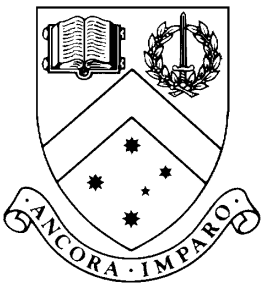
Right Ventricular Failure in Left Ventricular Assisted Patients



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Faculty of Medicine, Nursing and Health Sciences

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Thesis

Right Ventricular Failure in Left Ventricular Assisted Patients

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Declaration of originality

This thesis contains no material that has been accepted for the award of any other degree or diploma in any university or other institution. I affirm that, to the best of my knowledge, the thesis contains no material previously published or written by another person, except where due reference is made.

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Ethics approvals

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- Project: 243/13
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Publications arising out of this thesis (accepted to date)

- Right ventricular failure after implantation of continuous flow left ventricular assist device (LVAD): validation of published risk models

- Extracorporeal Membrane Oxygenation bridge to Ventricular Assist Device support; the double bridge strategy

- Long term right ventricular support with a centrifugal ventricular assist device is a reality

- Banding the Right Ventricular Assist Device outflow conduit: is it really necessary with current devices?

Summary

In patients with refractory end-stage heart failure, cardiac transplantation remains the only established, definitive treatment option endorsed by the current American Heart Association guidelines (1). However, owing to the limited number of available organs and the increasing numbers of patients surviving but remaining unsuitable for transplantation, there has been intense interest in the development of mechanical circulatory support options as destination therapy and bridge-to-transplant. This has led to the development and adoption of left ventricular assist devices (LVAD).

The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial demonstrated both survival benefit and quality of life improvement for patients with LVAD implanted (2). However, even with all the benefits it provides, LVAD technology has not proven to be the panacea that was hoped for. The most prominent amongst the technical challenges to be overcome has been the persistence in the right ventricular (RV) failure rate post LVAD implantation. The incidence of post-operative right ventricular dysfunction after LVAD implantation ranges from 20 to 50% (3). As well as increasing morbidity, the mortality of the peri-operative period increases from 19% to 43% (3). To further complicate matters, the transition from pulsatile flow left ventricular assist devices (LVAD) to continuous flow has necessitated a re-validation of knowledge in this technology.

In Victoria, The Alfred serves as the quaternary referral centre for cardiothoracic transplant and mechanical cardiovascular support services. At The Alfred, these patients are usually either heart transplant waiting list patients who deteriorate while awaiting donor organ availability for transplantation, or new rapidly deteriorating patients who

have not yet been assessed for eligibility for transplantation, but require urgent mechanical support. Mechanical support can be provided as either temporary (usually extra-corporeal membrane oxygenation [ECMO]) or 'permanent' (ventricular assist device [VAD]). The patients can then be bridged on these various devices to either a decision about further management, a more permanent mechanical assist device (i.e. convert ECMO to a VAD), or to transplant. Since the introduction of third-generation devices to the Alfred's VAD programme in 2001, 101 patients have been implanted with either VentrAssist [formerly VentraCor Ltd., now Thoratec Corp., Pleasanton CA, USA], HeartMate II [Thoratec Corp., op cit.] or Heartware HVAD [HeartWare Inc., Framingham MA, USA] third generation continuous flow devices.

The aim of this project is to establish and expand our knowledge of RV failure in LVAD patients in the context of the local population. We created a database to investigate the predictors of RV failure, validate the use of existing predictive models in the local population, study the efficacy of ECMO-to-LVAD bridging and then assess the application of 'permanent' RVAD support in LVAD patients. We also conducted in-vitro studies to assess the optimal on-table modifications required to configure an existing LVAD (the HeartWare HVAD) for 'off-label' permanent RVAD use.

Table of Contents

Chapter 1 – Overview and Literature Review of Topic

Part 1: Right ventricular (RV) anatomy

1.1.1 Introduction

Sitting retrosternally, the heart can be described as two pumps working in series to provide blood flow through two separate circuits. It is composed of primer pumps, the atria, and the circuit pumps, the ventricles. It is constructed around a fibrous skeleton, from which myocardial fibres originate, insert and contract against. The entire structure, together with the proximal great vessels, is encased in the pericardium.

The right heart is located anterior-medially in relation to the left heart and acts as a receptacle for returning de-oxygentated blood from the systemic circulation. It also acts as a pump to supply the low-resistance pulmonary system. The right heart is divided into its constituent chambers, the right atrium and ventricle, by its atrioventricular valve: the tricuspid valve. Embryological studies have found that the right heart originates from different progenitor cells from different sites to that of the left heart (4-6). Anatomical and physiological studies have discovered that the ventricles, although co-located and interdependent, are morphologically and functionally distinct and adapted to different physiological environments (6, 7). This carries implications that pathophysiology and management of failure of either ventricle may not be simply extrapolated from experience with the other.

The right ventricle is comprised of an inlet (sinus) and an outlet (infundibulum) distinct from one another and separated by the crista supraventricularis. In

transverse section, the right ventricle is a crescent-shaped structure secondary to the convexity of the interventricular septum towards the left ventricle. It is bound by the tricuspid valve at its inlet, a free-wall on its anterior surface, the interventricular septum posteriorly and the pulmonary valve at its outlet. Compared with the left ventricle, it is thin walled and has a larger cavity in the adult human (8).

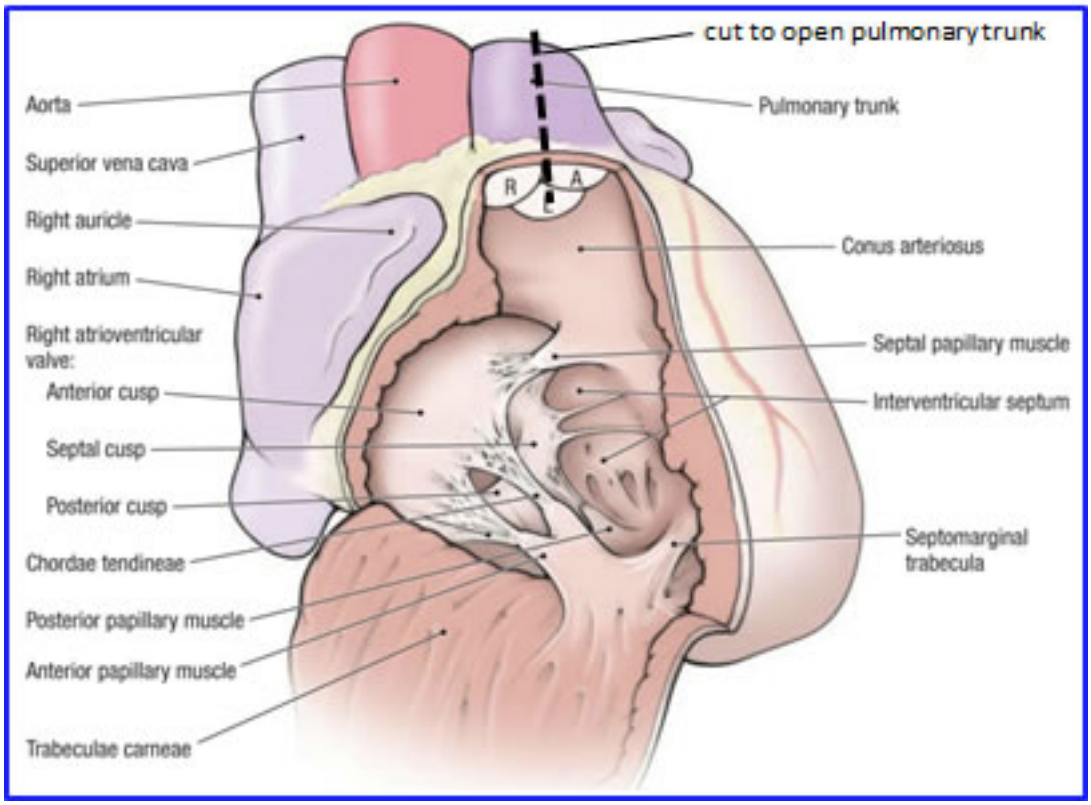

Figure 1 - Right ventricular anatomy (9)

1.1.2 Development of the RV

The cardiovascular system begins forming just before the 20th day of embryonic development (10). The heart itself starts to beat by day 22, as a tubular structure morphologically similar to that in fish (11). There are prominences and

constrictions defining precursors to future structures. At this stage, from cranial to caudal, it is comprised of the bulbus cordis, the ventricle and the atrium, with its inflow from the sinus venosus caudal to the atria and the outflow to the truncus arteriosis cranial to the bulbus (10).

The sinus and infundibulum of the right ventricle originate from different parts of the primitive heart, as was first described by Keith in 1924 (11). The sinus shares a common origin with the left ventricle, the primitive ventricle. The infundibulum, however, appears to be remnant of the proximal part of the bulbus cordis. Ventral-caudal folding of the heart positions the right ventricle in its anatomical anterior location. Thomas et al demonstrated with the manipulation of the Heart and Neural crest Derivatives (HAND) genes and the associated transcription factors in mice that this process is activated in each chamber by its own chamber-specific transcription factors (4).

Formation of the interventricular septum begins at approximately day 30, concurrently with the separation of the atria and ventricles via the growth and fusing of atrioventricular cushions (10). Odgers first observed this process through examination of embryos at various stages of development in 1938. As the developed interventricular septum anatomy suggests with its muscular and outflow components, this septum develops via two distinct processes (12).

The muscular septum arises from the caudal-anterior wall as a muscle fold with contributions from both ventricles. Concurrently, trabeculae from the right ventricular inflow tract coalesce to form a septum in the plane of the interatrial septum. As the fusion of these septa occurs, the point of contact will bulge and form the septomarginal trabecula (10).

Development of the outflow tract septum originates with the septation of the distal bulbus cordis to form the aorta and pulmonary artery. The specific sequence of events is still unclear with multiple theories presenting different origins for the septum. What is agreed is that caudal progression of the process, in combination with the growth of the muscular septum and the endocardial cushion tissue of the atrioventricular canal closes the communication between the ventricles (10).

During foetal life, biventricular wall thicknesses are approximately equal and the interventricular septum is midline and flat as the pulmonary circulation remains a mostly-bypassed high-resistance circuit and the systemic circulation is a low-resistance circuit. Alvarez et al suggested in an anatomical study that relative thickness of the walls of each ventricle bears correlation with birth weight (13). After birth, however, ventricular muscle mass begins to take its adult form. While the right ventricular muscle mass remains consistent with total body size, the left ventricle increases in mass as the increased preload secondary to

increased pulmonary flow and increased afterload secondary increased systemic pressure (14).

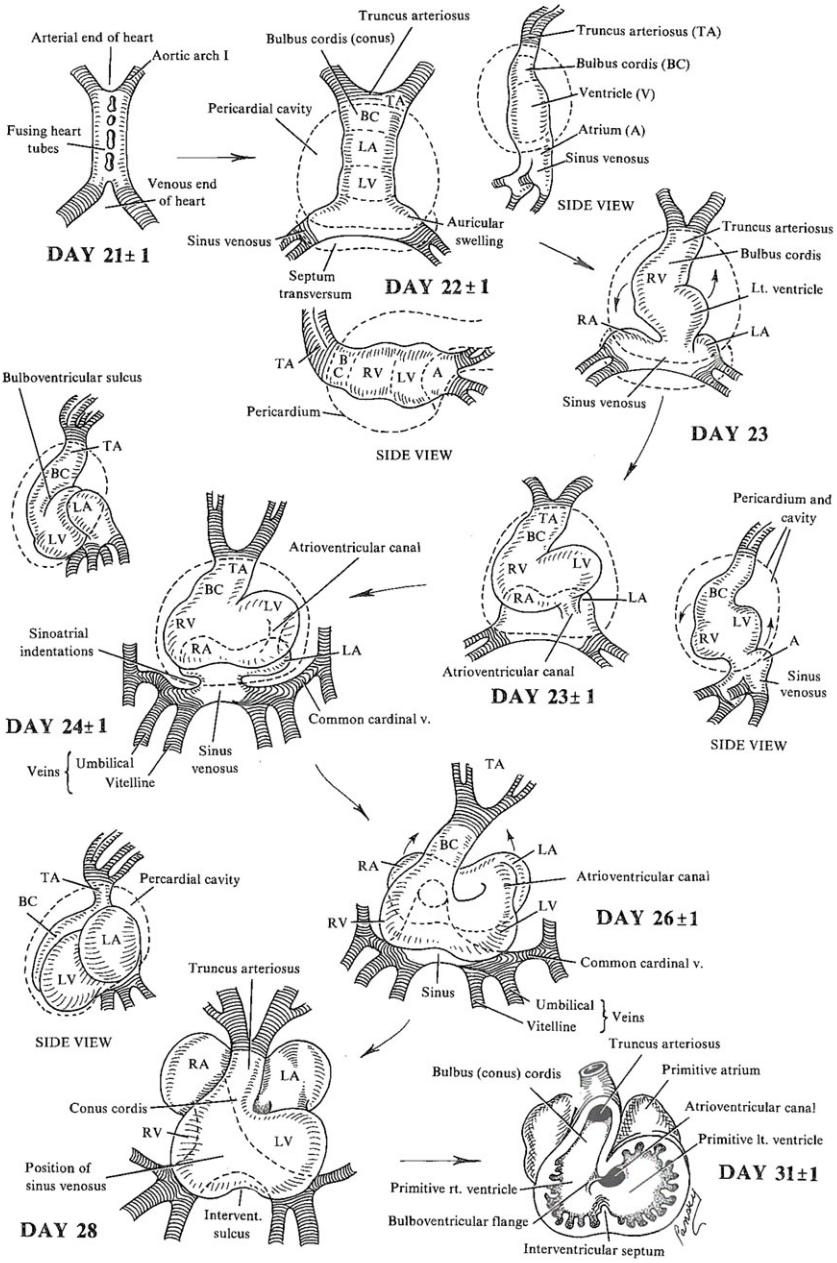

Figure 2 - development of the heart (15)

1.1.3 Normal RV

The right ventricle is a distensible and thin-walled structure adapted to the variable volume loading of the venous system and supplying the low-pressure pulmonary system. Superficially, the myocardium is continuous with that superficial to the left ventricle. Fibres encircling the chamber cause circumferential contraction, drawing the free wall towards the septum. Deeper myocardial fibres, however, are unique in their orientation according to their region, origin and function (7).

Guarding the orifice of the right ventricle is the tricuspid valve. The valve architecture consists of the annulus, the leaflets, the chordae tendineae and the papillary muscles. Despite the nomenclature, 72% of valves are not made up of three leaflets owing to fusion or clefts in the typical leaflets (16). Typically, the leaflets are the semilunar septal leaflet, quadrangular anterior leaflet and the triangular posterior leaflet. The papillary muscles contract to aid coaptation, and arise from the sinus of the ventricle. There are 3 groups of 4 to 5 muscles, each group attaching to the free edges of the 2 adjacent leaflets. The annulus lies within the fibrous skeleton of the heart, and dilates in diastole to aid ventricular filling (16).

The sinus or inflow tract begins at the annulus of the tricuspid valve, continuing in an apical direction. This region is characterised by the presence of trabecular carneae, the largest of which is the septomarginal trabeculae and the presence of

three muscular bands: the parietal band, the moderator band and the septomarginal band. The trabeculae extend from the origin of the anterior papillary muscle to the insertion of the crista superventricularis to the interventricular septum. The sinus is separated from the outflow tract by the U-shaped confluence of the parietal and septomaginal bands – the crista supraventricularis (17).

James described in 1985 the crista supraventricularis as providing the only attachment between the right ventricular free wall, the anterior leaflet of the tricuspid valve and the outlet portion of the interventricular septum (18). The circumferential orientation of fibres here both draw the free wall towards the septum while aiding coaptation of the tricuspid valve leaflets during systole. Thus, this structure provides a major anchor-point for the sinus free wall to the septum for traction during systole and contributes significantly to right ventricular function (7).

Myocardial fibres of the right ventricular sinus originate from the posterior skeletal triangle, and are oriented longitudinally between the tricuspid annulus and the apex. At the apex, the fibres begin to blend into those of the interventricular septum. Ventricular contraction begins in the sinus. It is noteworthy that the fibre orientation and contraction here is similar to that of the left ventricle, as the aforementioned embryology would suggest (7).

The outflow tract is unique to the right ventricle as a structure independent from the inflow tract. Keith suggested from his studies of mammalian and fish hearts that it is an adaption of the bulbus, which is structured to regulate the high pressures generated by contraction in the sinus, and thus protect the delicate pulmonary vasculature. It has been suggested that the developing left ventricle aIso has a similar structure, which completely regresses during foetal heart development as it is evolutionarily redundant (11).

Macroscopic examination of the infundibulum reveals a vertical, cylindrical structure with myocardial fibres originating in the anterior skeletal triangle, and stacked in a circumferential orientation. These fibres blend into those of the left ventricle (7).

The conus lies superficial to the sinus, beyond the crista supraventricularis. Cross-sectional examination reveals a thicker wall-to-cavity ratio than the sinus, and a smaller diameter (19). Contraction is in a peristaltic motion from apex to pulmonary valve (20).

Situated predominantly between the inlet of the right ventricle and outlet of the left ventricle lies the interventricular septum. It convexes into the right ventricle, leaving the chamber crescent shaped on transverse cross-section (21). The superior-posterior aspect of the septum is fibrous and of differing embryological origin to the rest of the septum as described above (6, 10, 12). Although barely

appreciable, it is important as it serves as the cranial attachment for the fibrous raphe where myocardial fibre contributions from both ventricles attach (7).

Septal myocardial fibres from the right run longitudinally, blending into the free wall towards the apex and making up only a small portion of the muscle mass. The bulk of the septum originates from the left, and is structurally is more complex. The upper muscular septum is composed of fibres fanning out from the outlet-end of the raphe. Towards the apex, however, fibre orientation gradually changes and begins to follow the orientation of the corresponding left ventricular free wall (22, 23).

1.1.4 Septal physiology

Interventricular septal contraction accounts for up to 50% of right ventricular output. Therefore, understanding the complex interplay between the factors that influence the form and function of the interventricular septum is integral to understanding the function of the chamber. It has been said that the septum is involved in the activation of the Frank-Starling mechanism and moderates interdependence between the ventricles. While affected by the pressure-gradient between the ventricles, the construction of the septum predisposes it to behave within certain parameters (8, 19).

As aforementioned, the bulk of septal musculature is continuous with that of the left ventricular free wall. The functional implication of this is that it behaves as

part of the left ventricle. Molaug et al demonstrated this in their study of myocardial function of the septum by measuring changes in myocardial fibre length throughout the cardiac cycle under different stresses. It was found that myocardial shortening of the septum was impaired along with the left ventricular free wall when the aorta was clamped, but not when the pulmonary artery was clamped. The same study also found that, in releasing pericardial pressure by pericardotomy, preload in the septum was increased, which was associated with an increase in myocardial shortening (23).

Scher et al discovered in 1955 that contraction in the septum begins halfway between the apex and the base on the left side, where the left bundle begins to branch. The right then follows in approximately 5 milliseconds, with excitation beginning near the base of the anterior papillary muscle group (24).

Armour et al went on to demonstrate that the caudal left septum contracted earlier than the rest of the septum and generated higher intramyocardial pressures. Using canine hearts, it was observed that the left septum contributed significantly to the output of the left ventricle, while the right, contracting with the sinus region of the free wall, was more in keeping with generating pressure within the sinus region (22).

Throughout the cardiac cycle, the septum remains in a convex position to varying degrees towards the right ventricle. This is important in maintaining efficiency of

right ventricular contraction as the septum provides anchorage to the free wall to generate pressure as well as generating pressure via contraction. Piene et al studied the influence of right ventricular pressure, left ventricular pressure, transseptal pressure and pericardial pressure on the septum to better understand this concept. They observed that, in a normally functioning canine heart, septal position was equally influenced by pressure from both sides. However, this influence was almost 10 times greater at end-diastole as it was at end-systole, indicating a significant increase in stiffness with contraction (21).

Seemingly paradoxical to this, however, was Guzman's previous finding that the septum, once flattened by RV loading using Mueller's maneuver in diastole, remained flattened during systole for two to three beats. The initial shift in interventricular septal position was, predictably, associated with a negative left-to-right transseptal pressure gradient. Still, it was observed that this septal position was maintained despite the gradient normalising by systole. This suggests that once a significant left shift in the septum is established, other forces override the influence of the pressure gradient to maintain the deformation (25).

1.1.5 Normal blood supply of the RV

The bulk of the blood supply of the right ventricle is supplied by the right coronary artery (RCA). In particular, epicardial branches of the RCA course through the right ventricular free wall, providing supply to all but the anterior margin abutting the left anterior descending (LAD) artery. The interventricular

septum receives the bulk of its perfusion from the LAD, with only the basal one-third being perfused from the posterior descending artery (PDA) (8).

Common anatomical variations to this include the conus artery, and PDA territories. The conus, in 30% of cases, is known to be supplied by an artery of a separate origin from the rest of the RCA. In such a setting, though, the flow physiology of the right coronary artery is retained. PDA territory, supplying the inferoseptal region, is determined by the dominance of coronary supply. In 80% of cases, this represents the RCA (8, 26).

Flow through the right coronary circulation continues consistently throughout the cardiac cycle, as opposed to the predominantly diastolic filling of the left circulation, albeit at a lower rate. In canine studies, myocardial oxygen extraction of the right ventricle has been found to be approximately one-half to one-third of that of the left ventricle. However, unlike the left ventricle, the right is capable of varying its oxygen extraction according to its need. These features have been postulated as potential protective factors accounting for the resilience of the right ventricle in ischaemia and infarction. With the onset of hypertrophy, however, there is a diminishing of these perfusion advantages (26, 27).

1.1.6 Contraction of the RV

Despite the mechanical disadvantage, the normally functioning right ventricle pumps blood at the same rate and volume as the left ventricle. This is owing to

the characteristics of the pulmonary circulation: low pressure and uniformly compliant. The normal ejection fraction of the right ventricle is approximately 40%.

Contraction and subsequent ejection of the right ventricle is a result of the complex interaction between the superficial myocardial layer, the deep myocardial layers of the free wall, the conus and the interventricular septum, and the left ventricle. It is regulated through staggered conduction of excitation. The mechanisms of contraction are the bellowing of the chamber via circumferential contraction of the superficial fibres and the crista superventricularis; the longitudinal shortening of fibre in the axis between the base and the apex; and traction from the left ventricle via the interventricular septum and anchorage points of right ventricular musculature (19, 26).

Beginning at the base, myocardial contraction initially spreads in a peristaltic manner throughout the sinus. After the conduction delay regulated by the autonomic nervous system, the infundibulum contracts. Owing to the low afterload, the isovolumetric contraction phase of the cardiac cycle is relatively short compared to the left. Multiple studies have observed that forward end-systolic flow into the pulmonary system continued as myocardial relaxation of the free wall and outflow tract began. However, septal contraction continues after this point and ceases with the cessation of forward pulmonary artery flow. These findings suggest that right ventricular output is initiated by the free wall

and infundibulum, but maintained with significant contribution from the septum (19, 26).

1.1.7 Interdependence and interaction of the ventricles

Bernheim first described the concept of ventricular interdependence in 1910 when he observed the effects of left ventricular hypertrophy on right ventricular function. It has since been defined as the forces that are transmitted from one ventricle to the other through the myocardium or pericardium, independent of neural, humoral or circulatory effects. These effects are secondary to the anatomical connection of the structures (28).

Ventricular interaction also occurs via their circulatory effects. These are described as interactions in series, as they are the result of series interaction of the left and right heart via their respective circuits. Unlike the instantaneous effects of interdependence, these interactions are delayed by a few beats as the flow-on effects to changes are conducted through the circulatory system (19, 26).

Slinker and Glantz sought to clarify the importance of these different types of ventricular interaction to overall function. Using statistical analyses of observed transient changes in left and right ventricular pressures in the setting of pulmonary artery and vena cavae constrictions in canine hearts, their team found that, with the pericardium closed, interdependence was half as important as series interaction at end diastole and one-third at end systole. In the absence

of pericardium, this decreased to one-fifth at end diastole and one-sixth at end systole. They conclude that although less significant than series interaction, interdependence still contributes significantly to output (29).

Interdependence can be described as diastolic or systolic. Diastolic interdependence is where the anatomical relationships between the ventricles and the pericardium affects diastolic function of each other. In the absence of pericardium, Bemis, Elzinga and Santamore et al have in separate in vivo studies demonstrated independent loading of one ventricle increases the pressure and decreases the volume in the other (30-32).

The pericardium acts as a significant, but non-essential, mediator to diastolic interdependence. Structurally, the pericardium is composed of three layers of collagen and elastin fibres embedded in a weak but viscous ground substance matrix, each layer aligned 60 degrees from its adjacent layer. Functionally, it acts to restrain acute increases in volume of the heart, while allowing enough compliance for normal physiological changes. While it has been demonstrated that interdependence occurs in the absence of pericardium, its presence is known to greatly accentuate the effect (19).

Systolic interdependence, on the other hand, describes the direct influence each ventricle has on the contralateral ventricle's output. While this is predominantly mediated through the interventricular septum, the free walls have also been

demonstrated to contribute. In the literature, studies have used canine hearts with electrically isolated ventricles where there is an active left ventricle and an electrically silent right to demonstrate the persistent generation of right ventricular pressure and output without specific right free-wall activity, and vice versa. It has been estimated that 20 – 40% of right ventricular systolic pressure is generated from the left, and 4 – 10% of left ventricular systolic pressure results from the right-sided activity (19, 26).

Part 2: RV Failure

1.2.1 Introduction

Heart failure is the inability for the heart to produce enough output to supply the body's haemodynamic requirements. This can be a result of direct changes to the heart, or flow on effects of other processes. The most common cause of right ventricular failure is left ventricular failure. In this scenario, left ventricular failure results in i) pressure and volume overload of the pulmonary system and ii) structural changes relating to interdepenence affecting efficiency of contraction. The resulting afterload increase results in myocardial hypertrophy of the right ventricle as an initial response. As progression from adaptive hypertension to maladaptive hypertrophy occurs, the equilibrium between maintaining wall tension and preload fails and dilatation occurs. As this progresses, myocardium loses its contractility and the preload passes the apex of the Starling curve to its descending arm of cardiac output.

The wall stress in a pressure overload situation such as pulmonary hypertension can be described by the Law of Laplace.

$$S=Pr/w$$

S=wall tension, P=intraluminal pressure, r=chamber internal radius, w=wall thickness

As this formula shows, the wall stress is increased by the increase in intraluminal pressure. As perfusion of the right ventricular free wall via right coronary artery is persistent throughout the cardiac cycle and depends on the low wall stress, proportional increase in wall thickness must occur (33).

1.2.2 Hypertrophy and maladaptive growth

In 1985, Marino et al noticed the marked contrast between the changes to the right ventricle's contractile abilities when exposed to volume versus pressure overload in the literature, and investigated the underlying histological changes (34). Feline subjects were used to create volume and pressure overload models and control groups, and were subjected to haemodynamic testing before being dissected for histological and electron microscopy examination after seven to ten weeks.

Both experimental protocols resulted in equal hypertrophy on macroscopic examination. Cardiocytes also hypertrophied in a similar manner: there were increases in mitochondrial, myofibrilar and nuclear mass. However, there was a significant increase in the cardiocyte size and no change in density in the volume overload group, while the pressure-overloaded group demonstrated an increase in connective tissue density in the extracellular matrix. In particular, collagen fibrils were found deposited throughout pressure-overloaded myocardium, with a drop in cardiocyte density compared with the volume overloaded and control groups. While the cause of this was unclear, it was suggested that the phenotype

changes with pressure versus volume overload are explained by this phenomenon.

A similar experiment was conducted in 2011 by Bartelds et al. (35). The same groups of experimental protocols were created. The subjects were examined using exercise testing after three weeks, and magnetic resonance imaging (MRI), haemodynamic testing and histological analysis after four weeks.

Mice from each group were exercise tested by being placed in cage wheels. Those with pressure overload of the right ventricle were exercising significantly less than the control and volume overload groups. Calculated stroke work and wall stress was significantly higher in the pressure overload group as opposed to volume overload, even though degree of hypertrophy was equal. The pressure overload group demonstrated a degree of dilatation.

As in Marino's experiment, marked histological differences were found between the volume and pressure overload groups. Pressure overloaded ventricles had a much more significant expression of natiuretic peptide A, alpha 1 skeletal muscle actin, modulatory calcineurin interacting protein-1, beta-Myosin Heavy Chain (MHC). There was also down regulation alpha-MHC and extracellular signal-regulated kinase (ERK) 1/2. Protein Kinase B (Akt) expression was the consistent across pressure and volume overload groups. The inversion of the expression of alpha versus beta-MHC represents a reversion to the foetal state,

which, as aforementioned, is also a pressure-loaded state of the RV. This shift in molecular isotype has significant consequences in myocardial function, as Herron et al demonstrated in 2002 (36). ERK and Akt are moderators of hypertrophy.

Li et al also investigated the cellular and molecular changes in the transition from hypertrophy to decompensated heart failure in myocardium (37). Using mice subjected to aortic constriction, they found that the rodent left ventricles were initially able to maintain contractility with increasing hypertrophy and fibrosis. However, 12 to 16 weeks after onset of pressure overload, subjects rapidly decompensated. Histological examination demonstrated significant apoptosis of myocytes with downregulation of regulatory proteins ERK 1/2, Akt and glycogen synthase kinase (GSK) 3β.

Pan et al further investigated molecular changes associated with hypertrophy and demonstrated in 1999 that mechanical stress, mediated by angiotensin II, interleukin-6 and calcium, activated Janus Kinase (JAK)/signal transducers and activation of transcription (STAT) pathway (38). Greater depth in the molecular response to mechanical stress causing contractile and regulatory protein expression changes leading hypertrophy was discussed by Ruwhof et al in 2000 (39). In this review, literature describing the stretch of myocardial integrens and stretch-activated ion channels (SACs) activating a cascade of intracellular biochemical changes was discussed. The subsequent expression of 'immediate-

early' genes(40-42), reactivation of foetal isoforms of genes encoding sarcomeric proteins (43) and shifts in isogene expression relating to energy metabolism (44, 45) were described to precede hypertrophy. Sadoshima et al's (46) finding that cells from stretch-conditioned medium induces hypertrophy when transplanted into non-stretched medium induces changes associated with hypertrophy was also described as evidence of autocrine and paracrine mechanisms. In particular, angiotensin II, endothelin-1 (ET-1) and transforming growth factor-beta were noted as known mediators. Cardiomyocyte protein synthesis in hypertrophy can thus be described as mediated by stretch and enhanced by autocrine, paracrine and neurohormonal influences (33).

Although none of the aforementioned changes suggest new myocyte growth, there is evidence of cardiac stem cells continuing to exist in a fully differentiated adult organ with multipotent potential (47). However, their role in this particular setting is, as yet, unclear.

Reversibility of hypertrophy was investigated by Kasimir et al, who reviewed the patients with primary pulmonary hypertension with isolated bilateral lung transplant treated at their centre over a two-year period and survived the peri-operative period (48). They measured physiological and echocardiographic changes. Although the sample size was small (n=14), they were able to demonstrate a statistically significant decrease in right ventricular dimensions, tricuspid annulus and heart failure class. While the focus of the study was to

investigate the suitability of lung transplantation as a treatment option, the results demonstrate reversibility of right ventricular changes secondary to pulmonary hypertension when the latter is removed from the equation.

Right ventricular hypertrophy is an independent predictor of mortality in cardiac disease. As part of their study, the Multi-Ethnic Study of Atherosclerosis (MESA) group reviewed right ventricular mass and volumes in their clinically well, multi-state American cohort (n=4144) via magnetic resonance imaging (MRI) (49). With a median follow-up of 5.8 years, five-year risk of mortality or heart failure for those with RV hypertrophy at baseline, adjusted for age sex, race, body mass index, education, C-reactive protein, hypertension and smoking status, was 2.52 times that of those without hypertrophy (C.I. 1.55 – 4.10, $P<0.001$).

1.2.3 Dilatation

Although a well recognised progression of the maladaptive remodeling process in heart failure, the molecular mechanisms governing dilatation is not as well understood as that of hypertrophy. It is believed that the aforementioned changes to the myocardium weaken its structural integrity and contractile force. In 1996, Tagawa et al reported observing persistent and progressive cytoskeletal changes in cardiomyocytes in the transition from hypertrophy to right heart failure, in particular that sarcomere mechanics are altered and microtubule density is increased (50).

As dilatation occurs, the Law of Laplace dictates increasing wall stresses, which in turn increase energy demand while simultaneously decreased oxygenation from compromised coronary perfusion and systemic and pulmonary hypoperfusion. This sets forward a downward spiral in contractility and dilatation. The aforementioned molecular mechanisms, in symphony with oxidative stresses (51), inflammation (52) and ischaemia (53) further exacerbate this spiral, and eventually leads to failure.

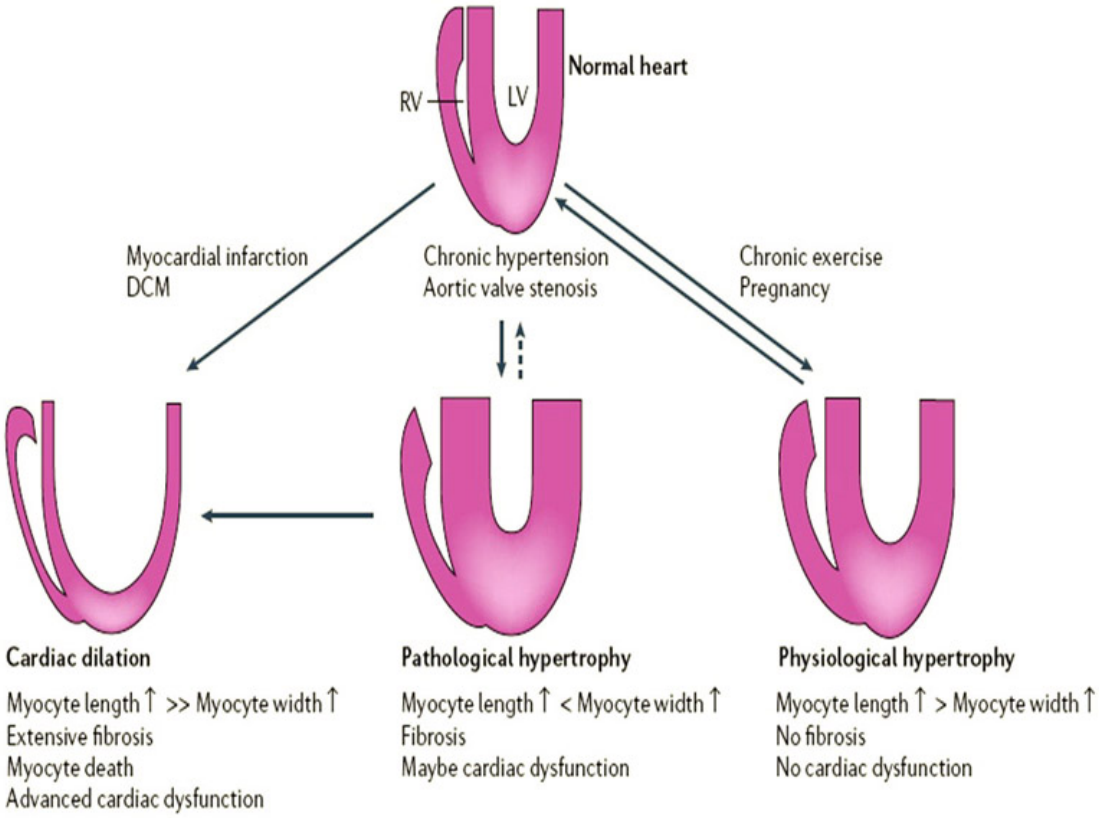

Figure 3 - Hypertrophy and dilatation (54)

1.2.4 Conduction changes

As the heart remodels and its myocardial composition changes, its conductive properties change. Using tissue from explanted human hearts of transplant

candidates, Kawara et al investigated the conductive properties of fibrosed myocardium (55). In this in vitro study, it was reported that the specific architecture of fibrosis, and not its density, was had the strongest correlation with conduction delay. In particular, long, compact strands of fibrosis were correlated with a significant decrease in a 40% decrease in conduction velocity.

As expression of regulatory protein ET-1 is so prominently altered in the haemodynamic changes leading to ventricular failure, Mueller et al investigated its role in the electrical remodeling process (56). This group reported that, in an in vivo and histological study of transgenic rodent models with cardiac-specific overexpression of human ET-1, significant ventricular conductive delays can be observed as early as 4-weeks post ET-1 overexpression. This preceded clinical heart failure, fibrosis and hypertrophy, and was progressively worse. This suggested the electrical remodeling process was a consequence of the same processes driving maladaptive changes altering the conductive pathway, not merely a consequence of the maladaptive changes alone.

However, as Massare et al reported in their 2008 study, the interstitial fibrosis contributes to ventricular electrical changes (57). Also using rodent models, this group subjected fibrosis-resistant mice to pressure overload and compared with normal mice, and demonstrated a decreased susceptibility to and duration of ventricular tachycardia in mice without significant fibrosis, despite similar degrees of hypertrophy.

Part 3: RV Failure with Left Ventricular Assist Device (LVAD)

1.3.1 Introduction

In patients with refractory end-stage heart failure, cardiac transplantation remains the only established, definitive treatment option endorsed by the current American Heart Association guidelines (1) and is described as the "gold-standard treatment" in the European guidelines (58). However, owing to the limited number of available organs and the increasing numbers of patients surviving but remaining unsuitable for transplantation, there has been intense interest in the development of mechanical circulatory support options. This has led to the development and adoption of left ventricular assist devices (LVAD).

The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial demonstrated both survival benefit and quality of life improvement for patients with LVAD implanted (2). Since, as aforementioned, the most common driver of right ventricular dysfunction is pressure overload from left ventricular failure, it is reasonable to expect the introduction of mechanical offloading of the left ventricle would reduce right ventricular afterload and thereby improving right ventricular function. However, owing to the complex interplay between the flow dynamics of the cardiovascular system, geometry of the ventricles and extra-cardiac influences of cardiac function, the behaviour of the RV is often not so predictable. To further complicate matters, the transition from pulsatile flow left ventricular assist devices (LVAD) to continuous flow has necessitated a re-validation of knowledge in this technology.

The incidence of post-operative right ventricular dysfunction after LVAD implantation ranges from 20 to 50% (3). As well as increasing morbidity, the mortality of the peri-operative period increases from 19% to 43% (3). Such wide variation in the incidence of can be attributed to variations in study size, protocols and definitions of RV failure used in studies. One commonly accepted definition was prescribed by INTERMACS as, "Symptoms and signs of persistent right ventricular dysfunction [central venous pressure (CVP) > 18mmHg with a cardiac index <2.3 L/min/m2 in the absence of elevated left atrial/pulmonary capillary wedge pressure (greater than 18 mmHg), tamponade, ventricular arrhythmias or pneumothorax] requiring RVAD implantation; or requiring inhaled nitric oxide or inotropic therapy for a duration of more than 1 week at any time after LVAD implantation" (59).

1.3.2 Overview of VAD

Extracorporal mechanical circulatory devices underwent their first proof-of-concept in humans in the early 1950's, as the advent of complex cardiac surgery necessitated a means to create a sustained bloodless operative field whilst protecting end-organs beyond that which hypothermia could provide (60-62). By the 1960's, this technology was adapted to specifically support the failing left ventricle for a period of weeks or longer in animal models, and in 1966, DeBakey et al successfully supported a series of critically ill humans with severe heart failure using experimental left ventricular bypass pumps that were produced in-house (63). The technology has since undergone further development and

commercialisation. Generations of refinement have resulted in the current selection of reliable and fully-implantable, continuous flow devices that can be calibrated for support of either ventricle.

Mechanical circulatory support (MCS) is now applied in the following circumstances (58):

Table 1 – Adapted from European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

Bridge to decision	Use of MCS in patients with drug-refractory acute circulatory collapse and at immediate risk of death to sustain life until a full clinical evaluation can be completed and additional therapeutic options can be evaluated.
Bridge to candidacy	Use of MCS to improve end-organ function in order to make an ineligible patient eligible for transplantation.
Bridge to transplantation	Use of MCS to keep a patient at high risk of death before transplantation alive until a donor organ becomes available.
Bridge to recovery	Use of MCS to keep patient alive until intrinsic cardiac function recovers sufficiently to remove MCS.
Destination therapy	Long-term use of MCS as an alternative to transplantation in patients with end-stage heart failure ineligible for transplantation.

The ESC's current recommendations regarding implantation of LVAD are (58):

Table 2 – Adapted from ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012

Recommendations	**Class**	**Evidence level**
An LVAD or BiVAD is recommended in selected patients with end-stage heart failure despite optimal pharmacological and device treatment and who are otherwise suitable for heart transplantation, to improve symptoms and reduce the risk of premature death while awaiting transplantation.	I	B
An LVAD should be considered in highly selected patients who have end-stage heart failure despite optimal pharmacological and device therapy and who are not suitable for heart transplantation but are expected to survive > 1 year with good functional status, to improve symptoms and reduce the risk of heart failure hospitalization and of premature death.	IIa	B

The era of FDA-approved, commercially available LVAD began in 1986 with the release of the pneumatically driven HeartMate LVAD, leading the development and implementation of the first generation systems (64). Although eventually miniaturised to an implantable size, these systems were still large, noisy and mechanically complicated, hence limiting the quality-of-life of patients. Pulsatile flow was established in a similar fashion to the native ventricle: passive filling followed by pumping action. Blood was vented directly from the heart, and pumped back into the pulmonary artery and the aorta. Pumping was, depending on the specific pump, actuated either by pneumatic or electrically driven forces, with back-up hand pumping in extracorporeal devices. They are capable of generating six to ten litres per minute in output. The REMATCH trial was

conducted on a cohort of patients implanted with the HeartMate VE, an example of this generation of devices (2).

The 1990's heralded the introduction of the second generation of LVAD. These devices had a single moving part: a rotor, which produced continuous axial flow (64). This allowed for further miniaturization, lower noise, greater comfort for the patient and greater reliability (65). The inflow cannula vents the left ventricle from the apex, while the outflow cannula pumps into the aorta. The rotations and flows are pre-set, and the device is capable of producing greater than ten litres per minute of flow (64, 65).

Third generation of LVAD is a further improvement on continuous flow technology by removing the single mechanical part. The rotor is suspended in the flow pathway and moved by haemodynamic levitation and/or magnetic levitation (64). Centrifugal flow is generated. The systems have been further minaturised, allowing for implantation of the entire device in the pericardium. The design theoretically allows for further improvements in durability and reliability.

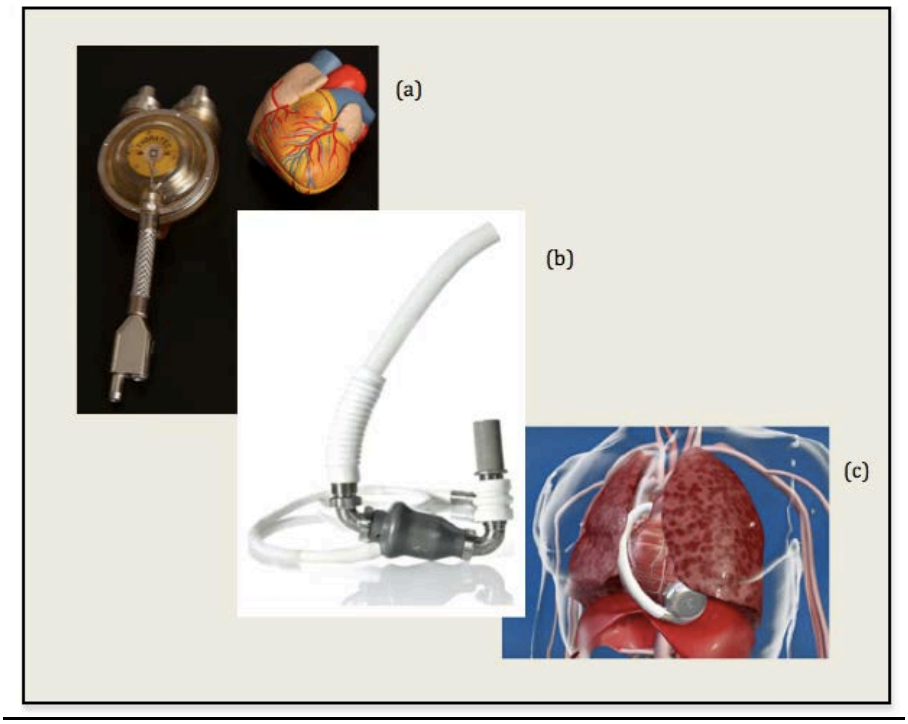

Figure 4 - (a) First-generation LVAD (66); (b) Second-generation LVAD (64); (c) Third-generation LVAD (67)

1.3.3 Cost of LVAD

The medical community is in agreement that LVAD remains an expensive management option. However, there remains intense debate on whether this high cost represents good value for money. Rogers et al (68) investigated the cost-effectiveness in the United States destination therapy LVAD in 2012. Combining data from multiple sources, a Markov model evaluating survival, from which hospitalization rates, quality of life and cost data could be extrapolated was developed for this purpose. These authors found that, although 5-year costs were significantly more expensive than optimally medically managed patients ($360,407 USD vs. $62,856), there was significant improvement in quality-adjusted life years (QALY) and life years. Furthermore, compared to pulsatile devices, there is a 75% improvement in cost-effectiveness ratio compared with quality-adjusted life year. Although the authors acknowledged the costs are still

higher than the established threshold for cost-effectiveness, they suggested that the improvements over time with cost, as well as the significant benefits in all other measure parameters, support the ongoing use of LVAD as destination therapy.

Clarke et al agreed with this finding in their 2014 study of the NHS. At the time of writing, estimated probabilistic incremental cost-effectiveness ratio (ICER) for end of life care in Britain was £53,527/QALY (95% CI £31,802 - £94,853). However, the cost of LVAD was £80,569/QALY. While the authors conclude that a cost-effectiveness argument cannot be made for this management strategy yet, they acknowledge that the ICER for LVAD is now approaching an acceptable level (69).

These findings are juxtaposed against a study conducted in the United Kingdom by Moreno et al (70). These authors assessed the cost-effectiveness of LVAD as a bridge-to-transplant. Using a similar Markov model based on NHS data, they found that the mean cost per QALY was £258,922. Although acknowledging the survival benefits described in the literature, the group noted that improvements to medical management have seen significant improvements in survival on medical therapy alone, and that the £94,200 initial cost of the device detract from its overall cost effectiveness. They conclude that, in terms of cost, this management strategy lacked justification.

There is now evidence that with accumulated clinical experience, modern systems decrease in cost over time. Mishra et al (71) evaluated their own experience. Comparing their earlier experience with extracorporeal Ventrassist systems and their current utilization of the Heartware device, they found that, even with more expensive unit cost, the improvement in logistics, selection and management in patients reduced total costs by $14,000 (3.6%) with each successive patient.

1.3.4 LVAD effects on the RV

Even prior to the commercialisation of LVAD technology, the effects of effective LVAD function on the right ventricle have been noted and studied (72). Although the left ventricle (LV) is offloaded and output to the systemic circulation is restored by the implantation of an LVAD, the interdependence of the ventricles, coupled with the already compromised state of the RV from congestive heart failure exposes the right heart to potentially detrimental dynamic changes. These changes may, in turn, predispose the RV to failing. Specifically, three physiological effects of LVAD on the RV are said to affect RV function: increase in RV preload, decrease in RV afterload and a change in RV contractility (73).

Acute increase in RV preload occurs owing to the aforementioned series interaction of the ventricles leading to increased venous return. As right ventricular pressure increases, the already compromised myocardium is quickly stretched beyond their peak performance on the Frank-Starling curve (73). This is compounded by the ensuing ischaemia as intracavity pressure exceeds

coronary perfusion pressure (3). These effects exacerbate dilatation of the chamber and the tricuspid annulus.

Offloading of the LV should result in a decrease in pulmonary artery pressure and hence RV afterload. Pauwaa et al evaluated the effectiveness of second and third generation devices in their cohort of patients (74). Although only a small cohort of fifteen patients, they were able to demonstrate a statistically and clinically significant reduction in mean pulmonary artery pressure post-implantation of LVAD (31.9 ± 10.6 mmHg vs. 22.1 ± 6.6 mmHg, $p = 0.001$). These results correlated closely with the authors' review of the literature. This improvement is observed even in patients with fixed pulmonary hypertension (75). However, the timing of improvement in unpredictable, and the exception to this is a non-cardiac cause for pulmonary hypertension (73).

The effects on RV contractility have already been described in detail in the "interdependence" section of this report. Specifically, suction to vent the LV distorts interventricular septal position and shape, myocardial fibres are disrupted in the implantation of LVAD, the leftward shift on the Starling curve from offloading the LV and subsequent decrease in the LV contribution to RV function, and the increase in pericardial pressure from space occupied by the device all negatively impact on RV function (73, 76).

1.3.5 Continuous vs. Pulsatile Flow

Successive generations of LVAD have begun to favour the use of continuous flow devices over pulsatile flow owing to the size and durability benefits of the devices. However, the overall advantage of continuous flow is not entirely uncontested. It has been hypothesized that pulsatile flow, more closely mimicking native cardiac function, provides physiological conditions more conducive to recovery.

The physiological consequence to the difference in flow was studied previously by Bartoli et al. In a bovine study with invasive monitoring, these authors found that the significant offloading of the left ventricle in continuous-flow devices deranged the physiological profile of myocardial and vascular haemodynamic energy consumption, which was not seen in pulsatile-flow supported subjects. This was postulated to retard myocardial recovery (77), and these effects have been demonstrated in a human study. Kato et al compared serial echocardiograms and biomarkers of patients implanted with continuous-flow devices and pulsatile devices. In patients with similar baseline fibrosis on histological examination, patients supported on pulsatile devices demonstrated improved LVEF ($p<0.0001$), dP/dt_{max} ($p<0.0001$) and mitral E/e' ($p<0.0001$), along with lower biomarkers for heart failure post LVAD implantation. However, this study does not specify the duration of follow-up with echocardiogram, and hence it is difficult to interpret the time-course of these histological changes.

A further concern raised regarding continuous flow devices is the development of aortic insufficiency (AI) post-LVAD implantation. Hatano et al investigated the aetiology of this in their own population with a prospective study. In their study of 37 patients, they did find a significantly higher incidence of AI in continuous-flow devices (7% vs 93%, OR 10.73, 95% CI 2.223 – 51.788, $p<0.01$). However, they noted a negative correlation between aortic valve opening frequency and the progression of AI (Correlation coefficient -0.451, $p<0.01$), and postulated that this was the likely culprit (78). Rajagopal et al's recent and much larger study (n=184) supports this hypothesis, with serial echocardiograms demonstrating worsening AI in all LVAD patients, but more pronounced in continuous-flow supported patients compared with pulsatile support ($p=0.0348$) (79).

Despite these haemodynamic and physiological disadvantages, there is much evidence to support the shift towards the use of continuous-flow devices. Deo et al recently conducted a retrospective review on their experience with continuous flow LVAD. Over a five-year period, this group transplanted 106 patients, of whom 37 required continuous-flow LVAD. Despite the continuous-flow LVAD group presenting with poorer pulmonary vasculature, renal and hepatic function ($p=0.0009$, $p=0.03$ and $p=0.02$ respectively), there was no difference at 5 year follow-up in survival (80).

Direct comparisons between pulsatile and continuous flow devices have also been made. Feller et al (81) and Garatti et al (82) conducted similar

retrospective studies on their patient databases, comparing their pulsatile supported patients with their continuous flow counterparts. Interestingly, a common factor in the early experience with continuous-flow devices was the patients' body surface area (BSA), with the rationale being better fit of the smaller device bodies. Lower BSA, however, has been demonstrated to be a significant risk factor for RV failure post LVAD (83, 84). However, these studies still did not find any difference in short and long-term mortality between continuous flow and pulsatile devices.

As well as mortality, morbidity of continuous-flow devices has also been examined. Acknowledging the hypothesis that pulsatility in the arterial system has an effect on overall outcomes in end-stage heart failure owing to organ perfusion (85), Radovancervic et al reviewed their own experience with pulsatile (n=58) and continuous-flow devices (n=12), comparing the end-organ function of patients between the modalities of support. Patients were similar pre-operatively, and were maintained on the same mean arterial pressure (80mmHg). In this study, the authors were not able to ascertain any difference between groups in creatinine, creatinine clearance, blood urea nitrate, albumin, bilirubin, serum glutamic-oxalocetic transaminase, serum glutamic-pyuvic transaminase nor lactate dehydrogenase with three-monthly follow-ups up to fifteen months (86). A similar (albeit larger) study by Sandner et al investigating specifically post-LVAD renal function had similar findings, with no difference in estimated glomerular filtration rate between device modality between implant and transplantation (87).

An extension to the concern regarding end-organ perfusion with the lack of pulsatility is the neurocognitive effects of such treatment. This was investigated in a sub-study of the HeartMate II DT trial, observing the neurocognitive effects of long-term continuous flow devices. This prospective trial tested visual-spatial perception, auditory memory, visual memory, executive function, confrontational language and processing speed in patients on long-term continuous flow (HeartMate II) and pulsatile (HeartMate XVE) devices. While they found an overall improvement across all tested neurocognitive areas over 24 months, they did not demonstrate any difference between the modalities of support.

The reason for the preservation of end-organ function was demonstrated in Tank et al's study of the baroreflex physiology in continuous-flow LVAD patients. In this study, a series of continuous-flow supported patients were age, size and gender matched to unsupported controls. Measuring muscle sympathetic nerve activity and correlating it with arterial pressure, these authors demonstrated that even a pulse pressure of 4mmHg in an LVAD patient was sufficient in maintaining the normal baroreflex function, and hence normal regulation of perfusion (88).

Ventrua et al went on to examining the implications of this in the wider transplant community by reviewing the United Network for Organ Sharing

(UNOS) Thoracic registry database. Examining the outcomes of 673 HeartMate XVE (pulsatile) and 484 HeartMate II (continuous-flow) devices between 2004 and 2009, and adjusting for the smaller patient size, female gender and higher serum bilirubin in the continuous-flow group, this study found no significant difference in the survival between the devices. Furthermore, the authors hypothesized that the increased invasiveness of the implantation of the pulsatile device would activate a greater inflammatory response. Whether this was specifically related to the higher transplanted allograft rejection rate in the pulsatile group (39.5% vs 27.5%, $p < 0.001$) was not investigated. This study also found a lower infection rate that required hospital admission in the continuous-flow group (29.3% vs 15.35%, $p < 0.001$) (89). Interestingly, during a similar era (2004 to 2008), using the same database, Hong et al demonstrated an interval improvement in post-transplant graft survival in continuous-flow device (hazard ratio of 2.314 vs 1.122 in the 2001-2004 era and 2005-2008 era respectively, $p=0.021$) (90). This is perhaps reflective of a learning curve to the use of these devices, however, there is suggestion in the literature that third-generation devices of different designs are associated with varying incidence of survival (91).

Nativi et al further expanded on this when they reviewed the International Society for Heart and Lung Transplantation (ISHLT) database during the era of transition between pulsatile to continuous flow devices. Of 8557 patients registered to the database between 2000 and 2008, 2397 were implanted with LVAD. The era was divided into the immediately pre-continuous flow device era

(pre June 2004) and the transitional era. Control groups of patients who were not implanted with LVAD, with and without inotropes, were established. The primary end-point was post-transplant mortality. In this study, it was found that, while the mortality for pulsatile LVAD was higher compared with medically managed patients (RR 1.21, 95% CI 1.02-1.43, p=0.03 for inotrope supported patients, RR 1.25, 95% CI 1.07-1.47, p=0.01 in patients not requiring inotrope support), there was no difference between the controls and either pulsatile or continuous-flow LVAD in the later period. Furthermore, there was no difference in overall survival between the two modes of LVAD (92).

As well as survival equivalence, there has been a reported improvement with infection rates using continuous flow devices. This seems to make biological sense, as the smaller devices require smaller incision, smaller device pockets and can often be implanted entirely within the thoracic cavity. While acknowledging Slaughter et al's review of continuous-flow device use associated with less sepsis than pulsatile devices (93), Schaffer et al sought to clarify the incidence of infection within their own population. In their study, they found that, while sepsis was more closely related to more recent implantation than the actual device, continuous-flow supported patients had improved freedom from sternal wound infections (94).

The theoretical durability of continuous-flow pumps is a much-touted benefit owing to the minimal moving parts. Holman et al sought to demonstrate this in

their Interagency Registry for Mechanically Assisted Circulatory Support INTERMACS database study. Over a five-year period between 2006 and 2011, 3302 devices were implanted (486 pulsatile, 2816 continuous flow). Three percent (n=111) of devices required exchange or resulted in mortality owing to device failure (1.8% of the continuous flow group vs. 12.1% of the pulsatile group). Kaplan Meier curve demonstrated that by 24 months, 50% of the pulsatile group suffered pump failure resulting in either device exchange or death, while less than 2% of the continuous-flow had the same ($p<0.0001$). The continuous-flow pumps that failed did so due to pump thrombosis, while the pulsatile pumps failed due to primary pump failure (95).

Perhaps because of the procedural, perfusion and device durability advantages, there is now evidence that continuous-flow supported patients have longer waitlist survival times than both pulsatile-supported patients and medically managed patients. Taghavi et al conducted another five-year review of the UNOS database between 2005 and 2012 comparing patients who received continuous flow devices and those who had pulsatile support and no mechanical support. Despite a waiting time of double that of pulsatile-device and non-supported patients (260 days vs 135 and 122 days respectively) in a well-matched population, waitlist survival time was better with continuous-flow devices compared to medical management and pulsatile devices ($p<0.001$). Overall survival is no different between groups. This is despite a higher frequency of status 1A patients exceeding the 30-day grace period for transplant when they are supported on continuous-flow LVAD (53.1% vs 40.4%, $p < 0.001$). This

demonstrated longer supported survival has been suggested to allow for better matching of organs in future (96).

1.3.6 Continuous-flow devices and the right ventricle

As aforementioned, one of the beneficial effects of LVAD is the relief in backpressure to the pulmonary circulation as a consequence of offloading the LV. However, under chronic backpressure from left ventricular failure, pulmonary vascular beds undergo significant remodeling (97). The rate of recovery of this under LVAD is often unpredictable (73). Furthermore, the effect of different modalities of support to this recovery requires investigation.

While not directly comparing the modalities of LVAD, Morgan et al sought to review the impact of continuous-flow on their population. 130 patients were implanted with LVAD over a six-year period and followed up at one and six months post implantation. During this follow-up period, there was significant improvement in pulmonary artery pressure, transpulmonary gradient and right ventricular stroke work index (all $p<0.001$). Furthermore, the overall proportion of patients who had severe RV failure dropped significantly between pre-operative and 1 month measurement, with a corresponding increase in the incidence of normal right heart function ($p=0.008$) (98). Atluri et al conducted a similar study on their patient population, with similar findings. In their study of 113 consecutive patients implanted with continuous-flow LVAD without concomitant tricuspid intervention or RVAD, they observed a mean pulmonary artery pressure decrease of 12 mmHg at six months (37.6 ± 5.3 mmHg to 26.1 ±

4.6 mmHg, p=0<0001). Furthermore, this translated to an improvement in RV function, with the RVSWI increasing from 6.05 ± 2.54 to 7.04 ± 2.60 (p=0.02), and decreased incidence of severe tricuspid regurgitation (10.19% to 3.26%, p=0.0004) (99).

Ozturk et al, meanwhile, actually observed the difference between continuous and pulsatile flow in a 2012 retrospective study. Of 90 consecutive patients presenting to their institution between November 2008 and July 2012, 27 had fixed pulmonary hypertension as demonstrated with sodium nitroprusside challenge. Fifteen of these cases received continuous flow devices and twelve received pulsatile-flow devices. The groups were well matched for their pre-operative characteristics, and received the same perioperative care. In this study, successive follow up catheterizations over a year demonstrated a significant improvement in pulmonary hypertension in both groups. However, at the final review, the continuous-flow supported group of patients demonstrated significant decrease in systolic pulmonary artery pressure as compared to the pulsatile group (22.2 ± 3.4 mmHg vs. 33.9 ± 6.4 mmHg, p=0.023) (100).

Previous concerns regarding the physiological impact of continuous-flow do not seem to be supported by the literature. Despite early physiological studies performed in a laboratory setting suggesting inadequate perfusion, it appears that the minimal residual pulsatility of the heart is sufficient to maintain perfusion in a clinical setting.

Chapter 2 – Right ventricular failure after implantation of a third-generation LVAD: a single centre experience

2.1.1 Introduction

The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial demonstrated both survival benefit and quality of life improvement for patients with LVAD implanted (2). Since the most common driver of right ventricular dysfunction is pressure overload from left ventricular failure, it is reasonable to expect the introduction of mechanical offloading of the left ventricle would reduce right ventricular afterload and thereby improving right ventricular function. However, owing to the complex interplay between the flow dynamics of the cardiovascular system, geometry of the ventricles and extra-cardiac influences of cardiac function, the behaviour of the RV is often not so predictable. To further complicate matters, the transition from pulsatile flow left ventricular assist devices (LVAD) to continuous flow has necessitated a re-validation of knowledge in this technology.

The recently published Sixth INTERMACS annual report has highlighted this issue. Since June 2006, 10,303 primary LVADs have been implanted in the United States, of which 931 were pulsatile devices. However, since 2008, there has been a dominance in continuous-flow device usage for patients requiring LVAD, now accounting for 100% of destination therapy implantations and >95% of all mechanical circulatory devices. This is opposed to a previous report of data from 2009, where 48% were pulsatile and 52% were continuous flow. The one- and two-year survival is now 80% and 70% respectively, while the reported mortality in the 2009 INTERMACS annual report was 74% and 55%. In the

earlier report, pulsatile pump was reported as a risk factor for death (p=0.001) (101, 102).

The incidence of post-operative right ventricular (RV) dysfunction after left ventricular assist device (LVAD) implantation in the literature ranges from 20 to 50%.(3) As well as increasing morbidity, the mortality of the peri-operative period increases from 19% to 43%.(3) The ability to predict such a common, yet highly morbid, complication is important in allowing pre-emptive right sided mechanical assist implantation and in improving outcomes for these patients.

In this study, we reviewed our experience of RV failure in patients undergoing continuous flow LVAD insertion over the last decade. The primary aim of this study was to establish predictive factors for RV failure post LVAD insertion in our own population of patients. We also reviewed a selection of studies looking at predictors of RV failure and aimed to validate those scoring systems against our own LVAD population.

2.2.1 Materials and Methods

We conducted a retrospective study, reviewing prospectively collected data from a single quaternary referral centre. All patients implanted with third-generation continuous-flow LVAD over a one-hundred-and-twenty-seven month period between June 2003 and December 2013 at The Alfred Hospital (Prahran VIC, Australia) were included in our study. Subjects were divided into two groups:

those who developed RV failure after LVAD implantation and those who didn't. Institutional ethics approval was given for the study and requirement for individual patient consent was waived. All patients who received LVAD implantation had New York Heart Association (NYHA) class III or IV symptoms despite maximal medical therapy. The decision for LVAD implantation followed multidisciplinary team review. All patients received either VentrAssist [formerly Ventracor Ltd., now Thoratec Corp., Pleasanton CA, USA], HeartMate II [Thoratec Corp., op cit] or Heartware [Heartware Inc., Framingham MA, USA]. A total of one hundred and one patients were implanted during this study period.

Data was sourced from clinical records, follow-up correspondence, the clinical unit's internal database, and data contributed to the Australia and New Zealand Society of Cardiac and Thoracic Surgery (ANZSCTS) database. It was then cross-referenced for verification between sources. RV failure was defined as requirement for mechanical right heart support, requirement for 14 days of inotropes, requirement for inhaled nitric oxide for more than 48 hours or discharge home with inotropes (103). Mortality was stratified into mortality within 30 days of LVAD, mortality within the admission of LVAD implantation, mortality before explantation of LVAD and overall mortality during the follow-up period. Right heart catheterisation data-points were collected at the final stages of elective therapy for all patients. Echocardiographic data-points were collected at presentation. Data was censored on 31st December 2013.

This data was then analysed using SAS® 9.4 [SAS Institute Inc., Cary NC, USA]. Data was initially assessed for normality. Parametric data was compared using student t-tests and reported as mean ± standard deviation, whilst non-parametric data was compared using Wilcoxon rank sum tests and presented as median with an interquartile range. Proportions were compared using chi-square tests for equal proportions and were reported as percentages. Patient survival was analysed using Cox proportional hazards regression models, reported as hazard ratios (95% CI) and presented using a Kaplan Meier curve. Multivariate models were constructed using both stepwise selection and backwards elimination techniques before undergoing final assessment for clinical and biological plausibility. All variables were considered for inclusion into the multivariate models. A two-sided p-value of 0.05 was considered to be statistically significant.

2.3 Results

2.3.1 Demographics

Of the 101 patients between January 2001 and December 2013, 88 patients were implanted with the intention of bridging-to-transplantation (BTT), nine were implanted as destination therapy (DT) owing to age at presentation, two were as a bridge-to-decision (BTD) owing to unclear prognosis at presentation and two were bridged-to-recovery (BTR). Although there was no statistical significance in difference between groups, there was a trend towards patients being bridged-to-transplant to develop RV failure (92.1% vs 78.9%, p=0.057). All patients received third-generation, continuous-flow devices (either VentrAssist [formerly VentraCor Ltd., now Thoratec Corp., Pleasanton CA, USA], HeartMate II [Thoratec

Corp., op cit.] or HeartWare [HeartWare Inc., Framingham MA, USA]). Twenty patients still had devices in situ at the census date (table 3).

Pre- and peri-operative characteristics of patients are detailed in table 1. The groups were well matched for all pre-operative characteristics on univariate analysis. There did not appear to be any difference in demographics or mortality risk modeling. Specifically, the Acute Physiology and Chronic Health Evaluation (APACHE) II and III scores (104, 105) were no different between groups (p=0.83 and p=0.31 respectively).

Serum bilirubin was noted to be statistically significantly higher in the RV failure group (p=0.05), however, the biological significance of the difference is questionable (28μmol/L vs 20μmol/L). Although not statistically significantly different, there was a trend towards higher serum creatinine in RV failure patients (135μmol/L vs 108μmol/L, p=0.06). Pre-operative systolic blood pressure was lower in the RV failure group (94.8mmHg vs 100mmHg, p=0.05) (Table 4).

The overall incidence of RV systolic dysfunction pre-operatively was not different. However, the severity of right ventricular compromise prior to LVAD implantation in the RV failure group was significantly greater on echocardiogram. In particular, RV systolic pressure and tricuspid valve regurgitation were both found to be statistically significantly higher (p=0.041

and p=0.0019). TAPSE also trended towards being lower in the RV failure group (p=0.06). There was no difference in right heart catheter data between groups.

Table 3 – Univariate analysis of pre-operative characteristics

Peri-operative characteristics (mean ± 95% C.I.)			
	RV Failure (n=63)	**No RV Failure (n=38)**	**p value**
Age (years)	48.3 ± 16.68	47.3 ± 15.01	0.76
Height (cm)	172.01 ± 14.66	174.79 ± 8.51	0.29
Weight (kg)	75.2 ± 14.53	80.44 ± 15.33	0.09
Gender (Male)	49 (77.8%)	34 (89.5%)	0.14
APACHE II	17.65 ± 8.12	17.29 ± 6.03	0.81
APACHE III	56.6 ± 33.12	50.11 ± 23.59	0.29
Heart rate (beats per minute)	92.89 ± 20.78	87.34 ± 21.9	0.23
Systolic Blood Pressure (mmHg)	94.85 ± 10.66	100.11 ± 15.78	0.05
Pre-op ICU admission	25 (39.7%)	15 (39.5%)	0.98
Pre-op ventilation	21 (36.2%)	9 (25%)	0.26
Pre-op inotropes	55 (87.3%)	34 (89.5%)	0.74
Pre-op haemofiltration	10 (15.9%)	2 (5.3%)	0.11
Cardiopulmonary bypass time (min)	90.9 ± 56.55	87.4 ± 32.38	0.71
Pre-VAD ECMO	16 (25.4%)	10 (26.3%)	0.92
Aetiology of heart failure			
Dilated idiopathic cardiomyopathy	27 (43%)	17 (45%)	0.85
Ischaemic cardiomyopathy	21 (33%)	10 (26%)	0.46
Other	15 (24%)	11 (29%)	0.57
Intention of LVAD implantation			
Bridge-to-decision	1 (1.6%)	1 (2.6%)	0.72
Bridge-to-transplant	58 (92.1%)	30 (78.9%)	0.06
Destination Therapy	4 (6.3%)	5 (13.2%)	0.25
Bridge-to-recovery	0	2 (5.3%)	0.07
LVAD implanted			
HeartMate II	4 (6.3%)	6 (15.8%)	0.12
HeartWare HVAD	12 (19%)	8 (21.1%)	0.81
VentrAssist	47 (74.6%)	24 (63.2%)	0.22

Table 4 – Univariate analysis of pre-operative investigations

Pre-operative Investigations			
Laboratory values (mean ± 95% C.I.)			
	RV Failure (n=63)	**No RV Failure (n=38)**	**p value**
APTT (secs)	44.32 ± 13.21	49.94 ± 25.82	0.15
INR	1.47 ± 0.53	1.38 ± 0.45	0.40
White Cell Count ($x10^9$ / L)	10.55 ± 3.66	10.15 ± 3.64	0.59
Platelets ($x10^9$ / L)	185.16 ± 90.88	191.29 ± 78.50	0.73
Haematocrit (%)	32.98 ± 7.04	33.37 ± 6.86	0.79
Creatinine (µmol / L)	135.13 ± 76.75	108.42 ± 49.24	0.06
ALT (U/L)	45 [27-157]	36.5 [23-62]	0.21
Bilirubin (µmol / L)	28 [19-38]	20 [14-30]	0.02
Echocardiographic data – last pre-VAD echocardiogram (mean ± 95% C.I.)			
RV systolic pressure (mmHg)	54 [45-64]	46 [40-59]	0.041
RV Dilatation	44 (72.1%)	24 (68.6%)	0.71
RV systolic dysfunction	57 (90.5%)	34 (89.5%)	0.87
RV systolic dysfunction severity (0 = none, 1 = mild, 2 = moderate, 3 = severe)	1.91 ± 0.89	1.92 ± 0.79	0.96
Pulmonary Hypertension	55 (90.2%)	33 (86.8%)	0.61
Pulmonary hypertension severity (0 = none, 1 = mild, 2 = moderate, 3 = severe)	1.83 ± 0.89	1.54 ± 0.95	0.13
TAPSE (cm)	1.2 [1-1.4]	1.4 [1.2-1.6]	0.06
Tricuspid regurgitation	60 (95.2%)	28 (73.7%)	0.002
Mitral regurgitation	59 (93.7%)	37 (97.4%)	0.41
Right heart catheter data (mean ± 95% C.I.)			
Cardiac output (L/min, inclusive of all supports)	3.43 ± 1.34	3.53 ± 0.94	0.70
Cardiac index	1.82 ± 0.72	1.8 ± 0.45	0.92
Mean RA pressure (mmHg)	11.12 ± 4.97	10.15 ± 8.95	0.52
Mean pulmonary artery pressure (mmHg)	36.53 ± 10.46	34.41 ± 9.71	0.36
Mean pulmonary capillary wedge pressure (mmHg)	25.75 ± 7.99	23.13 ± 7.57	0.15
Stroke volume index	21 ± 8.18	21 ± 5.62	0.68
RV stroke work index	6.76± 3.54	7.55 ± 4.22	0.38
Transpulmonary gradient (mmHg)	10.1 ± 5.61	10.7 ± 5.24	0.69
Pulmonary vascular resistance (Wood units)	3.54 ± 2.58	3.08 ± 1.56	0.37

2.3.2 Outcomes

Sixty-three patients (62.4%) developed RV failure. There was a three-fold increase in the incidence of mortality pre-explantation with patients who developed RV failure (31.7% vs 10.5%, p=0.015), with a significant portion of these patients dying within 30 days (11% vs 0%, p=0.043), and subsequently during the initial surgical admission (15.9% vs 2.6%, p=0.039). Mortality overall was also statistically significantly higher in the RV failure group (41.3% vs 15.8%, p=0.008) (table 5).

Of the 32 deaths during the census period, nine died after a cerebrovascular accident while supported on LVAD (32.3%), and the tenth patient suffered the same peri-transplant (3.1%). Five deaths occurred in the setting of septic shock (15.6%). A further five deaths occurred in the setting of multi-organ failure (15.6%), including one occurring peri-operatively after a pump change for pump-thrombosis. There was one death in theatre of a patient electively implanted with LVAD, but was unable to be weaned off cardiopulmonary bypass post-implantation (3.1%). Ventricular arrhythmia during support accounted for 2 deaths, including one where an attempted emergent re-sternotomy to relieve a pericardial effusion was unsuccessful (6.2%). Pump thrombosis after device exchange, ischaemic bowel and failure to thrive post-LVAD implantation each accounted for one death (9.3%). One more patient had treatment withdrawn after failure to thrive peri-transplant (3.1%). The remaining 6 patients died post-discharge from their transplant admission (18.6%), including two dying of complications after unrelated orthopaedic injuries.

Patients who developed RV failure had outcomes reflective of their poorer clinical condition, including longer ICU stay ($p<0.001$), higher incidence of transfusions ($p=0.026$) and re-intubation ($p=0.001$), longer ventilation duration ($p<0.001$) and higher incidence of returning to theatre ($p=0.0008$). RV failure was not, however, associated with early post-operative blood loss ($p=0.17$), re-admission to ICU ($p=0.72$) and post-operative renal failure ($p=0.13$) in this data set. The incidence of transplantation was not affected by the onset of RV failure in our population ($p=0.92$).

Table 5 - Univariate analysis of outcomes

Post-VAD Outcomes (mean ± 95% C.I.)			
	RV Failure (n=63)	**No RV Failure (n=38)**	**p value**
Mortality pre-explantation	20 (31.7%)	4 (10.5%)	0.02
Mortality within same admission as implantation	10 (15.9%)	1(2.6%)	0.049
Mortality (30 days)	7 (11%)	0	0.04
Mortality overall	26 (41.3%)	6 (15.8%)	0.01
Post-op ICU hours	418.76 [303.4-696.75]	159.31 [93.51-238.37]	< 0.001
Ventilation hours	143.27 [91.68-401.3]	23.87 [17.92-70.17]	< 0.001
Inhaled nitric oxide hours	90 [30-154]	0 [0-17]	< 0.001
Inotropy hours	306 [173-502]	73 [44-147]	< 0.001
logINOTROPY hours	5.76 ± 0.97	4.28 ± 0.85	< 0.001
Blood loss (mL, first 4 post-op hours)	370 [230-520]	320 [240-420]	0.17
Incidence post-op PRBC transfusion	60 (95.2%)	31 (81.6%)	0.03
Units PRBC transfused	13 [7-27]	6 [2-12]	0.0002
Post-op non-PRBC blood products	56 (88.9%)	27 (71.1%)	0.02
Re-intubation	33 (53.2%)	8 (21.1%)	0.001
Return to theatre	36 (58.1%)	9 (23.7%)	0.0008
Re-admission to ICU	8 (12.9%)	4 (10.5%)	0.72
New Renal Failure	16 (25.8%)	5 (13.2%)	0.13
Discharge home with IV inotropy	5 (8.3%)	0	0.15
Mechanical support of the RV	15 (24.2%)	0	0.0004
Transplanted	34 (66.7%)	19 (65.5%)	0.92

2.3.3 Predictors of RV Failure

Pre-operative characteristics were selected for their statistical and biological significance for multivariate analysis seeking predictors of RV failure. All characteristics except for ALT were selected with $p<0.15$ on univariate analysis. Given the literature (see next chapter) and the significance of bilirubin, ALT was selected as a clinically plausible factor. The other characteristics included pulmonary hypertension, pre-operative systolic blood pressure, haemofiltration, gender, RVSP, weight, bilirubin, creatinine, cardiac index < 2.2 and tricuspid regurgitation. (table 4) Logistic regression eliminated all but two variables: low cardiac index and tricuspid regurgitation (table 6).

Table 6 - Summary of backward elimination of pre-operative characteristics selected for statistical and biological significance

	Wald chi-square	Pr > chi-square
Pulmonary HTN	0.0087	0.9256
SBP	0.2317	0.6303
Haemofiltration	0.4261	0.5139
Male gender	0.4129	0.5205
ALT	0.9882	0.3202
RVSP	1.3287	0.2490
Weight	2.6335	0.1046
Bilirubin	2.7272	0.0986
Creatinine	3.2123	0.0731
C.I. < 2.2	10.4513	0.0012
TR	8.1789	0.0042

Table 7 - Odds ratio estimates of remaining significant pre-operative characteristics from Table 6

	Odds ratio	95% Wald Confidence Limits	p value
C.I. < 2.2	4.660	1.833 – 11.848	≤ 0.05
TR	8.108	1.932 – 34.026	≤ 0.05

2.3.4 Follow-up and Survival

Overall follow-up was between 0 and 3479 days. Mean ± standard deviation of follow-up was 945 ± 848 days. In the RV failure group, mean ± standard deviation of follow-up was 892 ± 900 days, and 1033 ± 758 days in the non-RV failure group. No patients were lost to follow-up, though 20 patients still had devices in situ at census date. Of the devices still in-situ, 2 were implanted as destination therapy, and the rest were awaiting transplant.

Patients who were still awaiting transplant with a device in-situ at census date were censored for survival calculation. Kaplan-Meier survival curves of the two groups demonstrated consistently poorer survival in the RV failure group throughout the follow-up period ($p<0.001$) (figure 5). Overall actuarial survival was 63.0%, while actuarial survival for the RV failure and non-RV failure groups were 53.0% and 79.8% respectively. There were too few mortalities within 30 days and primary admission for meaningful calculation of short term survival.

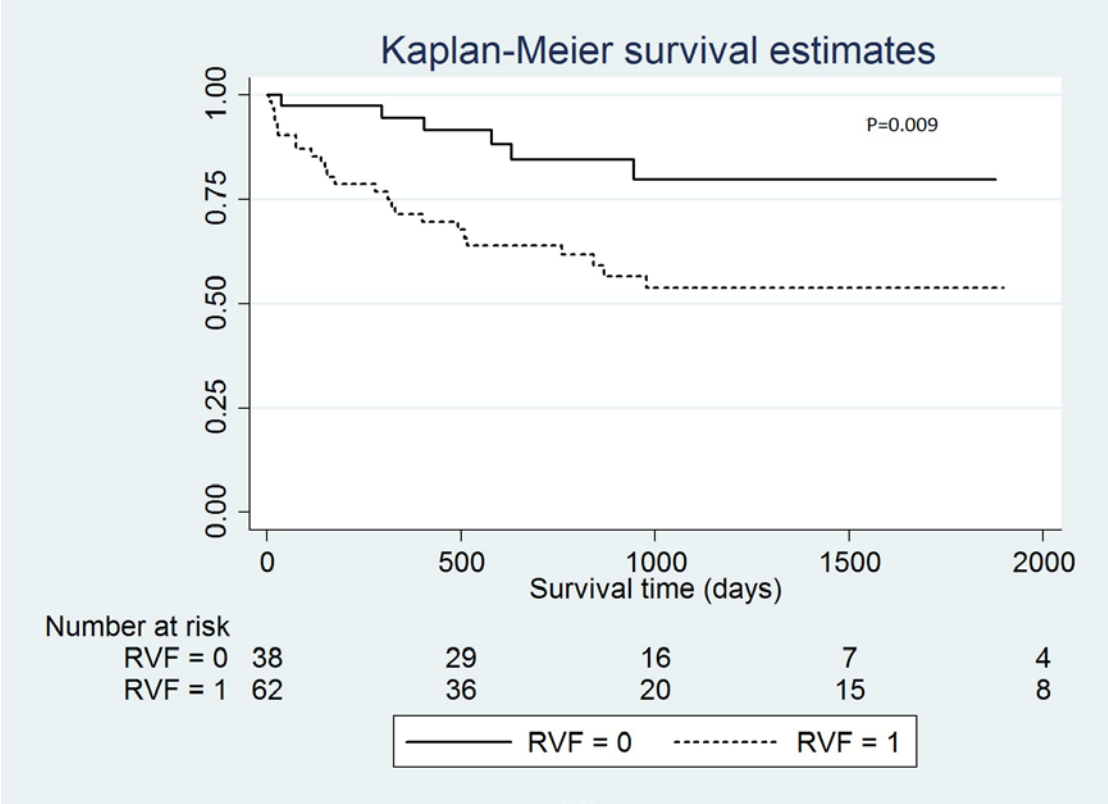

Figure 5 - Kaplan Meier survival after LVAD insertion: i) RV failure patients; ii) Non-RV failure patients, p=0.009

Table 8 - Number at risk at 0 days, 1 week, 30 days, 6 months, 1 year, 18 months, 2 years, 3 years, 4 years and 5 years post LVAD insertion.

Number at risk		
Days post-insertion	**RV Failure**	**Non-RV Failure**
0	63	38
7	62	38
30	57	38
183	47	35
365	40	32
548	33	29
730	29	21
1095	19	15
1460	15	7
1825	11	5
2190	6	4
2555	5	3
2920	3	2

2.4.1 Discussion

LVAD implantation is theoretically beneficial to RV function by reducing left atrial pressure and thus RV afterload. Previous studies have demonstrated reduction in pulmonary artery pressures after LVAD implantation in both pulsatile and continuous devices. For example, Pauwaa et al evaluated the effectiveness of second and third generation devices in their cohort of patients, and were able to demonstrate a statistically and clinically significant reduction in mean pulmonary artery pressure post-implantation of LVAD (31.9 ± 10.6 mmHg vs. 22.1 ± 6.6 mmHg, p = 0.001) (74). This improvement is observed even in patients with fixed pulmonary hypertension (75). However, the chronicity of improvement is unpredictable, and the lack of afterload relief in the interim, coupled with an increased preload, places an already compromised right ventricle at risk of failing.

Compounding the issue are the hypothesized effects of the LVAD's physical presence. Firstly, suction from the LVAD inflow distorts interventricular septal position and shape, myocardial fibres are disrupted in the implantation process. Secondly, there is a leftward shift on the Starling curve from offloading the LV and subsequent decrease in the LV contribution to RV function. Finally there is an increase in pericardial pressure from space occupied by the device (73, 76).

In our population RV failure was significantly more common than that reported in previous literature (3). However, the clinical significance of this is

questionable, as the definition of RV failure has varied within the existent literature. Furthermore, we postulate that this is at least a partial reflection of our liberal use of prophylactic nitric oxide and our extended use of IV inotropy. However, our overall mortality with RV failure is comparable to that which has been previously reported (3). In fact, by applying a recent INTERMACS definition of RV failure to our patients, where a longer duration of inhaled nitrous oxide was required to qualify for RV failure (59), the RV failure incidence drops to 40 (39.6%). However, the predictors of RV failure, and the mortality outcomes between RV failure patients and non-RV failure patients were not different.

The results of this study suggest a greater degree of RV compromise pre-existent in our patients who subsequently develop post-operative RV failure compared with those who don't. While there was no difference in overall demographics between groups, indicators of RV compromise including elevated bilirubin and tricuspid regurgitation, morphology and pathology of the tricuspid valve were more prevalent in the RV failure group. This was supported by our echocardiography and has also been observed in other studies (72). Unfortunately, the size of this study limited our ability to stratify patients further into a risk model for RV failure.

Although the left ventricle (LV) is offloaded and output to the systemic circulation is restored by the implantation of an LVAD, the interdependence of the ventricles, coupled with the already compromised state of the RV from

congestive heart failure exposes the right heart to potentially detrimental dynamic changes. These changes may, in turn, predispose the RV to failing. Specifically, three physiological effects of LVAD on the RV are said to affect RV function: increase in RV preload, decrease in RV afterload and a change in RV contractility (73).

Acute increase in RV preload occurs owing to the aforementioned series interaction of the ventricles leading to increased venous return. As right ventricular pressure increases, the already compromised myocardium is quickly stretched beyond its peak performance on the Frank-Starling curve (73). This is compounded by the ensuing ischaemia as intracavity pressure exceeds coronary perfusion pressure (3). These effects exacerbate dilatation of the chamber and the tricuspid annulus.

Morphology and pathology of the tricuspid valve is intimately related to right ventricular (RV) failure post left-ventricular assist (LVAD) implantation. Kukucka et al's recent prospective study found that echocardiographic evidence pre-operatively of tricuspid annular dilatation without tricuspid regurgitation (TR) was one of only two independent predictors of RV dysfunction and 30 day mortality, the other being age (106). This group postulated that the mechanism for this was secondary tricuspid annular dilatation, similar to that of concomitant tricuspid regurgitation with mitral valve disease. However, conflicting evidence exists with regards to the applicability of this in the context

of left ventricular assisted patients. Specifically, the effect that pre-operative and persistent tricuspid regurgitation has on morbidity and mortality is still under investigation.

Measurement of valvular pathology was based on previously established criteria, and all patients were considered to have varying degrees of severe MR and mild-to-moderate TR pre-operatively. Post implantation, it was recorded that MR had decreased to mild-to-moderate, while TR had worsened to moderate-to-severe. This accompanied significant improvement in systemic circulatory function. However, even though there was no demonstrable clinical failure of the right ventricle, there was noted structural deformation owing to negative pressure in the left ventricle generated by the ventricular assist device.

The following year, they went on to assess the medium-term changes to valvular function in the same patients (107). Echocardiogram obtained at 95 ± 32 days after implantation demonstrated persistence in the aforementioned changes. Noteworthy was that the observed changes in the right ventricle were not of statistical significance. End-organ dysfunction was demonstrated to have improved.

Piacentino et al (108) also found that tricuspid regurgitation was not reduced in their single-centre study of continuous-flow supported patients with TR but not undergoing concomitant valvular repair. Although statistical significance for

slight improvement in regurgitation was achieved in their study, it was not of clinical significance. Furthermore, patients with clinically significant tricuspid regurgitation pre- and post-procedure were observed to require longer inotropic support and overall hospital stay and a higher rate of RVAD implantation. Kaplan-Meier survival curves of significant and insignificant TR trended towards poorer survival from zero months to at least eighteen months in the significant TR group.

Although worsened TR has been demonstrated to increase mid-term morbidity and mortality (108, 109), repair concurrently with implantation of LVAD is still controversial owing to concerns of undue worsening of RV afterload and subsequent increase in morbidity and mortality. Piacentino et al subsequently went on to retrospectively study the clinical impact of concomitant tricuspid valve procedures in patients who received any type of LVAD.(110) Comparing pre-operative characteristic-matched groups of patients with significant tricuspid regurgitation undergoing either LVAD implantation only or concomitant tricuspid procedure, these authors found the LVAD only group had a longer duration of inotropic infusion (median 10 hours vs 8 hours, p=0.04) and hospital length of stay (median 26 days vs. 19 days, p=0.02). The LVAD only group in their study was also more likely to suffer renal insufficiency (39% vs 21%, p=0.05). These results were replicated when the same group studied their experience with specifically continuous-flow LVAD (111).

Maltais et al also recently studied this phenomenon. In their study, although patients undergoing tricuspid intervention had more tricuspid regurgitation, worse right ventricular dysfunction, and worse clinical heart failure preoperatively, the morbidity and mortality post-operatively of the tricuspid intervention group is similar to the LVAD-only group (112). They demonstrated significant reduction in right ventricular end-diastolic area with tricuspid intervention, and suggested that, in these sicker patients, tricuspid intervention promoted early RV remodeling.

A number of smaller studies, however, have suggested a lack of significant benefit from concomitant tricuspid intervention. Krishan et al investigated the outcomes of concomitant tricuspid repair with a retrospective study of 50 consecutive patients undergoing LVAD implantation at a single institution, with patients receiving tricuspid intervention if they had at least moderate-to-severe TR (113). These authors were unable to find statistically significant difference in morbidity or mortality at a median follow up of 170 days.

A prospective observational study conducted by Potapov et al demonstrated similar outcomes using continuous flow pumps (114). At a single centre, 25 patients presented during the study period with at least moderate TR. The assumptions in their study, based on their literature review, was that TV regurgitation is a marker for RV dysfunction. Untreated pre-operative RV dysfunction thus leads to early post-operative RV failure and that patients should

be pre-selected for RV intervention to prevent this outcome. Acknowledging the limitations of concomitant mechanical support of the right ventricle, these authors sought to study whether TV repair alone would yield different short-term outcomes to elective implementation of BiVAD or Total Artificial Heart support. No statistically significant difference in morbidity or mortality was demonstrated between interventions in this their study.

Saeed et al, likewise, reviewed retrospectively their cohort of patients undergoing LVAD implantation with significant TR and the in-hospital impact of concomitant tricuspid repair (115). Their study was very limited in power owing to size and perspective, and the only statistically significant result they could achieve was the higher need for blood products post-operatively in the tricuspid intervention group.

To address the limitations of these small, single centre studies, Robertson et al recently performed a retrospective review of six years of data from The Society of Thoracic Surgeons (STS) National Database (116). In a study of 2196 patients with moderate to severe TR receiving LVAD at 115 institutions in the USA, just over a quarter (n=588) received some form of tricuspid surgical intervention concomitantly with their LVAD implantation. These authors were not able to demonstrate the findings of improved outcomes with concomitant TV surgery from previous studies. Furthermore, they found that there was increased risk of re-operation, tamponade, prolonged ventilation and new renal impairment.

While concluding that tricuspid regurgitation alone is not a reason for intervening, these authors cautioned against closing the book on this intervention, suggesting that other methods of patient selection for tricuspid intervention may demonstrate benefit in the procedure. Although our own experience of concomitant TV intervention was too small for meaningful analysis (n=5), there were no mortalities associated with the procedure, and no increased incidence of RV failure (n=2).

One marker suggested to have potential use as a predictor of RV failure is the tricuspid annular plane systolic excursion (TAPSE). In general cardiology, TAPSE has already been demonstrated to have clinical applications in predicting both quality of life and prognosis in heart failure patients. Caminiti et al recently conducted a small prospective observational study (n=50) where patients were stratified into groups according to their pre-exercise training TAPSE (117). In their study, patients with a TAPSE of < 19mm (n=23) presented in a poorer clinical state with end-organ sequelae of RV dysfunction, and had less improvement in 6-minute-walk-test with the same training (20.3% improvement vs. 27.5% improvement, p=0.04).

While the prognostic value of TAPSE alone has been questioned (118), Guazzi et al has suggested that the relationship between TAPSE and PA systolic pressure (PASP) may, combined, be a more accurate description of the RV's condition. This was hypothesized and demonstrated to represent a stronger predictor of

poor outcomes in heart failure patients (119). In a study of 334 consecutive patients (with 14 exclusions for poor echocardiogram windows), these authors found a strong correlation between TAPSE and survival ($p<0.001$). Multivariate analysis found the TAPSE/PASP relationship to stratify well amongst NYHA functional classes ($p<0.05$), and hold a strong predictive value for non-survival, with an optimal dichotomous threshold on ROC curve analysis being </≥0.36 mm/mmHg (area under the curve: 0.78, 95% C.I., 83% sensitivity, 72% specificity, $P < 0.001$).

Given the aforementioned studies were conducted on patients still fit for medical management, the applicability of TAPSE in patients pre-LVAD must be investigated for its predictive value at this extreme of the heart failure spectrum. With this in mind, Puwanant et al retrospectively reviewed their experience. Although only a small study (n=33, RV failure n=11), these authors were able to demonstrate statistical significance in the difference in pre-operative TAPSE between patients who developed RV failure post LVAD and those who didn't. Interestingly, even their non-RV-failure patients had a mean TAPSE of 15 ±6mm, while their failure patients had a mean TAPSE of 8 ± 4mm (± SD, $p<0.01$). Furthermore, receiver operating characteristic curves demonstrated a specificity of 91% and a sensitivity of 46% for RV failure in a TAPSE of ≤7.5mm. This seemingly supports the hypothesis that all LVAD patients inherently have a degree of RV compromise, and that more sensitive methods for stratifying RV compromise is necessary to identify those who would benefit from early intervention (120).

While we were unable to reach statistical significance in the difference between groups in terms of pre-operative TAPSE, the trend of our data was clearly in the same direction as that which has been previously reported. That is, all patients are already suffering a degree of RV compromise by the time they are referred for LVAD. Those who are worse off to begin with appear to be the ones susceptible to developing post LVAD RV failure. We hypothesise that the lack of significance in our data with regards to TAPSE is a reflection of the size and power of our study. As this is already one of the larger studies in RV failure post-LVAD, it highlights the need for larger, multi-centre studies with regards to this all-too-common morbidity.

Although the ideal management of RV failure in LVAD patients is prevention, post-onset management is important in rescuing these patients. Management requires the careful assessment of aggravating factors to the RV, and involves clinical, haemodynamic and echocardiographic observations. As aforementioned, RV failure can be a consequence of exacerbation of pre-existing dysfunction, increased preload, insufficient afterload reduction and structural changes. Furthermore, contractile coordination may have a significant impact on overall ventricular function. Meineri et al recently reviewed the management strategies currently available, and suggested an algorithm involving assessing heart rate and rhythm, CVP, cardiac index, intraventricular septum position and afterload. Management suggested includes rate and/or rhythm reversion, astute fluid management, modulating LVAD rotational speed and pulmonary vasodilator

agents. The failure of these treatments would necessitate consideration of right-sided mechanical circulatory support (121).

2.5.1 Summary

Despite advances in technology and management, RV failure remains a highly morbid complication associated with a significantly increased risk of mortality. It appears that the patients who develop RV failure post LVAD implantation, in our experience, are already showing a degree of RV dysfunction pre-operatively. Given this, we postulate that, in order to decrease the incidence of this complication requires pre-implantation optimization of the patients, and we suggest that further study of strategies for this will improve LVAD outcomes.

Chapter 3 – Validation of existing risk models in the local population

3.1.1 Introduction

Despite the known clinical significance of the RV failure post-LVAD, studies stratifying the risk factors for RV failure in post-LVAD patients remain limited in their size, scope and power. They also lack consistency in defining the problem at hand, and are fundamentally undermined by a recent shift in technology from pulsatile-flow pumps to continuous-flow pumps.

In this chapter, we have reviewed a selection of studies looking at predictors of RV failure. These studies include a select few who have developed predictive models for RV failure after LVAD insertion. Based on a recent retrospective review of our own patient population, we have attempted to validate these models for use in our cohort. We hypothesise that at least some of the models will be predictive in our patient population.

3.2.1 Materials and methods

The dataset described in Chapter 2 formed the basis for this study. A thorough literature review was first conducted using the National Institutes of Health's United States National Library of Health database (Pubmed.gov) including the search terms "right ventricular failure," "left ventricular assist device," and "biventricular device." A selection of relevant papers were reviewed, including five studies which had developed a predictive model for RV failure (83, 84, 103, 122, 123). However, one paper required B-type natriuretic peptide (BNP) for the calculation of their score, which is not routinely tested in our institution, so it

had to be excluded from analysis (84). Each of the predictive models were then applied to the dataset, and the predicted outcomes were recorded. These predictions were then compared to the actual outcome of RV failure, and correlation between the predicted and actual outcomes was analysed using the same statistical analysis tools as aforementioned.

3.3.1 Results

Due to variations in the detail of pre-operative management, it was necessary to make minor adjustments to some of the scoring models in order to apply them to our population. The Matthews model (103) required the measurement of aspartate aminotransferase (AST). However, this is not a part of routine work-up for our population, with most of the samples having been long discarded by census date. Although in their study alanine aminotransferase (ALT) was not statistically significant for difference between RV failure and non-RV failure, there was a clear trend in the data towards favouring this as a predictor of RV failure (128 ± 200 vs. 84 ± 160 IU/L, p=0.16). As this was the only aminotrasferase routinely measured pre-operatively for our patients, this was used as an analogue. Similarly, in our data set, tricuspid regurgitation was only recorded as positive for greater than trivial regurgitation as the current evidence for the accuracy of gradation of severity on echocardiogram beyond this is lacking (124). As such, the criterion for severe TR on the Atluri model (123) was substituted for any significant tricuspid regurgitation.

All of the models showed at least a weak trend in the relationship between their predictions and our actual outcomes. Interestingly, despite our description of RV failure most closely correlating with that of Matthews (103), their model did not correlate significantly with our outcomes ($p = 0.15$). Two models demonstrated statistically significant difference in our population: Fitzpatrick (83) and Atluri (123) ($p = 0.003$ and $p=0.021$ respectively) (table 9).

Table 9 - Validation of scoring models in our population

Mean ± SD score from established RV failure risk models			
	RV Failure (n=63)	**No RV failure (n=38)**	
Matthews(103)	8.05 ± 2.23	7.46 ± 1.14	p = 0.15
Drakos(122)	5.27 ± 2.54 (n=59)	4.85 ± 2.48	p = 0.43
Fitzpatrick(83)	34.49 ± 15.33	24.8 ± 10.3	p = 0.003
Alturi(123)	1.632 ± 0.211	1.33 ± 1.12	p = 0.021

Table 10 - Previous risk scoring studies

Author, year	Study size	Indication for VAD	VAD	RVF incidence	RVF definition	Univariate predictors (OR > 1, 95% CI > 1, p > 0.05)	Multivariate predictors/Developed score (RVFRS)	Limitations
Matthews, 2008(103)	N=197	94% BTT 6% DT 48% ischaemic 52% non-ischaemic	8% HeartMate 1000 IP 33% HeartMate VE 39% HeartMate XVE 14% HeartMate II 4% Thoratec IVAD 1% Thoratec VAD 1% Novacor 1% Micromed	N=68 (35%) *58 cases occurred with first-generation HeartMate	Post-op need for: 1) IV inotropy > 14 days 2) iNO >/= 48 hrs 3) right sided mechanical support (inc. pre-op insertion) 4) hospital discharge with IV inotropy	TIA/CVA, code at anytime pre-operative, ventilator, renal replacement therapy, bridge-to-bridge therapy, pre-op vasopressor, pre-op IV antiarrhythmic, severe pre-op RV failure on echo, pre-op RVSWI <450, pre-op urea >48mg/dl, pre-op Cr >2.3mg/dl, pre-op WCC >12.2k/mm^3, pre-op Platelets <120k/mm^3, pre-op Albumin <3.0g/dl, pre-op AST > 80IU/L, pre-op bili > 2.0	1) vasopressor requirement (OR 3.9, 95% CI 1.5 – 9.8): 4 points 2) AST > 80 IU/L (OR 2.1, 95% CI 0.96 – 4.5): 2 points 3) bilirubin > 2.0 mg/dl (OR 2.4, 95% CI 1.1 – 5.2): 2.5 points 4) creatinine > 2.3 mg/dl (OR2.9, 95% CI 1.1 -7.7): 3 points RVFRS < 3.0, OR 0.49 (CI 0.37 – 0.64); 4.0 – 5.0, OR 2.8 (CI 1.4 – 5.9); > 5.5, OR 7.6 (CI 3.4 – 17.1)	Retrospective study, single centre, selection bias, both pulsatile and continuous devices included
Nakatani, 1996(125)	N = 28	All BTT with end stage heart failure	HeartMate LVAD	N=11 (39%)	RAp > 15mmHg despite diuresis, requires	Elevated End-Diastolic volume index, End-Systolic volume index, right atrial pressure, transpulmonary gradient	Any 2 of RAP (pre-LVAD) > 20mmHg, TPG (pre-LVAD) > 16mmHg or change in PAP < 10mmHg: - sensitivity 82%	Very small sample size, single centre, selection bias, all pulsatile devices

					RVAD	and pulmonary vascular resistance; lack of improvement in PAP post-implantation	- specificity 88% (P=0.937)	
Drakos, 2010(122)	N=175	Consecutive patients receiving LVAD: 58% BTT, 42% DT	HeartMate XVE (47%) HeartMate VE (24%) HeartMate 1000IP (10%) HeartMate II (14%) Novacor (5%)	N=77 (44%)	1) iNO > 48 hours 2) IV inotrophy > 14 days 3) RVAD	Pre-op IABP, intubation, higher bilirubin (higher RAp, smaller LVEDD/LVESD	Destination therapy (3.5 points); IABP (4 points); PVR (<1.7WU: 1pt, 1.8-2.7WU: 2pts, 2.8-4.2WU: 3pts, >4.3WU: 4pts); inotrope dependency (2.5 points); obesity (2 points); ACEi/ARB (-2.5points); β-blocker (2 points) Four risk groups (<5.0; 5.5-8.0; 8.5-12; >12.5): - RVF (11%, 37%, 56%, 83%) - 30-day survival (97%, 92%, 85%, 83%) - 180-day survival (94%, 85%, 75%, 72%) - 365-day survival (83%, 77%, 71%, 61%)	Single centre, retrospective, mostly pulsatile flow devices, possible selection bias for certain risk factors
Baumwol, 2011(126)	N=40	Consecutive patients receiving LVAD: 33 BTT, 7 DT	VentrAssist (75%) HeartWare (25%)	N=13 (32.5%)	As per Matthews et al(103)	TV insufficiency	n/a	Sample size, single centre, only assessed for early RV failure, retrospective study, selection bias

		22 patients INTERMACS level 1, 17 level 2						
Ochiai, 2002(127)	N=245	239 BTT, 2 Bridge to recovery, 4 DT 65% Ischaemic cardiomyopathy, 29%dilated cardiomyopathy	HeartMate (77%) Novacor (23%)	N=23 (9%)	RVAD: LVAD pump flow index < 2.0 L/min/m^2 despite maximal inotropy Recurrent VT (n=2) Infection (N=1)	Lower BSA, Female, Pre-op circulatory support, Pre-op ventilation, non-ischaemic cardiomyopathy, low pre-op RVSWI/RVSW	Preoperative circulatory support, female gender, non-ischaemic aetiology n/a (score)	Only considering severe RV failure requiring RVAD, single centre, pulsatile devices only, retrospective study, selection bias
Patel, 2008(128)	N=77	BTT/DT not specifically mentioned 40% idiopathic 36.4% ischaemic 23.6%	HeartMate I (n=43) HeartMate II (n=34)	N=29 (37.7%)	1) Inotropic/vasodilator support > 14 days 2) RVAD	Pre-op IABP	n/a	Small study, focused on comparing continuous flow and pulsatile flow devices, single centre, retrospective, selection bias

		miscellaneous						
Fitzpatrick, 2008(83)	N=266	Destination of therapy not mentioned. 44.4% ischaemic 65.6% non-ischaemic	TCI IP (n=45) TCI VE/HeartMate XVE (n=93) Abiomed BVS-5000 (n=21) Thoratec PVAD (n=99) HeartMate II (n=6) Biomedicus (n=1)	N=99 (37%)	RVAD as per surgeon discretion	Female gender, lower BSA, pre-op ventilation, previous cardiac surgery, severe pre-op RV dysfunction, pre-op IABP/circulatory support, non-separation from CPB, lower systolic/diastolic blood pressure, elevated CVP, lower PAP, lower CI, lower S_vO_2, depressed RVSWI, elevated WCC, lower platelets, higher INR, higher creatinine, higher bilirubin, lower albumin	Cardiac Index <2.2 (OR 5.7, CI 1.3 – 24.4, p = 0.0192): 18pts RVSWI < 0.25 (OR 5.1, CI 2.1 – 12.2, p = 0.0002): 18pts Severe pre-VAD RV dysfunction (OR 5.0, CI 2.0 – 12.5, p = 0.0006): 16pts Creatinine > 1.9mg/dl (OR4.8, CI 1.9 – 12.0, p = 0.0010): 17pts Previous cardiac surgery (OR 4.5, CI 1.7 – 11.8, p = 0.0023): 16pts SVP < 96mmHg (OR 2.9, CI 1.2 – 6.9, p = 0.0162): 13pts Maximum 98 pts, 50pts signifying high risk for RVAD	Single centre, limited and subjective definition of RV failure, retrospective analysis, variable devices implanted, limited scope of study
Topilsky, 2011(129)	N=76	65% DT 35% BTT 51% ischaemic 38% dilated cardiomyopath	HeartMate II	N=52 (68%)	Echocardiographic evidence of at least moderate RV dysfunction	Decreased tissue Doppler tricuspid valve lateral velocity, leftward interventricular septum deviation	n/a	High degree of subjectivity in data collection, RV failure not an endpoint or focus of study, sample size, single centre, retrospective analysis, only

		y 11% restrictive cardiomyopathy						looking at predictors from 30-day echocardiogram
Alba, 2009(130)	N=54	BTT 11 BTR 17 BTC 24 DT 2	Abiomed BVS 5000 Novacor Thoratec HeartMate XVE HeartMate II	N=28 (51%)	Low LVAD output, and high CVP (>15mmHg), and iNO >48hrs; or RVAD	Nil significant results	Nil significant results	Looking at correlation of INTERMACS score with poor outcome only, sample size, retrospective study
Santambrogio, 2006(131)	N=48	100% BTT	Novacor	N=8 (16%)	Systolic arterial pressure < 80mmHg, cardiac output < 2L/min, acute massive tricuspid regurgitation on TOE, evidence in theatre, IV inotropy, iNO or RV mechanical assistance	Blood urea nitrogen elevation, transaminase rise (ALT and AST), mechanical ventilation, creatinine rise	Not performed	Sample size, exclusion criteria, univariate analysis of data only, pulsatile device

					post LVAD			
Kavarana, 2002(132)	N=69	100% BTT	Thoratec	N=21 (30%)	Inotropy >14 days and/or RVAD	Elevated pre-op bilirubin, decreased pre-op RVSWI, intra/post-op bleeding secondary to coaguloapthy, post-op transfusion, platelets, cryo and elevation in bilirubin and creatinine, longer ICU length of stay	Not performed	Study size, sampling bias, nivariate analysis only
Kormos, 2010(133)	N=484	100% BTT	HeartMate II	N=65 (13%)	RVAD, inotropy > 14 days, late onset inotropy (after 14 days)	CVP > 15mmHg, CVP/PCWP > 0.63, RVSWI < 300mm, ventilatory support, haematocrit < 31%, WBC > 10.4 x 10^3/mL, re-operation for bleeding, bleeding > 6 units during implantation of LVAD, PRBC during first 48 hrs (early RV failure)	Pre-op ventilatory support, CVP/PCWP > 0.63, BUN > 39	Multiple authors affiliated with device manufacturer, multivariate analysis does not include all significant predictors found in univariate analysis, retrospective study
Dang, 2006(134)	N=108	73.1% BTT	HeartMate	N=42 (38.9%)	RVAD; >14 days of inotropy/pulmonary vasodilator therapy	Female gender, relative intraoperative hypotension, elevated intraoperative CVP	Nil	Sample size, single centre, univariate analysis of risk factors only
Puwanant, 2008(120)	N=33	67% BTT 21% DT 4% BTR	HeartMate II (55%) HeartMate	N=11 (33.3%)	Inotropy or pulmonary vasodilator > 14 days	Decreased pre-op tricuspid annular motion, elevated pre-op RVSP	Nil	Sample size, single centre

			XVE (21%) Thoratec LVAD (24%)					
Atluri, 2013(123)	N=218	Not discussed	Abiomed BVS-5000 (n=8) Biomedicus (n=1) CentriMag (n=10) HeartMate II (n=64) HeartWare HVAD (n=9) TCI VE/HeartMate XVE (n=38) Thoratec PVAD (n=82) VentrAssist (n=6)	N=51	BiVAD insertion	Pulmonary hypertension, Hypertension (negative predictor), hypercholesterolaemia (negative predictor), Prior stroke (negative predictor), chronic kidney disease (CR >2mg/dL) (negative predictor), mechanical ventilation, severe preoperative RV dysfunction, intra-aortic balloon pump, preoperative circulatory support, heart rate, central venous pressure, ALT, AST, INR, platelet count, white blood cell count, bicarbonate	One point for each of: (i) Severe right ventricular dysfunction (OR 3.7, 95% CI 1.7-8.1, p=0.001) (ii) Severe tricuspid regurgitation (OR 4.1, 95% CI 1.4-12.4, p=0.011) (iii) Preoperative mechanical ventilation (OR 4.3, 95% CI 1.9-9.6, p<0.001) (iv) Central venous pressure >15mmHg (OR 2.0, 95% CI 0.9-4.2, p=0.089) (v) Heart rate >100bpm (OR 2.0, 95% CI 0.9-4.3, p=0.086) If score ≤ 1, 93% freedom from BiVAD Score < 1, 84% sensitivity, 63% specificity for BiVAD Score < 3, 80% requirement for BiVAD	Small, single centre study, limited definition for RV failure, no data on intention of treatment
Shiga, 2012(84)	N=76	Not discussed	NIPRO-VAD (n=59) EVAHEART	N=6	BiVAD insertion	Age (≤23 years); BSA (≤1.40m^2); haemofiltration; LV diastolic diameter	CVP/PCWP ratio ≥0.5 – 11pts BSA ≤1.40m^2 – 7 pts	Very small study; some statistical inconsistencies; majority of VAD

			(n=9) DuraHeart (n=7) Jarvik2000 (n=3) HeartMate II (n=1)			(≤62mm); CVP/PCWP ratio; RVSWI (≤4.0); Plasma BNP (borderline insignificant)	Haemofiltration – 6pts BNP ≥ 1200pg/mL – 8pts LVDd ≤62mm – 13pts ≥ 20pts (out of 45) carries at least 80% specificity and 80% sensitivity for BiVAD requirement	designs used not common to other studies
Dandel, 2013(135)	N=205	Not discussed	Not discussed	N=45	Post-op need for: 1) IV inotropy > 10 days 2) iNO >/= 10 days 3) right sided mechanical support (inc. pre-op insertion)	Total serum Bilirubin, lactate dehydrogenase, creatinine, CRP, NT-proBNP; Blood urea nitrate; PAP, cardiac index, CVP, PCWP, PVR, End-diastolic RVOT diameter, RV end diastolic short-/long-axis ratio, TAPSE, TAPSm, peak systolic longitudinal strain rate, pressure gradient between RV and RA, RV load adaption index (see text), tricuspid regurgitation	No predictive model, but echocardiographic predictors of RV failure (sensitivity, specificity): RV end diastolic short-/long-axis ratio (84%, 74%) Pressure gradient between RV and RA (ΔP_{RV-RA}) (84%, 93%) Tricuspid lateral annulus peak systolic wall motion velocity (84%, 90%) Peak systolic longitudinal strain rate (PSSrL) (80%, 98%) PSSrL x ΔP_{RV-RA} (89%, 96%) Load adaption index (91%, 95%)	Single centre study, specifically assessing echocardiographic data

Table 11 - common to all studies

Common Pre-operative predictors for Right Ventricular Failure
• Inotrope/vasopressor support • Ventilatory support • Mechanical circulatory support • Right heart dysfunction – elevated CVP, decreased RVSWIs • Decreased tissue Doppler tricuspid valve annular motion • Low body surface area • Female gender • Hepatic dysfunction • Intra-operative bleeding and blood product use

3.4.1 Discussion

Despite advances in LVAD technology, significant technical issues remain to be resolved. Furthermore, owing to the rapid development of the technology, the specific criteria and goal posts for management has evolved rapidly. However, the overall physiological principles to be addressed remain unchanged. Although the specific criteria for diagnosis of right ventricular failure in all of the reviewed studies varies slightly, they all appear to assess the amount of support the ventricle required (mechanical, inotropy and or pulmonary vasodilation) and the sequelae of decreased function (venous and arterial pressure). To our knowledge, there are no studies to equate the different diagnostic criterion. Also, common to these studies are their small, single-centre and retrospective nature. As the technology is relatively new, expensive and rare, this is not unexpected. However, despite their differences and limitations, the studies consistently demonstrate the predictive values of a few pre-operative characteristics.

Matthews et al sought to develop a risk score based on their single centre experience of RV failure post LVAD (103). A wide variety of pre-operative variables were considered, including demographics, occurrence pre-operative clinical events, interventions, haemodynamic variables, laboratory values and echocardiographic data. Owing to the sample size, all variables where $p < 0.1$ were considered for risk score development. Although the developed score had a high specificity for excluding RV failure, sensitivity was lacking, with 20% of patients in the lowest risk strata developing RV failure. It was surprising, given that this is the source of our definition of RV failure, that this score did not have predictive capability in our population. We hypothesise that the large population

of pulsatile flow devices had an impact on their outcome, accounting for some of the difference. Furthermore, this study was conducted in an earlier era with a known higher morbidity and mortality rate in continuous-flow supported patients, possibly accounting for the rest of the difference (102).

In a manner similar to our study, Drakos et al were unable to validate the use of Matthews' score (103) in their population (122). Based on statistical analysis of the pre-operative characteristics of their cohort, they developed their own risk model. Elements that were significant on multivariate analysis were weighted for risk calculation, including intention of therapy, PVR, pre-operative inotrope dependency, obesity and baseline medications. While not identical to our findings, it does not take any major leaps of imagination to see that the bulk of their risk factors could, like our own, be attributed to RV dysfunction. However, their risk model was not predictive in our population. This may be due to their population being vastly different to our own. With a mean age 10 years older than our population (58.2 vs. 48.3 in RV failure patients, 56.5 vs. 47.3 in non-RV failure patients) presenting with greater degrees of end organ dysfunction (creatinine 159 vs. 135 and ALT 258 vs. 159 in RV failure patients; 141 vs. 108 and 130 vs. 75 respectively in non-RV failure patients), and a large proportion of patients being implanted with pulsatile devices (47% HeartMate XVE), it is little wonder this score was not a useful metric in our patients.

With the current literature supporting planned biventricular mechanical support (136, 137), emphasis in clinical care has begun shifting towards early mechanical intervention for RV. As such, research has shifted towards specifically predicting the need for BiVAD. The model developed by Fitzpatrick et al was thus developed to specifically predict the need for conversion to BiVAD (83). Retrospectively reviewing their centre's extensive experience with various device types, these authors found a similar incidence of severe RV failure according to this definition as Ochiai did. They reported six significant variables after multivariate analysis that bore strong correlation to severe right ventricular failure requiring RVAD. A weighted score based on strength of correlation was then developed, which was found to be highly sensitive and specific in this cohort. Out of a score of 98, patients scoring < 30 had a 96% chance of successful LVAD support, while those with scores > 65 had an 89% incidence of requiring BiVAD support. Interestingly, despite the difference in definition of RV failure, this model was the most predictive of RV failure in our patients. However, the threshold for significance was much lower in our population (mean score 34.49 in our RV failure patients, vs 50 points for "high risk" in Fitzpatrick's study), presumably due to our broader definition of RV failure. Unlike Drakos' model, this scoring system explicitly focused on pre-operative RV status. In our population, this scoring system may prove useful with some recalibration. However, Fitzpatrick's study does suffer from some of the criticisms of the other aforementioned studies, as it stems from a database of an earlier era of patients with a significant proportion of continuous flow devices. The presenting aetiology is also quite different from our own, with a

predominance of ischaemic cardiomyopathy in their dataset (56% vs 33% in RV failure group; 62% vs 26% in non-RV failure group).

Most recently, Atluri et al examined their population and identified using multivariable logistic regression analysis key predictors of severe RV failure requiring mechanical circulatory support.(123) In 218 patients receiving LVAD, 51 patients required BiVAD. Being a study of the current era, these authors' reported experience had a higher proportion of continuous flow devices. Risk factors identified were (i) central venous pressure greater than 15mmHg ($p=0.089$); (ii) severe RV dysfunction ($p=0.001$); (iii) pre-operative mechanical ventilation/intubation ($p<0.001$); (iv) severe TR ($p=0.011$); and (v) tachycardia ($p=0.086$). These variables were assigned a score of 1 each, and an overall score of less than 2 was suggested to predict a low risk for needing BiVAD (negative predictive value of 93%). A score of 2 or more was 84% sensitive and 63% specific for BiVAD. The score was validated against the predictive value of previously reported predictors, including Matthews' scoring model (103). Furthermore, it was valid in predicting RV failure in our patients.

Shiga et al had similar findings in their study of pre-operative risk factors for BiVAD requirement. However, their study was limited in its size, including only 79 patients, 3 of whom had to be excluded as they had presented in fulminant cardiogenic shock, and all of those excluded requiring BiVAD. The authors excluded these patients as they hypothesized that the final haemodynamic

measurements would not be reflective of the patient's pre-presentation status. The findings of this study correlated strongly with those of the aforementioned studies, however. Body surface area, left ventricular diastolic diameter, CRP, logarithmic BNP, CVP/PCWP and RVSWI were all found to be significantly correlating to BiVAD requirement ($p<0.05$), while the relationship with pre-operative haemofiltration was also trending towards significance ($p=0.059$). These variables were then used for multivariate analysis, finding only LV diastolic diameter ≤ 62 mm to carry significance ($p=0.025$, OR 12.81, 95% CI 1.387 – 118.4). Based on the Odds Ratios from the univariate analysis, this team then constructed their own weighted predictive model, which was 80% specific and 80% sensitive for BiVAD requirement in their population (84). Unfortunately, we were unable to validate this score against our patient population, as we did not routinely measure BNP in our patients.

Although we were unable to validate some of the scores for our own population, this may be a consequence of the limited size and power of our study rather than an actual difference. Certainly, we were able to show a trend (however weak) towards a difference between those who subsequently developed RV failure and those who didn't. Furthermore, the univariate analyses of our data set and those reviewed in the literature previously did show significant similarities in predictive factors. There were signs of RV compromise in all of our patients from both direct measurements and end-organ markers. However, this was significantly more prominent in those who subsequently developed RV failure post LVAD.

In conducting our own retrospective study, we sought to streamline our findings with the findings already in the literature. We hence selected the definition that, in our literature review, was most commonly referenced and validated against (103). While this may not be the most current definition (59), it addresses the physiological and clinical concerns in RV failure, and allows our results to be more easily compared with the rest of the literature. However, owing to this, our reported incidence of RV failure appears at the higher end of the spectrum that is reported.

In 2005, Dang et al reviewed the predictors, and outcomes of patients developing right ventricular failure (134). In developing their study these authors created a specific criteria for the diagnosis of right ventricular failure post LVAD which has since been adopted by the National Institutes of Health-sponsored Interagency Registry for Mechanically Assisted Circulatory Support's (INTERMACS) and is now widely quoted. Their analyses of predictors, however, was basic and revealed little that wasn't already known from previous studies.

Other authors have also previously studied predictors for RV failure with varying degrees of success. In 1996, Nakatani et al conducted the largest study of their time to assess for predictors of right ventricular failure following implantation of LVAD (125). Relative to more recent studies, however, it was quite small (n=28). Still, they were able to yield statistically significant results and identify some risk

factors. A rudimentary risk score was developed, based on the correlation between pre-implantation RAP > 20mmHg, TPG > 16mmHg and a change of PAP, and post-operative RV failure.

Santambrogio et al performed a similar study fifteen years later with data from their own cohort (131). Although still a small sample size and undertaking only limited statistical analysis of their data, these authors developed a much more sophisticated and specific definition of RV failure and focused on testing risk factors established in the literature. However, these authors did exercise a broad exclusion criteria aimed at removing known risk factors for implementation of biventricular support, such as post-cardiotomy heart failure and rejection of the transplanted heart.

Kavarana et al sought to conduct similar analysis on their patient population to the exclusion of device variation bias (132). They excluded all patients that were not implanted with a Thoratec device. Their definition of RV dysfunction, however, varies from the aforementioned studies. Multivariate analysis was not conducted. In this study, survival to transplant with right ventricular failure was 57.1% as opposed to 85.4% without failure. Significant results were yielded, including, interestingly, a correlation with coagulopathy and use of blood products.

Baumwol et al acknowledged the aforementioned studies, and instead aimed to fill the literature gap in describing risks of RV failure in the short term, and juxtaposing them against the quality-of-life focused parameter of "failure to thrive" (126). This study was conducted entirely using centrifugal flow VADs. Given the sample size and the short-term focus, though, the only predictor of statistical significance for RV failure was severe tricuspid valve regurgitation. RV failure in this cohort was associated with a mortality of 90.9%, compared with 45.5% in the group without RV failure (p=0.027).

Given the widespread use of the INTERMACS scale to stratify patients for purposes of communication and prognostication, Alba et al looked at the correlation between this scoring system and negative outcomes in their patient population (130). Although statistically significant results were yielded for correlation between higher INTERMACS levels and poorer overall survival, 30-day mortality and liver injury, the results did not specifically support correlation with right heart failure. Interestingly, the lower risk groups were at higher risk of infection and late mortality.

While all the studies have assessed the predictive value of pre-operative characteristics, Topilsky et al's study attempted to find predictors of adverse outcome in the mid-term at the 30-day post-operative echocardiogram (129). While the study was small, the parameters were subjective and it was not specifically focused on right ventricular dysfunction, the authors were able to

find significant predictive value in early leftward bulge of the interventricular septum and decreased tissue Doppler tricuspid valve lateral velocity. The end-points assessed in this study were 90-day mortality, readmission for heart failure and persistent New York Heart Association (NYHA) class III or higher, and leftward deviation of interventricular septum was associated with the worst outcome (odds ratio 3.03, 95% CI 1.21 – 13.3, p = 0.01).

Similarly, Puwanant et al reviewed their patients for echocardiographic predictors of RV failure (120). Although the sample size was small, the authors were able to demonstrate the predictive value of pre-operative tricuspid annular motion and right ventricular systolic pressure for severe right ventricular failure for patients with continuous flow VADs.

Unlike all of the aforementioned studies, Kormos et al performed a multi-centre study on the incidence, risk factors and effect on outcomes of right ventricular failure (133). Specifically, a database created for evaluation of the HeartMate II device was accessed for its large sample size (n=484). Pre-operative demographics were consistent between groups, and a variety of predictors were tested. These authors' results support predictors that have been suggested in previous studies.

Patel et al reviewed their patient population during the period of transition from pulsatile flow devices to continuous flow, and were interested in comparing

outcomes between implementation of the different devices (128). Although not implicitly described, the paper strongly hinted that all devices implanted during the study period were implanted for bridge-to-therapy (BTT). Strength of the study was that there was good correlation between the study groups in terms of characteristics, surgeons, techniques and even the devices themselves. However, it was a relatively small study, which was unable to demonstrate any significant difference between the devices that could not be accounted for by the learning curve in handling a new device. In terms of right ventricular dysfunction, the only predictor they identified was pre-operative intra-aortic balloon pump (IABP), possibly suggesting, like other studies, that sicker patients pre-operatively are more likely to develop right heart failure afterwards.

Ochiai et al sought to determine predictors of severe right ventricular failure post LVAD (127). Although conducted at a time when continuous flow pumps were available, the data was retrospective and only included patients with pulsatile pumps. On review of pre-operative patient characteristics, lab data and haemodynamic variables, then conducting multivariate logistic regression on significant variables, only pre-operative circulatory support, female gender and non-ischaemic aetiology was associated with severe RV failure. Also noteworthy was poor RV stroke work pre-operatively, as an analog to poor RV contractility, was suggested to be an important parameter.

To demonstrate the pre-existing RV compromise, Dandel et al recently conducted an echocardiographic study of their VAD candidates. Retrospective review of the pre-insertion echocardiography found that patients with pot-LVAD RV failure had higher CVP ($p=0.01$), longer right ventricular end-diastolic short-/long-axis ratio ($p<0.01$), shorter tricuspid annulus peak systolic excursion (TAPSE) (<0.01) and a lower RV load adaption index, which was derived from velocity-time integral, and RV end diastolic long-axis length and area ($p<0.01$). In a study of 205 patient, of whom 45 developed post-operative RV failure, these authors found that pre-operative compromise in RV geometry and velocity of contraction on echocardiogram was predictive for post-operative RV dysfunction (135).

3.5.1 Summary

Existing studies on RV failure post-LVAD suggest that the severity of RV compromise pre-operatively is the main factor in predicting post-operative RV failure. This appears to have been common across the different generations of VAD. From a clinical perspective, the ability to predict severe RV failure for pre-emptive treatment with mechanical circulatory assistance can be an important determinant of outcome. Existing models in the literature predicting this outcome appear to be valid in our population.

Chapter 4 – ECMO-to-LVAD double bridge

4.1.1 Introduction

In patients requiring left ventricular assist device (LVAD) support, acuity of presentation has been shown to be an accurate predictor of outcomes. Those presenting in the Interagency Registry for Mechanically Assisted Circulatory Support's (INTERMACS) profiles 1 and 2 have been demonstrated to carry a 30-day mortality risk of 38% compared with 11% in patients presenting in profiles 3 and 4 (130). In INTERMACS category 1 and 2 patients, it can be difficult to ascertain whether a patient will be suitable for long-term mechanical support with LVAD and eventual transplantation. Even in the absence of contraindications to LVAD or transplantation, implantation of LVAD may not be survivable in the acute setting. In these critically unwell patients, the evidence for utilisation of veno-arterial (VA) extracorporeal membrane oxygenator (ECMO) for mechanical cardiovascular support as a bridge to decision is growing, with various case reports describing success with this management protocol since the early 2000's.(138-140) ECMO has some advantages in this patient population in that it can be instituted peripherally, even in the setting of cardiopulmonary resuscitation, and stabilises the patient to allow for end-organ recovery from the insult of poor perfusion prior to invasive surgical intervention. This effectively allows a patient presenting in INTERMACS profile 1 or 2 to be stabilised to a less acute category.

In this study, we examine the utility of ECMO in stabilising the critically unwell patient prior to LVAD implantation. We will attempt to test the hypothesis that stabilising these patients provide better post-LVAD outcomes. We reviewed the experience of a single quaternary referral centre with ECMO double-bridging for

management of mechanical cardiac support and transplantation, and assessed the efficacy of such a management protocol for acutely deteriorating patients not suitable for immediate LVAD implantation.

4.2.1 Materials and methods

We conducted a retrospective review of prospectively collected data. All patients implanted with continuous-flow LVAD over a forty-two month period between January 2010 and December 2013 at The Alfred (Melbourne, Australia) were included in our study. Subjects were divided into two groups: those who received VA-ECMO prior to LVAD implantation and those who didn't. Institutional ethics approval was given for the study and requirement for individual patient consent was waived. Selection for ECMO was based on clinical need. All patients who were initiated on ECMO presented as INTERMACS category 1 and 2 patients in whom there was a reasonable expectation of long-term survival without disability. Contraindications included the presence of other organ severe chronic dysfunction, severe brain injury, malignancy and age of 65 years.

Peripheral cannulation of the femoral vasculature by Seldinger technique under ultrasound guidance was performed. The target mean arterial pressure (MAP) was 70mmHg. A distal perfusion catheter was placed percutaneously in the limb with arterial cannulation to provide antegrade limb perfusion in all cases. The VA-ECMO flow was optimized to provide circulatory support while avoiding blood trauma. Patients were anti-coagulated with intravenous heparin in the

absence of bleeding complications, aiming for an Activated Partial Thromboplastin Time of 55-75 seconds. Once the patients regained some pulsatility in their arterial waveform and were haemodynamically stable on ECMO support, usually at one week post-initiation of ECMO, weaning studies were conducted and it was determined whether the patients would tolerate further weaning and removal of support. Patients who were not able to wean went on to have VAD implantation, and were included in this study.

Two hundred and twenty three patients were instituted on ECMO at The Alfred Hospital during this study period. Of these, ninety-four were VA-ECMO patients and a further twenty-nine had no cardiac output and were receiving cardiopulmonary resuscitation while being instituted on VA-ECMO (ECMO/CPR). Forty-one patients did not survive VA-ECMO (including fifteen ECMO/CPR). Twenty-three of the remaining patients (including two ECMO/CPR patients) went on to have an LVAD implanted. During the same period, a further thirty-five patients underwent LVAD implantation without requiring ECMO bridge during this period, bringing a total of fifty-eight cases. Of the remaining VA-ECMO patients, 57/94 (61%) were successfully weaned and 16/94 (17%) were never weaned. Of the remaining ECMO/CPR group, 12/29 (41%) were successfully weaned and 15/29 (52%) were never weaned.

Data was sourced from clinical records, follow-up correspondence, the clinical unit's internal database, and data contributed to the Australia and New Zealand

Society of Cardiac and Thoracic Surgery (ANZSCTS) database. It was then cross-referenced for verification between sources. Definition of right ventricular (RV) failure was defined as requirement for mechanical right heart support, requirement for 14 days of inotropes, requirement for inhaled nitric oxide for more than 48 hours or discharge home with inotropes. Mortality was stratified into mortality before explantation of LVAD and overall mortality during the follow-up period. Data was censored on 31st December 2013.

Right heart catheterisation data-points were collected at the final stages of elective therapy for all patients. Echocardiographic data-points were collected at presentation. However, in the ECMO group, owing to acuity of presentation, data points were only scantily recorded in the medical history for a number of patients. The remaining data was too scantily recorded and amounted to too few cases for meaningful interpretation. The reported data-points for echocardiographic findings are thus from the final pre-VAD echocardiogram (weaning study for the ECMO group).

This data was then analysed using SAS® 9.4 [SAS Institute Inc., Cary NC, USA]. Data was initially assessed for normality. Parametric data was compared using student t-tests and reported as mean ± standard deviation, whilst non-parametric data was compared using Wilcoxon rank sum tests and presented as median with an interquartile range. Proportions were compared using chi-square tests for equal proportions and were reported as percentages. Patient

survival was analysed using Cox proportional hazards regression models, reported as hazard ratios (95% CI) and presented using a Kaplan Meier curve. Multivariate models were constructed using both stepwise selection and backwards elimination techniques before undergoing final assessment for clinical and biological plausibility. All variables were considered for inclusion into the multivariate models. A two-sided p-value of 0.05 was considered to be statistically significant.

4.3 Results

4.3.1 Demographics

Between January 2010 and December 2013, fifty-eight patients presenting with acute heart failure required LVAD. All patients received third-generation, continuous-flow devices (either VentrAssist [formerly Ventracor Ltd., now Thoratec Corp., Pleasanton CA, USA], HeartMate II [Thoratec Corp., op cit.] or Heartware [Heartware Inc., Framingham MA, USA]) (table 14). Of these, fifty-four were implanted with the intention of bridging-to-transplantation (BTT), three were implanted as destination therapy (DT) owing to age at presentation and one was as a bridge-to-decision (BTD) owing to unclear prognosis at presentation (table 15). Nineteen of these devices are still in situ at census date.

Pre and peri-operative characteristics of subjects are outlined in the tables 12 to 16. The groups were well matched for age, sex, height, weight, previous cardiovascular history and most pre-operative investigations. However, the ECMO group presented with significantly higher Acute Physiology and Chronic

Health Evaluation (APACHE) II and III scores (104, 105)(p=0.02 and p=0.001 respectively). These subjects were statistically more likely to have been admitted to ICU and ventilated pre-operatively (p<0.001 for both), and demonstrated a higher incidence of pre-operative haemofiltration (p=0.002), higher serum creatinine (p=0.045) and a faster resting heart rate (p=0.03). Liver function was not statistically significantly different between groups immediately pre-VAD.

Between the implementation of ECMO and insertion of LVAD, patients demonstrated a significant improvement in hepatic and renal function. At the time of ECMO, the patients were demonstrating marked hepatic and renal dysfunction (ALT 530 [123-1372]; bilirubin 47.9 ± 29.0 μmol/L; creatinine 161 μmol/L [110-264]). However, by the time of LVAD implantation, there was marked improvement (ALT 86 [31-242]; bilirubin 28.5 ± 21.5 μmol/L; creatinine 94 μmol/L [64-114], p=0.02, p=0.02 and p=0.004 respectively) (table 17).

By the final echocardiogram prior to implantation of LVAD, the ECMO group demonstrated less RV dilatation (p=0.009) and less mitral regurgitation (p=0.012). There was no difference in right heart catheter-measured parameters.

Table 12 - Pre-operative characteristics

Pre-operative characteristics			
	ECMO (n=23)	**Non-ECMO (n=35)**	**p value**
Age (years)(mean ± st. dev)	45.2 ± 14.74	45.9 ± 14.56	0.92
Height (cm)(mean ± st. dev)	169 ± 22.07	175 ± 7.28	0.33
Weight (kg)(mean ± st. dev)	76.1 ± 15.23	78.5 ± 15.63	0.44
Gender (Male)	19 (82.6%)	29 (82.9%)	0.99
APACHE II	22.8 ± 11.02	16.6 ± 4.92	0.02
APACHE III	78.5 ± 32.35	51.9 ± 16.9	0.001
Pre-op ICU admission	23 (100%)	7 (20%)	< 0.001
Pre-op ventilation	16 (69.6%)	4 (11.4%)	< 0.001
Pre-op inotropes	18 (78.3%)	32 (91.4%)	0.16
Pre-op haemofiltration	9 (39.1%)	2 (5.7%)	0.002
Pre-op systolic blood pressure (mmHg)	95.4 ± 11.6	102.2 ± 14.2	0.06
Pre-op resting heart rate (BPM)	100 [90-108]	85 [70-100]	0.03

Table 13 - Diagnosis

Aetiology of heart failure			
	ECMO (n=23)	**Non-ECMO (n=35)**	**p value**
Dilated idiopathic cardiomyopathy	11 (48%)	17 (49%)	0.96
Ischaemic cardiomyopathy	4 (17%)	10 (29%)	0.33
Other	8 (23%)	8 (35%)	0.32

Table 14 - Device implanted

LVAD implanted			
	ECMO (n=23)	**Non-ECMO (n=35)**	**p value**
HeartMate II	5 (22%)	5 (14%)	0.46
HeartWare HVAD	12 (52%)	8 (23%)	0.022
VentrAssist	6 (26%)	22 (63%)	0.006

Table 15 - Intention of implantation

Intention of LVAD implantation			
	ECMO (n=23)	**Non-ECMO (n=35)**	**p value**
Bridge-to-decision	1	0	0.221
Bridge-to-treatment	21	33	0.669
Destination Therapy	1	2	0.823

Table 16 – Peri-operative data-points

Perioperative data-points			
Laboratory investigations (mean ± st. dev)			
	ECMO (n=23)	**Non-ECMO (n=35)**	**p value**
APTT (secs)	52.7 ± 10.68	50.3 ± 4.61	0.66
INR	1.26 ± 0.14	1.32 ± 0.14	0.025
White Cell Count ($x10^9$/L)	14.5 ± 2.6	14.8 ± 2.05	0.16
Platelets ($x10^9$/L)	184 ± 54.04	194 ± 18.21	0.11
Haematocrit (%)	27 ± 1.43	27.3 ± 1.18	0.14
Creatinine (µmol/L)	101 ± 62.55	128 ± 80.06	0.045
ALT (U/L)	86 [31 – 242]	40 [22 – 88]	0.10
Bilirubin (µmol/L)	28.5 ± 21.45	29 ± 17.86	0.66
Echocardiographic data – last pre-VAD echocardiogram (mean ± st. dev)			
RV systolic pressure (mmHg)	50.4 ± 18.28	54.5 ± 15.09	0.19
Incidence of RV Dilatation	12 (54.5%)	27 (87.1%)	0.009
Incidence of RV systolic dysfunction	10 (87%)	33 (94.3%)	0.34
RV systolic dysfunction severity (0 = none, 1 = mild, 2 = moderate, 3 = severe)	1.83 ± 1	2.07 ± 0.72	0.40
TAPSE	1.22 ± 0.42	1.45 ± 0.45	0.23
Tricuspid regurgitation	20 (87%)	29 (82.9%)	0.69
Mitral regurgitation	19 (82.6%)	35 (100%)	0.012
Right heart catheter data (mean ± st. dev)			
Cardiac output (L/min, inclusive of all supports)	3.5 ± 2.09	3.47 ± 1	0.36
Cardiac index	1.84 ± 1.22	1.81 ± 0.5	0.26
Mean RA pressure (mmHg)	12.6 ± 11.08	10.4 ± 5.55	0.93
Mean pulmonary artery pressure (mmHg)	29.9 ± 7.32	36.3 ± 11.82	0.10
Mean pulmonary capillary wedge pressure (mmHg)	20.8 ± 7.23	24.8 ± 8.57	0.20
Stroke volume index	19 ± 10.18	21 ± 6.42	0.11
RV stroke work index	5.33 ± 4.98	7.34 ± 4.03	0.15
Pulmonary vascular resistance	3.36 ± 2.16	3.38 ± 2.17	0.98
Transpulmonary gradient (mmHg)	9.13 ± 4.46	10.91 ± 6.14	0.40
Operative Details (mean ± st. dev)			
Cardiopulmonary bypass time (min)	95.7 ± 38.27	93.7 ± 61.69	0.13

Table 17 - pre- and post-ECMO serum studies

Changes post-ECMO			
	Pre-ECMO	**Pre-VAD**	**p value**
ALT	530 [123-1372]	86 [31-242]	0.02
Bilirubin (µmol/L)	47.9 ± 29.0	28.5 ± 21.5	0.02
Creatinine (µmol/L)	161 [110-264]	94 [64-114]	0.004

4.3.2 Outcome

In this study population, the incidence of RV failure was 50% (n=29) and mortality was 15.5% (n=9). There was no statistically significant difference in the incidence of these outcomes between study groups (p=0.06 and p=0.25 respectively). Differences in post-operative transfusion (p=0.06), ventilation times (p=0.06) and inotrope requirements (p=0.33) were also insignificant. (table 17)

Of the nine deaths occurring pre-LVAD explantation, five (55.6%) died following cerebrovascular accidents. Two patients (22.2%) died of septic shock, including one where the source was never clear, but the patient's haemodynamics continued to deteriorate despite initiation of ECMO support and the family withdrew consent for further management, and another who developed outflow conduit sepsis, which precipitated thrombus formation and hence occlusion of flow. There was a single death (11.1%) in theatre, where the patient was unable to be weaned off bypass despite insertion of temporary RVAD. The final death (11.1%) was due to non-compliance to orthopaedic treatment, which occurred following a non-related neck of femur fracture. The patient self-discharged during the orthopaedic admission, only to re-present shortly afterwards in acute renal failure. He subsequently developed knee sepsis, which progressed to bacteraemia and endocarditis, and the patient was thus palliated by the orthopaedic team.

Two more patients died during the census period after explantation of LVAD. One patient clotted their LVAD and was urgently re-admitted for a change of LVAD. Unfortunately, they had already suffered hypoperfusion related multi-organ failure by the time of LVAD change, and died shortly after from multi-organ failure. The second survived four-months past transplant, but died from saddle pulmonary embolism after being admitted for an unrelated rib fracture post-fall.

Of the remaining patients, a total of twenty-nine patients from this cohort have been transplanted. Two patients were explanted owing to myocardial recovery. The final twenty-seven patients still had their LVAD in situ at census date.

Table 18 - Post-operative outcomes

Post-VAD Outcomes (mean ± st. dev)			
	ECMO (n=23)	**Non-ECMO (n=35)**	
RV failure	15 (65.2%)	14 (40%)	p = 0.06
Mortality pre-explantation of LVAD	2 (8.7%)	7 (20%)	p = 0.25
Mortality overall	3 (13%)	8 (22.9%)	p = 0.36
Explanted LVAD due to myocardial recovery	1 (4.3%)	1 (2.9%)	p = 0.08
Transplanted	8 (80%)	21 (77.8%)	p = 0.90
Post-op ICU hours	418 ± 270	251 ± 207	p = 0.004
Post-op ventilation hours	94.25 (95% C.I. 66.6 – 194.13)	57.71 (95% C.I. 19.85 – 149.87) (n=34)	p = 0.06
Post-op inhaled nitric oxide hours	0 (95% C.I. 0 – 45)	16.5 (95% C.I. 0 – 75)	p = 0.33
Post-op inotropy hours	215 (95% C.I. 89 – 384)	151 ± (95% C.I. 76 – 271)	p = 0.33
Blood loss (mL, first 4 post-op hours)	513 ± 338.56	419 ± 435.80	p = 0.39
Incidence of post-op PRBC transfusion	22 (95.7%)	27 (77.1%)	p = 0.06
Units of PRBC transfused	11 (95% C.I. 8 – 29)	5 (95% C.I. 1 – 13)	p = 0.003
Incidence of non-PRBC blood products post-operatively	22 (95.7%)	24 (68.6%)	p = 0.014
Return to theatre	9 (39.1%)	10 (29.4%)	p = 0.46
New Renal Failure	6 (26.1%)	1 (2.9%)	p = 0.01
Post-op RV failure			
Incidence of IV inotropes >14 days	7 (30%)	8 (24%)	p = 0.56
Post-operative inhaled nitric oxide hours	0 [0-45]	16.5 [0-75]	p = 0.33
Incidence of Discharge home with IV inotropy	1 (4.3%)	1 (3.1%)	p = 0.83
Incidence of Mechanical support of the right ventricle	6 (26.1%)	3 (8.8%)	p = 0.08

4.3.3 Survival

In this study, we did not demonstrate any survival difference between patients who were supported on ECMO and those who weren't (HR0.81, 95% CI 0.21-3.18, p=0.76) (figure 6). Statistically significant factors associated with survival on univariate analysis were transplantation, explanted VAD, pre-operative systolic blood pressure and male gender. There was a trend towards a negative survival benefit where logarithmic inotropy hours exceeded 5 hours, mean RA pressure was greater than 11 mmHg or serum creatinine was greater than 117, though this was not statistically significant (table 19).

Multivariate analysis of factors impacting on survival identified pre-operative systolic blood pressure (HR 0.93, 95% CI 0.88-0.98, p=0.01) and pre-operative creatinine (HR 1.006, 95% CI 1.001-1.012, p=0.04) to be the only statistically significant factors. In clinical terms, a 10 mmHg increase in systolic blood pressure was associated with a halving of the risk of death (HR 0.50, 95% CI 0.29-0.85) and a 10 μmol/L increase in creatinine was associated with an increased risk of death of 6% (HR 1.06, 95% CI 1.002-1.12).

Table 19 – Univariate survival data

Predictors of survival			
	Hazard ratio	**95% C.I.**	
Post-transplant	0.09	0.02 – 0.38	p = 0.001
Explanted VAD	0.16	0.04-0.66	p = 0.01
Pre-operative systolic blood pressure ≥ 100mmHg	0.94	0.9-0.99	p = 0.02
Male gender	0.29	0.08-1.00	p = 0.05
Logarithmic inotropy hours > 5	1.48	0.96-2.27	p = 0.067
Mean RA pressure >11 mmHg	1.08	0.99-1.18	p = 0.082
Pre-operative serum creatinine >117 µmol/L	1.01	1-1.01	p = 0.099

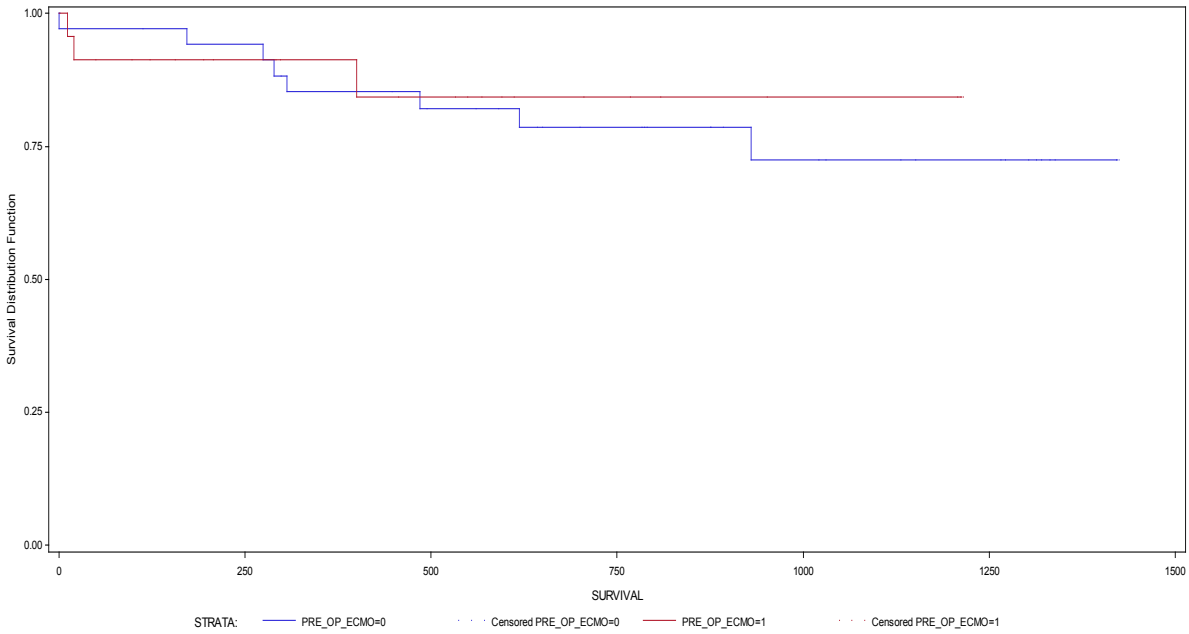

Figure 6 - Survival analysis

4.4.1 Discussion

Pre-VAD patient condition has been demonstrated to be a significant determinant of post-operative outcomes. In their study of pre-VAD patients, Alba et al were able to stratify post-operative the mortality of INTERMACS profiles I and II patients against that of profiles III and IV patients. They found a significant increase in 30-day mortality (38% vs 11%; OR 4.8, 95% CI 1.1-21, $p<0.05$) and poorer overall survival (HR 2.7, 95% CI 1.1-7, $p<0.05$) (130). These stratifications are analogous to the presenting profiles of our ECMO and non-ECMO groups respectively. Our ECMO patients had a poorer presenting condition by multiple metrics, including APACHE II and III scores (141), renal (142) and hepatic function (143) and a higher incidence of circulatory, respiratory or just general intensive care support. However, in our experience, a strategy of ECMO stabilization of INTERMACS I and II patients reduced their peri-operative risk to that of lower INTERMACS profile patients. The ECMO group's echocardiographic findings were comparable with elective patients by the time of LVAD implantation. Furthermore, there was a demonstrable end-organ recovery as evidenced in the improvement in liver and renal function after the period of support with ECMO.

APACHE II has been validated as a predictor of mortality of cardiothoracic surgical patients. Reviewing 811 consecutive patients in the Royal Brompton's intensive care unit, Turner et al demonstrated a strong correlation between the predicted and actual mortality, with an exponential increase in mortality with higher scores ($p<0.001$) (141). Schaffer et al went on to demonstrate that relationship between APACHE II score and mortality has been found to extend

specifically to insertion of continuous-flow LVAD. In their study of 86 continuous-flow supported patients, APACHE II was predictive of 90-day and one-year mortality with a hazard ratio of 1.10 (95% CI 1.01-1.21, p=0.04) (144).

This risk model has been expanded upon to form the APACHE III score (105), which has been demonstrated in a multicentre prospective trial to be predictive of ICU length of stay, resource use and mortality after coronary artery bypass grafting (145). In a 2009 study by Song et al, APACHE III was assessed for its predictive capacity in VA-ECMO supported patients. Studying 50 consecutive patients over a 2-year period, this group found an APACHE III score of ≥50 was highly predictive of in-hospital and long-term mortality (73.5% vs. 20%, HR 14.35, 95% CI 3.13-72.34, p=0.001), and suggested that earlier support of patients could improve post-support survival (146). While the majority of our patients breached this threshold, our ECMO supported patients were far worse (mean APACHE III 78.5 ± 32.35 vs. 51.9 ± 16.9, p=0.001).

Similarly, pre-cardiac surgery renal impairment, even at a mild-to-moderate level, has been demonstrated to be a predictor of adverse outcomes. Shavit et al conducted a retrospective review over a 13-year period between 1997 and 2010 of 5340 patients who underwent cardiac surgery at a single institution. A pre-operative serum creatinine level of just 106 μmol/L was demonstrated to be an independent risk factor of morbidity and mortality. This level of serum creatinine correlated with in-hospital mortality (OR2.2, 95% CI 1.4-3.4), dialysis

(OR 4, 95% CI 2-9.8) and post-operative infection (OR 1.2, 95% CI 1-1.5). Furthermore, there was a corresponding increase in mortality with increasing serum creatinine levels (147). With these predictions applied to our patients, ECMO support potentially represented an 80% reduction in mortality risk on the basis of renal recovery alone.

The relationship between pre-operative end-organ dysfunction and mortality can be described as a self-perpetuating spiral. Backpressure as a result of right heart failure has been demonstrated to be the cause of ischaemic hepatitis. In a retrospective study of 31 consecutive patients, Seeto et al found that all of their patients who developed ischaemic hepatitis to have underlying heart failure, and the development of ischaemic hepatitis was independent of acute circulatory collapse (148). Pre-operative hepatic dysfunction, however, has also been demonstrated to be an independent predictor of poorer post-VAD survival. In 255 retrospectively analysed VAD patients, Yang et al demonstrated using the Model of End-stage Liver Disease excluding INR (MELD-XI) that patients with MELD-XI < 17 had better supported and overall survival than their counterparts with poorer hepatic function ($p<0.0001$) (143). Furthermore, poor hepatic function is well known to negatively impact on post-operative bleeding. While the ECMO-bridged patients in our study did demonstrate greater peri-operative bleeding, we postulate that, without ECMO-bridging, bleeding may have been a much bigger problem with the poorer hepatic function pre-ECMO.

While the increased pre-operative morbidity of the ECMO-bridged patients was reflected in the increased post-operative intensive care duration, blood loss, blood product use and renal failure, this did not impact on the overall outcome. In the overall population, lower peri-operative systolic blood pressure, and higher pre-operative creatinine were both associated with poorer survival. However, RV failure, survival to transplantation and mortality were not statistically significantly different between patients who were bridged-to-LVAD on ECMO and those who were electively implanted with LVAD. The period of ECMO stabilization may also decrease bleeding by reducing venous filling pressures due to offloading the right ventricle. It can be inferred that the incidence of right heart failure might have been higher without ECMO stabilization.

With current evidence overwhelmingly supporting the efficacy of LVAD for managing end-stage heart failure, interest has surged in ECMO bridging for patients presenting with more acute INTERMACS profiles to buy time while assessing candidacy for LVAD support. As well as providing a bridge for patients who do not demonstrate sufficient myocardial recovery despite overall improvement of clinical state, early ECMO has been suggested to prevent myocardial insult that can lead to LVAD (149).

The efficacy of double-bridging was observed in Smedira et al's study of the long-term survival of 202 VA-ECMO patients. In their study, survival of ECMO-bridged

patients (n=42 to LVAD, n=6 directly to transplantation) was 85%, 67%, 54% and 44% at 7 days, 30 days, 1 year and 5 years. Over the same intervals, survival in their overall population was 58%, 38%, 29% and 24%. Survival in patients who were successfully weaned from ECMO without further mechanical circulatory support (n=71) was 72%, 52%, 43% and 40%. The improved mortality in the ECMO-bridged patients suggested that ECMO is an effective tool for stabilising acutely unwell patients. ECMO-bridging allowed for clearer stratification for further management, including mechanical support, weaning and non-survival (150). Our results correlate with this, as can be seen from the number of patients supported on ECMO during the study period. 61% of the VA-ECMO patients were successfully weaned, and 17% were never weaned. In the ECMO CPR group, 41% were weaned and 52% never weaned. A policy of earlier VAD support, without a period of ECMO stabilization and assessment would inevitably lead to a higher number of peri-operative deaths, particularly in this higher INTERMACS group.

Pagani et al. conducted a similar study to our own on a cohort of 33 patients in 2001. In 10 ECMO to LVAD (all pulsatile pumps) bridged patients, two were implanted with an RVAD as adjunct to an implanted LVAD. In this population, there was a 40% (n=4) incidence of RV failure. This was associated with an in-hospital mortality of 50% (n=2). While worsening end-organ dysfunction while ECMO-supported was shown to be a predictor of mortality, survival with ECMO-bridging was not different to overall survival (151). On the other hand, in a series of 28 ECMO-bridge to VAD patients, Hoefer et al. reported 50% mortality. They

implanted 19 BiVADs, 5 isolated RVADs and only 4 LVADs, perhaps indicating a very different population to ours. The VADs implanted in that series were pulsatile paracorporeal VADs, which presumably also contributed to the poor survival. Interestingly, they also found pre-ECMO and pre-VAD bilirubin levels to be significantly higher in non-survivors, perhaps indicating a failure to normalize hepatic function prior to proceeding with VAD implantation. We did not see an association of liver function tests with survival, although we did demonstrate significant improvements with ECMO support, perhaps negating the effect of liver dysfunction on outcomes. Other single-centre studies have shown mixed results (table 20).

Table 20 - Review of previous publications of ECMO bridge to LVAD

Publication	Number of ECMO-to-VAD	VAD used	Survival of ECMO-bridged	Other findings
Smedira 2001(150)	48 (including 6 ECMO-to-transplant)	Not specified	54% at 12 months	See text
Pagani 2001(151)	10	HeartMate LVAS	80 ± 12% at 12 months	See text
Chen 2001(152)	12	HeartMate LVAS, Biopump	33.3%	Divided into 2 groups: immediate ECMO cessation at LVAD/BiVAD insertion (Group 1) and step-wise weaning of right-sided support (Group 2) (see text) (n=6 each): - 4/6 RV failure Group I, 1/56 Group 2
Wang 2001(153)	5	Thoratec VAD, HeartMate LVAS	100%	Case series of 10 patients: 1 LVAD-transplant (survived), 4 ECMO-transplant (3/4 in-hospital mortality)
Bowen 2001(154)	9	Not specified	78% (survival to transplant)	Study of 23 consecutive ECMO patients: 3 weaned, 11 ECMO withdrawn, overall survival to transplant 43%
Hoefer 2006(155)	28	Thoratec PVAD, Berlin Heart EXCOR	50% at up to 39 months follow-up	See text
Scherer 2009(156)	5	HeartMate II	80% survival on LVAD	Prophylactic tricuspid annuloplasty concomitant with LVAD 1/5 left MCA CVA on ECMO Interval improvement between ECMO and VAD in: - glutamic-oxaloacetic transaminase (206 ± 107 vs 71 ± 33 IU/L) - glutamic-pyruvic transaminase (334 ± 207 vs 78 ± 40 IU/L) - creatinine (186 ± 88 vs 106 ± 18 µmol/L)
Chung 2010(157)	16	Continuous-flow: specific device not specified	50% survival on VAD	Protocol as per Chen et al (152). 70 total adult patients on ECMO, 39 withdrawn from treatment. 15 direct ECMO to transplant bridge (HT): - HT survival 73.3% - Overall predictors of poor outcomes o Older age (p=0.001) o Pre-ECMO CPR (p=0.002) o Ischaemic CM (=0.03) o Higher SOFA score (p=0.03)
Bermudez 2011	22 - 8 LVAD - 12 BiVAD - 2 RVAD	Not specified	53.3% survival of LVAD (transplanted (n=6) or weaned (n=2)), mean follow-up 774 days, mean VAD support	42 patients presenting for ECMO. - 33 post AMI o 48% at 1 year (n=16) o 15 ECMO-LVAD bridge LVAD n=6, BiVAD n=7, RVAD n=2) - 9 acute-decompensated chronic cardiomyopathy

			106 days	○ 11% at 1 year (n=1) ○ 7 ECMO-LVAD bridge (2 LVAD, 5 BiVAD) Overall mortality 40.4% Overall severe vascular complication 14.2% (n=6)
Lebreton 2011(158)	5	HeartMate II, HeartWare HVAD (not bridged to from ECMO), Jarvik 2000	Not specified	See text
Moraca 2012(159)	9	Not specified	66% during VAD support	Total 26 ECMO patients - 8 withdrawn from ECMO support - 5 successfully weaned off ECMO - 3 weaned after cardiac intervention - 1 direct ECMO to transplant - Overall mortality 65%
Chou 2012(160)	33 - 11 patients staged conversion of LVAD (152) - 19 conventional bridge to LVAD - 3 BiVAD - 1 RVAD	Thoratec PVAD, HeartMate II, Biopump	Not specified – unclear presentation of overall data	In the 23 patients bridged to the Thoratec PVAD, 62.5% survival to transplant
Karamlou 2013(161)	41 (UNOS dataset)	See text	79% at 12 months	See text
Riebandt 2014(162)	22	Heartmate II, Heartware HVAD (univentricular and bivad configuration), DeBakey LVAD	86.4% at 12 months	Interval improvement between ECMO and VAD in: - Creatinine (164 ± 80 vs 117 ± 46 µmol/L, p=0.02) - AST (1426 ±2176 vs 277 ± 259 IU/L, p=0.04) - ALT (982 ± 1466 vs 357 ± 447 IU/L, p=0.04) - Inspired oxygen (52 ± 18 vs 26 ± 23%, p<0.01) - Positive end-expiratory pressure (7 ± 3 vs 5 ± 4 mBar, p=0.02) - Noradrenaline (0.408 ± 0.355 vs 0.056 ± 0.097 µg/kg/min, p<0.01)

The largest study to date regarding ECMO double bridging is a recent review of the United Network for Organ Sharing (UNOS) Dataset, tracking survival of status-1 heart transplant candidates produced (161). While demonstrating better survival in patients receiving LVAD support only compared to any other form of mechanical circulatory support (HR0.707, 95% CI 0.593-0.844, p<0.001), these authors found that this survival benefit extended to any patient who successfully transitioned to LVAD-only support, including with the use of ECMO. Specifically, of 41 ECMO-to-LVAD bridged patients, 32 (79%) survived.

Physiological benefits aside, there remain concerns regarding the cost effectiveness of LVAD (2, 68, 70, 163). The ability to observe patients with ECMO-bridging extends to our ability to select likely survivors for LVAD, and hence optimize resource utilization(71). To examine this hypothesis properly, however, we would need to compare the resource utilization of contemporary INTERMACS I and II patients directly proceeding to LVAD implantation with ECMO-bridged patients. However, as the evidence mounts for the outcome disadvantages of directly implanting 'crash-and-burn' patients, the study of this would be impractical and unethical.

To our knowledge, there are no other studies of our size observing the outcomes of ECMO double-bridging exclusively to continuous-flow LVAD. This may be owing to the relatively rapid pace of development of generational change in VAD technology and the relative rarity of the intervention. However, with the known

haemodynamic differences between continuous-flow and pulsatile devices (164), and the trend towards the exclusive use of continuous-flow devices (102), it is important to specifically validate the use of this combination of supports in these already very fragile patients.

Various protocols for the bridging to LVAD have been described in the literature. Chen et al described a staged conversion of the ECMO circuit over 2 theatre visits from VA-ECMO configuration to temporary LVAD (second drainage cannula in left atrium) (152). Other authors have suggested leaving peripheral ECMO in situ for several days after VAD implantation as a way of protecting the right ventricle (156, 158). Our institution trialed the latter approach in the past, but found it difficult to adequately fill the VAD when VA-ECMO was running. Our preferred configuration for temporary right-right sided support is to have the ECMO circuit outflow cannula run directly into the main pulmonary artery by an 8mm Dacron conduit.

Our study is limited by its relatively boutique size owing to its single centre design and the rarity of the interventions investigated. While the findings are congruent with the existing literature in supporting the use of this treatment strategy, more multi-centred studies are required to verify our results. Furthermore, the retrospective collection of data inherently disadvantages the study as the consistency of peri-operative observations and investigations are

out of the control of our researchers, often resulting in sub-optimal data collection.

This series, however, suggests that the use of ECMO bridge-to-LVAD is a viable treatment option for patients presenting in INTERMACS profiles I and II, and may improve overall outcomes in the LVAD supported population. In this traditionally highly morbid group of patients, we did not experience any increase in post-operative mortality or RV failure when compared with patients electively implanted with LVAD.

4.5.1 Summary

In the past decade, LVAD has become an established treatment modality for patients in severe heart failure refractory to maximal medical therapy. However, with the high cost and invasiveness of the procedure, it is not possible or advisable to institute LVAD in all acutely deteriorating patients. Double-bridging using ECMO to allow sufficient systemic recovery for the implantation of LVAD appears to be a promising option. Further potential benefits include the ability to assess the RV in a controlled manner to determine the need for biventricular support. The results of this study suggest that, despite presenting with higher morbidity, patients instituted on ECMO do not appear to have worse outcomes than those electively implanted with LVAD. However, further research into this topic is warranted.

Chapter 5 – RVAD outflow conduit modifications

5.1.1 Introduction

Ventricular assist devices (VADs) implanted in the left ventricle (LVAD) have been demonstrated to provide both statistically and clinically significant improvement in the life expectancy and quality of life for end-stage heart failure patients.(165) However, with the high incidence of subsequent right ventricular failure and the associated increased morbidity and mortality,(3) and evidence of improved outcomes with early biventricular mechanical support,(136, 166) the ongoing development of mechanical biventricular assistance techniques remains pertinent.

All current commercially available continuous-flow centrifugal VADs for long term implantation are designed for left-sided use.(167, 168) As such, their design specifications are tailored to pump against left-sided afterload. For the purpose of right ventricular support, implantable VADs are thus adapted to function in the setting of the lower resistance of the right-side. This can either be achieved by decreasing pump speed or modification of the outflow conduit to avoid over-pumping.

Decreasing RVAD pump speed to below manufacturer's specifications moves away from the design point for pump function, and can influence pump washout and thus thrombus formation within the pump (169). Furthermore, with hydrodynamic suspension of the impeller within the device, insufficient pump speed may lead to impeller instability (169). Conversely, the inadequate adaption of the VAD for right-sided use has been demonstrated to carry its own

unique set of problems, chiefly with regards to excessive RVAD flow compared to LVAD. Previous in-vitro studies on RVAD support had already established the benefits of outflow cannula restriction and rotational speed reduction. Recent literature has thus focused on assessing either the degree of outflow cannula restriction required to simulate left-sided afterload, or the limitation of RVAD rotational speeds (167). However, anecdotally, the utility of outflow cannula restriction has been questioned, with suggestion that banding may be entirely unnecessary in an in-vivo setting. Although not described in the literature, there have been anecdotal suggestions that, in agreement with Poiseuille's Law, the same outflow resistance may be achieved by increasing graft length. Furthermore, many patients have a high pulmonary vascular resistance (PVR) at the time of VAD insertion that reduces over time. It is, therefore, important to assess the potential changes in flow through a RVAD as PVR changes, and how different outflow conduits may affect this.

In this in-vitro study, we observed the use of dual HeartWare HVAD devices (HeartWare Inc., Framingham MA, USA) in BiVAD configuration in a mock-circulation loop (MCL). We assessed the pumps' ability to maintain haemodynamic stability with and without banding; and with varying outflow cannulae length. We aimed to assess the suitability of the HeartWare HVAD for use in dual device biventricular support and establish the optimal settings for such use with various levels of PVR. We hypothesise that graft length will have a demonstrable impact on outflow conduit resistance, but that it would not equal

that of banding. This study will demonstrate whether the reduced incidence will still produce conditions that allow for normal pump function.

5.2 Methods

5.2.1 Mock Circulation Loop

A physical five-element Windkessel mock circulation loop (MCL) including systemic and pulmonary circulations was used for this study (Figure 7) (170, 171). In brief, ventricular systole was controlled through a series of electropneumatic regulators (ITV2030-012BS5, SMC Pneumatics, Tokyo, Japan) and 3/2 way solenoid valves (VT325-035DLS, SMC Pneumatics, Tokyo, Japan) to provide passively filled heart chambers and variable contractility, heart rate and systolic time. Heart rate and systolic time were maintained at 60 beats per minute and 35% respectively throughout this study. A Starling response was implemented in both left and right ventricles, which actively controlled ventricular contractility (through electropneumatic regulator supply current) based on ventricular preload (172). Mechanical check valves were used to simulate the mitral, aortic, tricuspid and pulmonary valves to ensure unidirectional flow throughout the circuit. Four independent Windkessel chambers were employed to simulate lumped systemic and pulmonary arterial and venous compliance. Socket valves (VMP025.03X.71, Alb. Klein Ohio, Plain City, OH) allowed easy manipulation of systemic and pulmonary vascular resistance respectively. The working fluid throughout this study was a water/glycerol mixture (60/40% by mass) with similar viscosity and density to that of blood. Inflow and outflow cannulation for the LVAD and RVAD was achieved via the ventricles for inflow and aorta / pulmonary artery for outflow.

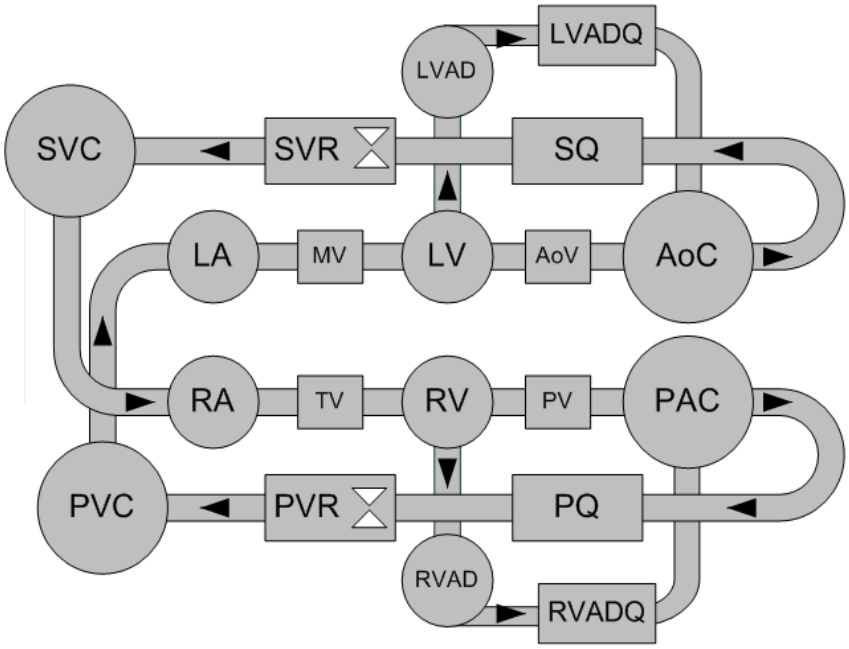

Figure 7: Schematic of the MCL setup for evaluation of a dual HeartWare biventricular support system. LA - left atrium, MV - mitral valve, LV - left ventricle, AoV - aortic valve, AoC - aortic compliance chamber, SQ - systemic flow meter, SVR - systemic vascular resistance valve, SVC - systemic venous compliance chamber, RA - right atrium, TV - tricuspid valve, RV - right ventricle, PV - pulmonary valve, PAC - pulmonary arterial compliance chamber, PQ - pulmonary flow meter, PVR - pulmonary vascular resistance valve, PVC - pulmonary venous compliance chamber, LVAD - left ventricular assist device, LVADQ - left ventricular assist device flow meter, RVAD - right ventricular assist device, RVADQ - right ventricular assist device flow meter.

5.2.2 Dual LVAD Evaluation

Severe LV failure was simulated in the MCL and supported using a HeartWare HVAD device at 2920 RPM to maintain 5 L/min aortic flow and mean aortic pressure (MAP) of 80 mmHg. Haemodynamics for supported and unsupported conditions are highlighted in Table 21. Severe RV failure was simulated and supported using a second HeartWare HVAD device, under test conditions of: unrestricted 10 mm diameter outflow cannulae of 20, 40 and 60 cm lengths and a 20 cm length cannula restricted to 5mm diameter. The shorter lengths were selected for clinical feasibility, while the long length was tested as an academic exercise to trend the effect of various graft lengths on pump function. Outflow cannulae were standard Dacron® (Kennesaw, Georgia, USA) vascular grafts

coated in petroleum jelly and wrapped loosely with cling-wrap for waterproofing. The conduits were carefully placed to avoid kinking.

Condition	MAP	MPAP	MSQ	MPQ	HR	SVR	PVR	LVADS	RVADS
	mmHg	*mmHg*	*L/min*	*L/min*	*BPM*	*dyne.s.cm^{-5}*	*dyne.s.cm^{-5}*	*rpm*	*rpm*
MRHF	56	13	2.8	2.8	60	1350	100	-	-
MRHF-S	80	16	5.0	5.0	60	1350	80	2920	2420
SRHF	48	9	2.3	2.3	60	1350	100	-	-
SRHF-S	80	16	5.0	5.0	60	1350	80	2920	2700

Table 21 – Haemodynamic parameters for steady state conditions of mild (MRHF) and severe (SRHF) right heart failure models with (MRHF-S and SRHF-s respectively) and without dual rotary blood pump support. Note severe left heart failure was simulated in all conditions. MAP – mean aortic pressure, MPAP – mean pulmonary artery pressure, MSQ – mean systemic flow rate, MPQ – mean pulmonary flow rate, HR – heart rate, SVR – systemic vascular resistance, PVR – pulmonary vascular resistance, LVADS – LVAD rotational speed, RVADS – RVAD rotational speed, rpm – revolutions per minute.

For each cannula length and banding simulation, PVR was successively increased from 40 to 560 Dynes.s.cm^{-5} (0.5 to 7 Wood units) in 40 Dynes.s.cm^{-5} (0.5 Wood unit) intervals. RVAD speed was manually manipulated to maintain haemodynamic stability with balanced systemic and pulmonary flow rates of 5.0 L/min for each level of PVR. All other conditions were kept consistent between tests. The experiment was repeated in mild RV systolic dysfunction to assess the clinical applicability of the findings.

5.2.3 Data Acquisition

Haemodynamic and VAD parameters were captured at 100 Hz using a dSPACE acquisition system (DS1104, dSPACE, Wixom, MI, USA). Systemic and pulmonary flow rates were recorded using magnetic flow meters (IFC010, KROHNE, Duisburg, Germany) while LVAD and RVAD outlet flow rates were recorded with clamp-on ultrasonic flow meters (TS410-10PXL, Transonic Systems, Ithaca, NY,

USA). Circulatory and VAD pressures were recorded using silicone-based transducers (PX181B-015C5V, Omega Engineering, Stamford, CT, USA).

5.3 Results

Results of the experiment were analysed to observe the changes in RVAD rotational speed, power consumption, outlet pressure measured directly after the pump and at the interface between the outflow cannula and pulmonary artery (mean pulmonary artery pressure - MPAP) with increasing pulmonary vascular resistance.

5.3.1 Severe RV failure

As expected, an increase in outflow cannula resistance or PVR required increased pump speed to maintain a flow rate of 5 L/min (Figure 8a). At a PVR of 40 dyne.s.cm^{-5} (0.5 Wood unit), the RVAD rotational speeds required to maintain 5L/min flow with a 20 cm outflow conduit with 5 mm banding and unbanded 60 cm, 40 cm and 20 cm outflow conduits were 3120, 2760, 2380 and 2160 rpm respectively. This increased to 3480, 3280, 2860 and 2700 rpm when PVR was increased to 560 dyne.s.cm^{-5} (7 Wood unit), with the increase in rotational speed following a progressive, linear relationship with PVR. The corresponding power consumption and pump outlet pressures behaved similarly. Power consumption at a PVR of 40 dyne.s.cm^{-5} was 7, 5.4, 4.5 and 3.7 Watts for the banded, 60 cm, 40 cm and 20 cm conduits respectively, and 9.2, 8.3, 6.5 and 5.6 Watts at 560 dyne.s.cm^{-5} (Figure 8b).

RVAD outlet pressures generated at the lowest tested PVR setting were 78, 48, 45 and 30 mmHg, and 112, 86, 79 and 65 mmHg in the highest (Figure 8c). This demonstrated that left-sided afterload was sufficiently simulated when the RVAD outflow was banded in the setting of severe RV failure. The unbanded conduits, however, resulted in reduced RVAD afterload of between 39% (60cm conduit, 40 dyne.s.cm^{-5}) and 77% (20cm conduit, 560 dyne.s.cm^{-5}) of that seen with the LVAD, depending on conduit length and PVR. However, the MPAP was similar in all outflow conduit conditions (Figure 8d).

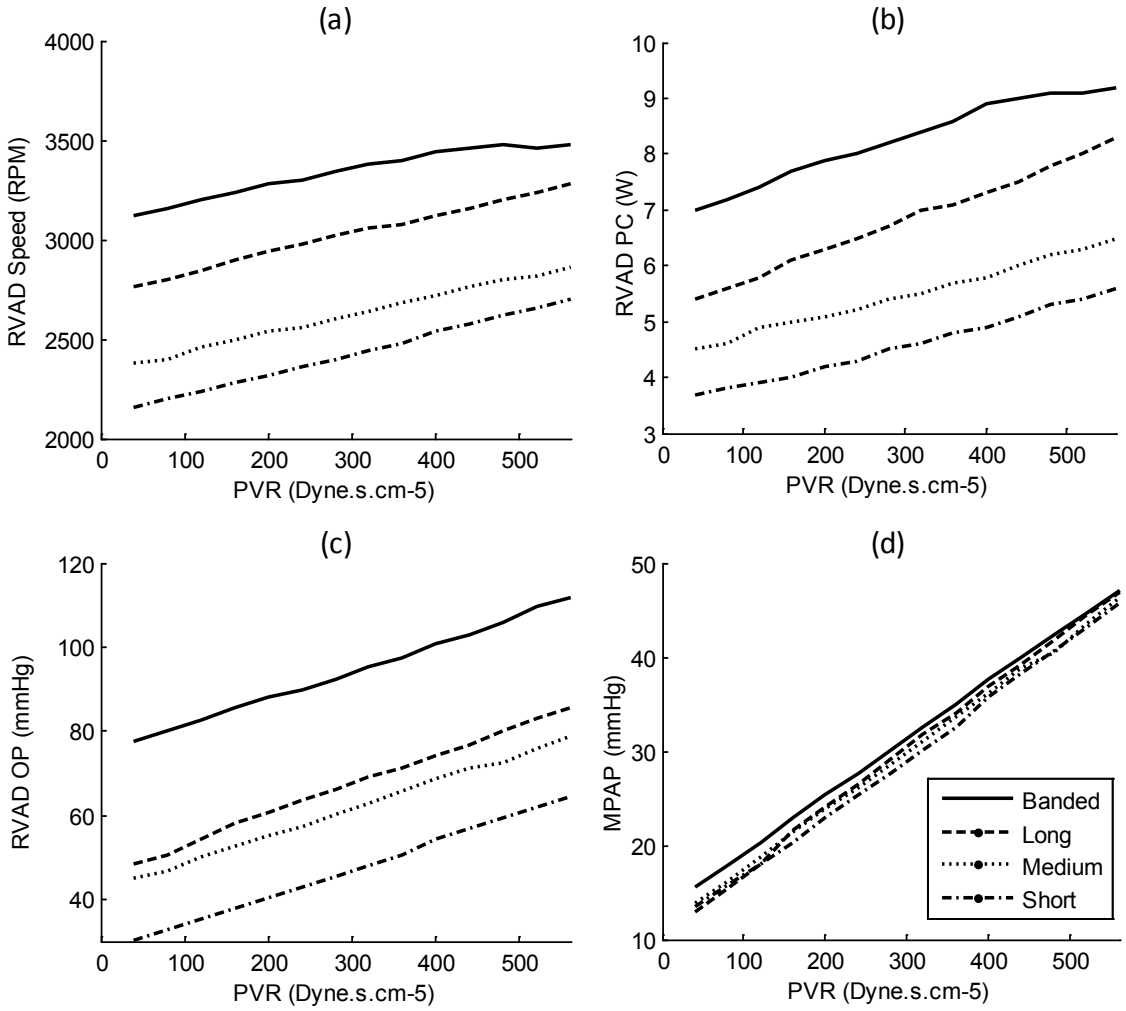

Figure 8 – Results for the severe biventricular heart failure condition with varying pulmonary vascular resistance (PVR) including (a) RVAD speed, (b) RVAD power consumption (PC), (c) RVAD outflow pressure (OP) and (d) mean pulmonary arterial pressure (MPAP). W – Watts.

5.3.2 Mild RV failure

Compared with severe RV failure, the same flow-rate and pressure was achieved with lower RVAD speed and power consumption in all outflow conduit conditions tested. With the exception of the unbanded conduits at a PVR of 40 dyne.s.cm^{-5}, the RVAD was able to function above the manufacturer's recommended minimum rotational speed in the setting of mild RV failure (2400 rpm) (67) and produce 5 L/min flow to match that of the LVAD (Figure 9a). This was similar to the findings in severe RV failure, where the shortest unbanded conduit required operation of the RVAD at a sub-optimal rotational speed. This effect was ameliorated with the application of 40 cm, 60 cm and banded conduits.

Overall, in the tested outflow conduit conditions, the corresponding rotational speed, and subsequent power consumption and outlet pressure generated was, on average, lower in mild RV failure than that in severe RV failure. The mean difference in RVAD rotational speed between severe RV and mild RV failure was 1.9%, mean difference in power consumption was 6.3% and mean difference in RVAD outlet pressure was 8.3%. However, the relationship of these three variables with PVR in the setting of mild RV failure differed from that in severe RV failure. For instance, from 40 to 120 dyne.s.cm^{-5}, the increase in mean RVAD rotational speed in the setting of mild RV failure was 22.7%, but from 120 to 560 dyne.s.cm^{-5}, the increase was only 4.0%. This is opposed to the linear relationship between these variables and PVR in severe RV failure, and was more marked in the unbanded conduits. This can be attributed to the RV contributing to forward flow at low levels of PVR where the RV end diastolic volume is higher.

Through the Starling response implemented in the MCL, this resulted in increased right ventricular contractility and subsequent ejection through the pulmonary valve. As PVR, and consequently MPAP, increased and ejection through the pulmonary valve decreased, greater changes in RVAD speed were required to overcome the reduced RV ejection and the increase in resistance. Once the RVAD was providing total circulatory support (PVR at 120 dyne.s.cm^{-5}), smaller changes in pump speed were required to maintain pulmonary flow rate (Figure 9b).

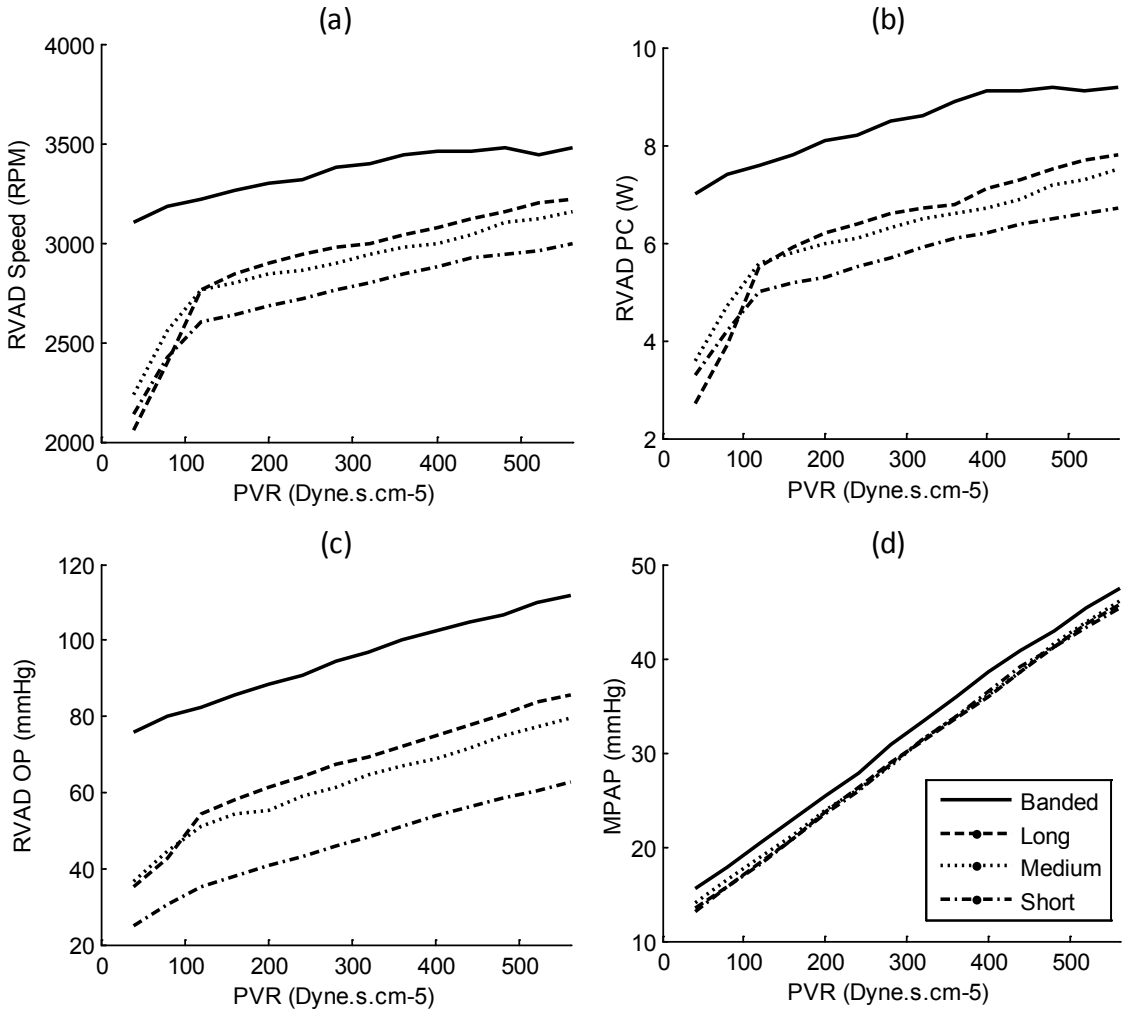

Figure 9 - Results for the mild biventricular heart failure condition with varying pulmonary vascular resistance (PVR) including (a) RVAD speed, (b) RVAD power consumption (PC), (c) RVAD outflow pressure (OP) and (d) mean pulmonary arterial pressure (MPAP). W – Watts.

5.4.1 Discussion

Although various mechanical circulatory support devices have been reportedly used successfully for right ventricular support (173), there remains to be a commercially available RVAD-specific third generation device. While devices are still being developed (174, 175), adopting existing devices for RVAD use presents challenges in their set-up that must be overcome. This includes device placement (176), operational parameters and the outflow tract dimensions (177).

Adaption of existing VADs for right-sided use is not a new concept. As early as the early 90's, successful animal in-vivo application of a fully-implantable continuous axial flow device in RVAD configuration had been described (178). This device was not physically altered on table, but instead regulated with slower pump speeds. However, the study was limited by the short duration of only 6 days of support.

In the case of the HeartWare HVAD used in this study, the device is fitted with a hydrodynamically levitated impeller, relying on sufficient speed to create a fluid film and thus may become unstable at lower speeds (179). However, increasing RVAD rotational speed and flow-rate raises pulmonary artery and capillary pressures (180). Guidelines for the operational parameters of these devices specifically in RVAD configuration were thus necessary.

Krabatsch et al described the currently prescribed method for adapting the HeartWare HVAD for RVAD use in 2011. Their method attempts to neutralize the pump's left-side specific features: the inflow cannula insertion is altered to prevent excessive intraventricular length to avoid suction events; and the outflow cannula diameter is restricted to simulate systemic afterload for the pump without causing barotrauma to the delicate pulmonary vasculature. Pump speed was set independently from the LVAD, but was generally similar (181). This was opposed to the method used by Strueber et al the year before: decreasing the RVAD speed to the lower limits of the manufacturer's specifications and compensating for pulmonary congestion by significantly increasing LVAD speed, but at the expense of increased LVAD power consumption (182).

Almost concurrently, Timms et al began studying the specific degree of banding required to achieve adequately balanced flow rates while maintaining pump speeds within the manufacturer's specifications (67). With their results also demonstrating excessive RVAD flow when no adjustments are made to the RVAD in a mock circulation loop setting, the authors determined that optimal adaption of the VAD required a restriction in the outflow cannula to 5.4mm in order to maintain adequate speed and prevent RVAD flow exceeding LVAD flow. However, in the context of our experiment, these results need to be interpreted with caution, as the third-generation devices used were from a different manufacturer, to a different design (167).

While our clinical experience with banding has been successful, we note the anecdotal suggestions of surgeons attempting to vary conduit length to achieve the same result. This was justified using Poiseuille's law stating that resistance of a lumen is a function of radius and tube length. However, the required increase in length to achieve the same resistance did not seem realistic for implantation. To the knowledge of our group, there is little to no discussion of this in the literature previously. As such, we aimed to observe the performance of a third generation VAD with varying outflow conduit conditions and compare this with performance of a banded conduit.

In this experiment, we found that all tested outflow conduit conditions caused the pump to run outside of manufacturer's recommended rotational speed (2400 rpm to 3200 rpm) (67) at some degree of PVR. However, we found that the banded conduit had the narrowest range of PVR conditions where it would function within the recommendations (40 dyne.s.cm^{-5} to 120 dyne.s.cm^{-5} in severe RV failure, and 40 dyne.s.cm^{-5} to 80 dyne.s.cm^{-5} in mild RV failure) and achieve a normal haemodynamic state. Higher resistance conditions forced the pump to be operated faster than 3200 rpm. Conversely, the lowest resistance conduit also required pump speed outside of the prescribed parameters in the lowest PVR setting. The optimal outflow conduit configuration for maintaining pump function within the guidelines seemed to be the 40 cm unbanded conduit. This conduit had the widest range of PVR where it would facilitate pump operation within manufacturer's guidelines. In clinical terms, where PVR has a reference range of 155 to 255 dyne.s.cm^{-5} (183), a conduit of 40 cm should

always function within manufacturer's guidelines based on our in-vitro results. This is important, as low-flow through devices have been reported as contributory factors to intra-pump thrombosis (184), while higher than recommended speeds result in excessive power consumption. These results can be used as a guide for clinicians to base the intra-operative decision of RVAD outflow conduit set-up, as well as pump speed adjustments throughout the supported duration depending on changes in the patient's right ventricular function and afterload.

While the length of the outflow conduit impacted on RVAD afterload, it should be noted that the longest length tested (60 cm) only produced half the outlet pressure of a 5 mm diameter band. However, the practicality is that such a long outflow conduit would never be used clinically as it would be susceptible to kinking and compression from adjacent viscera. Testing at this length in an in-vitro setting is useful, though, to demonstrate the effects of varying graft length. Clinically, the shorter lengths can be achieved by laying the conduit down along the diaphragm and then up over the RV to reach the pulmonary trunk.

It has been reported in the literature that right ventricular recovery can occur with both short (185) and long term (186) BiVAD support. Discerning the operational parameters within a spectrum of right heart failure severity is thus important to prevent over-pumping where myocardial recovery has occurred. With the repetition of the test with mild RV failure, this study also took into

account potential right-sided myocardial recovery and pulmonary vascular bed remodeling. We found that, even under improved right heart conditions, the RVAD did not need to drop below the recommended functional parameters to continue to produce an optimal haemodynamic state by simply extending the graft length.

Although the HeartWare HVAD has not received FDA approval for use as an RVAD, we believe this device has advantages warranting thorough evaluation for this application. The HVAD has a small device size with an integrated inflow cannula. This allows for direct intrathoracic implantation of the entire device, and less disruption to native viscera function. Furthermore, a recent study has demonstrated the reliability of the HVAD in long-term support, and hence suitability for long-term implantation. Using a mock circulation loop and 8 HVADs, Reyes et al ran the pumps for a cumulative runtime of 2408 ± 60 days without device failure (187).

A proposed disadvantage to the application of permanent BiVAD strategies such as the dual HVAD tested here has been the concern with the need to re-operate to explant the devices should myocardial recovery occur. However, Potapov et al have demonstrated with the HeartWare device that, should RV function recover prior to transplant, the device can be switched off and left in-situ safely. In ten consecutive patients implanted with HeartWare devices in BiVAD configuration, three patients on follow-up demonstrated sufficient RV recovery to no longer

require assistance. The devices were switched off and left in-situ, and follow-up/echocardiography demonstrated continued effective RV function without pump complications such as thromboemboli or regurgitation (188).

In this preliminary study, we utilised a previously validated mock circulation loop to avoid the complications involved in using animal models. Although we recognise the availability of numerical models to conduct a simulation (189, 190), we hypothesise that the physical testing of a device would be better able to detect unpredictable performance characteristics of the VAD system.

A similar study was recently conducted by Stevens et al, albeit with biventricular VentrAssist LVADs (formerly Ventracor Ltd, Sydney NSW, Australia, now Thoratec Corp. Pleasanton CA, USA) (179). These conditions were tested against a control of running the pump at normal operational parameters without modification while implanted to the right heart. They were then repeated in-vivo in a sheep model. While this group's findings were congruent with our own, the specific changes are not compatible simply because of differing pump design. In their experiment, the right-sided VentrAssist device was required to run at below manufacturer's specification speeds. This was not observed in our experiment. Furthermore, their animal study demonstrated increased RVAD afterload compared to the same degree of RV failure and PVR. Post-mortem examination revealed longer graft length and a thin, uniform layer of thrombus inside the graft as the likely causes, thus effectively banding the RVAD outflow

conduit. If this were also true with the HeartWare device, we hypothesise that it would function well within manufacturer's guidelines in-vivo under all of our tested conditions.

As an in-vivo study, we were limited by multiple factors that were impossible to simulate. The complex auto-regulatory systems of a biological circulation are only partially replicated. Also, while our system simulates the viscosity of blood in a healthy human, this can vary significantly with heart failure. Furthermore, the coagulation properties of blood were not simulated, which, as aforementioned, can have significant impact on outflow conduit conditions in an in-vivo setting.

As expected, the capacity to run the pumps at lower speeds also brings with it power consumption benefits. We found that the difference in power consumption was between 9.8% and 48% lower by varying cannula length rather than banding while operating the pump within recommended parameters. However, the increased power consumption with RVAD outflow banding could be reduced by decreasing the RVAD outflow restriction, and thus pump speeds.

We defined the minimum pump speeds required to maintain 5L/min flow with a variety of outflow conduits. Based on the literature, we postulate that the pump speed would be higher in an in-vivo setting. Therefore, an in-vivo study would be necessary to confirm our results.

5.5.1 Summary

In this study, using a sophisticated simulation of the human circulatory system, the HeartWare HVAD in an RVAD configuration was demonstrated to maintain physiological pulmonary flow rates with and without outflow cannula restriction in both severe and mild RV systolic dysfunction with varying levels of PVR. Increased length of the outflow conduit was found to produce significantly increased afterload to the device, and a graft length of 40 cm was found to provide optimal conditions for pump function. While results of this in-vitro study should be interpreted with caution, our results suggest that the utility of outflow conduit modification in the HeartWare HVAD may not be as great as previously believed. Further testing of this hypothesis in animal models is thus warranted to confirm these findings, and for the ongoing development of right ventricular mechanical support.

Chapter 6 – Biventricular support using HeartWare HVAD

6.1.1 Introduction

Despite the high incidence of RV failure post-LVAD and evidence for early right-sided mechanical support, there remains no fully-implantable, commercially available right ventricular assist device (RVAD) for long term support. We examine the off label use of the centrifugal HeartWare HVAD (HeartWare Inc., Framingham, MA) for long-term right sided support in our population.

Of the one-hundred and one patients reviewed in our retrospective study, fifteen patients patients required mechanical right ventricular support of either a temporary or permanent nature peri or post-operatively. Of these, eight were planned at the time of operation and seven were unplanned. Two from each of these groups were implanted with permanent BiVAD using right-sided HeartWare HVAD. These patients are discussed in detail in this chapter (table 22).

Table 22 - Patients with Permanent BiVAD

Patient	Age at LVAD	Gender	LVAD	RVAD	Outcome
A	17	F	Ventrassist: replaced with HeartWare HVAD	Biomedicus: unable to wean, thus HeartWare HVAD	Transplanted at day 117
B	21	F	Ventrassist	HeartWare HVAD	Transplanted at day 597
C	51	M	Heartware HVAD	HeartWare HVAD	Transplanted at day 546
D	56	M	HeartWare HVAD	HeartWare HVAD	Awaiting transplant (772 days)

6.2.1 Case Series

Patient A was a 17-year-old with post partum cardiomyopathy who had a Ventrassist LVAD inserted. Post operatively she immediately developed problems with low flow requiring insertion of a temporary (Biomedicus centrifugal pump) RVAD. She continued to have problems with low-flow, which seemed to be due to the Ventrassist inflow cannula position. Due to her small size and narrow costal margin, it was decided to remove the Ventrassist LVAD and replace it with a Heartware HVAD. The temporary RVAD support could be weaned and removed after 26 days but one week later increasing right heart failure necessitated the insertion of permanent right-sided support. The patient was adequately supported on the biventricular HVADs and was able to leave the hospital for day trips. However she had ongoing problems with sternal sepsis (requiring long term antibiotics), renal failure (requiring dialysis for a short period) and after a renal biopsy had a gastrointestinal bleed and then an LVAD thrombus requiring thrombolysis. Following these complications, she was urgently listed for transplantation and was successfully transplanted after 5 months of LVAD support and 117 days of right-sided HVAD support. Unfortunately at four months post transplant she died of disseminated cytomegalovirus infection.

Patient B was a 21-year-old female with lymphocytic myocarditis who underwent Ventrassist LVAD insertion with a temporary RVAD inserted at that time. After two weeks of temporary right-sided support, there was no evidence of improvement and a permanent right sided HVAD was implanted. The patient

improved to hospital discharge and was successfully transplanted after 597 days Ventrassist LVAD support and 580 days of Heartware RVAD support.

Patient C was a 51-year-old male with an initial presentation of severe idiopathic dilated cardiomyopathy. He deteriorated despite maximal medical management requiring urgent institution of peripheral extracorporeal membrane oxygenation (ECMO) support. After four days of support a Heartware LVAD was inserted. At one-week post operatively he required insertion of a permanent right sided HVAD. After 546 days of BiVAD support, the patient was successfully transplanted.

Patient D was a 56-year-old man with idiopathic dilated cardiomyopathy requiring urgent institution of peripheral ECMO due to rapid decompensation soon after admission. After one week of support an elective BiVAD implantation with Heartware HVADs was performed. The patient was discharged home after 49 days in hospital and has remained an outpatient for over 772 days awaiting transplant. The patient has not had complications of returning to theatre for bleeding, ongoing sepsis issues, nor other VAD related complications.

6.3.1 Discussion

Right-sided failure occurring concomitantly with end-stage left ventricular failure requiring biventricular mechanical assistance has been associated with poorer outcomes than single-chamber support (191-193). These patients present sicker (192, 193), and it has been postulated that the established end-organ sequalae of this poor pre-operative state is the cause of the excess

morbidity and mortality. However, there is growing support in the literature for the prompt and planned biventricular mechanical support to improve outcomes (136, 166, 191).

In 2005, Tsukui et al sought to justify this treatment strategy by examining their own experience with biventricular mechanical assistance over a thirteen-year period (166). Although no control group was established in this study for comparison of outcomes, the data produced from this study of planned BiVAD inserted patients suggested survival and complications comparable with historical datasets for LVAD supported only patients when pre-operative factors, other than established biventricular failure, were matched.

Fitzpatrick et al expanded on the topic, including 266 consecutive patients, of which 99 were BiVAD supported, in their study. With the BiVAD patients further subdivided into planned and delayed RVAD insertion groups, these authors compared the outcomes of each treatment strategy in the same population. They found that, while still inferior to the outcome of LVAD only in the same cohort, there was a significant difference in the survival between planned and delayed BiVAD conversion (51% vs 29%, $p<0.05$). This survival benefit continued throughout one year and long-term survival, as well as incidence of transplantation (136).

This relationship between early biventricular support and survival was further indirectly explored by Holman et al in their multicentre study (191). Specific VAD outcomes aside, these authors found that signs of severe pre-implant

hepatic dysfunction, interpreted as an analogue to the systemic sequelae to severe RV failure, was a strong predictor of mortality ($p<0.05$). These authors hence suggested early intervention prior to the onset of systemic sequelae to be important in improving survival.

As such, research is beginning to focus on selecting those patients who would benefit most from such a treatment strategy (84, 194). However, the bulk of the literature focuses on temporary, para-corporeal devices. Whilst effective, this strategy severely limits the quality of life experienced by supported patients, especially if they do not demonstrate any improvement in RV function and require long-term support. Hence, we examined the utility of permanently implanted biventricular devices.

The off label use of the Heartware HVAD as right-sided support is now well described (177, 181, 182). There are a variety of cannulation methods reported which include right ventricular apex, diaphragmatic surface of the right ventricle and the right atrium (176, 177, 182, 195). HVAD was implanted in the right atrium in all of our subjects, suspending the pump through a window in the right lateral pericardium (Figure 10).

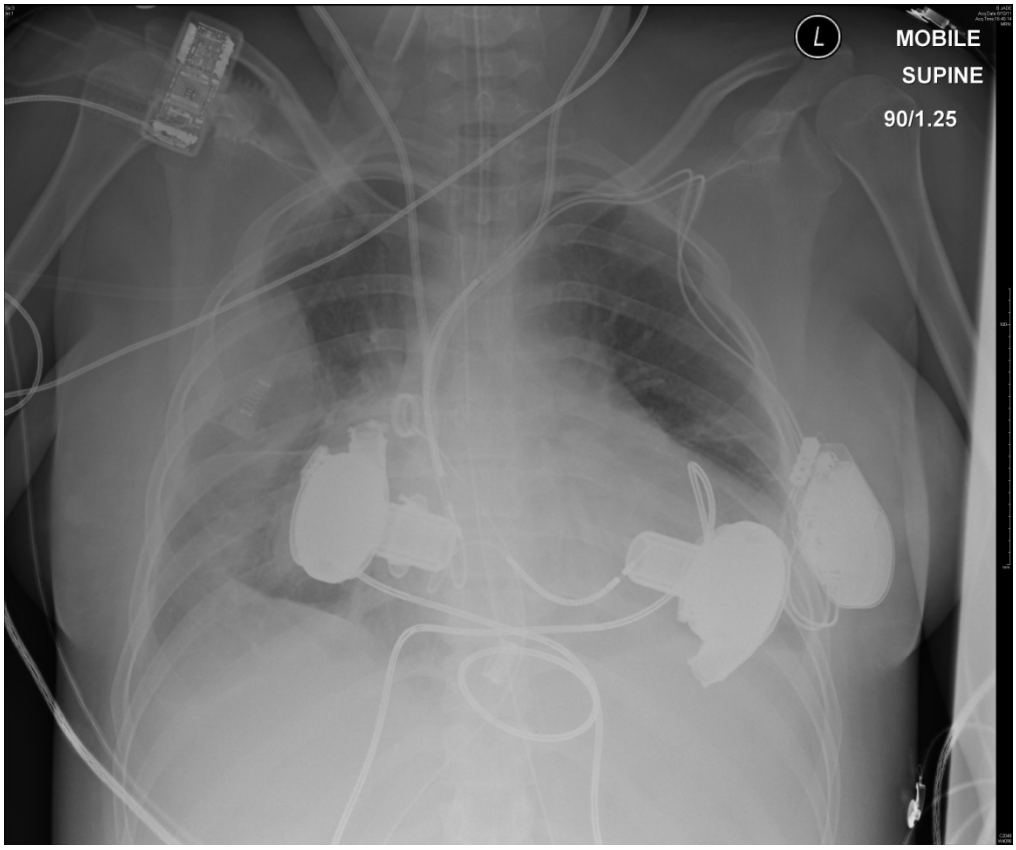

Figure 10 - Post-operative CXR showing positioning of both HVADs

The increase in pericardial pressure from the presence of LVADs have been documented to negatively impact on RV function (73, 76). Furthermore, consideration has to be given to inflow and outflow cannulae positions to avoid kinking and compression. While no research has been conducted on biventricular HeartWare HVADs specifically, an in vivo fitting study conducted by Ootaki et al with the larger DexAide device at the Cleaveland Clinic demonstrated the same problem, concluding that right thoracic cavity placement provided best-fit in humans (196).

Alternatively, placement in the right ventricle has been suggested as superior as it is more likely to allow for better decompression and improved likelihood of recovery. Schlensak et al randomised 31 consecutive long-term continuous-flow

BiVAD patients to atrial and ventricular cannulation and observed support adequacy (176). Using renal and hepatic function as analogues of left and right heart performance respectively, as well as directly observing pump flows, the group found better pump flow and renal recovery in the ventricularly implanted group ($p<0.001$). However, this study was conducted using a paracorporeal device, meaning space for the pump was not taken into consideration.

Gregory et al attempted to perform a similar study with third-generation devices in an in-vitro setting using a mock circulation loop to assess the effect of cannulation site on ventricular function (197). This group noted that right ventricular cannulation led to superior contractility and decreased stasis in the native ventricle, an effect that was more evident in severe RV failure. However, right atrial cannulation was observed to provide better ventricular decompression in mild RV failure, and was suggested in this condition to be more conducive to ventricular recovery.

In our cohort, the first three patients were physically very small with narrow costal margins and short anteroposterior diameter. It was felt the pump would be too bulky if placed anteriorly behind the sternum or on the diaphragmatic surface. Furthermore, use of this device as an RVAD requires effective shortening of the inflow cannula as it is designed to pass through the thicker, muscular left ventricular apex. Use of the inflow cannula's full length in the much thinner walled right heart would leave a much longer length of cannula in the chamber. Although no literature exists on the matter, it can be easily inferred from observation of the anatomy and biomechanics of the right ventricle that

insertion of the entire inflow cannula into the chamber would lead to suck down and malposition events owing to the proximity of the tip to the opposing chamber wall. Thus the intrachamber length of the inflow cannula was shortened by either placing spacers over the cannula between the epicardium and the sewing ring (181), or by creating a new 'washer' over the inflow cannula and 'overtightening' the hex screw on the sewing ring so that only about 15mm of the inflow cannula passes through the sewing ring (Figures 11 and 12).

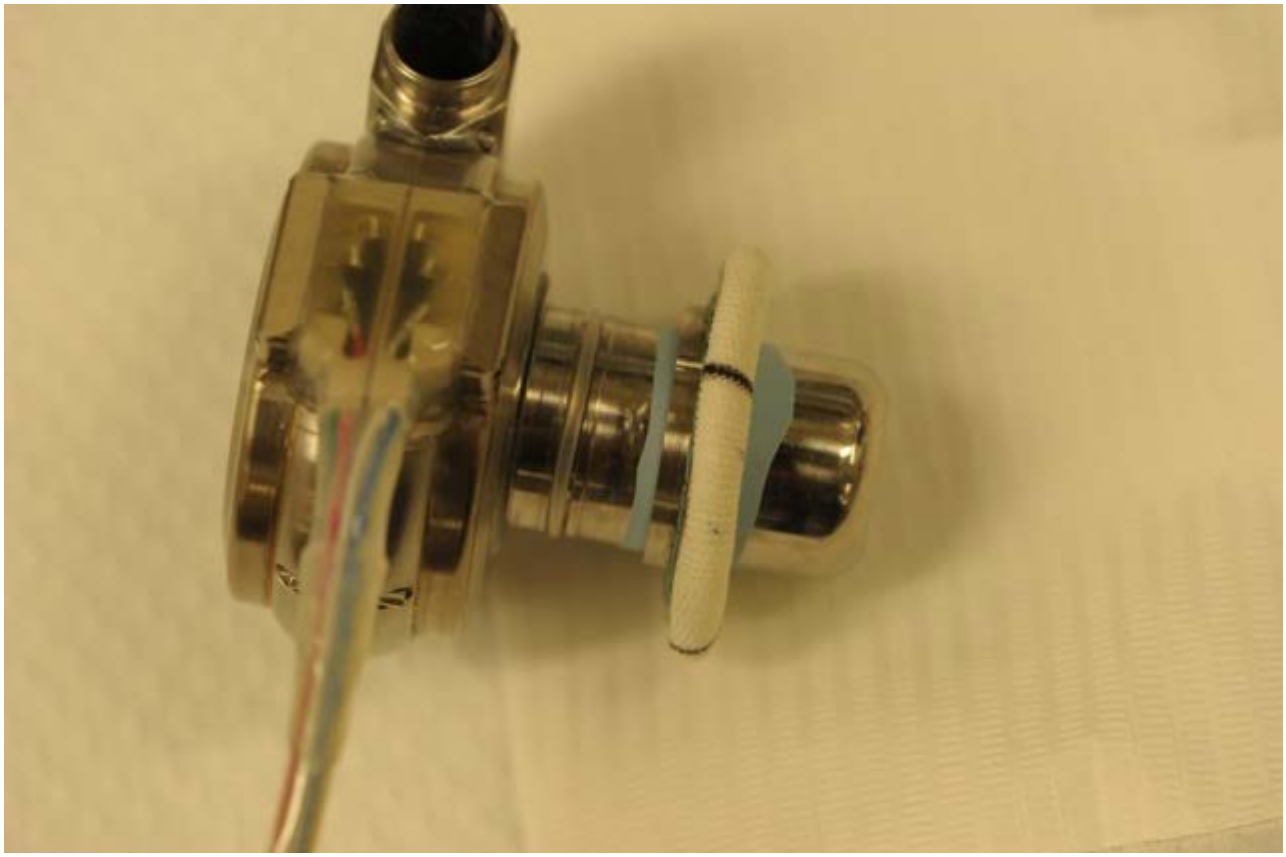

Figure 11 - Position of the sewing ring on the inflow cannula with a piece of rubber glove as the new washer

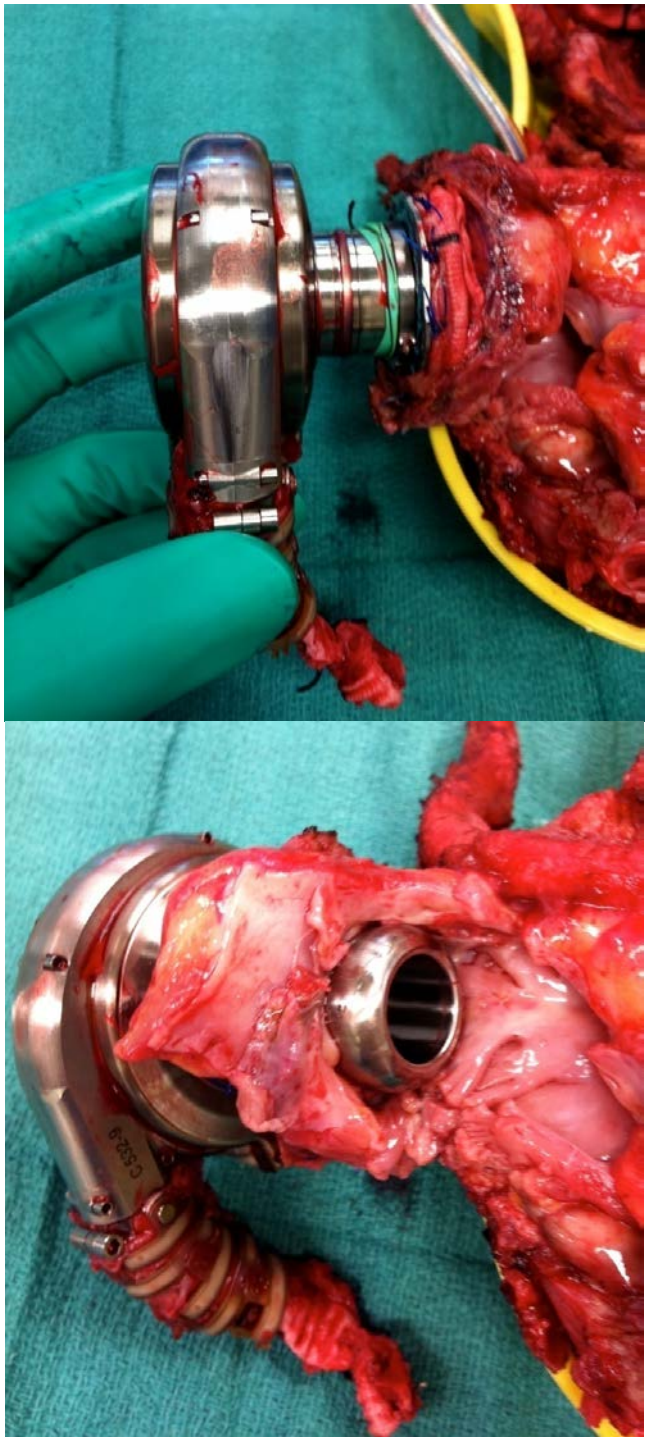

Figure 12 - Position of inflow cannula in right atrial wall in an explanted specimen

However, this technique leaves the pump sitting up away from the surface of the heart so that it does become a more bulky intrapericardial device. Leaving the pump outside the pericardium, with the cannula passing through a window in

either the right lateral pericardium or the diaphragm removes the bulk of the device out of the pericardium.

In all cases, the outflow graft was brought superiorly, crossing the left ventricular outflow tract to reach the main pulmonary artery. This left a fairly short length of outflow graft (about 10 cm) and it was thus necessary to reduce the bend relief length and crimp the diameter down to about 6mm with haemaclips over a 3 cm portion of the length to increase the afterload of the device (181) (Figure 13) .

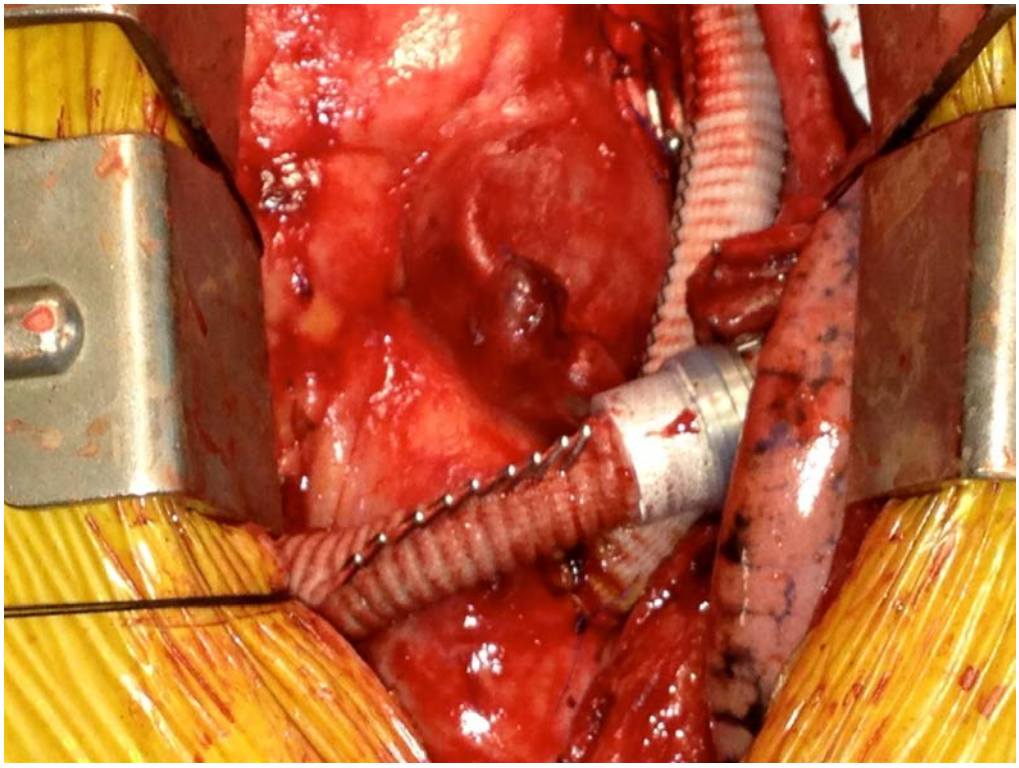

Figure 13 - RVAD outflow graft crossing the ascending aorta (patient's head is at the inferior aspect of the photo). Bend relief has been shortened and the graft has been crimped with Hemaclips

Over-crimping was immediately evident intraoperatively by increased power consumption by the RVAD and corrected on table. There were no episodes of

flooding of the lungs and pulmonary oedema with this technique. Despite good pulsatility seen on the VAD flow waveform on the left side, significant pulsatility on the right was not observed. This is in keeping with the placement of the cannula in a non-pulsatile chamber. As can be seen in Figure 14, the waveform of the RVAD flow is fairly flat. Suck-down events can still be clearly identified if and when they happen, however.

Figure 14 - Operational parameters of the left and right HVAD soon after implantation, prior to leaving the operating room

Inflow cannula low on the lateral right atrium, closer to the inferior vena cava rather than the superior vena cava was the preferred position in this cohort, as it appeared to give better, more reliable flows, with minimal suck-down events. Again, a lack of evidence on this matter demanded on-table improvisation. We hypothesise, however, that right atrial cannulation is likely to provide conditions for optimal flow and less suck-down events overall.

Post-operative management of the BiVAD patient group followed the same principles as for patients with LVAD alone. In particular, nutritional status was optimised with early enteral feeding, euvolaemia was restored with judicious diuresis, and infections prevented with strict infection control protocols and prophylactic antibiotics. Routine ICU management followed the same principles as for the LVAD group. Bridging heparin was commenced after 24 hours (to the exclusion of active bleeding issues). Warfarin was introduced once all chest drains and lines were removed with a target International Normalised Ratio of 2 to 3. Antiplatelet therapy in the form of aspirin 100mg daily was commenced on post-operative day 3 (again, to the exclusion of active bleeding issues), and dipyridamole was used as an adjunct agent where there was suspicion or evidence of clotting pre-disposition. One patient (C) had significant haemoptysis in the setting of chest sepsis, requiring bronchial artery embolisation to control this. He remained off all anti-coagulation and anti-platelet agents for several days but did not have any thrombotic complications.

Early post-operative haemodynamic management of BiVAD patients required frequent echocardiographic examinations. In contrast to LVAD support alone, haemodynamic monitoring using pulmonary artery catheters was not deemed adequate. Right atrial pressure, estimated VAD outputs and pulsatility waveform of the LVAD, mean arterial pressure and signs of end organ perfusion were used as markers of RVAD performance. Fine-tuning of flows required echocardiographic support, usually in the intensive care unit with transoesophageal echocardiography to avoid artefact from recent sternotomy. In

particular, interventricular septal movement and position, ventricular outflow valve opening and size of the ventricles were assessed for in optimising speed settings.

Interestingly, while the literature is lacking in the description of RVAD monitoring, regular serial echocardiograms have been suggested as useful in the monitoring of LVAD patients. Kato et al performed a prospective study in 2013 on their elective continuous flow LVAD population to determine the utility of transthoracic echocardiogram (TTE) in identifying patients with deteriorating RV function early for further medical or surgical intervention (198). Of the 68 patients in this study, 35.3% of patients overall developed RV failure. In addition to standard TTE techniques, the authors utilised spekle tracking imaging and tissue Doppler imaging to assess RV parameters including tricuspid annular plane systolic excursion (TAPSE), trans-tricuspid filling velocity/early diastolic velocity ratio (RV E/e') and absolute value of global RV longitudinal strain remained lower in the patients who developed RV failure ($p = 0.012$, 0.003 and <0.001 respectively). They reported that their sensitivity for RV failure was 87.5%, with a specificity of 70.4% and predictive accuracy of 76.5%. Furthermore, the authors reported no difficulty in obtaining any left or right-sided views and parameters. While not the primary aim of this paper, it does support the utility of echocardiography when VADs are in situ to accurately assess biventricular structure and function.

Patients A, B, and C all had delayed insertion of permanent right sided support and as a result suffered from bleeding complications, multiple returns to theatre

for bleeding and wash out of clot. As a result, patients A and C developed ongoing sepsis requiring long term antibiotics while on BiVAD support. In contrast, patient D, who had elective placement of permanent BiVAD support at the initial operation, had no peri-operative bleeding or requirement for reoperation. None of the patients have had any driveline infections, despite having two driveline exit sites. The velour covering of the driveline was routinely left completely implanted with the intention of decreasing infection rates.

All three transplant operations in patients A, B, and C were difficult with dense adhesions, presumably as a result of multiple re-entries and sepsis. Patient C sustained bilateral phrenic nerve injuries during the BiVAD explantation and has hypercapnoeic respiratory failure as a result. Use of artificial membrane wraps, such as GORE-TEX™ (W.L. Gore & Associates, Elkton, MD) or expanded polytetrafluoroethylene (ePTFE), around the pump housings and outflow conduits have been described to reduce the risk of damage on re-entry and damage to surrounding structures by limiting adhesions (199).

Device malfunctions or complications in the right-sided position were not observed in this population. Patient A, who had her anticoagulation stopped after bleeding post renal biopsy, developed evidence of pump thrombus in the LVAD requiring thrombolysis. Interestingly she did not develop evidence of thrombus in the RVAD despite the cessation of anticoagulation. Patients B, C and D were all able to achieve a good quality of life while awaiting transplantation. They are reviewed in the VAD clinic 4-6 weekly and have returned to school (patient B), exercise, and their normal daily activities while on BiVAD support.

While none of this cohort ever achieved sufficient right ventricular recovery for cessation of RVAD, evidence in the literature suggests conversion to LVAD only support has a strong correlation with survival. Saito et al first demonstrated this in their population (185). In 101 patients implanted with LVAD, 26 patients required BiVAD. Of these, 11 were able to be weaned to LVAD only, and demonstrated a similar survival to patients never requiring right-sided support. However, there was a statistically significant difference in survival between those who could be weaned, and could not (80% vs. 11% at 1 year, $p<0.001$). A recent review of the United Network for Organ Sharing (UNOS) Dataset tracking survival of status 1 heart transplant candidates produced results supports this.(161) LVAD support only compared to any other form of mechanical circulatory support had the strongest correlation with survival (HR0.707, 95% CI 0.593-0.844, $p<0.001$). However, these authors also found that the survival benefit extended to any patient who was successfully transitioned to LVAD only from ECMO or biventricular support. Although, both of these studies were predominantly made up of older generation devices, the capacity to cease right-sided support is hence important.

Given the fragility of these patients, re-operation to explant the RVAD in the event of RV recovery would be suboptimal. However, Potapov et al have demonstrated with the HeartWare device that, should RV function recover prior to transplant, the device can be switched off and left in situ safely (188). In ten consecutive patients implanted with HeartWare devices in BiVAD configuration, three patients on follow-up demonstrated sufficient RV recovery to no longer

require assistance. The devices were switched off and left in-situ, and follow-up echocardiography demonstrated continued effective RV function without pump complications such as thromboemboli or regurgitation.

The requirement for the development of an implantable RVAD has been mooted by members of the heart transplant community for some time now. Unfortunately, barriers identified to this progress include: (a) reversibility of failure in the RV compared to that in the LV; (b) poor predictability of RV failure; and (c) financial cost (200). However, given the mounting evidence of benefit, this seems to be the necessary direction for the next step of development in VAD technology. In the mean time, existing devices which may serve in a similar capacity need to be thoroughly researched for their utility in this application. In our experience, the HeartWare HVAD appears to fit this description.

6.4.1 Summary

Established biventricular failure prior to mechanical circulatory support has been well described as a predictor of poor outcomes in the literature. In this high-risk group of patients, there has been suggestion that early identification and management with biventricular assist devices may improve outcomes. Although there remains to be a specific device specifically designed for the purpose, this series suggests that the use of currently available devices with appropriate on-table modification is a safe treatment option, providing patients with an acceptable standard of living whilst awaiting transplantation.

Chapter 7 – Future Directions and Conclusions

7.1.1 Future Directions

With improving cost-effectiveness and demonstrable survival and quality of life benefits, LVAD is becoming a more common intervention for end-stage heart failure. However, in order to maintain the momentum in improving outcomes, technical challenges, such as RV failure, must be addressed.

In this study, we have demonstrated the importance of pre-implantation sub-clinical RV dysfunction in determining the outcome post-implantation. While this correlates with the existing literature, the size and scope of previous studies have not been sufficient to consistently demonstrate measurable markers that can be easily and universally applied for risk assessment. A more organized and coordinated effort to produce and analyse multi-centre registry data, as has been begun by Karamlou et al (161), will enable clinicians to identify and optimise patients prior to LVAD. We hypothesise that this will significantly decrease the incidence of post-LVAD RV failure. Where pre-LVAD RV dysfunction is refractory to optimisation, planned permanent BiVAD is becoming an increasingly attractive option. Our experience has not demonstrated any long-term issues with early biventricular support, and provides a pilot study for further research in the subject.

A stumbling block for research in LVAD has been the speed of rapid generational change of the devices. The fundamental, and initially controversial, change that has allowed longer-term therapy has been the development of continuous-flow devices, and the associated reduction in size, noise and complexity. With

research now supporting the efficacy and safety of continuous-flow devices (201), long-term LVAD support has become a reality. Miniaturisation (202) and reduction in external components (203) are the next frontiers in VAD technology overall. However, RVAD specific technology remains at its infancy. Necessary developments for adaption of existing technology include establishment of RVAD specific techniques and parameters, and development of controllers specific for monitoring RVAD function. These may be the prelude to eventual development of devices specific for RVAD use (173).

Improvements in VAD technology have led to the increasing use of LVAD as destination therapy. Survival with LVAD has now reached the point where carefully selected patients can achieve two-year survival comparable to that of heart transplantation (204). Furthermore, developments in wireless technology will allow for full implantation without external parts, further enhancing quality of life. Given the perennial struggle to find appropriate donor organs, development of VAD technology may evolve to become a viable alternative, rather than bridge to, transplantation.

7.2.1 Conclusion

In the past decade, LVAD has become an established treatment modality for patients in severe heart failure refractory to maximal medical therapy. However, with the high cost and invasiveness of the procedure, it is not possible to

institute LVAD in all acutely deteriorating patients. Careful patient optimization and selection is thus vital for the application of this treatment protocol.

Despite advances in technology and management, RV failure remains a highly morbid complication associated with a significantly increased risk of mortality in left ventricular supported patients. This project was a multi-faceted study on the aetiology, pathology and management of this phenomenon.

It appears that the patients who develop RV failure post LVAD implantation, in our experience, were already showing a degree of RV dysfunction pre-operatively. Existing studies on RV failure post-LVAD support the notion that the severity of RV compromise pre-operatively is the main factor in predicting post-operative RV failure. Furthermore, existing predictive models in the literature appear to have some predictive capability in our population, albeit with re-calibration.

While medical optimization to decrease likelihood of RV failure is possible in patients slowly deteriorating, this is not possible in acutely presenting shocked patients. For these patients, double-bridging using ECMO to allow sufficient systemic recovery for the implantation of LVAD appears to be a promising screening and management option. Further potential benefits include the ability to assess the RV in a controlled manner to determine the need for biventricular

support. Despite presenting with higher morbidity, our patients instituted on ECMO do not appear to do any worse than those electively implanted with LVAD.

For those with established biventricular failure prior to VAD implantation, but are otherwise candidates for long-term mechanical support, BiVAD appears to be a promising option. In this high-risk group of patients, there has been suggestion that early identification and application of biventricular mechanical assistance may improve outcomes. Although there remains to be a specific device specifically designed for the purpose, the use of currently available devices with appropriate on-table modification is a safe treatment option. Furthermore, fully-implantable devices are capable of providing patients with an acceptable standard of living whilst awaiting transplantation.

Appropriate on-table modifications were investigated using a sophisticated simulation of the human circulatory system. The HeartWare HVAD in an RVAD configuration was demonstrated to maintain physiological pulmonary flow rates with and without outflow cannula restriction in both severe and mild RV systolic dysfunction with varying levels of PVR. Increased length of the outflow conduit was found to produce significantly increased afterload to the device, and a graft length of 40 cm was found to provide optimal conditions for pump function.

LVAD appears to be a promising technology for the management of end-stage heart failure. As our understanding of its interactions with the native

components of the circulatory system improves, we will be better able to anticipate and prevent complications. RV failure, though, remains a serious consideration in these patients. While this project found useful predictors and early management strategies, it also highlighted large gaps in the literature. Further research to improve cost-effectiveness, streamline pre-operative assessment of all heart failure patients and ensure early and appropriate intervention is pertinent to improving patient outcomes.

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