefits of temporary RVAD includes better outcomes in patients with isolated LVAD compared to BiVAD support, and significantly lower costs associated with use of VPA-ECMO compared to VADs. These findings will provide valuable information to improve device/patient selection, recommendations, post-operative management and the distinction between irreversible right ventricular and borderline right ventricular failure. By publishing these novel clinical findings, we will be assisting other health professionals to make informed clinical decisions regarding their patient's condition and treatment.

Laboratory results showed no difference between implant and explant tissue in terms of long non-coding RNA. While the sample size was too small to make any conclusive statement, a reproducible methodology was demonstrated for tissue collection and extraction.

9.11 CONCLUSION

This thesis investigated the HeartWare HVAD within a clinical, in-vitro and laboratory setting. Clinical findings demonstrate acceptable outcomes with BiVAD support. In addition, they highlight the feasibility of a right atrial configuration for patients with contraindication to right ventricular support. The literature review described improved outcomes and enhanced quality of life via improved mobility and early hospital discharge. Short-term concomitant VPA-ECLS is possible with the HVAD as a long term LVAD for patients with borderline right ventricular failure. Survival was greater than many existing ECLS studies and registry databases. The in-vitro experimentations tackled many unanswered clinical questions. Various conditions were simulated including a healthy heart, a failing heart, left ventricular failure, biventricular failure, pulmonary hypertension and various forms of valvular regurgitation. The MCL was validated and demonstrated reversal of pathological delayed right ventricular failure post LVAD to normal hemodynamic conditions. Furthermore, continuous flow BiVAD proved capable of compensating for severe regurgitation during tricuspid and mitral regurgitation, eliminating the need for valvular repair/replacement. In addition, potential non-invasive markers for aortic regurgitation were identified for future investigation. Finally, laboratory findings demonstrated no difference between the long non-coding markers pre- and post BiVAD support. However, a valid and repeatable methodology for various aspects of the protocol including tissue collection, RNA extraction and analysis was developed in the process. Ventricular remodelling may be because of reduced strain on the

heart due to successfully ventricular support with the BiVADs. The data presented in this thesis has provided methodological rigor and pragmatic considerations for future clinical trials. The HeartWare HVAD proved to be a suitable device for biventricular support in patients with advanced heart failure.

APPENDICES

Appendix 1 RNA Ethics Approval Letter



St Vincent's Hospital

8 April 2011

Assoc Chris Hayward
Heart Failure and Transplant Unit
Xavier, Level 4
St Vincent's Hospital
Darlinghurst NSW 2010

Dear Chris

COPY

SVH File Number: 10/154

Project Title: Structural and functional adaptation of left and right ventricle following
implantation of continuous flow left ventricular assist device
(HREC Ref: HREC/10/SVH100)

Thank you for submitting an application for authorisation of this project. I am pleased to advise that the Executive Director on 1 April 2011 has granted authorisation for the above project to commence at St Vincent's Hospital.

Documents to be used at this site are

- Protocol LVAD Outcome Study Version 2.0 dated 6 January 2011
- Participant Information Sheet and Consent Form Version 2.0 dated 6 January 2011

The following conditions apply to this research project. These are additional to those conditions imposed by the Human Research Ethics Committee that granted ethical approval:

1. Please provide an amended Insurance Certificate with cover of \$20 Million on any one claim (as per NSW Health Policy Directive PD2011-006) within 3 months of study commencement.
2. Proposed amendments to the research protocol or conduct of the research which may affect the ethical acceptability of the project, and are submitted to the local HREC for review, are copied to the Research Governance Officer.
3. Proposed amendments to the research protocol or conduct of the research which may affect the ongoing site acceptability of the project are to be submitted to the Research Governance Officer.

Investigators holding an academic appointment (including conjoint appointments) at the University of New South Wales are required to provide a copy of the application form, all approved documents and a copy of the ethics approval letter to the UNSW HREC for ratification. These documents should be sent to UNSW, Ethics Secretariat, Research Services, Rupert Myers Building, 3rd floor, Kensington 2052.

Should you have any queries about your project please contact the Research Office. Tel: 6332-2075 or email research@stvincents.com.au. The HREC Terms of Reference, Standard Operating Procedures, National Statement on Ethical Conduct in Human Research (2007) and the CPMP/CI Note for Guidance on Good Clinical Practice and standard forms are available on the Research Office website: www.stvincents.com.au/researchoffice or internal at <http://www.stvincents.com.au/researchoffice>

Yours sincerely

Julie Charlton
Research Governance Officer
Research Office
D2011-14507

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Continuing the Mission of the
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UTS HREC Approval

Dear Applicant

[External Ratification: St Vincent's Hospital. Ethics approval HREC/10/SVH/100, 01/02/2011 to 01/02/2016]

The UTS Human Research Ethics Expedited Review Committee reviewed your application titled, "Structural and functional adaptation of left and right ventricle following implantation of continuous flow left ventricular assist device", and agreed that the application meets the requirements of the NHMRC National Statement on Ethical Conduct in Human Research (2007). I am pleased to inform you that your external ethics approval has been ratified.

Your approval number is UTS HREC REF NO. 2014000267

Please note that the ethical conduct of research is an on-going process. The National Statement on Ethical Conduct in Research Involving Humans requires us to obtain a report about the progress of the research, and in particular about any changes to the research which may have ethical implications. This report form must be completed at least annually, and at the end of the project (if it takes more than a year). The Ethics Secretariat will contact you when it is time to complete your first report.

I also refer you to the AVOC guidelines relating to the storage of data, which require that data be kept for a minimum of 5 years after publication of research. However, in NSW, longer retention requirements are required for research on human subjects with potential long-term effects, research with long-term environmental effects, or research considered of national or international significance, importance, or controversy. If the data from this research project falls into one of these categories, contact University Records for advice on long-term retention.

You should consider this your official letter of approval. If you require a hardcopy please contact Research.Ethics@uts.edu.au.

To access this application, please follow the URLs below:

* if accessing within the UTS network: <http://rmprod.itd.uts.edu.au/RMNet/HOM001N.aspx>

* if accessing outside of UTS network: <https://remote.uts.edu.au>, and click on "RMENet - ResearchMaster Enterprise" after logging in.

We value your feedback on the online ethics process. If you would like to provide feedback please go to:

<http://surveys.uts.edu.au/surveys/onlineethics/index.cfm>

If you have any queries about your ethics approval, or require any amendments to your research in the future, please do not hesitate to contact Research.Ethics@uts.edu.au.

Yours sincerely,

Professor Marion Haas

Chairperson

UTS Human Research Ethics Committee

C/- Research & Innovation Office

University of Technology, Sydney

T: (02) 9514 9645

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P: PO Box 123, BROADWAY NSW 2007

[Level 14, Building 1, Broadway Campus]

CB01.14.08.04

E:13

Quick-Start Protocol

Sajad's Copy.

miRNeasy Mini Kit

The miRNeasy Mini Kit (cat. no. 217004) can be stored dry at room temperature (15–25°C) for at least 9 months. QIAzol Lysis Reagent can be stored at room temperature or at 2–8°C.

For more information, including preparation of miRNA-enriched fractions, optional DNase treatment, and general handling advice, please refer to the miRNeasy Mini Handbook, which can be found at www.qiagen.com/handbooks.

For technical assistance, please call toll free 60800 22 44 6000, or find regional phone numbers at www.qiagen.com/contact.

Notes before starting

- This protocol is for purifying total RNA, including small RNAs, from animal cells and tissue.
- If necessary, re-dissolve any precipitate in RNeasy RWT by warming.
- Except for phase separation (step 5), all steps should be performed at room temperature (15–25°C). Work quickly.
- Add ethanol (96–100%) to Buffer RWT and Buffer RPE concentrates before use (see bottle label for volume).
- Before starting with step 1 for the first time, select disruption and homogenization methods according to recommendations in the miRNeasy Mini Kit Handbook.

1. Add 700 µl QIAzol Lysis Reagent to the sample and disrupt and homogenize using an appropriate method. $\frac{1000}{700} = 1.43$
2. incubate the homogenate at room temperature (15–25°C) for 5 min.
3. Add 400 µl chloroform ^{200 µl} and cap tube securely. Shake vigorously for 15 s. $140 \times 1.43 = 200.2 \mu\text{l}$
4. incubate at room temperature for 2–3 min.
5. Centrifuge for 15 min at 12,000 × g at 4°C.

For Material Safety Data Sheets, see www.qiagen.com/safety.

January 2011



miRNeasy Mini Handbook

second then mix thoroughly before eluting
 ↑
 tip

6. Transfer the upper aqueous phase to a new collection tube. Avoid transferring any interphase. Add 1.5 volumes (usually 525 μ l) of 100% ethanol, and mix thoroughly by pipetting. *is can do first*
7. Pipette 100 μ l sample, including any precipitate, into an RNeasy Mini column in a 2 ml collection tube. Close the lid and centrifuge at $\geq 8000 \times g$ for 15 s at room temperature. Discard the flow-through. *is*
8. Repeat step 7 using the remainder of the sample.
9. **Optional.** Perform DNase digest according to instructions in Appendix B of the Handbook (not required for detecting mature miRNA using the miScript PCR system).
10. Add 200 μ l Buffer RWT to the RNeasy Mini column. Close the lid, and centrifuge for 15 s at $\geq 8000 \times g$. Discard the flow-through.
 This step is optional if working with cultured cells.
11. Pipette 500 μ l Buffer RPE on to the RNeasy Mini column. Close the lid, and centrifuge for 15 s at $\geq 8000 \times g$. Discard the flow-through.
12. Add 500 μ l Buffer RPE to the RNeasy Mini column. Close the lid, and centrifuge for 2 min at $\geq 8000 \times g$.
13. **Optional:** Place the RNeasy Mini column into a new 2 ml collection tube. Centrifuge at full speed for 1 min to further dry the membrane.
14. Transfer the RNeasy Mini column to a new 1.5 ml collection tube. Pipette 30–50 μ l RNase-free water directly onto the RNeasy Mini column membrane. Close the lid, and centrifuge for 1 min at $\geq 8000 \times g$ to elute.
15. If expected RNA yield is $>30 \mu$ g, repeat step 14 using an additional 30–50 μ l RNase-free water or using the eluate from step 14 (if high RNA concentration is required). Reuse the collection tube from step 14.

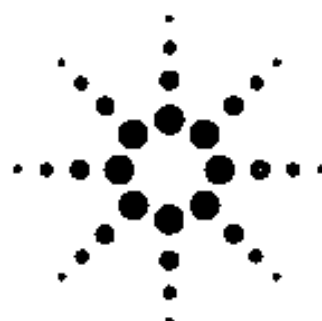
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Appendix 3 Agilent RNA 6000 Nano Kit Guide



Agilent RNA 6000 Nano Kit

Agilent RNA 6000 Nano Kit Quick Start Guide

Agilent RNA 6000 Nano Kit (reorder number 5067-1511)

RNA Chips

- 25 RNA Nano Chips
- 2 Electrode Cleaners

- Syringe Kit
- 1 Syringe

Reagents (reorder number 5067-1512) & Supplies

- (yellow) Agilent RNA 6000 Ladder (reorder number 5067-1526)
- (blue) RNA Nano Dye Concentrate
- (green) Agilent RNA 6000 Nano Marker (2 vials)
- (red) Agilent RNA 6000 Nano Gel Matrix (2 vials)
- 4 Spin Filters

Tubes for Gel-Dye Mix

30 Safe-Lock Eppendorf Tubes PCR o amp (C/Nase/4 Nase free) for gel-dye mix.

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Assay Principles

Agilent RNA kits contain chips and reagents designed for analysis of RNA fragments. Each RNA chip contains an interconnected set of microchannels that is used for separation of nucleic acid fragments based on their size as they are driven through it electrophoretically. Agilent RNA kits are designed for use with the Agilent 2100 bioanalyzer only.

Assay Kits

Agilent RNA kits are designed for the analysis of total RNA (eukaryotic and prokaryotic) and mRNA samples. The complete RNA 6000 Nano kit guide can be found in the online help of the 2100 expert software. Other RNA kits: Agilent RNA 6000 Pico Kit (reorder no 5067-1518), Agilent Small RNA Kit (reorder no 5067-1548).

Storage Conditions

- Freeze the unused RNA 6000 Nano Ladder at -20°C and keep all other reagents and reagent mixes refrigerated at 4 °C when not in use to avoid color variation caused by reagent decomposition.
- Protect dye and dye mixtures from light. Remove light covers only when operating. Dye decomposes when exposed to light.

Equipment Supplied with the Agilent 2100 Bioanalyzer

- Chip priming station (reorder number 5036-1451)
- RNA vortex mixer



Agilent Technologies

Agilent RNA 0000 Nano Kit Quick Start Guide

Additional Material Required (Not Supplied)

- RNaseZAP[®] recommended for chloride decontamination (Ambion, Inc. cat. no. 9790)
- RNase-free water
- Pipettes (10 μ l and 1000 μ l) with compatible tips (RNase-free)
- 0.5 ml and 1.5 ml microcentrifuge tubes (RNase-free)
- Microcentrifuge (> 1300 g)
- Heating block or water bath for lysis/sample preparation

Sample Preparation

- For total RNA or mRNA analysis, the sample concentration must be in the specified range. If concentration of your particular sample is above this range, dilute with RNase-free water.

Physical Specifications		Analytical Specifications		
Type	Specification	Specification	Total RNA Assay	mRNA Assay
Analysis run time	30 minutes	Quantitative range	25–500 ng/ μ l	25–250 ng/ μ l
Number of samples	12 samples/chip	Concentration range	0–500 ng/ μ l	25–250 ng/ μ l
Sample volume	1 μ l	Quantitation accuracy	20 % CV (for ladder as sample)	20 % CV (for ladder as sample)
Repeatability	7 months (Storage temperature sensitive indicators used)	Buffer compatibility [†]	10 mM Tris or 125 mM NaCl or 15 mM MgCl ₂	100 mM Tris or 125 mM NaCl or 15 mM MgCl ₂
		Reproducibility of quantitation	10 % CV	10 % CV

[†] Due to the high sensitivity of the assay, different ions and higher salt concentrations might influence the performance of the assay.

Setting up the Chip Priming Station

1. Replace the syringe:
 - a. Unscrew the old syringe from the tip of the chip priming station.
 - b. Release the old syringe from the clip. Discard the old syringe.
 - c. Remove the plastic cap of the new syringe and insert it into the clip.
 - d. Slide it into the hole of the luer lock adapter and screw it tightly to the chip priming station.
2. Adjust the base plate:
 - a. Open the chip priming station by pulling the latch.
 - b. Using a screwdriver, open the screws at the underside of the base plate.
 - c. Lift the base plate and insert it again in position C. Retighten the screws.



Agilent RNA 6000 Nano Kit Quick Start Guide

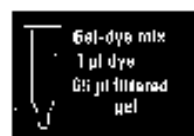
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Preparing the Gel

1. Pipette 550 µl of RNA 6000 Nano gel matrix (red ●) into a spin filter.
2. Centrifuge at 14000 g $\pm$ 20 % for 10 minutes at room temperature.
3. Aliquot 65 µl filtered gel into 0.5 ml RNase-free microfuge tubes. Use filtered gel within 4 weeks.

Preparing the Gel-Dye Mixture

1. Allow the PhA 6000 Nano dye concentrate (blue ●) to equilibrate to room temperature for 30 min.
2. Vortex RNA 6000 Nano dye concentrate (blue ●) for 10 seconds, spin down and add 1 µl of dye into a 65 µl aliquot of filtered gel.
3. Vortex solution well, spin tube at 13300 g for 10 min at room temperature. Use prepared gel-dye mix within one day.



Loading the Gel-Dye Mixture

1. Put a new RNA 6000 Nano chip on the chip priming station.
2. Pipette 9.0 µl gel-dye mix in the well marked @.
3. Make sure the plunger is positioned at 1 ml and then close the chip priming station.
4. Press plunger until it is held by the clip.
5. Wait for exactly 30 seconds then release clip.
6. Wait for 6 s. Slowly pull back plunger to 1 ml position.
7. Open chip priming station and pipette 9.0 µl of gel-dye mix in the wells marked @.
8. Discard the remaining gel-dye mix.



Loading the Agilent RNA 6000 Nano Marker

1. Pipette 5 µl of 44x RNA 6000 Nano marker (green ●) in all 12 sample wells and in the well marked @.



Loading the Ladder and Samples

1. Pipette 1 µl of prepared ladder in well marked @.
2. Pipette 1 µl of sample in each of the 12 sample wells. Pipette 1 µl of RNA 6000 Nano Marker (green ●) in each unused sample well.
3. Put the chip horizontally in the adapter of the IXA vortexer and vortex for 1 min at 2400 rpm.
4. Run the chip in the Agilent 2100 bioanalyzer within 5 min.



Technical Support In the U.S./Canada: 1-800-227-3770 (toll free); lscs-ibs-support@agilent.com. In Europe: call your local Customer Care Center; bio_solutions@agilent.com. In Japan: 0120-477-111; yscn_ccc@agilent.com. In Asia Pacific: call your local Customer Care Center; Bioanalyzers_ja@agilent.com.

Further Information Visit Agilent Technologies' unique Lab-on-a-Chip website. It is offering useful information, support and current developments about the product line and the technology: <http://www.agilent.com/chem/labonachip>.



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3 Adjust the syringe clip:

- a Release the lower of the clip and slide it up to the top position.



Essential Measurement Practices

- Handle and store all reagents according to the instructions on the label of the individual box.
- Avoid sources of dust or other contamination. Foreign material in reagents and samples or in the wells of the chip will interfere with assay results.
- Allow all reagents to equilibrate to room temperature for 30 minutes before use. Keep samples on ice.
- Protect dye and dye mixtures from light. Remove light covers only when pipetting. The dye decomposes when exposed to light and this reduces the signal intensity.
- Always insert the pipette tip to the bottom of the well when dispensing the liquid. Placing the pipette at the edge of the well may lead to poor results.
- Always wear gloves when handling RNA and use RNase-free tips, microfuge tubes and water.
- It is recommended to heat denature all RNA samples and RNA ladder before use ("Preparing the RNA ladder after arrival" on page 3 of the kit guide).
- Do not touch the Agilent 2100 bioanalyzer during analysis and never place it on vibrating surface.
- Always vortex the dye concentrate for 10 seconds before preparing the gel-dye mix.
- Use a new syringe and electrode cleaners with each new kit.
- Use loaded chips within 5 minutes after preparation. Reagents might evaporate, leading to poor results.
- To prevent contamination (e.g. RNase), it is strongly recommended to use a dedicated electrode cartridge for RNA assays. For running the RNA 6000 Pico Assay, the 16 pin bayonet cartridge is mandatory.
- Perform the RNase decontamination procedure for the electrodes daily before running any assays.



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WARNING



Handling DMSO

Kit components contain DMSO. Because the dye binds to nucleic acids, it should be treated as a potential mutagen and used with appropriate care.

Wear hand and eye protection and follow good laboratory practices when preparing and handling reagents and samples. Handle the DMSO stock solutions with particular caution as DMSO is known to facilitate the entry of organic molecules into tissues.

Preparing the RNA ladder after Arrival

1 After reagent kit arrival pipette the Ladder in RNase-free vial. 2 Heat denature it for 2 min at 70 °C. 3 Immediately cool down the vial on ice.	4 Prepare aliquots in RNase-free vials with the required amount for a typical daily use. 5 Store aliquots at -20 °C. After initial heat denaturing, the frozen aliquots needn't be heat denatured again. 6 Before use thaw ladder aliquots on ice (avoid extensive warming).

Appendix 4 Library Sequencing Protocol



Methods

Procedure guidelines

- Thaw components that contain enzymes—such as 5X Ion AmpliSeq™ HiFi Master Mix, FuPa Reagent, DNA Ligase, and Platinum® PCR SuperMix HiFi—on ice, and keep on ice during the procedure. All other components, including primer pools, may be thawed at room temperature. Gently vortex and spin down before use.
- If there is visible precipitate in the Switch Solution after thawing, pipet up and down at room temperature to resuspend.
- Minimize freeze-thawing of Ion AmpliSeq™ Primer Pools by aliquoting the pools as needed for your experiments.
- Use good laboratory practices to minimize cross-contamination of products. If possible, perform PCR setup in an area or room that is separate from template preparation. Always change pipette tips between samples.
- Use a calibrated thermal cycler specified in “Required materials and equipment” on page 9.
- Pipet viscous solutions slowly and ensure complete mixing.
- Always seal the reaction tubes or plate before loading into the thermal cycler, for consistency in replicate libraries.
 - For PCR strip tubes, cap the tubes completely to prevent evaporation.
 - For 96-well PCR plates, seal the plate with MicroAmp® adhesive film and place a MicroAmp® Optical Film Compression Pad on the plate.

Input RNA requirements

Each reverse transcription reaction requires 10 ng RNA, prepared from unfixed or FFPE tissue. Libraries have been successfully generated from as little as 500 pg of RNA from unfixed samples, and from 5 ng of fixed/FFPE samples.

In general, the library yield from high-quality RNA is higher than from degraded samples. However, libraries from degraded RNA samples will still give good sequencing results. Yield is not indicative of sequencing performance. See “Required materials and equipment” on page 9 for kits recommended for isolating high-quality RNA.

Note: RNA prepared from FFPE tissue must be heated before reverse transcription, as described in step 1 of the procedure.

Before using the kit for the first time

Complete the Wash Solution: add the indicated amount of 100% ethanol to each bottle of Wash Solution Concentrate and mix well. Mark the label on the bottle to indicate that you added ethanol. Store the completed Wash Solution at room temperature.



Kit size (Cat. no.)	Volume Wash Solution Concentrate per bottle	Volume 100% ethanol
8 rxn (Cat. no. 4482335)	2 mL	8 mL
96 rxn (Cat. no. 4482340)	6 mL	24 mL
384 rxn (Cat. no. 4482752)		

Reverse transcribe the RNA

1. If the input RNA was prepared from FFPE tissue, pre-heat the RNA at 80°C for 10 minutes, then cool on ice or leave the tube at room temperature, before assembling the reverse transcription mix in the next step.
2. Combine the following components in a tube on ice. For multiple reactions, prepare a master mix without RNA.

Component	Volume per rxn.
5X VILO™ RT Reaction Mix	2 µL
10X SuperScript® III Enzyme Mix	1 µL
Total RNA, 10 ng	≤6 µL
Nuclease-free Water	to 10 µL

3. Gently mix the tube contents, and centrifuge the tube briefly to collect the contents at the bottom.
4. Load the tube in the thermal cycler, and run the following program to synthesize cDNA.

Temperature	Time
42°C	30 min
85°C	5 min
4°C	∞ [1]

[1] Remove samples when ready to proceed to the next step.

Amplify targets

IMPORTANT! Primers and 5X Ion AmpliSeq™ HiFi Master Mix may be viscous. Pipet slowly and mix thoroughly. We recommend PCR setup on ice or a cold block.

1. Combine the following components on ice, in a PCR strip tube or plate.

Component	Volume per 10- μ L rxn.
5X Ion AmpliSeq™ HiFi Master Mix (red cap)	4 μ L
5X Ion RNA Panel	4 μ L
Nuclease-free Water	to 10 μ L

- Pipet the mixture up and down 5 times, or gently vortex, to mix gently but thoroughly.
- Add the entire contents of the reverse transcription reaction (the total volume is now 20 μ L), and gently mix again as in the previous step.
- Seal the tubes or plate, load the samples in the thermal cycler, and run the following program to amplify target cDNA regions.

Stage	Step	Temperature	Time
Hold	Activate the enzyme	99°C	2 min
Cycle; set number according to the following table	Denature	99°C	15 sec
	Anneal and extend	60°C	4 min
Hold	—	10°C	∞ ⁽¹⁾

⁽¹⁾ Remove samples when ready to proceed to the next step.

Number of amplification cycles		
Primer pairs per pool (see following table for Ready-to-use Panels)	Unfixed RNA	FFPE (fixed) RNA
12–24	21	24
25–48	20	23
49–96	19	22
97–192	18	21
193–384	17	20
385–768	16	19
769–1200	15	18

Ready-to-use Panels	Primer pairs per pool
Ion AmpliSeq™ RNA Apoptosis Panel	267
Ion AmpliSeq™ RNA Cancer Panel	50

STOPPING POINT (Optional) Store amplification products at 10°C overnight. For longer periods, store at –20°C.



Partially digest primer sequences

1. Carefully remove the cap or plate seal, and add 2 μ L of FuPa Reagent (brown cap) to each amplified sample. The total volume is 22 μ L.
2. Pipet the mixture up and down 5 times, or gently vortex, to mix gently but thoroughly.
3. Seal the tubes or plate, load the samples in the thermal cycler, and run the following program to partially digest the primer sequences.

Temperature	Time
50°C	10 min
55°C	10 min
60°C	20 min
10°C	Hold (for up to 1 hour)

Ligate adapters to the amplicons and purify

Barcoded libraries only: Combine and dilute adapters

If you are running multiple sample libraries on a single chip, you can assign a unique barcode to each library. For each barcode X chosen, prepare a mix of Ion P1 Adapter and Ion Xpress™ Barcode X at a final dilution of 1:4 for each adapter. Substitute 2 μ L of this barcode adapter mix for the Ion AmpliSeq™ Adapters in the ligation reaction. Store diluted adapters at –20°C.

For example, combine the volumes indicated in the following table. Scale volumes as necessary.

IMPORTANT! When handling barcoded adapters, be careful to avoid cross-contamination by changing gloves frequently and opening one tube at a time.

Example barcode adapter mix for up to 4 reactions (8 μ L total)	
Component	Volume
Ion P1 Adapter (violet cap)	2 μ L
Ion AmpliSeq™ Barcode X ⁽¹⁾ (white cap)	2 μ L
Nuclease-free Water	4 μ L

⁽¹⁾ X = barcode chosen

Set up and run the ligation reaction

1. If there is visible precipitate in the Switch Solution, pipet up and down at room temperature to resuspend.
2. Uncap the tubes or remove the plate seal, and add the following components to each tube or well containing digested sample. Switch Solution and Adapters can be combined before addition.



Methods

Ligate adapters to the amplicons and purify

Component	Volume
(Digested sample)	(22 µL)
Switch Solution (yellow cap)	4 µL
Ion AmpliSeq™ Adapters (for non-barcoded libraries; green cap) or Diluted barcode adapter mix (for barcoded libraries)	2 µL
Total volume	28 µL

3. Add 2 µL of DNA Ligase (blue cap) to each well (30 µL total volume).
4. Pipet up and down 5 times, or gently vortex, to mix gently but thoroughly.
5. Seal the tubes or plate, load the samples in the thermal cycler, and run the following program.

Temperature	Time	
	Unfixed samples	Fixed (FFPE) samples
22°C	30 min	60 min
72°C	10 min	10 min
10°C	≤24 hours ^[1]	≤24 hours ^[1]

^[1] Remove samples when ready to proceed to the next step.

STOPPING POINT (Optional) Samples may be stored at –20°C.

Purify the unamplified library (two-round purification)

Perform a two-round purification process with Dynabeads® Magnetic Beads to remove high molecular-weight DNA and primers from the library.

- **First round:** High molecular-weight DNA is bound to beads, while the amplicons and primers remain in solution. **Save the supernatant.**
- **Second round:** Amplicons are bound to beads, and primers remain in solution. **Save the bead pellet, and elute the amplicons from the beads.**

Important procedure guidelines and reagent preparation

- Ensure that the Wash Solution has been completed.
- If a white precipitate is present in the Binding Solution Concentrate, warm the solution at 37°C, then shake the solution to dissolve any precipitate before use.
- Incubate the Dynabeads® Magnetic Beads at room temperature for ≥10 minutes. Vortex to mix thoroughly immediately before pipetting. Do not substitute components from the Magnetic Bead Purification Module (Cat. no. 4475486) in this procedure.
- Pre-heat the elution solution—Nuclease-free Water or Low TE—at 37°C for ≥5 minutes.
- To reduce the chance of cross-contamination, we strongly recommend sealing unused wells on the 96-well Processing Plate with MicroAmp® Clear Adhesive Film. Alternatively, skip a row between sample rows on the 96-well plate.



- If the guidelines for reducing cross-contamination are followed, the same 96-well Processing Plate may be used for both bead purification procedures.
- Accurate pipetting of bead cleanup reagents is critical to successful size selection. Pre-wet pipette tips with 100% ethanol as described.
For optimal size selection, perform the bead cleanup steps exactly.

First-round purification

1. Vortex the Dynabeads® Magnetic Beads, and add 5 μ L of beads to each designated well in the 96-well Processing Plate.
2. Add 72 μ L of Binding Solution Concentrate to each bead-containing well, and pipet up and down 10 times to mix the beads and buffer.
3. Add 30 μ L of Nuclease-free Water to each 30- μ L ligation reaction (unamplified library), and mix gently.
4. Add the 60- μ L ligation reaction/unamplified library to the beads and Binding Solution mixture from step 2, and mix by pipetting up and down 5 times.
5. Pre-wet a pipette tip by pipetting 32 μ L of 100% ethanol up and down 3 times.
6. Without changing tips, add 32 μ L of 100% ethanol to each sample well and mix by pipetting up and down 10 times.
7. Incubate the samples for 5 minutes at room temperature (off the magnetic stand).
8. Place the plate on a magnetic stand for 1–2 minutes until the solution is clear, to capture the beads.
9. Keeping the plate on the magnetic stand, carefully remove the supernatant and transfer to a fresh well in the plate.

IMPORTANT! Keep the supernatant! It contains the desired library.

Second-round purification: Bind the library to the beads

1. Vortex the Dynabeads® Magnetic Beads thoroughly, and add 5 μ L of beads to the supernatant ($\approx$ 162 μ L) from the first-round purification.
2. Add 25 μ L of Binding Solution Concentrate to each bead-containing well, and pipet up and down 5 times to mix.
3. Pre-wet a pipette tip by pipetting 32 μ L of 100% ethanol up and down 3 times.
4. Without changing tips, add 32 μ L of 100% ethanol to each well, and pipet up and down 10 times to mix.
5. Incubate the samples for 5 minutes at room temperature (off the magnetic stand).
6. Place the plate on a magnetic stand for 5 minutes until the solution is clear, to capture the beads.



7. Keeping the plate on the magnetic stand, carefully remove and discard the supernatant.

IMPORTANT! Keep the beads! The library is bound to the beads.

Second-round purification: Wash the beads and elute the library

1. While the plate is on the magnetic stand, add 150 μ L of completed Wash Solution to each sample well, and incubate the samples for 30 seconds.
2. Keeping the plate on the magnetic stand, carefully aspirate and discard the supernatant without disturbing the beads.
3. Air dry the beads at room temperature for 3 minutes to remove all traces of ethanol.
4. Remove the plate from the magnetic stand, add 10 μ L of pre-heated (37°C) Nuclease-free Water to each well, and pipet up and down 10 times to mix.
5. Off the magnetic stand, incubate for 1 minute at room temperature.
6. Place the plate on the magnetic stand for 1 minute to capture the beads.
7. Keeping the plate on the magnetic stand, carefully remove the supernatant, which contains the purified library, and transfer to a fresh well or tube, without disturbing the beads.

IMPORTANT! Keep the supernatant! It contains the desired library.

Amplify the library and purify

Amplify the library

1. On ice, combine the following in a 0.2-mL PCR strip tube or 96-well reaction plate (the SuperMix and Primer Mix may be combined before addition):

Component	Volume per rxn.
Platinum® PCR SuperMix HiFi (black cap)	50 μ L
Library Amplification Primer Mix (white cap)	2 μ L
Purified, unamplified library	10 μ L

2. Seal the tubes or plate, load the samples in the thermal cycler, and run the following program.



Stage	Step	Temperature	Time
Hold	Activate the enzyme	98°C	2 min
5 cycles	Denature	98°C	15 sec
	Anneal and extend	60°C	1 min
Hold	—	10°C	≤24 hours ^[1]

^[1] Remove samples when ready to proceed to the next step.

STOPPING POINT (Optional) Store the amplified library at –20°C.

Purify the amplified library

A single-round purification with Dynabeads® Magnetic Beads removes high molecular-weight DNA and primers from the amplified library.

Important procedure guidelines and reagent preparation

- Ensure that the Wash Solution has been completed.
- If a white precipitate is present in the Binding Solution Concentrate, warm the solution at 37°C, then shake the solution to dissolve any precipitate before use.
- Incubate the Dynabeads® Magnetic Beads at room temperature for ≥10 minutes. Vortex to mix thoroughly immediately before pipetting. Do not substitute components from the Magnetic Bead Purification Module (Cat. no. 4475486) in this procedure.
- Pre-heat the elution solution—Nuclease-free Water or Low TE—at 37°C for ≥5 minutes.
- To reduce the chance of cross-contamination, we strongly recommend sealing unused wells on the 96-well Processing Plate with MicroAmp® Clear Adhesive Film. Alternatively, skip a row between sample rows on the 96-well plate.
- If the guidelines for reducing cross-contamination are followed, the same 96-well Processing Plate may be used for both bead purification procedures.
- Accurate pipetting of bead cleanup reagents is critical to successful size selection. Pre-wet pipette tips with 100% ethanol as described. For optimal size selection, perform the bead cleanup steps exactly.

Bind the library to the beads

1. Vortex the Dynabeads® Magnetic Beads thoroughly, and add 10 µL of Dynabeads® Magnetic Beads to each designated well in the 96-well Processing Plate.
2. Add 72 µL of Binding Solution Concentrate to each bead-containing well, and pipet up and down 10 times to mix thoroughly.
3. Add 62 µL of the amplification reaction/amplified library to the beads and Binding Solution mixture from step 2, and mix by pipetting up and down 5 times. (Total volume 144 µL.)
4. Pre-wet a pipette tip by pipetting 45 µL of 100% ethanol up and down 3 times.



Methods

Quantify the library and dilute for template preparation

5. Without changing tips, add 45 μ L of 100% ethanol to each sample well and mix by pipetting up and down 10 times.
6. Incubate the samples for 5 minutes at room temperature (off the magnetic stand).
7. Place the plate on a magnetic stand for 1–2 minutes until the solution is clear, to capture the beads.
8. Keeping the plate on the magnetic stand, carefully remove and discard the supernatant.

IMPORTANT! Keep the beads! The library is bound to the beads.

Wash the beads and elute the library

1. While the plate is on the magnetic stand, add 150 μ L of completed Wash Solution to each sample well, and incubate the samples for 30 seconds.
2. Keeping the plate on the magnetic stand, carefully aspirate and discard the supernatant without disturbing the beads.
3. Air dry the beads at room temperature for 3 minutes to remove all traces of ethanol.
4. Remove the plate from the magnetic stand, add 15 μ L of pre-heated (37°C) Low TE to each well, and pipet up and down 10 times to mix.
5. Off the magnetic stand, incubate for 1 minute at room temperature.
6. Place the plate on the magnetic stand for 1 minute to capture the beads. Place the plate on the magnetic stand for 1 minute.
7. Keeping the plate on the magnetic stand, carefully remove the supernatant, containing the purified library, and transfer to a fresh well or tube, without disturbing the beads.

IMPORTANT! Keep the supernatant! It contains the desired library.

Quantify the library and dilute for template preparation

Quantify the amplified library by one of the following methods, then dilute the library for downstream template preparation (clonal amplification on ISPs).

The concentration of amplified libraries is typically up to 15 nM for unfixed RNA input, and is typically less than 1 nM for FFPE RNA input.

- Use the Ion Library Quantitation Kit to quantify the library by qPCR.
- Use the Agilent® Bioanalyzer® instrument with the Agilent® High Sensitivity DNA Kit.
- Use the Qubit® 2.0 Fluorometer with the Qubit® dsDNA HS Assay Kit.



In practice, the chip-to-chip variation in library quantification by the Bioanalyzer® instrument is higher than the variation seen by qPCR. The qPCR method may be more accurate for low-input or FFPE-source libraries.

Quantify the library by qPCR and dilute

Determine the concentration of each Ion AmpliSeq™ library by qPCR with the Ion Library Quantitation Kit using the following procedure. Each sample, standard, and negative control should be analyzed in duplicate 20-μL reactions.

1. Prepare five 10-fold serial dilutions of the *E. coli* DH10B Ion Control Library (~68 pM; included in the Ion Library Quantitation Kit) at 6.8 pM, 0.68 pM, 0.068 pM, 0.0068 pM, and 0.00068 pM (standards 1–5). Mark these as standards and use these concentrations in the qPCR instrument.
2. Prepare serial dilutions of the sample library as follows:
 - a. Prepare an initial 1:10 dilution of the sample library in Nuclease-free Water, in a non-stick microcentrifuge tube, on ice.
 - b. Prepare serial dilutions at 1:1000 and 1:5000 for use in the qPCR:

Dilution	Library	Nuclease-free Water ^[1]
1:1000	1 μL of 1:10	99 μL
1:5000	10 μL of 1:1000	40 μL

^[1] Not DEPC-treated

Higher dilutions of libraries prepared from unfixed RNA may be necessary to achieve a dilution that falls between standards 3 and 4 of the DH10B standard curve. Conversely, lower dilutions may be necessary for libraries prepared from FFPE or low-input samples.

3. Prepare a reaction mix and dispense 11 μL to the wells of a PCR plate. Set up two wells for each library sample, DHB10 library standard, and negative control.

Component	Volume per sample (duplicate reactions)
2X TaqMan® MasterMix	20 μL
20X Ion TaqMan® Assay	2 μL

4. Add 9 μL of each library dilution or 9 μL of each control dilution to each well (two wells per sample as noted before), for a total reaction volume of 20 μL.
5. Program the real-time instrument as follows:
 - Enter the concentrations of the control library standards.
 - Use ROX™ Reference Dye as the passive reference dye.
 - Select a reaction volume of 20 μL.
 - Select FAM™ dye/MGB as the TaqMan® probe reporter/quencher
 - The Ion Library TaqMan® qPCR Mix can be used on a variety of instruments, as listed below. The fast cycling program was developed using the StepOnePlus™ System in Fast mode.



Methods

Quantify the library and dilute for template preparation

Real-time PCR system	Stage	Temp	Time
7900 HT System	Hold	50°C	2 min
7900 HT Fast System (Fast 96-Well, Standard 96-Well, or 384-Well Block Modules)	Hold	95°C	20 sec
ViiA™ 7 System	Cycle (40 cycles)	95°C	1 sec
StepOne™ System		60°C	20 sec
StepOnePlus™ System			
7500 Fast System	Hold	50°C	2 min
7500 System	Hold	95°C	20 sec
7300 System	Cycle (40 cycles)	95°C	3 sec
		60°C	30 sec

- Calculate the average concentration of the undiluted library by multiplying the concentration determined with qPCR by the library dilution used in the assay. Use the library dilution that falls between standards 3 and 4 of the DH10B standard curve.
- Based on the calculated concentration of the undiluted library, determine the dilution factor (Template Dilution Factor) that results in a library concentration of 100 pM.
For example:
 - The undiluted library concentration is 300 pM.
 - The library dilution factor is $300 \text{ pM} / 100 \text{ pM} = 3$.
 - Therefore, 1 µL of library mixed with 2 µL of Low TE (1:3 dilution) yields approximately 100 pM.
- Prior to combining libraries or proceeding to template preparation, dilute an aliquot of each library to a concentration of approximately 100 pM.
Store diluted libraries at 4–8°C and use within 48 hours. Store undiluted libraries at 4–8°C for 48 hours; store at –20°C for long-term storage.

Quantify the library with the Agilent® Bioanalyzer® instrument and dilute

Analyze 1 µL of amplified library on the Agilent® Bioanalyzer® instrument with the Agilent® High Sensitivity DNA Kit. Amplicon libraries should have multiple peaks in the 125–300 bp size range. If the library concentration is over 20,000 pM, dilute the library 1:10 and repeat the quantification to obtain a more accurate measurement. Alternatively, use the Agilent® DNA 1000 Kit.

- Determine the molar concentration of the amplified library using the Bioanalyzer® software. Ensure that the upper and lower marker peaks are identified and assigned correctly. Follow the manufacturer's instructions to perform a region analysis (smear analysis). Briefly:
 - Select the **Data** icon in the Contexts panel, and view the electropherogram of the sample to be quantified.
 - Select the **Region Table** tab below, and create a region spanning the desired amplicon peaks. Correct the baseline if needed.
 - The molarity is automatically calculated and displayed in the table in pM (pmol/L).
- Determine the library dilution that gives a concentration of 100 pM.



For example:

- The library concentration is 3000 pM.
 - The library dilution is $3000 \text{ pM} / 100 \text{ pM} = 30$.
 - Therefore, 1 μL of library mixed with 29 μL of Low TE (1:30 dilution) yields approximately 100 pM.
3. Prior to combining libraries or template preparation as described in the following sections, dilute an aliquot of each library to a concentration of approximately 100 pM.
- Store diluted libraries at 4–8°C and use within 48 hours. Store undiluted libraries at 4–8°C for 48 hours; store at –20°C for long-term storage.

Quantify the library and dilute: Qubit® 2.0 Fluorometer

Analyze each amplified library using the Qubit® 2.0 Fluorometer (Cat. no. Q32866) and the Qubit® dsDNA HS Assay Kit. For detailed instructions, see the *Qubit® dsDNA HS Assay Kits User Guide*.

Amplified libraries typically have concentrations of 300–1500 ng/mL. This quantification method may not be appropriate for low-yield libraries, for example from low-input or FFPE samples.

1. Determine the amplified library concentration:
 - a. Make a 1:200 working dilution of Qubit® dsDNA HS reagent using the Qubit® dsDNA HS Buffer.
 - b. Mix the amplified library with the diluted dye reagent:
 - For high-quality input RNA, prepare a 1:10 dilution of the amplified library in Nuclease-free Water, and add 10 μL of the diluted library to 190 μL of diluted dye reagent.
 - For FFPE or low-input samples, mix 3 μL of the (undiluted) amplified library with 197 μL of diluted dye reagent.

Several library dilutions may be necessary to get an accurate reading.

- c. Prepare each Qubit® standard as directed in the user guide.
 - d. Measure the concentration on the Qubit® 2.0 Fluorometer.
 - e. Calculate the concentration of the undiluted library by multiplying by 20. This can be calculated automatically using the “Calculate Stock Concentration” button.
2. Determine the library dilution that gives a concentration of approximately 15 ng/mL.
- For example:
- The library concentration is 450 ng/mL.
 - The library dilution is $450 \text{ ng/mL} / 15 \text{ ng/mL} = 30$.
 - Therefore, 1 μL of library mixed with 29 μL of Low TE (1:30 dilution) yields approximately 15 ng/mL.
3. Prior to combining libraries or template preparation, dilute an aliquot of each library to a concentration of approximately 15 ng/mL.
- Store diluted libraries stored at 4–8°C and use within 48 hours. Store undiluted libraries at 4–8°C for 48 hours; store at –20°C for long-term storage.



Methods

(Optional) Combine barcoded libraries from different samples

(Optional) Combine barcoded libraries from different samples

You can prepare barcoded libraries from different samples using Ion Xpress™ Barcode Adapters 1–96 Kits. Multiple uniquely barcoded libraries can be combined as shown in the following figure and loaded on a single Ion Chip to minimize the sequencing run time and cost and to allow for accurate sample-to-sample comparisons.

Store diluted combined libraries at 4–8°C and use within 48 hours.

Ion Xpress™ Barcode Adapters 1–16

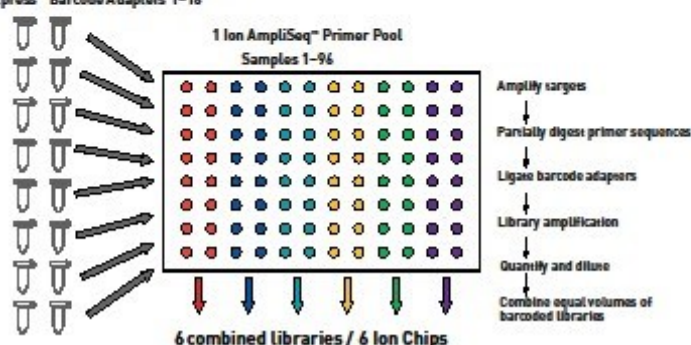


Figure 1 Multiple barcoded libraries prepared from different samples using the same primer pool.

Example library combination algorithm: 96 samples and 16 barcodes. In this example, 1 barcoded library is generated from each sample using the same Ion AmpliSeq™ Primer Pool. After quantifying and diluting the libraries according to their Template Dilution Factors, equal volumes of the barcoded libraries are combined in sets of 16 barcodes. In this example, one 96-well plate yields 6 combined libraries (each combined library contains 16 barcoded libraries from 16 samples), for sequencing on 6 Ion Chips.

Proceed to template preparation

The diluted library or combined libraries are ready for downstream template preparation using an appropriate Ion template preparation kit. Dilute the library immediately before template preparation, or store the dilution in a sealed plate at 4–8°C for up to 48 hours.

In general, Ion AmpliSeq™ libraries at 100 pM (or 15 ng/mL) yield sufficient monoclonal Ion Sphere™ Particles (ISPs).

Template preparation documentation is available on the Ion Torrent™ user community at ioncommunity.lifetechnologies.com. Follow the links under **Systems & Software > Ion PGM System > User Guides and Bulletins > Prepare Template**.



PARTICIPANT INFORMATION SHEET AND CONSENT FORM

CLINICAL RESEARCH

The effect of mechanical heart support on underlying heart structure and function

Invitation

You are invited to participate in a research study into investigating the effect of mechanical heart support on underlying heart structure and function.

The study is being conducted by Associate Professor Christopher Hayward, (Consultant Cardiologist), and Dr Kavitha Muthiah (Cardiology Research Fellow).

Before you decide whether or not you wish to participate in this study, it is important for you to understand why the research is being done and what it will involve. Please take the time to read the following information carefully and discuss it with others if you wish.

1. 'What is the purpose of this study?'

The purpose is to investigate what the effect of mechanical heart support is on the underlying structure and function of the heart.

This will help to provide a framework to help work out which patients may be able to have their LVAD removed, depending on the recovery of their own heart.

2. 'Why have I been invited to participate in this study?'

You are eligible to participate in this study because you have/ will be implanted with the left ventricular assist device (LVAD as part of your management for heart failure. If you do not have an LVAD or will not be implanted with this device, your participation is limited to use of your explanted heart tissue material.

3. 'What if I don't want to take part in this study, or if I want to withdraw later?'

Participation in this study is voluntary. It is completely up to you whether or not you participate. If you decide not to participate, it will not affect the treatment you receive now or in the future. Whatever your decision, it will not affect your relationship with the staff caring for you.

New information about the treatment being studied may become available during the course of the study. You will be kept informed of any significant new findings that may affect your willingness to continue in the study.

If you wish to withdraw from the study once it has started, you can do so at any time without having to give a reason. However, it may not be possible to return your samples to you or withdraw your data from the study results if these have already had your identifying details removed

4. 'What does this study involve?'

If you agree to participate in this study, you will be asked to sign the Participant Consent Form.

This study will be conducted over 2 years or until heart transplantation. If you agree to participate in this trial, you will then be asked to undergo the following procedures:

1. Blood sampling whereby samples of blood taken from a vein will be required. The amount of blood taken will be equivalent to 15 millilitres (approximately one and a half a teaspoon full) taken up to 7 separate occasions (at LVAD implant, at 1 week post implantation of LVAD, at 1 month, at 3 months, 6 months, 12 months, 18 months and 2 years). The blood samples will be tested for various biochemical markers to assess for recovery of the heart.
2. At the time of the LVAD implantation, a sample of the heart muscle/tissue will be obtained and also be sent off for analysis. At transplant, the explanted heart will also be analysed.
3. At LVAD implant, at 1 week post implantation of LVAD, at 1 month, at 3 months, 6 months, 12 months, data from the LVAD will be down-loaded and analysed. Graphs will then be plotted to assess pumping function of the heart.
4. 3-D echocardiography to assess heart function. This is a non-invasive test. A cardiac ultrasound probe will be placed upon your chest wall to obtain these measurements while you are lying comfortably on your side. It uses the same type of ultrasound machine that has been used for your previous echocardiograms. This test will also be performed at LVAD implant, at 1 week post implantation of LVAD, at 1 month, at 3 months, 6 months, 12 months.
5. A physical examination will be performed whereby a stethoscope will be used to listen to heart sounds, and observations of fluid status will be made. The mean arterial blood pressure will be recorded using a BP cuff and Doppler. Pulse rate will be recorded. This data will be collected at LVAD implant, at 1 week post implantation of LVAD, at 1 month, at 3 months, 6 months, 12 months.
6. **If you do not have a LVAD implanted**, we would like to collect and analyse a small sample (5mmx5mm) for heart failure gene analysis.

Please note that if you have already been implanted with the LVAD, you will only be eligible to have the 3-D echocardiography analysis and LVAD data download studied

Please note that collection of blood samples at the specified intervals is standard of care. It is not however standard of care to test specifically for biochemical markers. Similarly, it is standard of care to obtain tissue samples from the heart at the time of LVAD implantation. We will in this study be testing for additional factors that determine recovery of the heart. It is also standard of care to down-load data of pump flows at the mentioned timed intervals. A similarly, it is also standard of care to perform 2-D echocardiography however we will be using a different echocardiography probe (3-D probe) in this study. Performance of a physical examination is standard of care.

In addition, the researchers would like to have access to your medical record to obtain information relevant to the study.

5. 'How is this study being paid for?'

The study will be supported by dedicated heart failure research trust funds.

6. 'Are there risks to me in taking part in this study?'

All medical procedures involve some risk of injury. In addition, there may be risks associated with this study that are presently unknown or unforeseeable. In spite of all reasonable precautions, you might develop medical complications from participating in this study.

The known risks of this study are bruising associated with having blood taken. The risk is small and is performed using a very fine needle and blood tubes. The procedure is similar to that taken in the course of your normal treatment.

There are operative risks associated with placement of the LVAD for which you should refer to information available concerning LVAD and ask your implanting surgeon / cardiologist concerning those risks. The current study does not alter your treatment.

Risk associated with the performance of 3-D echocardiography includes mild musculoskeletal chest discomfort from placement of the echocardiography probe on the chest wall.

Testing on tissue specimens will be performed on segment of the heart that will be removed as part of the routine involved in implantation of the LVAD and is included as part of the surgical risks associated with the LVAD implantation.

The current study will not alter your management.

7. 'What happens if I suffer injury or complications as a result of the study?'

If you suffer any injuries or complications as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment.

You may have a right to take legal action to obtain compensation for any injuries or complications resulting from the study. Compensation may be available if your injury or complication is caused by the drugs or procedures, or by the negligence of any of the parties involved in the study. If you receive compensation that includes an amount for medical expenses, you will be required to pay for your medical treatment from those compensation monies.

If you are not eligible for compensation for your injury or complication under the law, but are eligible for Medicare, then you can receive any medical treatment required for your injury or complication free of charge as a public patient in any Australian public hospital.

8. 'Will I benefit from the study?'

This study aims to further medical knowledge and may improve future treatment and management of patients with the LVAD / mechanical heart support however it may not directly benefit you.

9. 'Will taking part in this study cost me anything, and will I be paid?'

Participation in this study will not cost you anything. You will be reimbursed for your time and reasonable travel expenses for visits not associated with your usual care.

10. 'What will happen to my tissue sample after it has been used?'

The blood or tissue(heart muscle)sample/s you provide during the study will be stored at the completion of the study. If the researchers wish to store (or 'bank') the samples, you will be asked whether you agree to this and, if so, will be asked to sign a specific consent form. If this is done, the blood and tissue (heart muscle) samples will be stored for a duration of 15 years.

If you do agree to your tissue samples being stored, they will not be used for other research projects, except with your written consent or, under some circumstances, with the approval of a Human Research Ethics Committee at that time.

11. 'How will my confidentiality be protected?'

Of the people treating you, only your treating doctors and nurses will know whether or not you are participating in this study. Any identifiable information that is collected about you in connection with this study will remain confidential and will be disclosed only with your permission, or except as required by law. Only the researchers named above will have access to your research details and results that will be held securely at St Vincent's Hospital.

12. 'What happens with the results?'

If you give us your permission by signing the consent document, we plan to discuss / publish the results as part of a thesis and submit it for publication in peer reviewed journals. In any publication, information will be provided in such a way that you cannot be identified. Results of the study will be provided to you, if you wish.

13. 'What happens to my treatment when the study is finished?'

There is no disruption to standard treatment by participating in this study

14. 'What should I do if I want to discuss this study further before I decide?'

When you have read this information, Associate Professor Christopher Hayward or Dr. Kavitha Muthiah will discuss it with you and any queries you may have. If you would like to know more at any stage, please do not hesitate to contact him/her on 02-83821111 and ask to be put through to their mobile phone.

15. 'Who should I contact if I have concerns about the conduct of this study?'

This study has been approved by St Vincent's Hospital HREC. Any person with concerns or complaints about the conduct of this study should contact the Research Office who is nominated to receive complaints from research participants. You should contact them on 02 8382 2075 and quote HREC reference number HREC/10/SVH/100.

Thank you for taking the time to consider this study.

If you wish to take part in it, please sign the attached consent form.

This information sheet is for you to keep.



CONSENT FORM

LVAD Outcome Study

1. I, ...
of
agree to participate as a participant in the study described in the St.Vincent's Hospital Participant Information Sheet set out above.
2. I acknowledge that I have read the Participant Information Sheet, which explains why I have been selected, the aims of the study and the nature and the possible risks of the investigation, and the information sheet has been explained to me to my satisfaction.
3. Before signing this consent form, I have been given the opportunity of asking any questions relating to any possible physical and mental harm I might suffer as a result of my participation and I have received satisfactory answers.
4. I understand that I can withdraw from the study at any time without prejudice to my relationship to St Vincent's Hospital.
5. I agree that research data gathered from the results of the study may be published, provided that I cannot be identified.
6. I understand that if I have any questions relating to my participation in this research, I may contact Assoc Prof Chris Hayward on telephone 02 8382 6880, who will be happy to answer them.
7. I acknowledge receipt of a copy of this Consent Form and the Participant Information Sheet.

Complaints may be directed to the, Research Office on 02 8382 2075.

Signature of participant	Please PRINT name	Date

Signature of witness	Please PRINT name	Date

Signature of investigator	Please PRINT name	Date



LVAD Outcomes Study

REVOCATION OF CONSENT

I hereby wish to **WITHDRAW** my consent to participate in the study described above and understand that such withdrawal **WILL NOT** jeopardise any treatment or my relationship with the *(insert name of university and/or Hospital)* or my medical attendants.

Signature

Date

Please PRINT Name

The section for Revocation of Consent should be forwarded to:

Associate Professor Chris Hayward,
Heart Failure Transplant Unit, - Level 4 Heart and Lung Clinic,
St Vincent's Hospital,
Victoria Street,
Darlinghurst 2010, NSW.

Appendix 6 Mock Loop Data Collection forms

Name of collector

Date:

dd/mm/yyyy

Data Collection form Date

Condition simulated: _____

SynCardia Settings:

Left CO		Right CO		Heart Rate		% Systole	
Left AVG. CO		Right AVG. CO		Left Pressure		Right Pressure	
Left Fill		Right Fill		Left Vacuum		Right Vacuum	

Abbreviations: CO; Cardiac output, AVG. CO; Cardiac Output Average, Vac; Vacuum.

S/S Monitor and CDAS values:

Time started:	Real time:	CDAS time:	S/S collect time:
Time Finished:	Real time:	CDAS time:	S/S collect time:

CDAS time	S/S time	RA	PA	LA	Ao	RP Speed	RP Power	RP Flow	LP Speed	LP Power	LP Flow	AoV	Pulm V	SVR	PVR	Flow rate	Heart rate
												O I C	O I C				
												O I C	O I C				
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Abbreviations: RA: Right atrium, PA: Pulmonary artery, LA: left atrium, Ao: Aortic, RP: Right Pump, LP: Left pump, "O | I | C", O: Open, I: Intermittent, C: Closed, AoV: Aortic Valve, Pulm V: pulmonary valve, SVR: Systemic vascular resistance, PVR: Pulmonary vascular resistance.

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Appendix 8 Publications associated with this thesis



The Journal of
Heart and Lung
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ORIGINAL CLINICAL SCIENCE

Long-term biventricular HeartWare ventricular assist device support—Case series of right atrial and right ventricular implantation outcomes



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KEYWORDS:

chronic mechanical
circulatory support;
biventricular ventricular
assist device;
severe heart failure;
outcomes;
thrombosis

BACKGROUND: There is limited information on outcomes using the HeartWare ventricular assist device (HVAD; HeartWare, Framingham, MA) as a biventricular assist device, especially with respect to site of right ventricular assist device (RVAD) implantation.

METHODS: Outcomes in 13 patients with dilated cardiomyopathy and severe biventricular failure who underwent dual HVAD implantation as bridge to transplantation between August 2011 and October 2014 were reviewed.

RESULTS: Of 13 patients, 10 were INTERMACS Level 1, and 3 were INTERMACS Level 2. Mean age was 45 ± 11 years, and mean body mass index was 26 ± 4 kg/m². There were 7 patients on temporary mechanical support preoperatively (extracorporeal life support, $n = 5$; intra-aortic balloon pump, $n = 2$). The median hospital length of stay was 53 days (interquartile range [IQR] 33–70 days) with a median intensive care unit length of stay of 14 days (IQR 8–36 days). The median length of support on device was 269 days (IQR 93–426 days). The right HVAD was implanted in the right ventricular (RV) free wall in 6 patients and in the right atrial (RA) free wall in 7 patients. Transplantation was successfully performed in 5 patients, and overall survival for the entire cohort was 54%. RVAD pump thrombosis occurred in 3 of 6 RV pumps and 1 of 7 RA pumps. No left ventricular assist device pump thrombosis was observed. Bleeding tended to be higher in the RV implantation group (3 of 6 vs 0 of 7). During follow up, 6 patients died (4 of 7 in the RA group vs 2 of 6 in the RV group). Cause of death was multiple-organ failure in 3 patients, sepsis in 2 patients, and intracerebral hemorrhage in 1 patient.

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CONCLUSIONS: Critically ill patients who require biventricular support can be successfully bridged to transplant using 2 HVADs. RA implantation may allow right heart support with lower pump thrombosis and bleeding complications, although this was at the expense of a higher mortality in this cohort. *J Heart Lung Transplant* 2016;35:466–473
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As a result of superior outcomes with continuous-flow left ventricular assist devices (LVADs) compared with pulsatile pumps, continuous-flow LVADs have become the therapy of choice for long-term support in patients with advanced heart failure.¹ Data are limited on long-term continuous-flow biventricular assist device (BiVAD) support. Established options for biventricular support include total artificial heart replacement and long-term pulsatile paracorporeal ventricular assist devices (VADs) and rely on large drivers, which limit full patient mobility.^{2,3} Widespread use of dual continuous-flow LVADs is limited because of logistic issues with separate controllers, reimbursement issues for the second pump, and poor reported long-term prognosis compared with patients on isolated left ventricular support.⁴ Early reports showed the feasibility of dual HeartWare ventricular assist device (HVAD; HeartWare, Framingham, MA) implantation for biventricular support.^{5–7} The aim of this case series was to report our experience with the HVAD as a BiVAD in patients who were considered to be unsuitable for isolated LVAD support and to compare right ventricular (RV) and right atrial (RA) right ventricular assist device (RVAD) implantation.

Methods

Patients

From August 2011 through October 2014, 13 patients with dilated cardiomyopathy (10 men) underwent implantation of 2 HeartWare HVAD pumps at St Vincent's Hospital, Sydney, for biventricular support. Approval for collection of data reported in this study was obtained from the St Vincent's and Mater Health Human Research Ethics Committee. All patients had advanced heart failure (INTERMACS Level 1–2). Before implantation, 7 patients required inotropes and temporary mechanical support preoperatively (extracorporeal life support [ECLS], $n = 5$; intra-aortic balloon pump, $n = 2$), and the remaining 6 patients required inotropic support alone.

Biventricular implantation decision

The decision to implant dual HVADs was based on a combination of hemodynamic parameters (RV stroke work index, mean pulmonary arterial pressure, transpulmonary gradient) and echocardiographic markers (degree of RV dilation, RV systolic impairment, estimated pulmonary arterial systolic pressure, and severity of tricuspid regurgitation) of RV dysfunction. The dominant reason for considering biventricular support was the severity of RV impairment and dilation before LVAD placement. Two patients underwent delayed RVAD implantation (at 1 week

after LVAD) because of inability to wean from temporary mechanical RV support used in association with the initial LVAD procedure.

The RVAD was implanted in the RV free wall in the first 6 consecutive patients (RV group) and in the RA free wall in the subsequent 7 consecutive patients (RA group). All patients were implanted as bridge to transplantation and were followed up until heart transplantation, until death on mechanical support, or until last observed (February 2015). Of patients, 11 underwent planned biventricular implantation, and 2 underwent delayed RV implantation within 2 weeks after isolated LVAD implantation because of intractable right heart failure (Patient 4 and Patient 13). Preoperative demographics for all patients are shown in Table 1.

Implantation procedure

In all 13 patients, the left HVAD was implanted into the apex of the left ventricle, with the outflow graft attached to the ascending aorta. The right HVAD was implanted at 2 different sites. The first 6 consecutive patients received an implant in the free wall of the right ventricle opposite the interventricular septum (RV group). In the course of monitoring these patients, it was recognized that after RV remodeling, RV thrombosis was occurring at a higher than expected rate. A decision was made to change the implantation technique in the future, and the next 7 consecutive patients underwent RA implantation (RA group). For HVAD implantation into the right ventricle, 4 layers of polytetrafluoroethylene (Teflon, DuPont Co., Wilmington, DE) felt were cut into donut shapes and placed between the sewing ring and right ventricle to allow for a 7-mm reduction in the intraventricular protrusion distance of the inflow cannula, similar to that described by Krahatsch et al.⁸ No spacers were used for RA HVAD implantation; however, the inflow cannula was maximally retracted with only 5 mm of the inflow cannula protruding beyond the sewing ring into the right atrium. However, the sewing ring was "overtightened" beyond that allowed for by the supplied torque wrench. After coring of the RV free wall, any trabeculae in the immediate vicinity of the planned inflow cannula were resected. No atrial trabecular resection was needed; however, pacing wires coursing through the right atrium were sutured to the atrial free wall out of the way of the inflow cannula in patients receiving an atrial RVAD. No pacemakers or pacemaker wires were removed, and the tricuspid valve was not operated on in any of the patients. The RVAD outflow graft for all patients was attached to the main pulmonary artery, which was restricted according to the patient's pulmonary vascular resistance. The outflow graft was narrowed to a diameter of 5–7 mm over a distance of 35 mm for all patients as per Krahatsch et al.⁸

Anti-coagulation

Postoperative anti-coagulation with intravenous heparin began 8 to 12 hours after surgery, and only after blood loss from drain

Table 1 Pre-operative Data

Patient no.	Sex	Age	BMI (kg/m ²)	INTERMACS	Etiology	Previous procedures	Creatinine (μmol/liter)	eGFR (ml/minute/BSA) ^a	Bilirubin (μmol/liter)	RA/PAWP ratio	TR grade	RAP	RVSWI	LVEF (%)	LVEDD (mm)
RV (n = 6)															
1	M	37	28.6	Level 2	DCM	ICD	130	60	100	0.58	3	15	0.91	25	83
2	M	33	29.4	Level 1	DCM	None	60	126	25	0.68	1	27	0.26	20	85
3	M	33	22	Level 1	CCTGA	IABP, ICD	111	75	32	0.77	2	23	1.09	15	74
4	F	36	19.4	Level 1	DCM	TVA + ASD repair, V-PA ECLS, LVAD	135	43	22	NA	NA	NA	NA	25	42
5	M	51	29.1	Level 1	DCM	CVVHD, ICD	137	51	18	0.60	3	18	0.44	25	76
6	M	31	23.5	Level 1	DCM	IABP, ICD	202	37	35	0.24	1	7	0.41	20	83
RA (n = 7)															
7	M	49	24.6	Level 1	DCM	ICD	91	85	41	0.73	2	19	0.20	20	64
8	M	64	28.6	Level 2	DCM	ICD	108	62	17	1	4	21	0.24	35	61
9	M	55	24.6	Level 2	DCM	ICD	109	65	39	0.54	2	15	0.82	40	75
10	M	44	34.6	Level 1	DCM	VA ECLS, ICD	82	100	35	NA	NA	NA	NA	15	80
11	M	62	26.8	Level 1	DCM	VA ECLS, ICD	109	62	50	NA	NA	NA	NA	39	80
12	F	40	22.1	Level 1	GCM	VA ECLS	91	68	14	NA	NA	NA	NA	Akinetic	NA
13	F	54	22.9	Level 1	DCM	V-PA ECLS, LVAD	124	42	29	NA	NA	NA	NA	40%	54
Mean (SD)		45 (11)	26 (4)	10 Level 1, 3 Level 2		5 VA ECLS, 2 IABP (46%)	115 (34)	67 (25)	35 (22)	0.66 (0.21)	2 (1.3)	18 (6)	0.55 (0.34)	27 (10)	71 (13)

BMI, body mass index; CCTGA, congenitally corrected transposition of the great arteries; CVVHD, continuous veno-venous hemodialysis; DCM, dilated cardiomyopathy; ECLS, extracorporeal life support; eGFR, estimated glomerular filtration rate; GCM, giant cell myocarditis; IABP, intra-aortic balloon pump; ICD, implantable cardioverter defibrillator; IDCM, idiopathic dilated cardiomyopathy; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NA, not available (right ventricular parameters not applicable in patients on ECLS); RA, right atrial; RA/PAWP, right atrial pressure to pulmonary artery wedge pressure (ratio); RAP, right atrial pressure; RV, right ventricular; RVSWI, right ventricular stroke work index; TR, tricuspid regurgitation; VA, veno-arterial; V-PA, veno-pulmonary arterial.

^aml/min/1.73m²

tubes reached <50 mL/hour, to derive an activated partial thromboplastin time between 50 and 75 seconds. Oral anti-coagulation began after the removal of mediastinal or chest drain tubes. A combination of aspirin (100 mg), clopidogrel (75 mg), and warfarin (international normalized ratio 2–2.5) was used until 2014. All patients with RV implantation were treated with dual anti-platelet therapy as well as warfarin; however, the second anti-platelet agent had to be stopped in 3 patients with RV implantation because of bleeding. From 2014 to the present, the post-operative anti-thrombotic regimen included aspirin (100 mg) and warfarin (international normalized ratio 2–3) only. To detect clinically significant hemolysis resulting from the use of 2 HVAD pumps, free hemoglobin, bilirubin, haptoglobin, and lactate dehydrogenase blood levels were analyzed on a daily basis during the intensive care unit stay and then on a monthly basis for outpatient visits.

Post-operative management

All patients received routine post-operative care for VAD support, including prophylactic broad-spectrum antibiotics for the first 3 days after implantation and close monitoring and correction of coagulation profiles. Within 1 week of restoring the patient's hemodynamic profile, echocardiography was performed to determine structural improvements and pump performances.

Statistical analysis

Statistical analysis was performed using SPSS for Windows version 10.00 (SPSS, Inc., Chicago, IL). Results are presented as mean (SD) for normally distributed data, and median (interquartile range [IQR]) for non-normally distributed data. Fisher exact test was used to assess the association between post-operative outcomes and adverse events and implantation technique (RV vs RA).

Results

Patient characteristics

Between August 2011 and October 2014, 13 patients (10 men) underwent biventricular implantation of 2 HVADs. Of patients, 11 had dilated cardiomyopathy, 1 had end-stage congenitally corrected transposition of the great arteries, and 1 had end-stage giant cell myocarditis. Patient age ranged from 31 to 64 years (mean 45.3 ± 11.3 years), and body mass index ranged from 22 to 39.4 kg/m^2 (mean $25.8 \pm 4.1 \text{ kg/m}^2$). Ten patients (77%) were Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) Level 1, and 3 patients (23%) were INTERMACS Level 1 before BiVAD implantation. There were 3 patients on veno-arterial ECLS before LVAD placement, and the 2 patients who underwent delayed RVAD placement were supported after LVAD placement with venous-pulmonary artery ECLS. With the exception of Patient 4 and Patient 13 (supported on venous-pulmonary artery ECLS for right heart failure after LVAD placement), all patients had clinically elevated RA pressures. In addition, Patient 4 and Patient 12 were transferred to our institution on veno-arterial

ECLS, and it was not possible to obtain some pre-operative cardiac measurements.

Right and Left Pump flows

The mean pump speeds were $2,531 \pm 259 \text{ rpm}$ for the right HVAD and $2,746 \pm 190 \text{ rpm}$ for the left HVAD. There were no differences in the pump speed settings for RV compared with RA support. Estimated pump flows were $5.1 \pm 1.0 \text{ liters/minute}$ on the right and $5.4 \pm 0.9 \text{ liters/minute}$ on the left. There was no significant difference in flow in the right HVAD according to RA vs RV implantation. The concordance in flow between the RVAD and LVAD was very close in 10 of 13 patients. In 1 patient with moderately severe pulmonary regurgitation, RVAD flow was significantly greater than LVAD flow ($6.6 \text{ liters/minute}$ vs $4.4 \text{ liters/minute}$); 1 patient had significant aortic regurgitation (RVAD $3.8 \text{ liters/minute}$ vs LVAD $6.5 \text{ liters/minute}$); and in 1 patient with recurrent pericardial effusions and mediastinal sepsis, there was no apparent valvular abnormality (RVAD $4.0 \text{ liters/minute}$ vs LVAD $6.0 \text{ liters/minute}$)—this difference was unexplained. In the other 10 patients, the RVAD and LVAD flows corresponded well ($r^2 = 0.77$, $p < 0.001$, mean difference $0.17 \pm 0.46 \text{ liters/minute}$).

Post-operative outcomes

We report outcomes from a cumulative BiVAD support duration across all patients of 3,807 days. The median duration of support was 269 days (IQR 93–426 days)—329 days (IQR 187–543 days) for the RV group and 132 days (IQR 78–391 days) for the RA group. All post-operative outcomes were censored at the time of transplantation. Peri-operative (30-day) and 1-year survival were 100% and 62%, respectively. At 30 days, serum creatinine improved from $115 \pm 34 \mu\text{mol/liter}$ to $79 \pm 24 \mu\text{mol/liter}$, and estimated glomerular filtration rate improved from $67 \pm 25 \text{ mL/minute (BSAc)}$ to $95 \pm 28 \text{ mL/minute (BSAc)}$. Discharge after BiVAD implantation was successfully achieved in 69% of patients, and overall survival at 2 years was 54%. During VAD support, 6 patients (46%) (4 of 7 in the RA group vs 2 of 6 in the RV group) died, typically early in the BiVAD support period, after a median 78 days (IQR 61–122 days). The cause of death was multiple organ failure in 3 patients, sepsis (unrelated to driveline) in 2 patients, and intracerebral hemorrhage in 1 patient. After a median of 513 days (IQR 269–594 days) of support, 5 patients (38%) were successfully bridged to transplantation, and 2 patients remained supported at 356 days and 426 days after implantation. Post-operative outcomes are reported in Table 2. No significant difference between the RA group and the RV group for any outcome was observed using Fisher exact test.

Adverse events

Adverse events during VAD support are listed in Table 2 and were classified according to the INTERMACS definitions. As

Table 2 Post-operative Outcomes and Adverse Events

Variables	Number of patients (%)		
	All patients (n = 13)	RV group (n = 6)	RA group (n = 7)
Post-operative outcomes			
Length of stay, days	53 (33–70)	41 (28–73)	60 (37–70)
ICU length of stay, days	14 (8–36)	8 (8–43)	15 (12–27)
Duration of support, days	269 (93–420)	329 (187–543)	132 (77–391)
TR grade	1.5 ± 1.3	1.6 ± 1.5	1.4 ± 1.2
Survived to discharge	9 (69%)	5/6 (83%)	4/7 (57%)
Transplantation	5 (38%)	4/6 (67%)	1/7 (14%)
Ongoing support	2 (15%)	0 (0)	2/7 (29%)
Died on support	6 (46%)	2/6 (33%)	4/7 (57%)
Adverse events			
Death	6 (46%)	2/6 (33%)	4/7 (57%)
LVAD thrombosis	0 (0%)	0 (0)	0 (0)
RVAD thrombosis	4 (31%)	3/6 (50%)	1/7 (14%)
Bleeding	3 (23%)	3/6 (50%)	0 (0)
Infection			
Driveline	1 (8%)	1/6 (17%)	0 (0)
Sternal wound	2 (15%)	2/6 (33%)	0 (0)
Blood culture >0	5 (38%)	2/6 (33%)	3/7 (43%)
Renal dysfunction	4 (38%)	2/6 (33%)	2/7 (29%)
Neurologic	2 (15%)	1/6 (17%)	1/7 (14%)
Respiratory dysfunction	3 (23%)	2/6 (33%)	1/7 (14%)

ICU, intensive care unit; LVAD, left ventricular assist device; RA, right atrial; RV, right ventricular; RVAD, right ventricular assist device.

Data are reported as median (interquartile range) for continuous variables or number (percent) where appropriate. Fisher exact test showed no significant difference between RV and RA groups in terms of postoperative outcomes and adverse events for any variable.

expected for this patient population, the rates of infection, renal failure, and thrombus formation were elevated. Infections occurred in 7 patients (54%); 1 patient (8%) developed a driveline infection, 2 patients (15%) had sternal wound sepsis, and 5 patients (38%) returned positive blood cultures (in the absence of a driveline infection). Of these patients, 3 experienced multiple infectious complications. Acute renal failure requiring hemodialysis occurred in 4 patients; 3 of the patients (2 in RV and 1 in RA group) successfully recovered. The patient whose renal function did not recover during the immediate postoperative period died. RVAD thrombosis was mainly observed in the RV group (3 of 6 patients) at an average of 13 months (range 8–20 months). It was treated with thrombolysis and was recurrent in 1 patient. One patient in the RA group had RVAD thrombosis, which was treated successfully with thrombolysis at 18 months. One patient (Patient 1) experienced multiple RV thrombotic events. The high rate of pump thrombosis with RV implantation is thought to be related to reverse remodeling of the right ventricle with long-term support. In Patient 1, the RV dimension normalized with the inflow cannula abutting the septum with expiration (confirmed on echocardiography), resulting in repetitive suction seen on review of the RVAD flow waveforms (Figure 1). There were only relatively minor changes in the LVAD flow waveform. No thrombus events occurred in the LVADs. Bleeding was more frequent in the RV implantation group (3 of 6 patients) compared with the RA implantation group (0 of 7). Low rates of respiratory failure and neurologic complications were also reported (Table 2).

Discussion

Continuous-flow LVAD therapy is the standard treatment option for patients with advanced heart failure with preserved RV function. In patients with significant concomitant RV dysfunction, options include the use of a total artificial heart or short-term pulsatile displacement BiVADs. Because of the barriers associated with large pulsatile flow pumps and driver consoles used in short-term BiVADs, the use of 2 continuous-flow LVADs for biventricular support has been suggested. The use of dual HVADs as a means of biventricular support is still in its infancy with limited experience reported.^{5–7,9} This is the largest reported series of RA support and provides a comparison with RV implantation in a contemporaneous cohort.

Implantation site

The impact of RV placement with a higher rate of pump thrombosis than is seen with LVADs is highlighted by the current series. A case report of pump decommissioning from RV remodeling and pump thrombosis was published previously,³⁰ and the present study suggests a solution to this problem with RA placement of the right-sided HVAD. Likely causes for the high rate of thrombosis include microtrauma from repetitive suction events abutting the septum as described earlier and the possibility of ingestion of small emboli from distant venous sites. Pacemaker/defibrillator leads were not removed in the current cohort, although that has also been suggested as a possible source

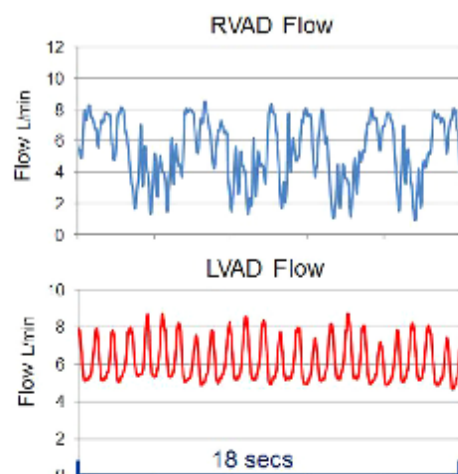


Figure 1 Flow waveforms demonstrating recurrent suction events according to respiratory cycle. With expiration, the decreased venous return to the right heart is associated with abutment of the right ventricular assist device (RVAD) onto the ventricular septum and results in suction, with a sudden decrease in RVAD flow. Only minor changes in flow are seen in the simultaneous left ventricular assist device (LVAD) flow waveform.

thrombus. The fact that 1 of the patients with RA implantation also experienced pump thrombus is consistent with ingestion from a distant source. In 3 patients right-sided VAD thrombosis, treatment with thrombolysis was successful. In 1 patient in whom thrombolysis was contraindicated, the pump driveline was cut and left in place. There was no retrograde flow, as the pump had thrombosed, and the patient underwent successful transplantation 6 months later. The selection of RA implantation in our series was largely based on the high rates of RVAD thrombosis observed early in our experience, and the right atrium was the site of choice for the last 7 consecutive patients supported with dual HVAD therapy. All patients with RV implantation were initially treated with dual anti-platelet therapy and warfarin, but the second anti-platelet agent was withdrawn because of bleeding in 3 patients. Therefore, it is unlikely that more intensive anti-coagulation would have been successful in this group because of the bleeding risks.

RA implantation also reduces the risk of occlusion from interactions with different chambers of the heart. It eliminates the need for additional surgical correction in the presence of severe tricuspid regurgitation and potentially increases RV cardiac output in such patients. Additionally, the RA site enables implantation in smaller patients without the risk of VAD positional changes after sternum closure. As shown in Table 2, length of stay and adverse events were similar in both groups. Although the main difference noted was the reduced rate of post-operative bleeding and right pump thrombosis in the RA group, there was a non-significant trend toward higher mortality in the RA group. Further studies with larger cohorts are required to clarify the risk/benefit ratio.

BiVAD Outcomes

The present study reports our experience with dual VAD support using dual HVADs as a bridge to transplantation. Our findings show 1-year survival rates (62%) similar to outcomes reported in another study by Krabatsch et al⁶ using the same device (47%) and rates similar to published registry data for pulsatile and continuous-flow BiVADs (46% and 63%, respectively).⁴ Our institutional 1-year and 2-year alive/transplanted outcomes for isolated bridge to transplantation LVAD use are 78% and 72%, respectively. Of the entire cohort, 6 patients died during support (2 in the RV group and 4 in the RA group). All patients who died (except Patient 8) were INTERMACS Level 1 status and were supported with either ECLS or intra-aortic balloon pump before BiVAD implantation. The use of ECLS before VAD implantation has been associated with high rates of morbidity and mortality¹¹ and has been identified as a predictor of RV failure after LVAD insertion.¹² It has been associated with exacerbating respiratory complications,¹³ increasing the risk of bleeding and infection, and contributing to inflammatory and/or metabolic complications before VAD implantation.¹¹ However, the use of ECLS or any short-term mechanical support before LVAD implantation can also just be a marker of sicker patients, indicating a higher degree of initial hemodynamic instability, because of patients who did not undergo implantation after short-term mechanical circulatory support, only 1 died. Of the 6 deaths, 5 occurred without hospital discharge, suggesting very late stage implantation without organ recovery or rehabilitation. All but 1 of the patients who were able to be discharged did well with good clinical status. Nonetheless, the results of this case series suggest that BiVAD placement is still insufficient to overcome multiorgan failure complicated by cardiogenic shock with predictable outcomes.

Pre-operative prediction of BiVAD support remains challenging despite much research in this area.^{14,15} Many standard hemodynamic measurements, such as pulmonary pressures, transpulmonary gradient, and RV stroke work index, provide low predictive indices for RV performance.¹⁵⁻¹⁷ Delayed RVAD implantation has also been associated with high mortality rates.¹⁸ Our results were consistent with this association, as both patients (Patient 4 and Patient 13) who were supported with LVAD and venous-pulmonary artery ECLS for 6 to 10 days before RVAD implantation were among the earliest deaths (at postoperative day 60 and 59, respectively). In addition, these patients tended to have a worse clinical course among our cohort and remained in the acute hospital setting for the duration of support.

Although our initial experience demonstrated acceptable outcomes, better results may be expected with accumulated experience. The small controllers and pumps of dual HVAD therapy promote mobility and are less surgically invasive than larger pumps. Although many pulsatile BiVADs have now introduced portable drivers,^{19,20} their driver consoles remain a significant impediment for full mobility. Aside from clinical outcomes, once discharged, the patients with HVADs were able to mobilize fully post-implantation,

allowing them to resume their daily routine, with 2 patients returning to full-time work while waiting for transplant and able to participate in vigorous activities such as cycling. Although preliminary data demonstrate feasibility and applicability of the HVAD as a means of biventricular support,^{5-7,21-23} more data are needed before such an intervention can be considered for widespread use, and use of the HVAD to support the right heart remains off-label. Our institutional experience with the SynCardia total artificial heart (SynCardia Systems, Inc., Tucson, AZ) includes 7 patients in the last 5 years. Survival for the patients is similar to the BiVAD cohort (57% alive or transplanted at 1 year). All the female patients and 1 male patient with small stature would not have qualified for total artificial heart implantation on the basis of size. The remaining patients had HVADs implanted because of greater institutional experience with HVAD therapy.

Limitations

Although lower pump thrombosis and bleeding complications may have been observed with RA support, they were not demonstrated to be statistically different from RV support. One explanation for these lower complication rates related to bleeding and thrombosis may be the higher mortality rates of our RA cohort. Using Fisher exact test, the null hypotheses of equal rates of post-operative outcomes or adverse events across the 2 techniques cannot be rejected for any given variable. Because of the small sample size, further comparisons, including mortality, between the 2 groups could not be made. The consecutive nature of the study cohorts may have resulted in a time bias, owing to the above-mentioned lessons learned and increased experience with patient selection. Additional limitations, such as changes to the anti-coagulation strategy between the 2 groups and initial experience with RA implantation and refinement of patient selection, may have further confounded any comparison between the groups.

In conclusion, our experience supports the use of dual HVAD pumps for biventricular support in critically ill patients who are deemed unsuitable for isolated left ventricular support. The use of RA implantation may be an acceptable alternative for patients with unsuitable RV dimensions or severe tricuspid regurgitation. Although reduced rates of thrombotic events were achieved with RA support, larger cohorts are required to confirm long-term outcomes. As such, outcomes remain guarded in light of the complexity of the patient population.

Disclosure statement

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REVIEW

Biventricular mechanical support devices – clinical perspectives

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ABSTRACT

Cardiac transplantation remains the optimal treatment for end stage heart failure in selected patients. However, the shortage of donor hearts, rigorous eligibility criteria and long waiting lists have increased the demand for alternative treatment strategies such as mechanical circulatory support. While many patients are adequately supported with left ventricular assist devices, frequently there is right heart failure or involvement of the right ventricle, requiring biventricular support. Pulsatile flow biventricular devices and total artificial hearts approved for temporary biventricular support have limitations including size, high rates of adverse events and restricted mobility which makes them unsuitable for long term support. A number of centres have reported dual continuous flow left ventricular assist devices as a means of supporting the left and right heart. This review will summarise the literature on the outcomes and complications from current biventricular support devices and assess the role of dual continuous flow VAD therapy, and the new continuous flow total heart replacement devices.

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Introduction

Chronic heart failure (CHF) is a progressive syndrome associated with high morbidity and mortality [1–3]. Management strategies vary depending on the stage of disease and severity of symptoms. Early stages of CHF can be managed with a combination of lifestyle modifications, pharmacological therapies, and cardiac devices [4]. However, these therapeutic options are often ineffective in patients suffering from advanced CHF. In these cases, cardiac transplantation for those without other contraindications is the preferred treatment option, but is limited by the scarcity of donor hearts, stringent eligibility criteria and long waiting lists [5]. Moreover, critically ill patients have poorer outcomes [6,7], and many such patients require 'bridging' with circulatory support to transplant [8,9].

While many patients with advanced CHF can be managed with isolated left ventricular assist devices (LVADs), up to 30% of patients suffer from concomitant right heart failure, requiring biventricular support [10]. Patients with biventricular failure have higher mortality and greater end organ compromise compared to LVAD recipients, and are generally classified Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACs) status 1 or 2 [11]. The decision to implant biventricular assist devices (BIVADs) can be difficult and vary among institutions. The main indications for early biventricular support has been acute circulatory collapse, due to fulminant myocarditis, acute decompensation of dilated cardiomyopathy, massive myocardial infarction, and acute deterioration following toxic cardiomyopathy. In addition to biventricular failure, BIVAD support may be more suitable in

the presence of other cardiac pathologies such as infiltrative cardiomyopathy, restrictive cardiomyopathy and other cardiac malignancies that may be contraindicated to isolated LVAD support only.

Most predictors of right ventricular failure assess the performance and structural integrity of the right ventricle. Right ventricular failure has been associated with severe tricuspid regurgitation, an ejection fraction <30%, and RA >50 mm [12,13]. However, as evident from the variety of algorithms proposed to predict right heart failure post-LVAD insertion [14,15], no single predictive tool has been accepted as the gold standard. Standard hemodynamic measurements such as pulmonary pressures, transpulmonary gradient and right ventricular stroke work index each provide low predictive indices for right ventricular performance [15–17]. Implantation of a sequential right ventricular assist devices (RVADs) in the setting of right heart failure after LVAD insertion has been associated with mortality rates of greater than 50% in early series [18]. Thus early BIVAD implantation for suitable candidates has been suggested to improve patient survival [19].

Options for biventricular support have previously involved the use of a total artificial heart (TAH) or pulsatile displacement biventricular assist devices. Short-term BIVADs continue to use pulsatile flow pumps, which remain too large for hospital discharge and are limited by their large driver consoles to adequately restore patients' mobility and improve quality of life [20,21]. Biventricular support with the TAH and pulsatile BIVADs have been associated with lower survival rates than patients with continuous flow LVADs [10]. Recent evidence indicates improved survival rates and outcomes produced with the use of simultaneous short-

term RVAD implantation during LVAD implantation [22–24]. The successful selection of patients and high RVAD wean rates have been largely responsible for these favorable outcomes. In patients who were not weaned or were converted into long-term support however, mortality remained poor [22,23]. It is important to note, however, that RVAD support was achieved with a third generation, continuous flow device and thus may be more reflective of current LVAD technology than older generation pulsatile BIVADs or the TAH system. These reports have brought to light a debate whether outcomes for critically ill patients requiring biventricular support may be improved with durable continuous flow devices.

Thus, with the advancement in VAD design and miniaturization of pumps, the use of two continuous flow LVADs has been suggested for biventricular support [25]. As many case series are only of a limited number of patients, outcomes are heavily affected by patient selection, as well as device type. This review summarizes current literature investigating biventricular support device outcomes and complications and discuss the evolution of these devices over the past two decades.

Device types

Ventricular assist devices can be classified according to their flow profiles (pulsatile vs. continuous), operational characteristics (first, second, and third generation), intended length of support (short, intermittent, and long), and form of implantation (extra-, para-, and intracorporeal). LVAD have a broad spectrum of devices available and can thus accommodate a wider range of patient profiles, particularly those ineligible for cardiac transplantation in need of long term, or destination, support. BIVADs have fewer options. Most of the BIVADs approved by the US FDA consist of first generation, pulsatile flow pumps which contain large and restrictive drivers. Their application is limited to short or intermittent term support and are generally extra- or paracorporeal in nature. Table 1 summarizes the list of devices capable of providing biventricular support, and Table 2 summarizes the clinical outcomes of current devices as reported in the literature.

Extracorporeal biventricular support devices

Extracorporeal BIVADs were among the first devices to be approved by the FDA as a bridge to transplant (BTT) or bridge to recovery (BTR). The Abiomed BVS5000 was one of the first dual chambered ventricular assist systems capable of providing complete uni- and biventricular support. It was originally approved by the FDA in 1992 as a short-term support system for BTT. However, its applicability in a 'bridge to bridge' (BTB) and BTR have also been documented [20,60]. Its widespread use, particularly for the treatment of acute cardiogenic shock was attributed to its simplicity, low cost and the limited commercial availability of other BIVAD systems [48]. Consistent with its role as a last resort device in cardiogenic shock, the survival rate is poor [36,37], and as most experiences were accrued prior to the initiation of INTERMACS in 2005 [61], survival rates remain elusive. While it has been shown to support patients for short periods, long-term support is associated with a high incidence of multiple organ failure (40%) [20,62] and excessive bleeding [20,63,64]. The BVS5000 has been superseded by more compact and reliable paracorporeal and extracorporeal devices.

In contrast to the BVS5000, the Levitronix CentriMag (Figure 1) provides continuous blood flow. It is a third generation, extracorporeal, centrifugal blood pump that also provides short-term support in a left, right and biventricular failure setting. It is FDA approved to support patients as bridge to decision device, and in Europe, its support has been approved for up to 30 days [65], with survival rates of up to 75–80%. In comparison to other first-generation pulsatile BIVADs, the CentriMag impeller is magnetically levitated, without the need for mechanical bearings. This eliminates friction and wearing during operation, thereby improving durability and decreasing the risk of hematological damage [66]. Its applicability in the treatment of primary graft failure has safely demonstrated positive outcomes [67]. While high survival rates at 30 days and 1 year have been reported (pre- and post-explant, respectively) [44,46], evidence also suggests a high mortality rate of patients supported with the CentriMag for right ventricular support after LVAD implantation [45]. As described by Takeda and colleagues, patients who required late unplanned right ventricular support after LVAD had much higher in-hospital mortality (74%) compared to those with

Table 1. Clinically applied and under development devices providing biventricular support.

Device	Type	Drive mechanism	Flow profile	Target therapy	Clinical purpose
<i>Clinically applied</i>					
Abiomed BVS5000 [26]	Extracorporeal	PQ, FP	Pulsatile	BTB, BTR, BTT	Short term
Abiomed AB5000 [27]	Paracorporeal	PQ, FP	Pulsatile	BTB, BTR, BTT	Short term
Thoratec PVAD [28]	Paracorporeal	PQ, FV	Pulsatile	BTB, BTR, BTT	Medium term
Thoratec IVAD [28]	Implantable	PQ, FV	Pulsatile	BTR, BTT, DT	Medium term
Levitronix CentriMag [29]	Extracorporeal	ED, CE	Continuous	BTB, BTR, BTT	Short term
Berlin Heart Excor [30]	Paracorporeal	PQ, FV	Pulsatile	BTR, BTT	Medium term
Heartware HVAD [31]	Implantable	ED, CE	Continuous	BTT, DT	Long term
SynCardia TAH [32]	Implantable	PD	Pulsatile	BTT	Long term
<i>Under development</i>					
Cleveland Clinic cTAH [33]	Implantable	ED	Continuous	BTT, DT	Long term
BIVACOR BV Assist [34]	Implantable	ED, CE	Continuous	BTT, DT	Long term

PVAD, paracorporeal ventricular assist device; IVAD, implantable ventricular assist device; TAH, total artificial heart; TH, Texas Heart Institute; cTAH, continuous flow total artificial heart; PQ, pneumatically driven; ED, electrically driven; FP, filled passively; FV, vacuum assisted filling; CE, centrifugal flow pump; BTB, bridge to bridge; BTR, bridge to recovery; BTT, bridge to transplantation; DT, destination therapy.

Table 2. Clinical outcomes of current devices.

Device	Year	Patient (n)	30-Day mortality	1-Year mortality	Overall survival	Wean rate	Transplant rate	Discharge rate ^a	DoS (days)	Infection rate	Renal failure	Liver failure	Bleeding	Neurological complication
Clinically applied														
Abiomed BVS000														
Kaan et al. [35]	1991	2	0%	–	100%	100%	–	–	4.3 (4.9–3.7)	0%	50%	–	100%	0%
Dekkers et al. [36]	2001	11	–	–	23.3%	54.5%	–	–	–	–	–	–	–	–
Group a		4					75%							
Group b														
Morgan et al. [37]	2004	22	36.4	–	65.6%	40.9%	13.6%	–	5.1 ± 4.4	12.5% ^b	–	–	25% ^b	37.5% ^b
Abiomed ABS000														
Samuels et al. [38]	2005	4	–	–	75%	75%	–	–	–	–	–	–	–	–
Thoratec PVAD														
Famar et al. [39]	1989	21	–	–	–	–	76%	–	–	–	–	–	–	–
Group c		29					58%			90% ^c			34%	52% ^c
Group d		44						48%		30% ^c				20% ^c
Kirsch et al. [41]	2009	62	–	–	63%	5%	58%	–	42 (2.3–268.0)	71%	32%	15%	26%	29%
Schlessak et al. [42]	2011	31	–	–	52%	13%	39%	–	84 ± 72	–	–	–	–	–
Brehm et al. [21]	2012	39	13%	27%	73%	33%	53%	–	137 ± 109	20%	33%	–	40%	26%
Group e		24					42%		65 ± 61	46%	38%	–	50%	21%
Group f							83%		100 ± 65	11%	–	–	17%	4%
Creaser et al. [43]	2014	24	–	–	83%	–	–	–	–	–	–	–	–	–
Levitronik CentriMag														
Ranjit et al. [44]	2007	12	17%	–	83% ^d	17%	–	–	–	–	–	–	–	–
Shuhaiber et al. [45]	2008	14	64%	–	36%	0%	–	–	11 (1–51)	–	–	–	–	–
De Roberts et al. [46]	2008	10	10%	–	80%	–	–	–	–	–	–	–	–	–
Haj-Yahia et al. [47]	2009	4	0%	0%	100%	0%	–	–	87 (26–105)	0%	0%	0%	25%	0%
John et al. [48]	2011	18	–	–	–	–	–	–	15 (1–60)	11%	0%	0%	11%	6%
Group g		23					35%		–	26%	74%	–	61%	22%
Group h		37					54%		–	16%	46%	–	43%	11%
Berlin Heart Exor														
Rockett et al. [50]	2008	4	–	–	50%	0%	50%	–	–	–	–	–	–	–
Potapov et al. [51]	2010	69	33%	–	67%	–	–	–	–	22% ^b	–	–	–	–
Moreno et al. [52]	2011	4	0%	–	100%	0%	100%	–	94 (3–264)	–	–	–	0%	–
Morales et al. [53]	2011	31	–	–	36%	0%	97%	–	–	–	–	–	–	–
Fan et al. [54]	2011	15	21%	73%	47%	7%	33%	–	–	40%	27%	–	27%	27%
Schweiger et al. [55]	2013	4	25%	–	50%	–	50%	–	218.8 (4–525)	50%	25%	–	25%	25%
Heartware HVAD														
Stepanenko et al. [56]	2011	10	10%	30%	70%	–	10%	–	–	10%	–	–	30%	–
Krabatsch et al. [25]	2011	17	18%	47%	47%	12% ^e	6%	59%	39	6%	–	–	33%	–
SynCardia TAH														
Copeland et al. [57]	2012	101	23% ^f	77%	68%	–	68%	–	87 ± 94.8	63%	–	–	43%	15.8%
Demorion et al. [58]	2013	27	–	–	44%	–	44%	–	254 (79–403)	44%	–	–	41%	15%
Torregrossa et al. [59]	2014	47	–	–	74%	–	72%	85%	554(365–1374)	27% ^g –53% ^h	26%	–	–	19%

PVAD, paracorporeal ventricular assist device; IVAD, implantable ventricular assist device; TAH, total artificial heart; TH, Texas Heart Institute; cTAH, continuous flow total artificial heart; DoS, duration of support; Group a, postcardiotomy patients; Group b, BVAD bridge to transplant patients; Group c, implanted between 1990–1999; Group d, implanted between 2000–2003; Group e, acute heart failure; Group f, chronic heart failure; Group g, unplanned right ventricular support (unable to wean); Group h, planned biventricular support.

^aRefers to discharge while on mechanical support.

^bOutcomes based on cause of death.

^cOutcomes based on actuary freedom.

^dSurvival based on direct transplant or bridge to another device.

^eRVAD weaned only.

^f34-Day mortality only.

^gDriveline related infection.

^hSystemic infection requiring antibiotics.



Figure 1. The Levitronix CentriMag ventricular assist system. (A) bearingless magnetic motor. (B) Single use disposable pump head. (Courtesy of Thoratec Corporation [65]).

initial planned BIVAD support (24%) [49]. Although the CentriMag is widely used, the large driver console (6.6 kg) and the requirement for prophylactic pump exchange every 28 days [63] means that patients are unable to be discharged from hospital. Major complications associated with the CentriMag include bleeding, infection, respiratory failure, liver dysfunction, hemolysis, and neurological dysfunction [45,68,69].

Paracorporeal biventricular support devices

The Thoratec PVAD (Figure 2) is a first generation, pulsatile flow pump approved for both uni- and biventricular support. Although initially approved in 1995 for BTT, indication for use was broadened to include postcardiotomy support in 1998 and has since demonstrated applicability as a BTR and BTB circumstances. The PVAD initially required a large driver console (Dual Drive Console), however the TLC-II portable pneumatic driver has since been introduced to improve patient mobility. Since then there have been a number of small case series demonstrating the feasibility of home discharge [43,70].

In terms of adverse events, Tsukul et al. reported reduced rates of driveline infection, bloodstream infection and neurological events in patients implanted after the year 2000 who remained supported with the Dual Drive Console [40].

Improvements to management, better patient selection or adjustments to surgical procedure could explain these outcomes. However, the rates of infection, bleeding, renal failure, and neurological events are still widely reported in other studies [21,41], as shown in Table 1. Despite the adverse events, overall survival remains greater than 50%, indicating effective post-operative management. In a comparison between BIVAD and LVAD support, no significant differences in survival between LVAD and BIVAD (45% vs. 63%, respectively) were observed ($p = 0.18$) [41].

After successful introduction of the Thoratec PVAD, the new Abiomed AB5000, gained FDA approval in 2003 for BTT, BTR, and BTB circumstances. The AB5000 is a portable adaptation of the BV55000, designed specifically to improve patient mobility through the use of a smaller driver console [71]. Similar to its predecessor, it is a first generation, pneumatically actuated pump that generates pulsatile blood flow. A major difference is the paracorporeal implantation and in its ability to provide intermediate term support [27] in patients with surface area of 1.3 m^2 or greater. Moreover, the drivelines are compatible with the older extracorporeal model, and it is able to replace the BV55000 without the need for repeat operation [38]. However, despite slight improvements in patient mobility and the length of support, adverse events such as device related thrombus formation and mechanical failure remain a major impediment for its continued use [20]. To date, the literature for AB5000 is limited to short case series insufficient to draw conclusions from in terms of survival and wean rates.

The more contemporary Berlin Heart EXCOR (Figure 3) is a first-generation pulsatile, paracorporeal, pediatric-specific VAD. It was the first device capable of providing complete left, right, and biventricular support in patients as small as infants to adult-sized adolescents [53]. However, similar to the earlier models, its large driver console (93 kg) and the high rates of thromboembolic events remained significant limitations. It was FDA approved in 2008 for investigational purposes and has since been approved for compassionate use only after conventional treatment modalities have failed. Although preliminary studies have demonstrated great potential in the applicability of the Berlin Heart EXCOR [50,72], small BIVAD sample size and reporting method make it difficult to determine the outcomes contributed by biventricular support.

Some evidence suggests that higher mortality rates are associated with increased age, temperature and overall



Figure 2. The Thoratec PVAD ventricular assist system. (A) PVAD pump. (B) Dual Driver Console. (C) TLC-II portable driver console with battery (Courtesy of Thoratec Corporation [67]).



Figure 3. Berlin Heart EXCOR ventricular assist device system. (A) Berlin Heart EXCOR pump. (B) Stationary driving unit Iku. (C) EXCOR mobile driving system (Courtesy of Berlin Heart GmbH).

total of the Sequential Organ Failure Assessment (SOFA) score [51,55,73]. Contrary to these findings, the Initial North American Multicentre Study, consisting of 73 patients (42 LVAD, 31 BIVAD), reported that younger age and BIVAD implantation were associated with higher rates of mortality [53]. The mortality in patients with BIVAD was 36% (11/31) compared to 12% of LVAD (5/42). This increase in the mortality rate was evident in all three age groups assessed (<1 year, between 1–5 years and >5 years old, respectively) [53]. However, one of the biggest limitations of the study is the exclusion of patients with adverse events such as stroke, thromboembolism, device malfunction and infection. These must be considered when assessing the limitations and advantages of the device, especially when complications such as bleeding [51,55], neurological complications [74], thromboembolism, and multiple splenic infarctions due to septic embolization [75] are still reported in the literature.

In terms of technical advancements, the EXCOR comes in many different sizes (10, 15, 20, 35, 50, 60, and 80 mL). Despite a bioactive coating on all blood contacting surfaces of the device, a high rate of thrombus formation is still reported. While this remains an issue, new surgical techniques proposed by Bigdell et al. [76], have demonstrated reduced intra- and postoperative complications such as bleeding, and may allow intensification of anticoagulation in selected patients. While adult pumps are capable of being supported with a mobile driving system (9 kg), biventricular support can only be maintained for a maximum of five hours prior to recharging and patients are often restricted to hospitals and other specialist facilities [77].

The Medos HIA VAD is very similar to the Berlin Heart EXCOR system as it shares many features. Aside from also being a first generation, pulsatile flow, paracorporeal device capable of providing uni- and biventricular support in both adults and pediatric populations, it also comes in a wide variety of pump size ranging from 10–80 mL. Unlike the EXCOR however, the RVAD of the Medos device produces 10% lower stroke volume, reducing the risk of pulmonary edema [78]. While promising, studies remain limited to a handful of case reports and small single center experiences, whose BIVAD samples are

too small to derive meaningful survival and outcomes data [79,80].

The Medos HIA VAD and the Berlin Heart EXCOR system remain the only two devices capable of providing intermittent to long-term mechanical support in children and neonates. Although previous studies have demonstrated successful support of young adolescence with the off-label of the HeartMate VAD [81] and the Thoratec PVAD [82], support remains limited to patients with a large surface area and those not contraindicated from adult pump support. A series of pediatric specific pulsatile and continuous flow devices are currently under development [78].

Implantable biventricular support devices

The Intracorporeal Thoratec IVAD (Figure 4) was the first implantable BIVAD to be introduced, approved in 2004 for intermediate and long-term support as BTR and BTT. Similar to the PVAD, the Thoratec IVAD is also pneumatically actuated; generating pulsatile blood flow with the same valves and polyurethane pump. While it maintains most of the features



Figure 4. The Thoratec IVAD titanium alloy pump and driveline (Courtesy of Thoratec Corporation [76]).

of its predecessor, there are major differences between the two models. In comparison to the polyurethane used in the PVAD, the IVAD utilizes titanium alloy housing for improved external surface biocompatibility [28]. Its smaller weight and size was designed to improve patient mobility and reduce the risk of infection [83]. When compared to 4400 patients implanted with the PVAD, the IVAD has only been used in 560 patients. These differences in numbers may be explained by the ease of pump exchange in the case of device malfunction or adverse events with the PVAD, and the limitations that the IVAD does not allow visualization of thrombus formation in the pump and remains too large to be implanted in children and small women. At present there is little information on the biventricular outcomes of the Thoratec IVAD. While there are studies published as conference abstracts, these studies do not provide detailed information on outcomes of the device but rather as a combined outcome of both the PVAD and IVAD [84].

Total artificial heart

The total artificial heart (TAH) (Figure 5) is a permanent orthotropic pulsatile system that enables biventricular support. Unlike pulsatile BIVAD devices, the TAH completely replaces the native heart. The SynCardia 70 cc TAH (CardioWest) is the first FDA approved completely implantable organ and has been implanted in approximately 1400 patients worldwide [32]. Survival to transplantation and the 1-year survival were initially reported to be 26% and 50%, respectively [85], but more recent experience with better patient selection and post-operative management has resulted in improved outcomes (transplantation and 1-year survival data (68% and 77% respectively) [57]. With the exception of infection, all other complications associated with the SynCardia were similar to those of other pulsatile BIVAD devices. As evident from more recent outcomes, infection remains the biggest adverse event, with 53% suffering from systemic infection (25/47) and 27% from driveline infections (13/47) [59] in long-term patients (median support time of 554 days). With a minimum support of at least one year, 72% were successfully transplanted, 24% died on support and 2% remained on support. It is clear that the SynCardia-TAH represents a significant improvement on previous options for severe biventricular failure and allows long-term hospital discharge. With the

introduction of a smaller 'Freedom' driver, patients are significantly more mobile, with improved quality of life. The noise associated with the four metallic valves and pneumatic driver, while initially confronting, is actually tolerated very well by patients and care givers. Until recently, the SynCardia-TAH system has been limited to patients with a surface area greater than 1.7 m². However, with the introduction of the smaller 50 cc model, which is currently undergoing an Investigational Device Exemption clinical trial, patients with a much smaller surface such as adolescents and smaller women can now be supported.

The most recent option for total heart replacement is the Carmat device, a pulsatile pump with pericardial tissue valves. At present, most of the information available is reported in the form of conference abstracts and published *in vitro* or animal trials. There are currently only three patients implanted with the Carmat TAH with no formal human publications in the literature. While it is hypothesized that the tissue valves will result in less blood trauma compared to the SynCardia device, ongoing anticoagulation is required, due to the large exposure to foreign surfaces. The initial analysis of the second patient implanted demonstrated effective 9-month support prior to complications associated with reduced cardiac output caused by irregularities with the steering of the pumps motor. These findings will help improve future performance and patient outcomes. Additional outcome data is awaited.

Dual VAD continuous flow devices

The use of continuous flow LVAD therapy has become a standard treatment option for patients suffering from advanced heart failure with preserved right ventricular function. Despite initial concerns due to lack of significant arterial pulsation, continuous flow LVADs are tolerated well physiologically [86,87]. Unlike pulsatile BIVADs and the TAH, these LVADs are smaller, lighter, and do not require valves. These features have improved the durability and longevity of the device, as well as significantly restoring patient mobility. It is with these improvements in mind that current effort has been directed into implementing these LVADs within a biventricular setting. There are numerous cases of hybrid application of a LVAD combined with a temporary BIVAD device; however, the use of dual LVADs for both left and right ventricular support



Figure 5. The CardioWest SynCardia Total Artificial Heart. (A) SynCardia pumps. (B) C2 driver caddy (C) Freedom driver. (Courtesy: SynCardia Systems, Inc [78]).

remains novel with only small case series or reports documenting outcomes.

The Jarvik 2000 is a second generation, axial flow LVAD and was the first device to attempt biventricular support using dual LVAD pumps [88]. Initial implants directed the outflow conduit to the descending aorta, which made removal during subsequent heart transplantation difficult. A similar case of biventricular replacement with the HeartMate II LVAD has also been reported [89]. Despite stabilizing hemodynamic parameters, the patient died from neurological complications. The study demonstrated the feasibility of dual VAD therapy with the HeartMate II LVAD but recommended further testing prior to larger scale human trials.

The third-generation HeartWare LVAD (HVAD) (Figure 6), being smaller has also been used for biventricular support. An initial study of 17 patients with the HVAD, biventricular support was successful and with good long-term support [25]. The 30-day survival was reported at 82% [25], an incremental improvement on the 70% survival rate of pulsatile BIVADs [90]. To date, long-term outcomes remain limited. While the 6-month survival rate has been reported to reach 50%, these outcomes were derived from initial experiences and may be improved with increased experience, better patient selection and management. Discharge while on support has been reported in 10/17 patients (59%) with a mean length of stay of 39 days [25]. Three patients died on support and one patient required reoperation to relocate the RVAD from the right ventricle to the right atrium due to interaction with the interventricular septum [25].

While preliminary outcomes are favorable, there are still a number of challenges that must be overcome before dual VAD therapy can become part of clinical practice. Given that the HVAD was originally designed for left ventricular support [25], its hemodynamic performance and physical characteristics are not necessarily compatible for right ventricular support. Various recommendations to modify pump function have been suggested including increasing the resistance of the outflow graft through banding/restricting of the outflow cannula to a smaller diameter [91,92], or running the RVAD at lower speed [93]. However, there is little data available that

can help establish the degree of banding necessary and how this may vary between person to person [91,94].

Secondly, inserting the HVAD into the free wall of the right ventricle may cause the HVAD's inflow cannula to interact with the opposite interventricular wall of the septum, occluding the blood flow through the right HVAD. This may be avoided by reducing the inflow cannula's insertion length [25,92,94] by adding spacers between the HVAD and the wall of the right ventricle [91,94]. Finally, interaction between the inflow cannula and the opposite interventricular wall of the septum can potentially occur after right ventricular remodeling. As the right ventricle becomes smaller in size after RVAD implantation, an appropriately positioned cannula at implant may start to abut the septum at end-systole. Repetitive intermittent occlusion by the inlet cannula hitting the septum results in an increase in the risk of ingested clot and RVAD thrombus. At this point, once that the RV has remodeled, it has been suggested the RVAD can be decommissioned with the driveline severed and the pump left *in situ* [95], eliminating the need for invasive reoperation. To circumvent this, some investigators have placed the HVAD to the right atrial free wall [96], however little data is available on the long-term outcomes of this approach. While preliminary data demonstrates feasibility and applicability of the HVAD as biventricular support [22,25,91,92,95,97,98], more data is required before such an intervention can be considered for approval. A formal outcome registry of BIVAD therapy has been suggested.

Outcomes

The rapid evolution of mechanical assist circulatory support (MCS) devices has significantly contributed to the way patients with advanced CHF are managed. With improved durability, interim mechanical support of a patient with advanced CHF before transplant has become standard of care for those unlikely to survive while waiting. Survival rates in patients ineligible for transplant supported with LVADs have demonstrated to be superior compared to medical therapy alone [99], with the benefit further enhanced with the introduction of continuous flow devices [100]. While randomized controlled trials for BIVAD recipients have not been conducted, based on



Figure 6. HeartWare HVAD ventricular assist system. (A) HVAD pump. (B) HVAD battery powered portable carrycase driver. (Courtesy of HeartWare Inc [84]).

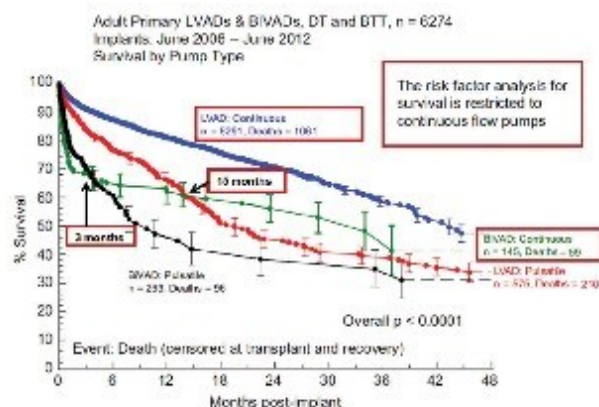


Figure 7. Adult left ventricular assist devices (LVADs) and biventricular assist devices (BIVADs) are shown stratified by continuous flow vs pulsatile flow pumps. Adapted and modified with permission from Kirklin et al (2013) [101].

the Fifth INTERMAC's Annual Report (Figure 7), continuous flow BIVADs (cfBIVADs) have also been shown to be superior to pulsatile BIVADs [101]. In terms of BIVAD support, outcomes have long since depended on careful patient and device selection. It is likely that some of the difference in outcomes with BIVAD patients is due to the significantly greater comorbidity as demonstrated in the very early postoperative mortality. After the first 3 months, the rate of mortality in cfBIVADs appears less than isolated continuous flow LVADs (cfLVADs) (Figure 7).

The main adverse events reported with BIVAD support include infection, bleeding, thrombus related complication, neurological complications and mechanical failure.

These complications differ between pediatric and adult populations and are largely influenced by the type of device used. The use of adult pumps in pediatric patients has been associated with intracranial hemorrhage and systolic hypertension as a consequence of large stroke volumes caused by device mismatch. In addition, the mandatory attachment of four adult sized pumps into a limited pericardial space has been associated with increased rate of infection and elevated rate of adverse events due to excessive surgical procedure [102]. While the Berlin Heart EXCOR and the Medos HIA VAD are able to overcome many of the limitations imposed by adult pumps, these devices are associated with increased rates of neurological complications resulting in death [50,72]. Although increasing experience has resulted in significant improvements, neurological complications and infection remain the greatest complications in pediatric patients. With the increasing number of devices available; each which have different configurations and contraindications, direct comparisons are difficult to make. Nonetheless, it is evident that a similar shift towards smaller, durable and more mobile cfBIVADs are necessary for further improving outcomes in these critically ill patients.

Expert commentary

Over the past 20 years there have been massive gains in terms of acute and long-term management with severe biventricular

heart failure. These patients are, by definition, the sickest chronic cardiac patients, and their heart failure is often associated with other significant organ dysfunction. Furthermore, the chronicity and severity of advanced heart failure, results in a state of physiological frailty, previously termed cachexia, which has been shown to have marked survival implications, independent of whichever therapy is required – routine cardiac surgery, transplant or mechanical support. It is into this milieu that biventricular support is applied, and the high mortality and complication rates need to be seen in this context.

The emphasis for whichever device is used is initially adequate hemodynamic support. Beyond that, immediate surgical invasiveness, short- and long-term complications, and finally durability and quality of life considerations. These latter issues are only applicable due to the success of earlier devices to navigate patients through life-threatening illness.

Application of dual cfLVAD therapy remains novel, with clinical outcomes expected to improve with better patient selection and accumulated experience. With the continuing miniaturization of pump designs, less invasive, more durable and cost-effective pumps become available for dual cfLVAD therapy in these critically ill patients. Newer smaller pumps, such as the HeartWare Miniaturized Ventricular Assist Device (MVAD) may offer a further option of dual cfVAD support, with smaller device burden. Should dual cfVAD therapy become established, it would be expected that the controller and battery packs be incorporated into a single unit.

Size is an important consideration for biventricular support. Not only does it dictate whether the heart needs to be completely excised (as with dual HeartMate II pumps), it is likely to contribute to the risk of infection. Current devices require external pneumatic or electric drivelines offering a portal for introduction of infection into the mediastinum. Notwithstanding this, even the short-lived Lion Heart experience, which was completely implantable without a driveline due to transcutaneous power induction, was associated with a significant infection risk, suggesting the volume (or surface

area) of material within the chest itself is a major risk factor for late sepsis. Future efforts to develop transcutaneous energy transfer (TET) technology need to acknowledge the importance of this, with emphasis on the minimization of device size. A further advantage of the smaller continuous flow pumps in this light, is the fact they can be implanted without median sternotomy, reducing the risk of infection related complications.

Aside from the miniaturization of ventricular pump, there has also been a push for the miniaturization of driver consoles. With the increasing emphasis on patient's quality of life and hospital discharge, a number of driver consoles have been reduced in size to restore patient mobility over the past 5 years. Combination driver for left and right sided cBIVAD should be part of their development. A significant advantage of the cTAH devices is the requirement for only one controller, and the simplicity and decreased size associated with that.

Thrombosis remains one of the biggest issues in biventricular support. Due to the position of the right sided support, RVADs are at a significantly increased risk of venous thrombus ingestion. This is exacerbated by the fact that many of these patients have implantable defibrillators or pacemakers, with associated lead thrombus commonly detected at transplantation, even in non-VAD patients. The reality of right sided thrombus needs to be addressed in ongoing development, should these pumps be considered for long-term support. An advantage of the newer LVADs and cTAH devices is the option for intermittent pump speed modulation which may provide washout to areas of stasis and within the pump. This hypothesis remains to be tested clinically, and is currently in trial in current generation LVADs (MVAD and HeartMate-III).

Five-year view

The three major issues for the field of biventricular mechanical support are device durability, adverse events and miniaturization with improved quality of life. Just as continuous flow LVADs have completely supplanted pulsatile LVADs due to improved device durability, it is likely that continuous flow TAH will supplant current pulsatile devices over time. Although still within the early stages of the development process, two CTAH models have been proposed for future application. While the dual LVADs discussed above function independently, the CTAH devices incorporate flow balancing algorithms between the left and right sides. The Cleveland Clinic has produced a CTAH with a single motor and one rotary assembly maintained by a hydrodynamic bearing [33]. *In vivo* testing has demonstrated excellent, hemodynamic status, end-organ function and pump performance. In a recent study, a calf implanted with CTAH achieved a steady state blood flow and pressure for 90 days [103]. During this, the calf did not show any signs of hemolysis or thrombosis, with good end-organ and vasomotor function. However, this is the first study in which the Cleveland CTAH support was observed in an animal model.



Original

Figure 8. The BIVACOR BV Assist ventricular assist system (Image © Texas Heart Institute, www.texasheart.org).

A second device under development and testing is the BIVACOR BV Assist (Figure 8), a third-generation device, able to provide complete circulatory support for patients with advanced heart failure. There have been nine short-term pre-clinical studies successfully performed in 2007 as a 'proof of concept'. Both *in vitro* and *in vivo* testing confirm that the device was able to balance left and right outflow to prevent atrial collapse in response to simulated changes in posture and extreme changes in systemic and pulmonary resistance [104,105]. The first chronic implant was completed without complication in 2014 [106]. The BIVACOR rotary device is smaller than previous BIVADs as both the LVAD and the RVAD impellers have a common rotating hub. With these promising devices becoming available for human use within the next five years, their superior features such as their smaller size, improved mobility, superior durability and continuous flow design may supersede existing devices; potentially allowing long-term support, and perhaps even be considered for destination therapy.

The adverse event profile of biventricular support, in common with isolated LVAD therapy, includes pump thrombus/embolic events, bleeding and infection. Improvements in pump design to minimize pump related thrombosis will likely come through software modulation to provide pump washout and possibly contribute to decrease gastrointestinal bleeding due to controlled arterial pulsatility. Miniaturization will allow decreased operative risks, and improved patient mobility. Infection remains a significant long-term obstacle to success, and enthusiasm for completely implantable systems needs to be balanced with an awareness of the risk of infection associated with large surface area of implanted devices.

Improved battery design will further decrease the imposition of having to carry power source (either internally or externally). Improved characterization of suitable patients

and evidence of reversal of the frailty phenotype, often associated with the biventricular heart failure patients, will allow improved patient survival and outcomes. It is likely that a durable chronic heart replacement device will be developed, but at present does not seem likely within a 5-year timeframe.

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Key issues

- Pulsatile displacement biventricular assist devices and the total artificial heart have successfully supported patient for BTB, BTR, and BTT circumstances.
- Primarily due to differences in patient cohorts, clinical outcomes in BIVAD or TAH patients remain inferior compared to isolated LVAD patients.
- Use of chronic dual continuous flow VADs is feasible and may provide similar outcomes compared to TAH with increasing experience.
- Miniaturization of both pump devices and controllers has allowed discharge and improved quality of life in selected patients.
- Ongoing issues of infection and pump thrombus/embolic events limit durability beyond bridge to transplant patients, destination therapy is not currently realistic.
- Pump size impacts both surgical morbidity, but may also be an important consideration in risk of late infection. This needs to be incorporated into development of transcatheter energy transfer technologies.
- Application of continuous flow technology into total heart replacement holds some promise, and further developments are awaited.

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Right Ventricular Failure Post LVAD Implantation Corrected with Biventricular Support: An *In Vitro* Model

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Right ventricular failure after left ventricular assist device (LVAD) implantation is associated with high mortality. Management remains limited to pharmacologic therapy and temporary mechanical support. Delayed right ventricular assist device (RVAD) support after LVAD implantation is associated with poorer outcomes. With the advent of miniaturized, durable, continuous flow ventricular assist device systems, chronic RVAD and biventricular assist device (BiVAD) support has been used with some success. The purpose of this study was to assess combined BiVAD and LVAD with delayed RVAD support within a four-elemental mock circulatory loop (MCL) simulating the human cardiovascular system. Our hypothesis was that delayed continuous flow RVAD (RVAD) would produce similar hemodynamic and flow parameters to those of initial BiVAD support. Using the MCL, baseline biventricular heart failure with elevated right and left filling pressures with low cardiac output was simulated. The addition of LVAD within a biventricular configuration improved cardiac output somewhat, but was associated with persistent right heart failure with elevated right-sided filling pressures. The addition of an RVAD significantly improved LVAD outputs and returned filling pressures to normal throughout the circulation. In conclusion, RVAD support successfully restored hemodynamics and flow parameters of biventricular failure supported with isolated LVAD with persistent elevated right atrial pressure. *ASAIO Journal* 2017; 63:41–47.

Key Words: mock circulatory loop, HVAD, biventricular failure, biventricular support

Lack of donor heart availability and improved short-term outcomes with durable left ventricular assist devices (LVADs) have resulted in a rapid rise in long-term mechanical circulatory support. Although LVADs are a well-established form of

practice, long-term effects on the right ventricle remain controversial.¹ The development of right ventricular failure (RVF) occurs in up to 30% of patients following LVAD implantation and has been associated with mortality rates of up to 40%.² Although inotropic therapy, nitric oxide, and prostaglandins are mainstays of acute therapy, management for periods greater than 14 days without recovery is associated with worse clinical outcomes.³ Thus, in patients at high risk or with symptomatic RVF, early biventricular assist device (BiVAD) support has been suggested.³ Biventricular support with existing paracorporeal BiVADs and the total artificial heart systems have, however, been associated with lower survival rates than isolated LVAD systems.⁴ These findings may be one of the main reasons why many institutions opt to provide isolated LVAD and use only temporary extra-paracorporeal support.^{5–8} There is a common misconception that the BiVADs themselves are responsible for the decreased survival rates of BiVAD patients. However, patients requiring BiVAD support are more critically unstable than those capable of being managed with isolated LVADs.^{3,4} Although RVF may be reversed in some instances, patients with persistent RVF will require bridging with a durable right ventricular assist device (RVAD).^{6,7}

Because of the advantages of miniaturized third generation devices, current focus has shifted to providing biventricular support with continuous flow devices. Although right ventricular (RV) support using the HeartWare HVAD is not currently FDA approved, the successful use of dual HeartWare HVAD in a BiVAD configuration has been reported.^{9–11} Anecdotal experience suggests delayed RVAD implantation support for persistent right heart failure after LVAD is not as well tolerated as planned BiVAD implantation although this has not been formally tested. We hypothesized that delayed continuous flow RVAD (RVAD) support would produce hemodynamic and flow parameters similar to patients receiving initial BiVAD support. Therefore, the aim of this study was to assess the hemodynamic performance of isolated LVAD, BiVAD, and isolated LVAD with delayed RVAD in a model of biventricular failure within a four-elemental mock circulatory loop (MCL).

Methods

Mock Circulatory Loop Design

The MCL in this study incorporated the systemic and the pulmonary circulation; systemic vascular resistance (SVR); pulmonary vascular resistance (PVR); VAD implantation sites; valves; left and right heart functions; aortic, pulmonary, and venous compliance; physiologic viscosity; and the resistance of blood vessels. An illustration of the MCL is shown in **Figure 1**. The left and right ventricles were constructed using a truncated ellipsoid-shaped deformable silicone diaphragm (77 mm × 49 mm)

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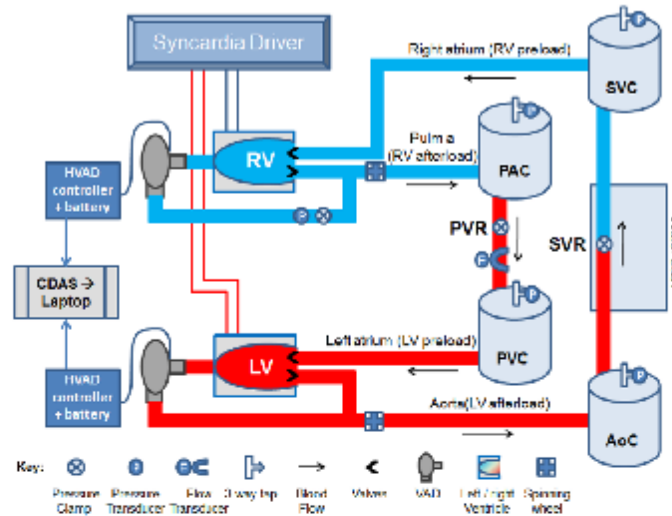


Figure 1. Mock loop configuration. AoC, aortic compliance; CDAS, continuous data acquisition system; LV, left ventricle; PAC, pulmonary arterial compliance; PVC, pulmonary venous compliance; PVR, pulmonary vascular resistance; RV, right ventricle; SVC, systemic venous compliance; SVR, systemic vascular resistance.

encased inside a transparent sealed air chamber, measuring 170 mm in length and 95 mm in width at the base. HeartWare HVADs (HeartWare, Framingham, MA) were attached to the apex of each ventricle, which directed flow to their respective systemic or pulmonary pathways (Figure 1) via mechanical bileaflet valves (On-X, On-X Life Technologies, Inc., Austin, TX).

Contractility

Ventricular contraction and pressures were generated by the 70 cc SynCardia companion driver system (SynCardia Systems, Inc., Tucson, AZ) as has been previously described.¹² The SynCardia driver provides pulsatile flow by pneumatic compression of the silicon ventricles with ejection both through the aortic valve and through the pump in pump systole. Systolic ratio and pneumatic driving pressures were varied for each ventricle to simulate pathologic ventricular function. The pneumatic driving pressure for left and right ventricles were reduced to minimum performance, valued at 100 and 40 mm Hg, respectively. Heart rate was maintained at 90 beats per minutes and systolic ejection ratio at 40%. These low range pneumatic driving pressures and systolic ejection ratios were used to generate hemodynamics to model the impaired ventricular contractility with short ejection duration (270 msec) and low cardiac output seen in advanced heart failure patients. Suction settings were not altered throughout the study.

Circulation Model

Four identical hermetically sealed cylinder shaped chambers (100 mm diameter × 320 mm height), commonly referred to as Windkessel chambers, were used to simulate the pulmonary artery compliance, left atrium/pulmonary venous compliance,

aortic compliance, and the right atrium/systemic venous compliance. Each chamber contained a certain level of fluid and air. Compliance was calculated using validated formula which takes into consideration the relationship between air pressure and volume, and fluid pressure and volume.¹³ On top of each chamber, valves were placed to help regulate pressure/volume. These valves were attached to an air-filled syringe that was able to adjust the amount of air present within the sealed chamber. Although the Windkessel configuration does not account for fluid inertia,^{13,14} these changes are very small. By allowing the system to stabilize before data collection, any changes due to inertia were minimized.

The major components of the MCL were connected via clear pulmonary venous compliance (PVC) tygon tubing (15.9 mm × 2.4 mm) which provided venous and systemic flow resistance. Additional resistance was added using tuning clamps to replicate the SVR and PVR. Flow was measured using TS410 transit-time tubing flow meter (Transonic System, Inc., Ithaca, NY) between the pulmonary arterial compliance (PAC) and PVC chamber, after the PVR clamp (Figure 1). The total volume of fluid (40% glycerol solution) within the MCL was approximately 5 L and maintained at 37° by in-line water bath to simulate the viscosity of blood with a hematocrit of 34%.

Experimental Method

The MCL was run in steady state, and real-time flow waveforms and pressures were monitored using an Aespire anesthesia machine (Datex-Ohmeda, Inc., Madison, WI). Four cardiac conditions were simulated with and without the HVAD operating (Table 1). These include 1) biventricular failure, 2) biventricular failure with isolated continuous flow LVAD (LVAD) support, 3) biventricular failure supported with LVAD receiving delayed

Table 1. Biventricular Heart Failure With and Without Ventricular Assist Device Support: Mock Loop and Clinical Hemodynamics

Condition	HR (per min)	Ao (mm Hg)	MAP (mm Hg)	LA (mm Hg)	Mean PA (mm Hg)	RA (mm Hg)	SVR Dyn. sec cm ⁻⁵	PVR Dyn. sec cm ⁻⁵	LVP (mm Hg)	RVP (mm Hg)	Flow (CO) (L/ min)	LVAD Flow Speed (L/min)	RVAD Flow Speed (L/min)	RVAD Speed (rpm)
A. Mock circulatory loop—VAD off (n = 4 runs)														
Heart failure pre-VAD	90	70 (0.28)	25 (0.5)	37 (0.7)	25 (0.32)	15 (0.6)	406 (13.6)		120	40	2.3 (0.1)	-	-	-
Mock circulatory loop—VAD on (n = 4 runs)														
BVVF with isolated LVAD	90	89 (1.1)	8 (0.1)	15 (0.3)	17 (0.3)	16 (0.4)	157 (9)		120	40	3.5 (0.1)	3.8 (0.5)	2600 (20.6)	-
BVVF + LVAD + delayed RVAD	90	115/72	86 (1.4)	8 (0.4)	18 (0.6)	3 (0.3)	1509 (36)	184 (3)	120	40	4.4 (0.2)	4.5 (0.7)	2600 (22.7)	4.5 (0.6)
BVVF + BVVAD	90	100/71	81 (1.6)	8 (0.3)	13 (0.7)	4 (0.2)	1311 (28)	85 (9)	120	40	4.7 (1.1)	4.9 (1.8)	2600 (22.8)	4.4 (0.7)
B. Hemodynamics in patients with biventricular failure, requiring mechanical support (n = 36 patients)														
Heart failure	87 (17)	77 (11)	27 (5)	40 (8)	16 (6)	1485 (56.0)	290 (173)		-	-	3.7 (1.1)	-	-	-
Pre-VAD (all, n = 36)														
LVAD + VPA ECMO (acute, n = 22)	93 (14)	78 (10)	15 (6)	28 (7)	10 (6)	1189 (44.5)	189 (102)		-	-	4.9 (1.0)	5.3 (0.7)	2700 (21.8)	-
Post-BVAD (chronic, n = 14)	76 (14)	77 (16)	13 (6)	22 (7)	12 (6)	994 (34.3)	125 (54)		-	-	5.6 (1.2)	5.2 (0.8)	2694 (19.2)	5.2 (0.7)

LVAD flow and RVAD flow were recorded directly from HVAD controller. Mock loop flow measured using transonic flow meter. Data shown as mean (standard deviation). Ao, aortic pressure; BVAD, biventricular assist device; CO, cardiac output; HR, heart rate; LA, left atrium; LVAD, left ventricular assist device; LVP, left ventricular pressure (pneumatic generated); MAP, mean arterial pressure; mean PA, mean pulmonary artery; PVR, pulmonary vascular resistance; RA, right atrium; RVAD, right ventricular assist device; RVP, right ventricular pressure (pneumatic generated); SVR, systemic vascular resistance; VPA, ECMO, veno-pulmonary artery extracorporeal membrane oxygenation; VAD, ventricular assist device.

RVAD support, and 4) biventricular failure with initial concomitant LVAD and RVAD support providing BiVAD support. Each experiment was run on four separate occasions. Before the introduction or changes to pump speed, a waiting period of 2–3 minutes was incorporated to allow the system to achieve steady state. For the first experiment, biventricular failure was simulated and recorded (condition 1). Both HVADs (LVAD and RVAD) were then turned on, and SVR and PVR were adjusted to accommodate the changing flows. This demonstrated the effects of initial BiVAD support (condition 4). The two VADs were then turned off, and SVR and PVR were reversed to simulate biventricular failure again. Once recorded, only the LVAD was turned on to represent biventricular failure support with isolated LVAD support (condition 2). Again, slight modifications were made to SVR and PVR. After all measurements were recorded, the RVAD was then turned on to simulate the hemodynamic consequences of delayed RVAD support following LVAD (condition 3). As before, SVR and PVR alterations were required to balance pressures. Data shown are the average of both the pressure and flow values across the four runs (mean ± standard deviation). The “aortic” and “pulmonary” valves were monitored throughout all experiments at 2 minute intervals, before and after any changes and during transitional changes between experimental states, for example, VAD versus no-VAD support. The valves did not open during any of the experiments. Pump speed remained constant for all experiments with an LVAD of 2600 rpm and RVAD of 2200 rpm.

Data Acquisition and Analysis

Flow and pressure waveforms were recorded using Labchart 7 (ADInstruments Pty Ltd, Bella Vista, Australia) and Datex-Ohmeda S/5 Collect software (GE Healthcare, Helsinki, Finland), respectively. Parameters of the LVAD and RVAD pumps were recorded directly from pump controllers onto laptop using proprietary software (continuous digital acquisition system) sampled at 50 Hz. All data were analyzed using Matlab software (The MathWorks, Inc., Natick, MA). All waveforms were smoothed with a low-pass filter using Savitzky-Golay method and were averaged over four cycles. This study was observational. As the pressures and flows were all measured in steady state at the same pump speeds and pneumatic ventricular rate, no statistical tests are available.

Results

The MCL produced physiologic equivalent hemodynamic waveform magnitudes and morphology for each condition targeted for simulation (Table 1 and Figure 2). As expected, higher calculated SVR and PVR values were observed in baseline biventricular failure compared with VAD-supported conditions. Initial BiVAD support was closest to achieving normal ranges but remained within expected values for VAD-supported patients. It can be seen that the elevated left- and right-sided filling pressures (25 mm Hg each) were normalized under BiVAD support. Although isolated LVAD improved cardiac output (from 2.3 to 3.5 L/min), the addition of RVAD markedly increased LVAD pump flow as well as overall circuit flow. Flow rates of the RVAD and LVAD pumps were well matched, despite not actively adjusting speed to achieve this. The mechanical “aortic” and “pulmonary” valves were monitored throughout and remained closed during all studies.

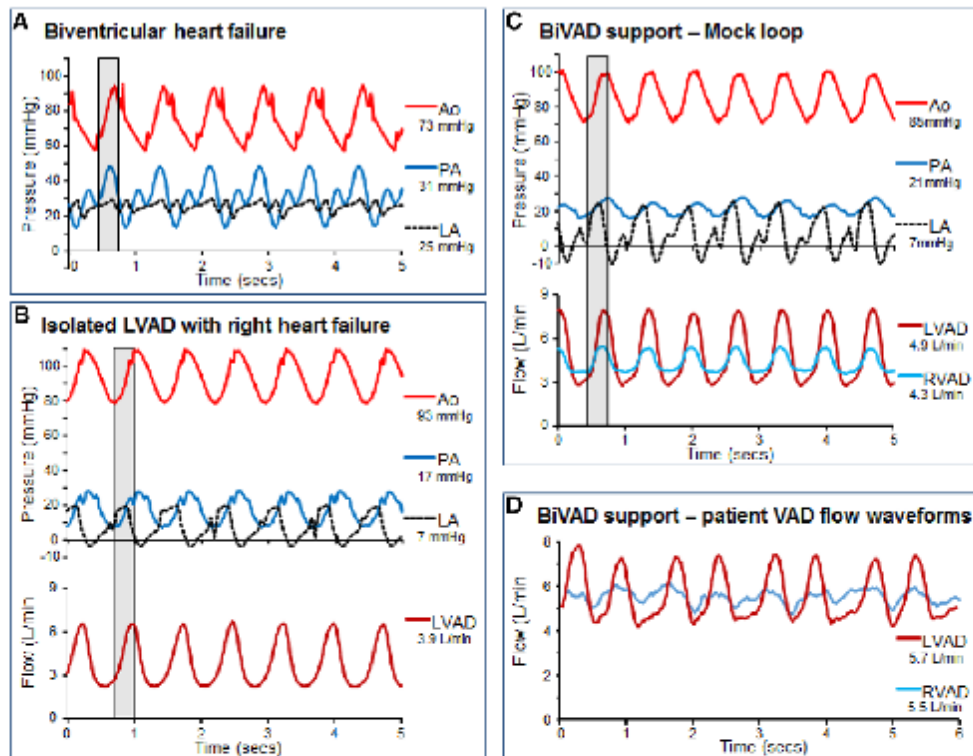


Figure 2. Baseline physiologic and pathologic cardiac pressures without VAD support for the three physiologic states created: (A) biventricular failure; (B) biventricular failure with isolated LVAD support; (C) biventricular failure with BiVAD support. D: The LVAD and RVAD flow waveforms in a clinical patient, confirming the close similarity of the waveforms to those generated by the MCL. BiVAD, biventricular assist device; LVAD, left ventricular assist device; MCL, mock circulatory loop; RVAD, right ventricular assist device.

Figure 2 shows pressure and flow waveforms for all experimental conditions with and without HVAD support. The SynCardia ejection period, which is approximated as a square wave ejection pulse,¹² has been added to the waveforms. It can be seen that the aortic pressure and the VAD flow rise in a linear fashion during the pneumatic compression of the silicon ventricles. The atrial pressure also increases somewhat as further flow is impeded entering the ventricle and then rapidly decreases on cessation of pneumatic support, as the silicon ventricle returns to its neutral noncompressed form. Biventricular supported with simultaneous RVAD and LVAD support resulted in restoration of hemodynamic parameters to normal and best overall flow (4.7 L/min). Biventricular failure supported with isolated LVAD resulted in improved overall flows compared with biventricular failure without VADs (3.5 ± 0.1 vs. 2.3 ± 0.1 L/min); however, there remained persistently elevated right atrial pressure with low pulmonary pressures and left atrial pressures consistent with right heart failure. Delayed RVAD support then reduced right atrial pressures from 17 to 3 mm Hg and increased systemic flow from 3.5 ± 0.1 to 4.4 ± 0.2 L/min. When RVAD was introduced after completion of isolated LVAD, the

hemodynamic outcome was similar to that obtained with combined initial BiVAD. Slight variations between delayed compared with initial BiVAD may be explained by the increased clamping of the SVR and PVR during delayed RVAD support. Nonetheless, in both cases of initial and delayed biventricular support, pathologic states were reversed and normal physiologic filling pressures and flow were restored.

In Table 1 (hemodynamics in patients with biventricular failure, requiring mechanical support ($n = 36$ patients)), it can be seen that the pressures generated by the MCL (both supported and unsupported) are similar to a population of patients with biventricular failure who go on to have biventricular support. In the clinical population, the RVAD pump speed was slightly higher than used in the current MCL. In Figure 2D, LVAD and RVAD flow waveforms from a patient with chronic BiVAD support is demonstrated. It can be seen that the low RVAD flow pulsatility shown in the MCL matches closely the waveforms in clinical patients. *In vivo*, there is significant respiratory inflow variation, which is not modeled in the current MCL. The shape of the LVAD waveform is also similar to that generated by the SynCardia driver.

Discussion

In this study, we developed an MCL to investigate the impact of BiVAD support in the setting of biventricular failure. We generated hemodynamically realistic biventricular failure with low cardiac output and elevated filling pressures at rest, as well as right heart failure with isolated LVAD, both of which were reversed by dual HVAD support. The stability of this MCL allows for assessment of the impact of changes in flow or other conditions on the pump function, flow waveforms, and hemodynamic parameters. We have also shown the pressure and flow waveforms generated in this MCL are very similar to those seen clinically.

The reported incidence rate of RVF after isolated LVAD implantation varies with most reports approximately 30%,^{3,16} with higher rates noted with paracorporeal LVAD systems compared with LVAD.^{16–18} Clinical manifestation of RVF following LVAD support is associated with high mortality and morbidity.^{18–20} Improvements to patient survival with planned biventricular support is suggested⁹ yet remains limited by the challenges associated with identifying RVF pre-LVAD implantation.^{2,21} Although RV recovery may occur, many patients continue to suffer with RVF managed with medical therapy and short-term surgical alternatives such as IABP which are associated with increased mortality. One of the biggest barriers to initiating early BiVAD support or delayed RVAD implantation is the higher mortality associated with BiVAD or delayed RVAD support compared with patients who only require isolated LVAD configurations.^{1,2} These findings, however, relate largely to pulsatile BiVADs with few short-term BiVADs assessed. Dual HVAD therapy is a novel and promising approach for patients with biventricular failure requiring long-term BiVAD support. It is less surgically invasive and more durable and does not require subsequent explantation following RV remodeling.²² We have shown that the hemodynamics of persistent right heart failure with isolated LVAD are reversed with an RVAD. Portable controllers enable hospital discharge and improved patient quality of life by allowing patients to return to their daily activities. The small pump size also allows for different implant configurations (atrial or ventricular RVAD implantation).¹¹

With the advent of more durable, long-term, miniaturized implantable continuous flow LVAD, RVAD, and BiVAD systems,^{23,24} clinical application of a second VAD may overcome the current limitations of delayed RVAD support following LVAD implantation. Our clinical experience is that sequential, delayed durable RVAD in patients with severe RV failure with isolated LVAD is associated with increased short-term mortality.¹¹ This has also been shown in a larger clinical study of planned (temporary) compared with unplanned RVAD support.² Whether costs and length of stay and other clinical outcomes are enhanced by planned BiVAD implantation is not answered in the case cohort studies, and population differences make comparisons difficult.

Our findings demonstrate the expected hemodynamic improvements seen with the use of delayed RVAD support in the setting of isolated LVAD with persistently deranged hemodynamics consistent with RV failure. Isolated LVAD resulted in persistent elevated right atrial pressures, with only slight flow improvements to those of baseline biventricular failure. Delayed RVAD support restored normal hemodynamic parameters and significantly increased LVAD and circuit flows.

Higher flow waveforms were achieved with initial biventricular support (Figure 2), which was influenced by the level of SVR and PVR clamping. Both clamps were slightly more restrictive in the delayed RVAD experiment as two sets of alterations to the SVR and PVR were made. Although restrictions to RVAD flow via narrowing of the outflow cannula are recommended by some investigators to avoid overflowing the pulmonary arteries and preventing pulmonary edema,^{10,11} the level of restriction varies between patients and remains at the discretion of the surgeon.¹¹

The baseline “biventricular heart failure” settings for the mock loop were set based on clinical experience. As shown in Table 1, this accorded well with the biventricular heart failure patient cohort, although RA pressure was slightly lower in the patients before implantation. After implantation, the isolated-LVAD and BiVAD-supported mock loop more successfully unloaded preload compared with patients. This is despite higher flows in the patients, and likely relates to the impact of pharmacologic management of VAD patients decreasing SVR to aggressively maintain MAP < 80 mm Hg, as is current clinical practice at our institution. As can be seen, both the MAP and SVR were lower, and cardiac output was higher in patients compared with the mock loop. The greater ability to titrate preload and generation of higher MAP in the mock loop using mechanical support is likely related to the lack of the distributive vascular tree and compliant proximal arteries seen in patients. Despite these discrepancies, the MCL fundamentally reflects the overall trends seen in the clinical cohort—cardiac output is enhanced with BiVAD support, and right atrial pressure (RAP) and pulmonary artery pressure are reduced.

Both combined BiVAD and LVAD with subsequent delayed RVAD achieved physiologic hemodynamic conditions (Figure 2). Isolated LVAD use results in increased venous return. This has been shown to overload the right ventricle, causing increased interventricular pressure and promoting ventricular overdistension.¹ In the setting of right heart failure, the significantly lower pressure in the left ventricular (LV) cavity caused by LVADs results in the interventricular septum shifting toward the left. Its inability to remain neutral further impairs RV function and thus reduces cardiac output. The importance of ventricular interaction with the achievement of a “neutral” septal position¹⁸ is well recognized, and often used in determining appropriate continuous flow pump speeds. As both the RV and LV chambers were encased in the current MCL, there was no detrimental impact of increased flow on contractility efficiency as may be seen in acute RVF. Notwithstanding this, the current MCL did manifest impaired outputs in the unsupported, failing RV as well as elevated right atrial pressures in the setting of isolated LVAD support, as is seen clinically. Future studies should focus on assessing a cardiac chamber which allows for visualization of left and right ventricular septal shifts in response to pump changes and pathologic conditions.

Despite successfully demonstrating restored hemodynamics with delayed RVAD support similar to those seen with initial BiVAD support, it is important to recognize that all outcomes achieved are limited to clinical observations from a purely hemodynamic viewpoint. The MCL is not intended to circumvent *in vivo* trials, but rather to act as testing platforms to assess the feasibility of the intervention and derive an idea of expected outcomes. The impact of return to theatre for placement of a second VAD, rather than both being placed in the

same operation, needs to be further considered. Furthermore, patients who undergo delayed RVAD placement are, by definition, failing isolated LVAD and are a higher risk population, with likely incipient organ dysfunction. Assessment of ventricular remodeling, genetic phenotype, or activation of regulatory proteins cannot be determined with the MCL.

Limitations

The left and right ventricles were identical in dimension, which is an inaccurate depiction of the natural geometry of the heart. However, we found that this did not affect cardiac output as flows for the left and right ventricles were able to be achieved using different pneumatic driving pressures with the SynCardia controller. The pressures recorded in the MCL are comparable to those of the natural cardiovascular system and are adequate for testing cardiac devices. Both HVADs were implanted into the apex of the left and right silicon ventricles. Although this remains a valid approach, RVAD placement has been achieved in the body of the ventricle, as well as in the right atrium.¹¹

Although pneumatic drivers such as SynCardia can provide physiologically appropriate systolic pressure, the characteristics of both the driver and of the silicon mock ventricle do not mirror diastolic properties including ventricular compliance. Furthermore, although the SynCardia driver does not demonstrate time varying elastance, and is afterload insensitive (within operating limits), outputs do vary in an apparent Starling-like behavior because of some preload sensitivity.¹² Also, although the performance characteristics of the SynCardia pneumatic drive on the silicon ventricles are likely to be different to clinical SynCardia pumps but, as discussed above, despite this limitation, the pressures and waveforms are very close to those seen clinically. As the current MCL houses the RV and LV separately, the impact of ventricular interdependence is not able to be modeled. Although the MCL is unable to assess interventricular interaction between the various pathologic states, it is able to successfully simulate decreased RV contractility (observed during experimentation), simulate LV collapse during excessive pump speeds, and control LV and RV filling with the SynCardia driver, all of which have been associated with VAD-induced shifts to the interventricular septum.^{1,25} Despite all of these limitations, the current MCL successfully models the hemodynamics of BiVF, right heart failure with isolated LVAD, acute correction with acute right heart support (LVAD + veno-pulmonary artery extracorporeal membrane oxygenation), and in the setting of chronic BiVAD support.

The use of mechanical valves may also impair the accurate reproduction of physiologic waveforms. As shown in this study (seen particularly in Figure 2A in the absence of VAD support), mechanical valves produce pressure spikes and oscillations attributed by the water hammer effect during valve leaflet closure. However, these disruptions to waveform morphology were minimized using a low-pass filter, and pressure and flow waveforms are similar to those reported in patients with mechanical valves.²⁶ A significant difference to *in vivo* circulation is the lack of ventriculo-vascular coupling through arterial baroreceptor modulation of vascular tone and sympathetic outflow. Longer term changes of ventricular remodeling are not able to be simulated by the MCL. Despite these limitations,

the MCL presented here has demonstrated to be an effective tool for *in vitro* assessment of mechanical assist devices, developing experimental protocols and training personnel on the maintenance and operation of mechanical assist devices.

Conclusion

Through the use of a four-elemental Windkessel model, we have reproduced the clinical syndrome of biventricular failure, with RVF after isolated LVAD, and shown reversal with initial and delayed BiVAD with normalized output and decreased filling pressures. These hemodynamic findings are consistent with the clinical benefit seen in patients and warrant further evaluation. Future MCLs incorporating ventricular interdependence and vascular feedback may further enhance these physical models. With their reduced invasiveness and complication profiles, durable RVADs may be suitable options for patients previously contraindicated for current paracorporeal systems.

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