Mechanical Circulatory Support

Monash University

Faculty of Medicine, Nursing and Health Sciences

James Farag

Masters of Surgery

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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. I have not knowingly added copyright content to my work without the owner's permission.

Editorial assistance has been provided by:

Prof Silvana Marasco FRACS

Prof David McGiffin FRACS

Prof Shaun Gregory PhD

Dr Andrew Stephens PhD

Data collection assistance has been provided by:

Ms Robyn Summerhayes RN

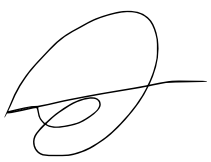
Ms Christina Kure PhD

Dr Andrew Stephens PhD

Ms Wei Chong

Statistical analysis assistance provided by:

A/Prof Michael Bailey PhD



Signed _____ Date 30th August, 2019

Dr James Farag MBBS, Dip Surg Anat, student ID 20710884 Master of Surgery Candidate 2018/2019

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I have / have not renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Student name: James Farag

Student signature: **Date:** 30th August, 2019

I hereby certify that the above declaration correctly reflects the nature and extent of the student's and co-authors' contributions to this work. In instances where I am not the responsible author I have consulted with the responsible author to agree on the respective contributions of the authors.

Main Supervisor name: Professor Silvana F Marasco

Main Supervisor signature: MARASCO **Date:** 30th August, 2019

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INTRODUCTION – MECHANICAL CIRCULATORY SUPPORT

Mechanical circulatory support is becoming more frequently utilised in the intensive care and cardiac surgical setting. From extra-corporal membrane oxygenation (ECMO) to ventricular assist devices (VADs), there are newer models, and variations in configurations to accommodate expanding indications. Cardiac failure can be managed in the immediate setting with Veno-Arterial ECMO (VA-ECMO), and in the mid- to long-term with Biventricular or Left Ventricular Assist Devices (Bi-VAD, LVAD).

This thesis aims to determine the current progress of mechanical circulatory support in the cardiac surgical setting. This ranges from the use of VA-ECMO in the post-cardiotomy period, simultaneous mechanical device usage (IABP and ECMO, ECMO and VADs), and the latest in ventricular assist device advancement (HeartMate III).

Throughout this thesis, several studies have been performed, aiming to determine the most optimal use of these devices, and ensure the best outcomes for patients.

EXTRA-CORPOREAL MEMBRANE OXYGENATION – AN OVERVIEW

Introduction

Extracorporeal membrane oxygenation (ECMO) has various configurations and indications, but essentially has two major roles:

- to replace the role of the lungs in oxygenating the blood (Venovenous-ECMO)
- to replace the role of the heart in propulsion of oxygenated blood (Venoarterial-ECMO)

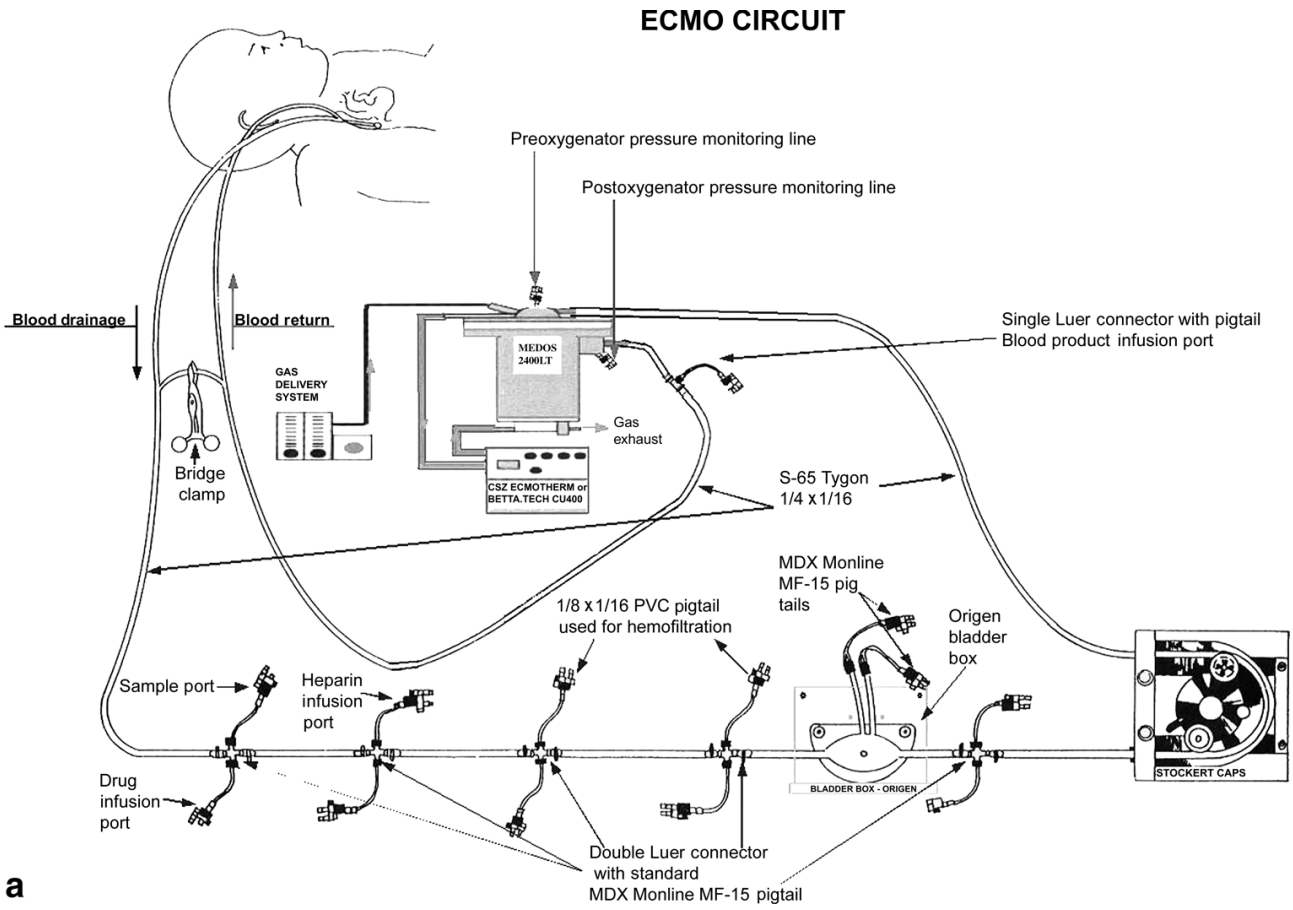
Essentially, indications for ECMO are dependent on the failed organ, generally unresponsive to all other therapy. ECMO is not in and of itself a cure to the underlying disease process either. It replaces the heart and/or lungs' vital function until the organ recovers, or allows a bridge to a destination therapy. In the case of VA-ECMO, this includes ventricular-assist devices (VADs) or heart transplantation.

In venovenous ECMO (VV-ECMO) a cannula is placed in a large vein, draining to the ECMO-circuit. Another cannula is placed in another vein, returning newly oxygenated blood. In venoarterial ECMO (VA-ECMO), a cannula is placed in a large vein, once again, draining to the ECMO circuit whilst a return cannula is placed in a large artery. The choice of vein and artery is dependant upon the configuration, either central or peripheral, or a combination, further described below.

Components of the Circuit

The following are the vital components of an ECMO circuit:

- Cannulae (venous +/- arterial)
- Circuit tubing
- Pump
- Oxygenator
- Heat exchanger
- Monitoring devices



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(Ghosh et al, 2009)

Although quite similar to a cardiopulmonary bypass circuit, the major difference is that there is no reservoir, hence acting as a closed-circuit. As a result there is no volume-buffer, and the haemodynamics are still dependant on the patient's volume status.

Cannulae -

The size of the cannula is calculated according to body surface area (BSA). Venous cannulae are larger than their arterial counterparts, allowing a larger flow rate with lower resistance. This is vital to ensure that haemolysis as well as collapse (and therefore, occlusion) of the cannulated vein does not occur.

Tubing -

The circuit tubing is known to cause complement, platelet and coagulation cascade activation that invariably occurs whilst on ECMO. This is thought to lead to an increased risk of bleeding, coagulation, and vasoplegia. Most cannulae available on the market currently are heparin or bio-coated. These are hypothesised to reduce this risk, although evidence only shows a reduction in blood cell trauma (1), complement activation (2), and granulocyte activation (3). Bio-coated circuits have been studied in the clinical setting with phosphorylcholine coating being a major focus. In a

study performed by Lorusso et al in 2009 (4), patients on ECMO were randomised to non- and phosphorylcholene- coated (PC) circuits. PC-circuits were found to reduce platelet consumption as well as reduce pressure gradients across oxygenators. Although there was a trend, there was still no statistically significant reduction in blood-loss however.

Pump -

Two types of pumps exist: centrifugal and roller pumps. Generally, centrifugal pumps are more widely utilised in ECMO, whilst roller-pumps are reserved for CPB circuits. Venous drainage is passive in both cases.

Oxygenator -

Essentially the gas-exchange component of the ECMO circuit. It both serves to oxygenate the blood and remove carbon-dioxide. Most circuits utilise PMP (poly-methyl pentene) hollow-fibre oxygenators.

Monitoring devices -

Ultrasonic flow measurement probes are placed around the ECMO circuit. Also, line pressure monitors are placed on the venous drainage cannula, as well as pre- and post-oxygenator lines to assess resistance. With regards to the venous drainage line pressure, it is vital to ensure it is not so negative that the vein collapses or haemolysis occurs. If there is high oxygenator membrane resistance, this often suggests clotting of the oxygenator.

Configurations

As mentioned, ECMO circuits are configured according to the indication, as well as the accessible and suitable vessels.

For central VA-ECMO cannulation, a venous cannula drains the right atrium, whilst an arterial cannula returns to the ascending aorta, much like a cardiopulmonary bypass set-up. This configuration is generally instituted in the operating theatre, often when patients fail to wean off cardiopulmonary bypass. The existing cannula may be reconnected to a primed ECMO circuit to simplify the process. In more recent times, new cannulae have been made to be tunnelled out of the abdominal wall so that the chest may be closed, including the Abiomed Cardiovascular cannula (5). This reduces the risk of bleeding from the sternum as well as infection, as the bone marrow is opposed and the mediastinum is protected from the external environment. Nonetheless, this

technique requires re-sternotomy at time of decannulation, although other tunnelled approaches obviating the need for re-sternotomy have been described (6).

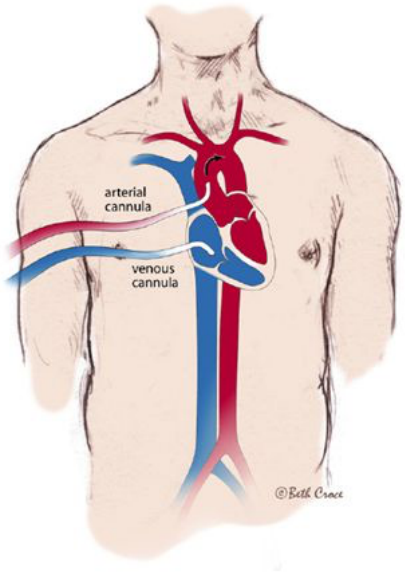


Figure 1. *Central ECMO cannulation.*

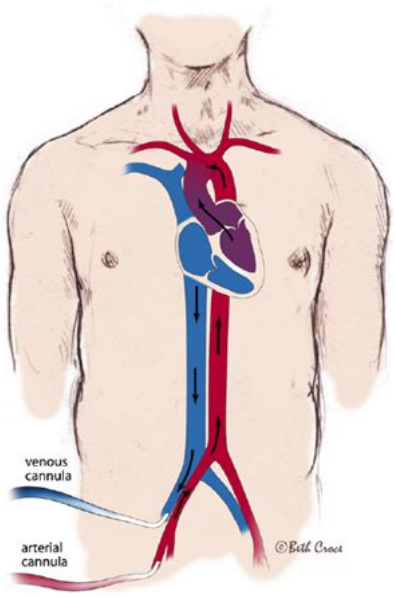
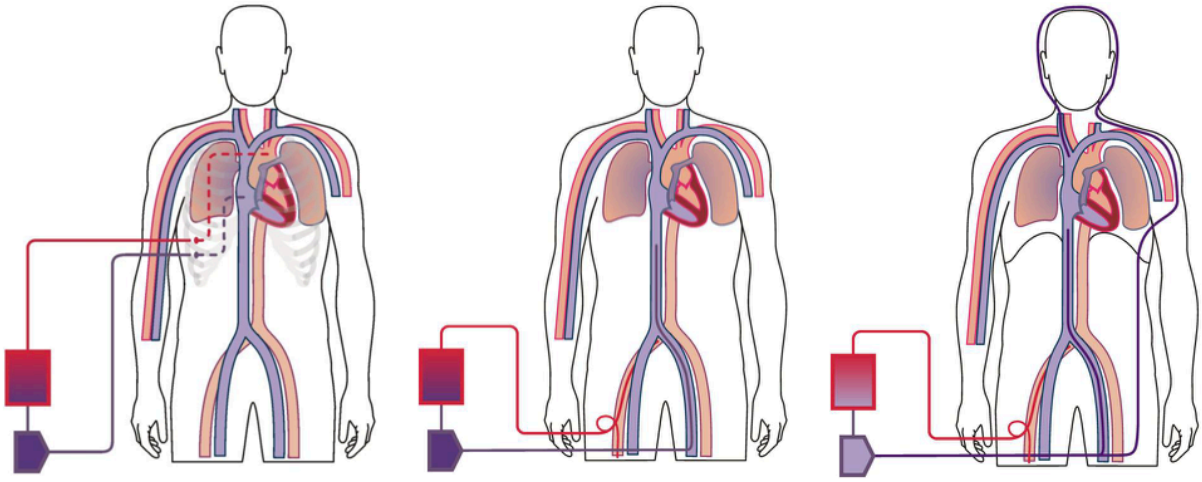


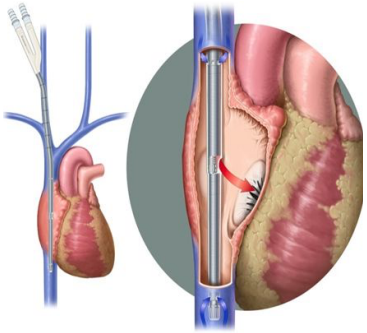
Figure 2. *Peripheral ECMO cannulation.*

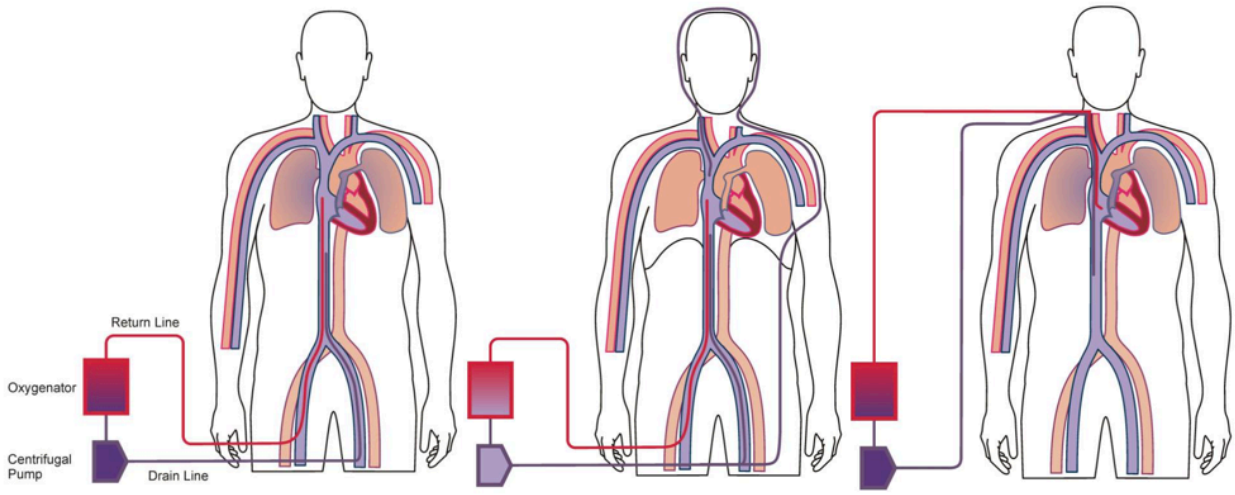
For peripheral VA-ECMO, the femoral vein or internal jugular vein may be used to drain to the circuit, whilst the arterial cannula may reside in the femoral or right common carotid artery. The most



common configuration in this case is femoral for both, however.

With regards to VV-ECMO, both internal jugular and femoral veins may be utilised. The Avalon cannula (Maquet, Rastatt, Germany) is a dual-lumen single bicaval cannula which has recently been released and approved for use in Australia. As opposed to the usual jugulo-femoral or femoro-femoral configuration, a single cannula is advanced through the right internal jugular vein, with its tip positioned in the IVC, and side-hole at the Tricuspid valve (TV) in the right atrium. Being a dual lumen cannula, the lumen extending to the tip is the inflow cannula, with the outflow cannula positioned towards the TV. Benefits of this cannula include single-vessel cannulation, ability to mobilise patients, as well as lay patients prone to assist in pulmonary recovery (7). However draw-backs are the need for more material, technical and physician experience, as well as cost.





Other configurations exist which may include a combination of vessels. These are clinically indicated, and may be prompted by volume drainage issues, whereby a second venous cannula may need to be inserted, for example.

Indications

VV-ECMO is instituted for respiratory failure, unresponsive to other medical therapy, and is deemed to be reversible. In some cases, it is indicated as a bridge-to-transplant (8).

Conditions that are commonly indicated for VV-ECMO are:

- severe pneumonia (including severe aspiration-pneumonia)
- Adult Respiratory Distress Syndrome (ARDS)
- severe bronchial asthma / status asthmaticus
- severe lung contusions
- smoke-inhalation injury
- diffuse pulmonary embolism not causing haemodynamic compromise (although VA-ECMO may still be advisable)
- *Paediatric conditions*

- maeconium aspiration syndrome
- persistent pulmonary hypertension
- congenital diaphragmatic hernia

Conditions commonly indicated for VA-ECMO are:

- cardiac arrest
- cardiogenic shock
- fulminant myocarditis
- failure to wean from cardio-pulmonary bypass
- cardiac trauma / contusions
- non-retractable cardiac arrhythmia with haemodynamic instability
- drug overdose (complicated by cardiogenic shock)
- hypothermia
- pulmonary embolism
- status asthmaticus
- procedural support in particular cases, such as
    - donor-organ preservation
    - abdominal aortic surgery / endovascular graft
    - tracheal surgery
    - pulmonary embolectomy
    - VAD placement

Contraindications

Important considerations are as follows:

Age

No absolute age contraindication exists, particularly when it comes to the elderly undergoing cardiopulmonary bypass surgery, however most surgeons deem patients over the age of 75 years to be unsuitable.

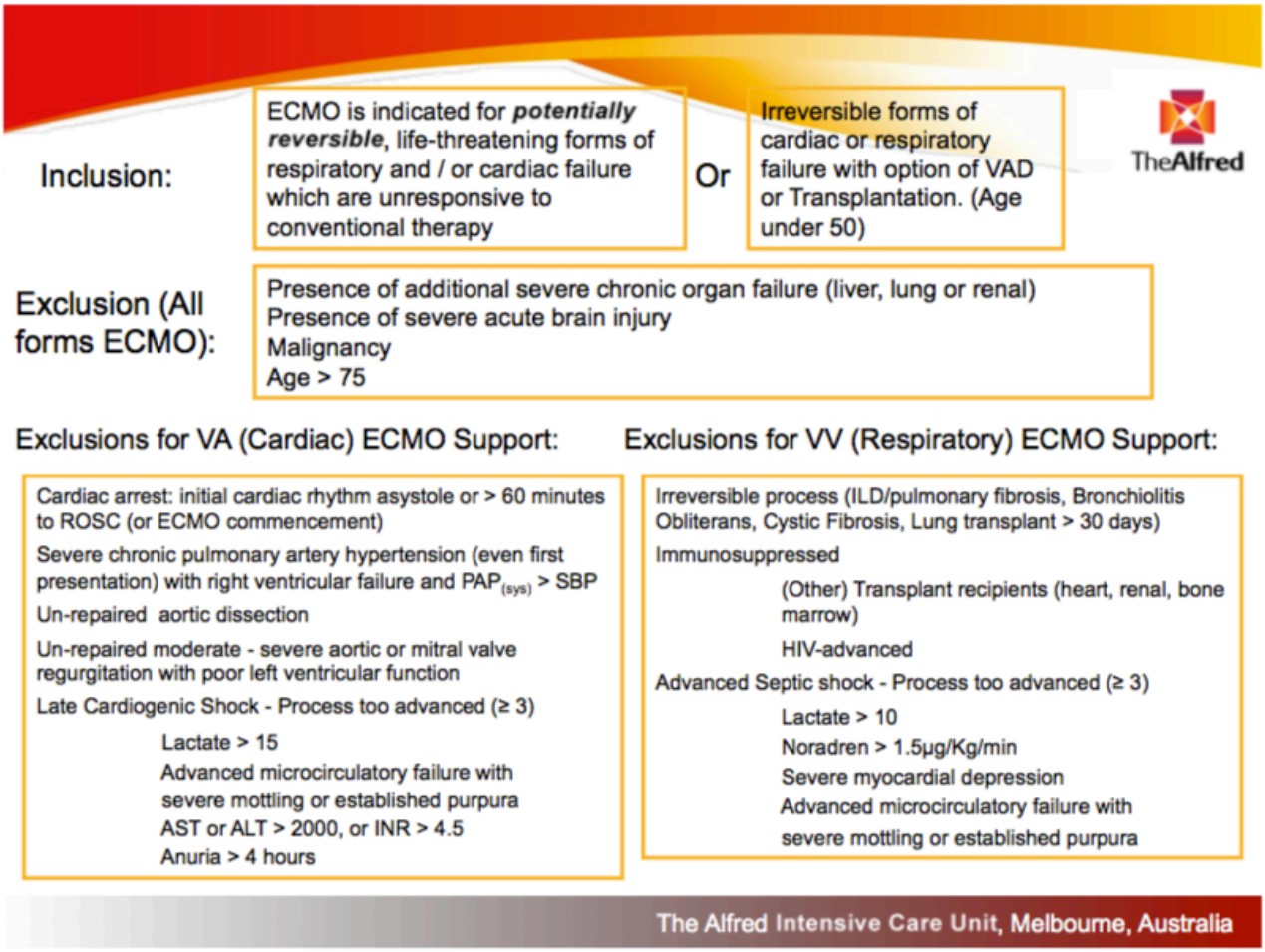
Comorbidities

Disseminated cancer is reported to be a contraindication in most guidelines. Other ailments including stroke and renal failure, need to be considered, as well as pre-morbid cardiac function.

Functional status

This is an important question, relating to patient frailty - essentially the physiologic burden of disease upon a patient, and quality of life. Multiple studies have already established that frailty has a negative impact upon outcomes in the cardiac surgical population (9).

Below are our centre's guidelines for inclusion and exclusion, which align with most institutions Australia- and world-wide.



Establishing ECMO

There are several measures required prior to establishing ECMO. It is vital to ensure that the suitability of the patient, condition, and goals of care have been discussed amongst the senior

medical and surgical staff who will be caring for the patient. It is a multi-disciplinary effort, and should be recognised as such. This most often primarily includes the cardiac surgeon, an intensivist where available, as well as other relevant senior physicians whose expertise is specific to the case (eg cardiologist, respiratory physician).

Often, especially in VA-ECMO, establishing ECMO is in a particularly emergent situation, frequently peri-arrest. Hence guidelines for establishing ECMO exist and protocol should be followed by experienced practitioners.

Necessary equipment and staff should be at hand and prepared. Vital staff for the procedure include the following:

- senior cardiac surgeon
- intensivist (if out of theatre)
- perfusionist
- appropriately trained cardiac surgical trainee / junior medical staff
- cardiac theatre nursing staff
- intensive care nursing staff (if out of theatre)

All team members are required to know their roles, and specific guidelines are available that suggest recommended roles and set-up.

Heparinisation prior to cannulation is necessary in order to prevent clotting of the circuit, particularly the oxygenator. Each institution and country may have its own practice, however it often involves a heparin bolus to achieve an activated coagulation time (ACT) of 160-180 seconds or activated partial thromboplastin time (apTT) of 50-70 seconds, and is maintained at such with an infusion. The dosage is calculated by BSA and/or weight of the patient. Generally, in emergent situations outside of theatre, peripheral VA-ECMO is established, whereas in the operating theatre - particularly if a cardiac surgical case - central may be preferable. This is due to convenience, ease and safety of exposure of the required vessels.

Cannulation in peripheral VA-ECMO or VV-ECMO can be percutaneous or open (i.e. surgical). The operator experience and clinical scenario often dictate the most appropriate method.

Cannulation

	Advantages	Disadvantages
Central	- Easily established post-cardiotomy - exchange of CPB lines with ECMO circuit - Larger cannula calibre, therefore higher flow rates may be delivered - Antegrade oxygenated blood flow to coronaries and cerebral circulation	- Risk of bleeding and infection from open sternum - If tunnelled, need for re-sternotomy for decannulation
Peripheral	- Ease of access - Rapid deployment - Seldinger approach reduces risk of bleeding and infection in experienced hands - Lesser risk of bleeding and infection, and especially suitable over long durations of support	- Smaller cannula may not deliver adequate flows - Cardiac output of failing heart may compete with retrograde ECMO flow —> admixing in thoracic aorta (perfusing arch and coronaries with desaturated blood - In femoral arterial cannulation, risk of limb ischaemia if no downstream cannula attached

Various configurations have been described above, with vessels accessible for VV- and VA-ECMO described. Generally, femoral vein and artery are preferred by most centres for peripheral VA-ECMO, whilst internal jugular is also accessible for the venous cannula, and the axillary/subclavian artery for the outflow cannula. In femoral approach, it is recommended that a down-stream cannula is always performed (10), in order to avoid the very high risk of peripheral limb ischaemia. In some institutions the signs of ischaemia prompt this cannulation, however as the complications are not always reversible it may be wise to pre-empt them.

Central Cannulation

As mentioned, this is often set up in post-cardiotomy cases, and after ceasing cardio-pulmonary bypass flows and clamping the cannula, the circuits are rapidly exchanged, with tubing to a de-aired

and primed ECMO circuit. It is at this stage that a left-ventricular vent may be inserted if there are any signs of ventricular distension. The chest is usually left open, packed, and covered with a sterile film to be left whilst in ICU. A method has been described to tunnel the cannula via the abdomen and close the chest, in order to reduce the higher risk of bleeding from and infection of the sternum. In either case, return to theatre is necessary to decannulate. If the chest has been closed, a sternotomy will need to be performed again.

Peripheral cannulation

The axillary / subclavian approach is most often also in the peri-operative setting, where these vessels can be easily identified. Otherwise, in the more emergent settings in ICU or otherwise, the femoral vessels are most easily accessible. These vessels can be approached with ultrasound guidance for a Seldinger approach, or an open 'cut-down' if this is not successful / preferable by the attempting clinician. Seldinger approach is particularly difficult considering a lack of pulsatility in the case of cardiac arrest, so formal open cannulation may be required with discretion (10). Once the guide-wires are in, heparin is bolused as described above. The venous cannula is advanced to the right atrium (RA), with the tip aimed at the superior vena cava (SVC) to ensure adequate drainage. The arterial cannula is advanced to the iliac artery (its whole length generally. A distal leg perfusion cannula (6-8Fr) is performed on the ipsilateral femoral artery and spliced into the arterial perfusion limb of the ECMO circuit. If this is not successful (severe PVD, for example) then a side-arm can be sewn onto the femoral artery and connected to the arterial limb.

Management

Basic nursing care

Regular hygiene measures including washes, as well as prevention of pressure injuries is vital to prevent systemic infection. Some suggest moving the endo-tracheal tube 2-3 times a day to prevent mucosal pressure ulcers of the oral cavity and airways.

Cannulation site checks

This should be performed several times a day by nursing and medical staff to ensure there is no bleeding, kinking, mal-positioning or movement, as well as infection has or is likely to occur.

Peripheral limb vascular checks

It is vital to monitor for haematomas at cannulation sites, as well as frequent peripheral vascular observations on the cannulated limb. This usually involves checking pulses, colour, capillary refill time, temperature, and - if the patient is awake - sensation and motor response.

Airway and ventilator settings

Ventilator settings should be protective to prevent barotrauma and hyperoxic lung injury. This is particularly important in VV-ECMO indicated for severe pneumonia or ARDS, and the Extracorporeal Life Support Organisation (ELSO) have recommendations (10), suggesting targets of PEEP as 10cmH2O, PIP 20cmH2O, and RR 5-10.

Haemodynamic and volume status

In VV-ECMO, a pulmonary artery catheter may be employed to measure cardiac output, as there is minimal effect on haemodynamics with this configuration. With VA-ECMO however, a PA catheter is not able to reflect upon cardiac function until the patient has been weaned off flows. In both cases, regular echocardiography - preferably trans-oesophageal echocardiography (TOE) - is a more accurate assessment of cardiac contractility. This can be useful in VA-ECMO to assess whether there is left-ventricular distention and the need for an LV-vent to prevent myocardial stretching and ischaemia.

Oxygenation status

In patients on VV-ECMO, SvO2 is not useful, owing to the fact that it has already been oxygenated by the circuit. The venous drainage limb of the ECMO circuit is most reflective of the oxygenation of end-organs. Patients on VA-ECMO will demonstrate an SvO2 that reflects their true central venous oxygenation. Of note, in peripheral ECMO there is the risk of admixture of saturated and unsaturated blood as the cardiac function recovers. This is particularly true if pulmonary function is impaired, and blood ejected from the left ventricle is not adequately oxygenated. In this case, well oxygenated blood is driven by the femoral arterial ECMO cannula retrograde, but only as far as the arch. The potentially poorly oxygenated blood in the ventricle then supplies the brachiocephalic vessels, and may lead to cerebral hypoxia. To monitor for this, a right radial arterial line should be in place, where arterial blood gases are taken, to detect upper body hypoxaemia (11). Also, oxygen saturation probes should be placed in both upper limbs. Finally, the pulmonary function should be optimised, and whilst weaning should be expected to provide optimal oxygenation.

Anticoagulation

The current ELSO guidelines recommend the following anticoagulation aims:

- ACT 180-200s

- aPTT 40-50s

This is generally achieved with a heparin bolus prior to cannulation as mentioned prior, followed by a heparin infusion to maintain adequate anticoagulation. Platelet count should be maintained at more than 50,000 / microLitre.

Nutritional requirements

Meeting nutritional requirements whilst on ECMO, as with any other critically ill patient, is of particular importance and should not be neglected. The greatest hindrance to adequate administration of nutrition seems to be clinician neglect more than any clinical contraindication (12). No serious adverse events seem to be caused by early nutritional intervention for ECMO patients (13).

Hepatic and renal function

Need to be continuously monitored. Liver impairment is common and the insult needs to be identified and reversed if possible. Reversible causes that are not related to ischaemia or resuscitation include haemolysis, sepsis and medication toxicity. Renal injury is almost universal, and the need for continuous renal replacement therapy (CRRT) is very frequent. Guidelines exist on how to manage CRRT in conjunction with ECMO (14).

Suggested Routine investigations

- Daily CXR
  - Useful in identifying venous cannulation position, as well as central cannulae positions
  - Monitoring for pulmonary oedema, pneumothorax, haemothorax, and other complications
- Daily bloods
  - FBE, UEC, LFT, apTT, INR, d-dimer, fibrinogen
  - apTT measured 6-hourly
  - Plasma-free Hb (<0.01g/dL)
- Blood cultures only taken if clinically indicated - i.e. when there are signs of local / systemic infection
- Peripheral VA-ECMO patients require doppler ultrasound studies to be performed on lower limbs on day 1, and as clinically indicated thereafter

Venting

Left ventricular distention may be noted on echocardiography at the time of ECMO implantation or during routine reviews of cardiac function. This is a common sequelae, resulting from poor ejection in the failed heart, as well as increased afterload by the ECMO flow, leading to reduced ejection

through the aortic valve, and thus distention of the left ventricle. This distention results in increased wall tension, increased myocardial oxygen consumption, and reduced perfusion (to the endocardium in particular), leading to ischaemia and cellular damage.

Early signs of left ventricular distension include raised left atrial pressure and resultant pulmonary oedema. If not too severe, this can sometimes be managed by changing the ventilatory settings to increase the pulmonary end expiratory pressure (PEEP) which can reduce the pulmonary oedema.

If ventricular distention is noted on echocardiography, steps should be taken to 'vent', or decompress the left ventricle. Various techniques are possible (15, 16), and listed below:

- Left atrial vent (surgical)
- Left ventricular vent (surgical)
- Aortic root vent (surgical)
- Percutaneous aortic root or left ventricular vent

Those denoted as 'surgical' are either performed in the operating theatre (usually post-cardiotomy during the establishment of ECMO), or via a thoracotomy later in the course of recovery. If not instituted in the peri-operative phase, it is considered safer to perform percutaneous venting, in order to reduce risk of bleeding that would be far higher with a thoracotomy on established ECMO (15). A percutaneous left ventricular vent has been described by various studies (16, 17). Flow Rate Through Pigtail Catheter Used for Left Heart Decompression in an Arti cial Model of Extracorporeal Membrane Oxygenation, where - under echocardiographic guidance and Seldinger access - a pigtail is passed through the aortic valve during systole. In all cases the vent is connected to the venous access / inflow cannula. Risks of percutaneous LV venting include aortic valve injury (eg perforation or prolapse).

Weaning VA-ECMO

When to wean:

Clinical, haemodynamic, laboratory, and echocardiographic findings are all markers to guide when suitable to commence weaning an ECMO patient. Biological markers of haemodynamics, such as blood lactate level and SvO2, are routinely monitored prior to decannulation. These markers, particularly lactate, are often trending towards baseline prior to weaning is attempted.

When to wean is indication-dependant. Essentially, the insult that necessitated ECMO needs to have been treated and reversed prior to weaning. In post-cardiotomy patients suffering myocardial stunning, recovery is not expected until at least 72-96 hours post-operatively.

When a patient is stable for 24-48 hours without excessive inotropic support (with or without an intra-aortic balloon pump (IABP)) and echocardiographic findings are favourable, a weaning attempt can be made. Echocardiography has been shown to be of great use in the monitoring and weaning of patients on ECMO (18).

Various institutions have their own guidelines, but some publications recommend several parameters that should be satisfied prior to the weaning of ECMO (19):

- mean arterial pressure (MAP) > 70 mmHg
- Low vasopressor requirement (inotropic score < 10)
- Sp02 > 95%
- Sv02 > 70%
- Adequate pulmonary oxygenation (chest X-rays not showing significant pulmonary oedema
- Improving echocardiographic assessments, including EF > 25-30%.

How to wean

The following description outlines our centre's current practice [10]:

1) Circuit flow is reduced by 0.5L/min increments down to 1L/min
2) Haemodynamic and echocardiographic data are gathered
3) Lung ventilation is increased progressively to match progressive rise in pulmonary blood flow, whilst oxygenator Fresh Gas Flow is reduced
4) Additional heparin may be instituted, maintaining an ACT 180-200s, as with reduced flow there is increased risk of stasis and clotting in the circuit
5) Once haemodynamic measures are deemed stable, flow rates are increased back to 2.5L/min so as not to clot the circuit

Haemodynamic measures are considered to be stable when there is no need for increasing inotrope doses, an LVEF > 25-30%, adequate cardiac indices, and a not excessive CVP.

Weaning VV-ECMO

When to wean

According to the ELSO guidelines (20), VV-ECMO decannulation can be considered when the native lung is supporting at least 50-80% of total gas-exchange. At our institution, our guidelines recommend the following, prior to weaning VV-ECMO:

- tidal volume (TV) < 6ml/kg
- PIP < 30 cmH2O
- FiO2 < 60%

All the above maintaining an SaO2 of 88-94%, and with arterial blood gases with normal pH and adequate CO2 and PO2 levels.

How to wean

The circuit flow need not be reduced in the weaning process, as opposed to VA-ECMO.

1) progressive reduction in the fresh gas flow (FGF)
2) An increase in lung ventilation to ensure adequate oxygenation as well as CO2 clearance
3) Once the FGF reaches 0L/min, VV-ECMO is maintained at normal flows for 4-24 hours prior to decannulation

Decannulation

Central ECMO must be removed by the cardiothoracic team in theatre. In our centre, femoral arterial cannulae (whether inserted percutaneously or open) and femoral venous cannulae inserted via surgical cut down approach must be removed in theatre by the vascular or Cardiothoracic surgical team. There are reports of percutaneous closure devices being utilised on the femoral artery, however. A study published by Majunke et al in 2016, showed that percutaneous closure devices were successful, and none of the sample size of 15 patients had to go to theatre for further haemostasis (20). The closure devices used were the Perclose Proglide and the AngioSeal, which are routinely used in vascular procedures, percutaneous coronary procedures and TAVI (21, 22).

Complications

Circuit related complications

Clot formation

Can occur in any part of the circuit, particularly the oxygenator and at the connectors - sites of highest turbulence. These clots may embolise systemically or lead to increased resistance and occlusion of the circuit. As mentioned previously, the circuit is particularly prone to thrombosis due to activation of inflammatory and coagulation markers.

Circuit fractures

Fissure or breakage can also occur at any point in the circuit leading to either minor or major blood loss. Air entrainment can also occur if a fracture occurs on the venous limb of the circuit.

Gas embolism

Air may entrain into the circuit, particularly at the venous end where the centrifugal pump may generate enough negative pressure. Similarly to clots, the air may embolise systemically to the patient, or occlude the circuit.

Patient related complications

Vascular access complications

Particularly high risk during the emergent cannulation, especially for VA-ECMO. Perforation of the posterior wall of the arterial access vessel can occur, leading to retroperitoneal haematoma. Similarly, arteriovenous fistulas may occur, as can dissection of vessels during insertion of guide-wires and dilators.

Leg ischaemia

This is a complication of peripheral VA-ECMO. At our institution, as with many others, the insertion of a distal-perfusion cannula (connected to the return-tubing via a T-connector) for the femoral artery is compulsory. Other institutions may only indicate insertion of this if there are signs of ischaemia. This is often performed easiest via femoral cut-down by an experienced surgeon, as percutaneous insertion can be difficult once pulsatility is lost.

Cannulation site bleeding

Is a common complication, and is best managed by checking the position of the cannulae prior to further intervention. Central ECMO cannulation site bleeding will most definitely need surgical revision as tamponade is likely to ensue.

Other bleeding

It is important to note the ECMO patient is not only therapeutically anticoagulated, but almost certainly has platelet dysfunction and coagulopathy secondary to the circuit as described. Bleeding from mucous membranes is commonly secondary to minor trauma. This may manifest from the endotracheal tube, nasogastric tube or other. Similarly, pre-existing pathologies such as gastrointestinal polyps or ulcers may bleed excessively.

Coagulopathy

It is a delicate balance between haemostasis and thrombosis, and needs continuous monitoring as well as repletion of consumed coagulation factors and platelets. Thrombocytopaenia and coagulopathy are common in ECMO, being induced by blood exposure to the circuit surface. It is vital to rule out other reversible causes (HITTS, other drug-induced, primary) of this and not attribute it to the circuit without further thought. The mechanism, although not fully understood, is believed to be fibrinogen and other protein absorption, leading to a self-propagating cycle of platelet activation and thrombus formation. The activation of the intrinsic pathway leads to the release of inflammatory mediators and thrombin production [9]. Not only do platelet counts drop, but their function is impaired due to this process, and the addition of factors that stabilise the platelet function, such as tranexamic acid (a kallikrein inhibitor) are recommended (14). In extreme cases, disseminated intravascular coagulopathy (DIC) may result from excessive activation of these factors and inflammatory and coagulation cascades. The heparin infusion itself, maintaining therapeutic anticoagulation to avoid clotting in the circuit, may be of harm, rarely, where heparin-induced thrombotic thrombocytopaenic syndrome (HITTS) is encountered. In this scenario, other agents may be used, such as danaparoid sodium or bivalirudin. In extreme cases, disseminated intravascular coagulopathy (DIC) may result from excessive activation of these factors and inflammatory and coagulation cascades.

Haemolysis

When pump suction pressures are too high, the negative pressure can cause shear-stress, which may induce haemolysis. similarly, high levels of occlusion in the post-pump circuit, usually secondary to clots, can induce haemolysis. Haemolysis can be measured by plasma-free haemoglobin, with safe levels generally < 10g/dL. Haemolysis can itself trigger coagulopathy.

Neurological

Both haemorrhagic and ischaemic stroke can occur. A study on 74 patients by the Cleveland Clinic (23) reported an incidence of 18.9%. Being of female gender and a low platelet count (particularly if < 50,000 / microLitre) were the most statistically significant predictors ($p = 0.02$ and 0.007, respectively) of intracranial haemorrhage. Intra-cerebral haemorrhage (ICH) obviously was a significantly negative influence on mortality (92.3% vs 61%, $p = 0.027$). Other neurological

complications include ischaemia, likely secondary to embolic events or hypo-perfusion, as well as seizures, secondary to ischaemia or oedema.

Cardiac

Cardiac tamponade may complicate patient recovery whilst on ECMO, and is best noted on echocardiography. Left ventricular distention is a complication unique to VA-ECMO, and is most likely to occur in patients with severe aortic regurgitation (AR), were blood returned from the circuit flows retrogradely past an incompetent aortic valve, into the left ventricle. This is why uncorrected moderate to severe AR is a contraindication to VA-ECMO. This LV distention leads to myocardial ischaemia and reduced likelihood of ventricular recovery. Either surgical or percutaneous LV vent insertion is vital to unloading the left ventricle in cases where distention is shown on echocardiography.

Sepsis

With multiple lines and invasive devices, as well as prolonged intubation and ventilation, sepsis is a major concern in ECMO. Patients may also be immunosuppressed due to their underlying condition or being transplant candidates, with fevers often masked by the temperature regulating system of the circuit, making sepsis difficult to identify. Broad-spectrum antibiotics should be instituted as early as possible when sepsis is suspected.

POST-CARDIOTOMY EXTRA-CORPOREAL MEMBRANE OXYGENATION

Post-cardiotomy ECMO – A Literature Review

Introduction

Extra-corporeal membrane oxygenation (ECMO) has been utilised for cardiac and / or respiratory failure in its various implementations (veno-arterial and veno-venous). Over recent years, veno-arterial (VA) ECMO has been indicated for use in post-cardiac surgery cardiac shock, often termed post-cardiotomy cardiac shock (PCCS).

PCCS has been defined by most literature as cardiac failure that results in inability to wean off cardiopulmonary bypass or cardiac failure that occurs in the immediate post-operative period. More specific parameters include systolic blood pressure < 100mmHg, mean pulmonary artery pressure > 25mmHg, central venous pressure > 15mmHg, and cardiac index < 2.01 L/min/m2 (24). The aetiology is often difficult to ascertain but often attributed to myocardial infarction, stunning, or poor preservation peri-operatively.

The incidence of myocardial dysfunction after cardiac surgery has been shown to reach 3-5%, however use of inotropes and an intra-aortic balloon pump (IABP) is usually sufficient management to bridge to recovery (25, 26). A smaller subset however - approximately 1% of patients - require mechanical circulatory support beyond this, once maximal inotropic therapy and IABP has proven insufficient. This is often in the form of VA-ECMO, although support devices such as bi- and left-ventricular assist devices (BiVAD, LVAD) and other such variations have been utilised. These alternatives will not be considered in this study due to minimal use - often restricted to transplant centres only, and as it is not part of the focus of the studies reviewed in this piece.

Methods

Utilising Ovid Medline, Medline, and PubMed databases, the following search terms were combined with 'and / or', with headings, titles and keywords all being searched in various strategies.

Search terms included the following:

- ECMO
- extracorporeal membrane oxygenation
- extra-corporeal membrane oxygenation
- extra corporeal membrane oxygenation

the above combined with 'OR'

- post cardiotomy
- post-cardiotomy
- post cardiac surgery
- post-cardiac surgery

the above combined with 'OR'

The 2 sets of search results were combined with 'AND', with results reviewed.

Based on selection of titles and abstracts, only relevant papers were included in the literature review. Furthermore, a close review of bibliographies elicited further studies not found using this search method. This was particularly true of the references of a meta-analysis by Khorsandi in 2017 (27). Interestingly, this paper describes using similar methods of searching for publications, and using the same databases, yet there was some difference in publications yielded. This may be due to differing access to journals across countries.

A total of 16 papers were found to be most relevant upon examination, and their methods, analysis, and results were compared in tabulated format as displayed below. Studies included in the review were those focusing on adult patients post cardiac surgery who required implementation of ECMO. Exclusion criteria were papers focused on transplant patients (although some included papers did have a small subset of transplant patients), the paediatric population, and studies including non-cardiotomy patients. Also excluded were opinion pieces, letters to the editor and studies not published in English. Finally, studies published earlier than the year 2000 were excluded on the basis that ECMO practices were quite different; specifically, the use of oxygenators available, heparin-

/bio-coated tubing and cannulas as well as experience across centres and guidelines available on indication and practice.

Results of 16 cohort studies will be discussed and compared, whilst a meta-analysis by Khorsandi et al (2017) will be compared with said discussion thereafter (27-43). The methodology of the studies is compared in table 1.

Table 1: Methods

PAPER	N	DATA COLLECTION
El Sharkawy et al, Outcome in Patients Who Require VA ECMO Support post cardiac surgery J Cardiothor Vasc Anaes 2010:24;6 pp946-951	233	retrospective cohort single centre study 1995-2005
Khorsandi et al, 20-year multicentre outcome analysis of salvage mechanical circulatory support for refractory cardiogenic shock after cardiac surgery *J Cardiothor Surg 2016:11:151*	27	retrospective cohort multi-center 1995-2015
Rastan et al, Early and late outcomes of 517 patients treated with ECMO for refractory PCCS *J Thorac Cardiovasc Surg 2010 139:2 pp302-11*	517	retrospective cohort multi-centre 1996-2008
Saxena et al, ECMO support in PC elderly patients: The Mayo Clinic experience *Ann Thorac Surg 2015; 99:pp2053-60*	45	retrospective cohort single centre 2003-2013
Zhao et al, Extra-corporeal cardiopulmonary resuscitation in adults who underwent post cardiac surgery (cardiac arrest) *Eur J Med Res 2015; 20:83*	24	retrospective cohort single centre 2004-2012
Hsu et al, ECMO for refractory shock after cardiac surgery: predictors of early mortality and outcome from 51 adult patients	51	retrospective cohort single centre 2002-2006

Table 1: Methods

PAPER	N	DATA COLLECTION
Eur J of Cardiothor Surg 2010:37:328-33		
Bakhtiary et al, VA ECMO for treatment of cardiogenic shock: clinical experience in 45 adults patients *J Thorac and Cardiovasc Surg 2008;135:382-8*	45	prospectively cohort single centre
Doll et al, Temporary ECMO in patients with refractory postoperative cariogenic shock - a single center experience *J Cardiac Surg, 2003;18:6:512-8*	95	retrospective cohort single centre 1997-2000
Pokersnik et al. Have changes in ECMO technology impacted outcomes in adult patients developing postcardiotomy cardiogenic shock? *J Card Surg. 2012;27:246-52*	49	retrospective cohort single centre 2005-2010
Doll et al. five-year results of 219 consecutive patients treated with ECMO for refractory postoperative cardiogenic shock. *Ann Thorac Surg 2004;77:151-7*	219	Prospective cohort single centre 1997-2002
Guihaire et al. Clinical outcomes in patients after ECMO support for PCCS: a single-centre experience of 92 cases. *Inter CardiVasc Thorac Surg 2017;25:363-9*	92	Retrospective cohort single centre 2005-2014

Table 1: Methods

PAPER	N	DATA COLLECTION
Wu et al. Using extracorporeal life support to resuscitate adult PCCS: treatment strategies and predictors of short-term and midterm survival. *Resusc. 2010;81:1111-16*	110	Retrospective cohort single centre 2003-2009
Li et al. The early dynamic behaviour of lactate is linked to mortality in postcardiotomy patients with ECMO support: a retrospective observational study *J Thorac Cardiovasc Surg. 2015;149:1445-50*	123	Retrospective cohort single centre 2011-2012
Slottosch et al. Outcomes after peripheral ECMO therapy for PCCS: a single-centre experience. *J Surg Res. 2013;181:47-55*	77	Retrospective cohort single centre 2006-2010
Unosawa et al. Long-term outcomes of patients undergoing ECMO for refractory PCCS. *Surg Today 2013;46:264-70*	47	Retrospective cohort single centre 1992-2007
Ko et al. ECMO support for adult PCCS *Ann Thorac Surg 2002;73:538-45*	76	retrospective cohort single centre 1994-2000

Results

Indications for ECMO - Similarities and Variances

Most studies conferred with standardised practice for indication of establishing VA-ECMO for cardiogenic shock post cardiac surgery. That is, the inability to treat cardiogenic shock simply with chemical vasopressors and inotropes, and intra-aortic balloon pumps (IABPs). Interestingly, maximal therapy of these treatments was not specified in any paper, which may lead to variation in how early ECMO was implemented As is often the case in clinical practice, treatment is individualised for each patient, with clinician experience and preference playing a role. Thus, institution of ECMO is not standardised across centres or even within centres. However, this may eventually affect outcome, in that patients placed too early on ECMO may have unexpectedly better outcomes, especially in comparison with more conservative approaches.

Implementation of ECMO was often ascribed to haemodynamic measurements that could not be attained despite maximal therapy, however these parameters were not included in all papers. Hsu et al (2010) describes their practice as a failure to maintain SBP >90 caused by poor cardiac contractility despite adequate filling volumes, large dose inotropes, and IABP support. Doll et al (2003) utilised cardiac index < 2.0 L / min / m2 despite adequate filling volumes, multiple inotropes, and IABP support. El-Sharkawy et al (2010) of the Cleveland Clinic, specified SBP <85mmHg or CI < 1.5 l / min / m2. These specific indications were described in single centre studies, rather than large retrospective multi-centre studies, owing to more standardised practice.

A notable exception in practice was the study by Zhao et al (2015) of the Beijing Anzhen Hospital. This retrospective study focused on patients who had post-cardiotomy cardiac arrest. Cardiac arrest was defined as the need for chest compression or direct, open-chest cardiac massage. Interestingly, as will be discussed when outcomes are reviewed, those weaned off ECMO, and survival to hospital discharge was similar to most studies whereby patients were not arrested prior to ECMO implementation.

ECMO practices

All patients in these cohort studies underwent veno-arterial ECMO. In a small subset of patients of one study (Khorsandi, 2016), short-term VADs were compared with the outcomes of ECMO for similar indications (BiVAD = 1, RVAD = 1, LVAD = 2).

Most studies distinguished between use of central versus peripheral ECMO cannulation, and the various implementations of such. Central cannulation was often reserved for those whom had been placed on ECMO in the operating theatre, often secondary to an inability to wean off cardio-pulmonary bypass (CPB). Central cannulation was implemented more often as described by Rastan et al (2010) in his study of 517 patients (60.8%), similarly with Khorsandi (61%). A notable exception once again is the ECMO-CPR method described by Zhao where most patients (96%) were cannulated peripherally. This is suitable in that all patents were already weaned off CPB. It is unclear whether Outcomes of mortality were affected across studies according to rate of peripheral versus central cannulation, however complication rates would differ in regards to peripheral limb ischaemia. This is discussed further in the complications section.

Kitamura et al (1999) was a unique paper in that it compared VA-ECMO with biventricular bypass (BVB), left ventricular bypass (LVB), and LVAD for similar indications of PCCS. As BVB and LVB are not commonly used they warrant explanation. BVB utilises either a centrifugal or roller pump, with an oxygenator. Its main difference to central VA-ECMO is the cannulation of both the left and right atria for drainage, as well as a reservoir. Due to bi-atrial cannulation, clamping and un-clamping can bypass one or both ventricles (44). An LVB is the same configuration as described for BVB, but the drainage cannula is reserved for the LA only. These devices were implemented according to indications for failure to thrive post-cardiotomy. VA-ECMO being implanted for acute cardiac failure with respiratory insufficiency, BVB for left-dominant bi-ventricular failure, and LVB/LVAD for isolated left-ventricular failure. VA-ECMO implemented emergently was also converted to the other devices if suitable.

Heparinisation practice varied little, and often was not even described. Rastan's described practice was the only outlier, with an activated clotting time (ACT) > 300 seconds at time of implementation, and then partially reversed by protamine in order to maintain an ACT of 160s. Most studies do not describe such a practice on cannulation, but once established the anticoagulation aims seem to correlate. Zhao's centre aimed for ACT 160-180s and the protocol at the Mayo Clinic (Saxena, 2015) aimed for an ACT 140-170s. This is similar to the rest of the studies which described their anticoagulation practice.

Duration of ECMO support varied substantially, once again highlighting differences in practice. From 32 hours average ECMO duration (Kitamura,1999), to 180 hours average (Hsu, 2010). However, as

discussed later, there was little difference in the rate of patients weaned off ECMO, and survival to discharge (50 vs 53%; and 26.7 vs 33.3%, respectively).

Weaning practices, once again not always described, were varied somewhat. Elsharkawy et al (2010) describes the Cleveland Clinic's practice of offering LVAD as destination or bridging therapy (n = 28; 12%), whilst even cardiac transplant was offered to 25 patients (10.7%).This may have contributed to the higher survival to discharge in their centre (36% vs 30.8%). Similarly, Kitamura et al of the Heart institute of Japan offered varied forms of bypass and LVAD to bridge patients during the weaning process. In this study - which also included results of biventricular bypass (BVB) and left ventricular bypass (LVB) - the longer the duration of assistance the worse the outcome. 47.6% survived to discharge if on support less than 24 hours, in contrast to 23.5% if between 24-96 hours, and 20% if over 96 hours.

Patient Characteristics

Overall patient characteristics were quite similar (see table 2). Sex was predominantly male across the board, and average age of patients ranged from 53-77 years old. However amongst all but one study (Saxena, 2015) had average ages of 53-66 years of age (39). This study focused particularly on post-cardiotomy ECMO in the *elderly* - defined as those 70 years or older.

Heart failure / NYHA status and ejection fraction were evaluated by most studies, but once again in a varied fashion. Elsharkawy et al (2010) evaluated survival amongst variables including characteristics such as 'normal LVEF', 'history of CHF', and 'new-onset cardiogenic shock' (31). In contrast, Doll et al (2003) simply compared the average LVEF% across CABG, AVR, and combined CABG/AVR patients (29). This did not allow for an assessment of pre-operative ventricular function, (or, in fact, any patient characteristics) affecting outcome of survival. As such, comparisons across centres / studies is difficult to determine if there was any variation in case load difficulty, and whether this affected outcomes.

Furthermore, Euroscore, logistic Euroscore, and Euroscore II were reported in various studies, but none uniformly across all cohorts. This is similar to the above measurements of cardiac function, and makes any comparison of patient selection impossible.

Table 2: Patient Variables

PAPER	PCCS needing VA ECMO	mean age	peripheral cannulation	central cannulation	primary ECMO implantation	secondary ECMO implantaation	other devices	mean age of surviving patients	mean age of non-surviving patients
El Sharkawy 2010	n = 233 (40,116) 0.58%	57yo	n = 156 67%	n = 77 33%	-	-	0	53.5yo	59.7yo (p < 001)
Khorsandi 2016	n = 23	59yo	n = 9 39%	n = 14 61%	-	-	4 / 27 LVAD 2 RVAD 1 BiVAD 1	-	-
Rastan 2010	n = 517 (of 40,538) 1.28%	63.5yo	n = 159 30.2%	n = 358 60.8%	n = 216 41.9%	n = 301 51.8%	0	60.4yo	64yo (p <0.002)
Saxena 2015	n = 45	76.8yo	n = 15 33.3%	n = 30 66.6%	n = 26 57.8%	n = 19 42.2%	0		
Zhao 2015	n = 24	59yo	n = 23 95.8%	n = 1 4.2%	0	n = 24	0	56.6yo	64.5yo
Hsu 2010	51(1764) 2.9%	63yo	51	0	-	-	0	-	-

Table 2: Patient Variables

PAPER	PCCS needing VA ECMO	mean age	peripheral cannulation	central cannulation	primary ECMO implantation	secondary ECMO implantaation	other devices	mean age of surviving patients	mean age of non-surviving patients
Bakhtiary 2008	45 (5750) 0.7%	60.1yo			n = 30 67%	n = 15 33%			
Doll 2003	n = 95 (7900) 1.2%	59.8yo	n = 26 27%	n = 69 73%	-	-	0	-	-
Pokersnik 2012	n = 49	66yo	n = 32 65.3%	n = 17 34.7%	-	-	0	59yo	68yo
Doll 2004	n = 219 (18,150) 1.2%		n = 60 27.4%	n = 159 72.6%	n = 194 (89%) *in OT*	n = 25 (11%) *in ICU*	0	-	-
Guihaire 2017	n = 92 (13,131) 0.7%	63yo	n = 81 88%	n = 11 12%	n = 80 86.9%	n = 12 13.1%	0	57yo	63yo
Wu 2010	n = 110 (4180) 2.6%	60yo	-	-	n = 102 89%	n = 12 11%	0	54.8yo	64.6yo

Table 2: Patient Variables

PAPER	PCCS needing VA ECMO	mean age	peripheral cannulation	central cannulation	primary ECMO implantation	secondary ECMO implantaation	other devices	mean age of surviving patients	mean age of non-surviving patients
Li 2015	n = 123 (13,538) 0.9%	56.2yo	? 100% (unclear)	? 0% (unclear)	n = 61 49.6%	n = 62 50.4%	0	51yo	58.9yo
Slottosch 2013	n = 77	60yo	n = 77 100%	n = 0 0%	n = 34 44.2%	n = 43 55.8%	0	52yo	63yo
Unosawa 2013	n = 47	64.4yo	n = 32 68.1%	n = 15 31.9%	-	-	0	67.3yo	62.7yo
Ko 2002	n = 76 (2,912) 2.6%	56.8yo	n = 61 80.2%	n = 15 19.7%	n = 39 51.3%	n = 37 48.7%	0	54yo	53-54yo

Patient procedures

Procedures amongst most studies was particularly heterogenous, with varying proportions of surgery type, as well as varying surgery types in general. These are summarized in table 3. For example, *isolated* coronary artery bypass graft surgery (CABG) was obviously performed by all centres, yet ranged from 6.7% of the case-load (Saxena, 2015) to 67% (Doll, 2003) (29, 39). In contrast, transplant (heart and/or lung) was only performed in 6 of the 16 studies. This ranged from 1.8% (Doll, 2004), to 15.8% (Ko, 2002) of the caseload (30, 35).

There was not complete consistency in the reported procedures performed nor the state of urgency. Redo- cardiac surgery was reported in half the papers, and ranged from 8.5% of patients (Unosawa, 2013), to 57.8% in Saxena's cohort (39, 41). This is consistent with the variation in average age between these two ends of the spectrum, with Unosawa's cohort averaging 64.4 years old, compared with Saxena's 76.8.

1 paper (Pokersnik, 2012) reports all its candidates were elective (37), whilst emergency cardiac surgery was recorded as such in 6 studies. Once again, of the 6 papers recording it, emergency cardiac surgery ranged from 8.9% in Saxena's cohort, to 46.8% in Unosawa's group. It is unclear why there is such a distinct difference, but in all likelihood, Saxena's older population were less likely to be emergency surgery candidates, and Unosawa may have inadvertently selected a higher proportion of patients placed on ECMO prior to revascularisation (eg presenting with AMI, proceeding to ECMO before or after emergency CABG) (41). The implications of this upon survival are described below, and discussed later.

Table 3: Operations Performed

	emergency procedure	isol CAGS	single/multiple VALVE	Combined CAGS / valve	Aortic dissection / aneurysm	redo	transplant	other
Elsharkawy 2010	n = 84 (36%)	n = 86 (36.9%)	n = 69 (29.6%)	not clear	-	n = 116 (49.8%)	0	
Khorsandi 2016	-	n = 6 (22.2%) (isol CAGS)	n = 10 (37%) (isol valve)	n = 4 (14.8%)	n = 3 (11.1%)	n = 4 (14.8%)	0	n = 1 (aortic transection)
Rastan 2010	n = 205 (39.7%)	n = 193 (37.4%)	n = 96 (18.6%)	n = 72 (14%)	n = 20 (3.9%) - dissection	n = 123 (23.8%)	n = 34 (6.5%)	
Saxena 2015	n = 4 (8.9%)	n = 3 (6.7%)	n = 6 (13.3%)	n = 8 (17.8%)	unclear	n = 26 (57.8%)	0	
Zhao 2015	unclear	-	-	-	-	-	-	-
Hsu 2010	unclear	-	-	-	-	-	-	-
Bakhtiary 2008	-	n = 20 (44.4%)	n = 2 (4.4%) - AVR only	n = 8 (17.8%)	unclear	unclear	n =2 (4.4%)	n = 5 (13.3%)
Doll 2003	n = 10 (11%)	n = 63 (67%)	n = 16 (17%) AVR only	n = 8 (8%) CAGS + AVR	-	-	-	8 (8%)
Pokersnik 2012	0, all patients *elective*	-	-	-	-	n = 27 (55.1%)	0	-
Doll 2004	-	n = 119 (54.3%)	n = 33 (15.1%)	n = 33 (9.6%)	n = 12 (5.5%)	n = 41 (18.7%)	n = 4 (1.8%)	n = 28 (12.8%)
Guihaire 2017	n = 30 (33%)	n = 8 (9%)	n = 61 (66%)	n = 34 (37%)	n = 9 (10%)	n =22 (24%)	-	-
Wu 2010	-	n = 31 (28.2%)	n = 42 (38.2%)	n = 19 (17.3%)	n = 8 (7.3%)	-	-	n = 10 (9.1%)
Li 2015	-	n = 44 (35.8%)	n = 40 (32.5%)	n = 15 (12.2%)	-	-	n = 11 (8.9%)	n = 13 (10.6%)
Slottosch 2013	-	n = 43 (55.8%)	n = 10 (13%)	n = 11 (14.3%)	n = 5 (6.5%)	-	n = 2 (2.6%)	n = 6 (7.8%)
Unosawa 2013	n = 22 (46.8%)	n = 19 (40.7%)	n = 8 (17%)	n = 2 (42.3%)	n = 5 (10.6%)	n = 4 (8.5%)	0	n = 4 (8.5%)
Ko 2002	-	n = 37 (48.7%)	n = 14 (18.4%)	n = 6 (7.9%)	n = 2 (2.6%)	-	n = 12 (15.8%)	n = 5 (6.6%)

Outcomes

The outcomes of short and long-term survival, and weaning from ECMO are summarised in table 4 below.

Weaned off ECMO

Only 2 papers did not describe whether patients were successfully weaned off ECMO (Khorsandi 2016, Elsharkawy 2010) (31, 34). Results of those patients who survived weaning ranged from 46.7% (Saxena 2015) to 66.7% (Zhao 2015) (39, 43). Of interest, the greatest percentage of patients successfully weaned off ECMO was in the cohort of Zhao et al (2015) which evaluated patients undergoing resuscitation prior to ECMO implantation. Furthermore, cause of cardiac arrest as well as location of ECMO CPR (ECPR) - whether in theatre or intensive care unit, did not affect outcome of weaning or survival to discharge in this group.

Of note, the lowest rate of successfully weaned patients of Saxena's was recorded only if they survived weaning after 24 hours. Apart from Rastan's study, no other paper declared if weaning was successful at 24 hours (38). Hence, this may skew the results significantly. This can be exemplified by both Rastan and Saxena showing approximately 7% difference between those successfully weaned, and those alive at 24 hours.

Kitamura's study at the Heart Institute of Japan, which compared BVB/LVB/LVAD with VA-ECMO showed interesting results in weaning (45). Of the 30 patients placed on VA-ECMO, 50% were weaned successfully, whilst BVB and LVB had greater success rates (76, and 60%, respectively). This may be explained by the likelihood that VA-ECMO is often implemented in a more emergent setting where the cause of failure to thrive post-cardiotomy is less readily apparent. With BVB, LVB, and LVAD there are quite specific indications that may reflect more reversible pathology and this may also suggest a more controlled setting of implantation.

Survival

Once again, this varied significantly across studies, with the lowest rate of survival to discharge from Saxena's group of 24.4% to 41.8% in Wu's cohort. Saxena's lower survival to discharge diverged from the trend of dropping survival at 1 year - remaining at 24.4%. At 5 years however, this did not

hold, and overall 8.8% survival was still lowest for those followed up that long. This is in contrast to Unosawa's cohort that had a survival of 20.1% at 5 year follow up (39, 41).

Survival to discharge was the most common endpoint for follow-up, with all papers reviewing this result. Only 6 out of the 16 papers reported 1 year survival, and 5 reported on 5 year survival.

Survival to discharge

An interesting comparison at 2 ends of the spectrum would be between Saxena and Khorsandi's studies. Saxena's cohort of 45 had a survival rate of 24.4% (n = 11), being the lowest, with Khorsandi's group (n = 27) having a survival rate of 40.7% (n = 11), second only to Wu et al (41.8%). Comparing the two ends of the spectrum provides insight into why these results may have been obtained. The major difference in practice between these 2 groups is noted to be the average age, and the use of other devices. Saxena's cohort's average age was 76.8 compared with 59 years old in Khorsandi's cohort. This is unsurprising, considering Saxena focused on the results of PCCS-ECMO in the elderly, being 70 years or older. Neither author commented on the average age of surviving patients, unfortunately (34, 39).

Khorsandi et al utilised 2 LVADs, 1RVAD, and 1BiVAD *instead* of ECMO. 3 out of the 4 VAD patients survived, suggesting that, in the correct circumstances, salvage ventricular assist devices are of great benefit. This is in keeping with established evidence on this subject. A review of the STS database over a 10 year period by Hernandez et al (5) reported a 54.1% survival rate in their study on 5735 patients undergoing VAD for refractory PCCS. Interestingly, in the case of Khorsandi's study being a particularly small sample size, with 3 out of the 11 survivors having had VAD devices *rather* than ECMO per se suggests this may have contributed. Were all VAD patients excluded, survival to discharge of only the ECMO patients would be 34.8%, (n = 8 survivors of 23 in cohort). This suggests that ventricular assist devices greatly skewed results in favour of survival in this trial, but does not explain how both Guihaire and Wu had favourable results, with neither group utilising VADs *instead* of ECMO (32). Rather, Guihaire's group were converted to VAD in 2 cases, and 2 received heart transplants following ECMO. 3 of 4 of these patients survived to discharge, and it is quite likely they would not have survived had they not been bridged to this treatment modality.

Another reason that may indicate why Khorsandi's faired better, is that Saxena's cohort, apart from being older, consisted of far more complex surgery. 57.8% of Saxena's group had redo- surgery

compared with 14.8%. Redo- cardiac surgery is known to have a higher mortality and morbidity rate, and this may well carry over to post-cardiotomy ECMO results (34, 39).

Apart from the two studies mentioned above, the other studies' survival to discharge ranged from 24.4% to 36%. The average survival to discharge rate of all studies reviewed was 31.9%, suggesting Wu, Khorsandi, and Guihaire were outliers (32, 34).

Mean duration of ECMO did not impact survival to discharge, and cause of death was reasonably uniform amongst all cohorts. Cause of death (COD) is particularly difficult to properly define, however, as cardiac failure and multi-organ failure (MOF) - the most frequently reported CODs - have significant cross-over in pathology. Similarly, the true COD in most of these cases is actually withdrawal of care, and may be prompted by MOF or clinical indicators suggesting a failure to thrive. Due to the vague nature of this process - where haemodynamics are maintained, but the indication to withdraw or sustain ECMO is undefined - this may significantly affect outcomes. Guidelines to assist practitioners in the decision should be created, if only to assist in standardising evidence.

Long-term survival

Few studies published the results for 1 year, and 2 for 5 year survival. This is unfortunate, and suggests the need for further evaluation, especially as these results vary grossly from survival to discharge, as well as amongst those that do report long-term survival.

Both Rastan and Saxena reported similar survival to discharge (24.7% and 24.4%, respectively), however their 1 year survival was significantly different (38, 39). Saxena's cohort held strong with all survivors remaining alive (n = 11, 24.4%), whilst Rastan reported only 16.5% remaining at 1 year follow up. This is surprising, considering Saxena's older population (avg age 76.8 vs 63.5 yo). It may be posited that selection of fitter surgical candidates may account for this, but a closer inspection of patient pre-morbid state shows that incidence of diabetes was similar, with Saxena reporting 35.6% and Rastan 32.5%, and Saxena having a higher incidence of COPD (22% vs 13%). Similarly, chronic kidney disease was in favour of Rastan's cohort. Unfortunately, pre-operative cardiac function cannot be compared, as Saxena reported simply on 'congestive cardiac failure', whilst Rastan reported specific ejection fraction and NYHA classes. Finally, as mentioned prior, Saxena's group had arguably more complex procedures, with redo-surgery accounting for 57.8% of cases, compared with 14%. Hsu's study, which focused on the patients whom underwent emergent VA-ECMO for

cardiac arrest post-cardiotomy, had similar results, with 29.4% survival at 1 year. Similar to Saxena's group this was a generally low attrition rate only falling from 33.3% from discharge.

Interestingly, although Wu's cohort had a particularly high survival to discharge of 42%, a comparable 25.5% of all patients remained alive at 1 year. Unosawa and Ko, (29.8% and 23.4%, respectively) followed suit with Wu and Saxena at 1 year (35, 39, 41, 42). Age did not seem to play a role in the decline in overall survival at this end-point.

Once again, there was another outlier with a particularly high success rate in long-term survival for Guihaire's cohort. Although they did not report 1 year survival, at 2 years 34 patients were alive (37%), grossly outperforming the other publications. This may be attributed simply to carry-on from a generally high survival to discharge (not specified, but 39% survival at 6 months). Yet, as shown above, Wu also has shown relatively successful survival to discharge (40.7%), with a drop to 25.5% at 1 year. Review of patient selection between Wu and Guihaire does not show any variation in sample size (110 vs 123, respectively) or average age (60 vs 63 years old). Similarly with ECMO practices, including implementation (central and peripheral, primary and secondary very similar). Unfortunately, it is not possible to compare and contrast pre-morbid state with any scientific method, as even Euroscore was utilised in its different formats between these 2 studies (32, 42).

Interestingly, whatever advantage Saxena's cohort had at 1 year did not hold till 5, with survival dropping to 8.8%. This is a significant drop from 24.4%, but is easily explained by the fact that his group was of the 70 years and older cohort (average age 76.8 vs 63.5 years), and were likely reaching their expected life-spans. There remains significant variability, however, in 5 year survival, with Unosawa reporting 20.1% (10 of 47 patients), and Wu reporting 8.2% (at 3 years). Unlike Saxena's cohort, Wu's group is not easily explained with age, as the average of surviving patients was 55 years (39, 41, 42).

Whatever is contributing to the variability in long-term survival is not distinguishable by the datasets provided. There seems to be no obvious differences in pre-morbid state that clearly explain why some cohorts faired better than others. ECMO indications, although vague, were essentially identical, and practices of ECMO management varied little (time of implementation, peripheral vs central, and anticoagulation strategies, for example). Similarly, it does not correlate with publication dates of these studies, ruling out advances in ECMO equipment, practice, or surgical techniques.

Table 4: Outcomes

PAPER	WEANED OFF ECMO	SURVIVAL TO DISCHARGE	SURVIVAL AT 1 YEAR	SURVIVAL AT 5 YEARS	RECEIVED CARDIAC TRANSPLANT	conversion to LVAD/other	mean duration of ECMO	most common COD
Elsharkawy 2010	*not specified*	n = 84 36%	-	-	n = 25 10.7%	n = 28 12%	-	-
Khorsandi 2016	*not specified*	n = 11 40.7%	-	-	-	-	5.43 days (including VADs) (130 hours)	refractory biventricular failure n = 22
Rastan 2010	n = 328 63.5% survived weaning n = 185 (56.4%)at 24h	n = 128 24.7%	n = 85 16.5%	n = 71 13.7%	n = 5 (2 survived)	-	3.3 days (79.2 hours)	cardiac failure 79.9%
Saxena 2015	n = 24 53% 46.7% survived weaning	n = 11 24.4%	n = 11 24.4%	n = 4 8.8%	0	0	4.3 days (103.8 hours)	cardiac cause (88.2%) MOF (38.2%) sepsis (17.6%)
Zhao 2015	n = 16 66.7%	n = 8 33.3%	-	-	-	-	4.8 days (115.2 hours)	MSOF n = 12 (75%)

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Hsu 2010	n = 27 53%	n = 17 33.3%	n = 15 29.4%	-	n = 4 (pre-ECMO)	17	7.5 days (180 hours)	not weaned: heart failure and MOF 20/24 (83%) weaned: Pulm infection (n = 4)
Bakhtiary 2008	n = 25 55%	n = 13 29%			n = 2 post-ECMO (of 5 LVAD patients) 4.4%	n = 5 11%	6.5 days (156 hours)	not weaned: persistent heart failure 18/20; weaned: pulm infection / sepsis and subsequent MOF

Table 4: Outcomes

PAPER	WEANED OFF ECMO	SURVIVAL TO DISCHARGE	SURVIVAL AT 1 YEAR	SURVIVAL AT 5 YEARS	RECEIVED CARDIAC TRANSPLANT	conversion to LVAD/other	mean duration of ECMO	most common COD
Doll 2003	n = 45 47%	n = 28 29%	-	-	n = 3 3%	n = 8 8%	2.8 days (67 hours)	refractory myocardial failure (71%); MOF 13% Sepsis 7%
Pokersnik 2012	n = 27 55%	n = 16 32.6%	-	-	0	n = 2 (BiVAD) Neither survived	3.8-4.3 days	
Doll 2004	n = 133 61%	n = 52 23.7% 30d surv 34%		n = 37 18%	n = 4 2% (all survived)	n = 8 (LVAD) 4% (3 survived)	2.2 days	Low cardiac output (71%); MOF (14%)
Guihaire 2017	n = 44 48%	1mo n = 39 (42%) 6mo n = 36 (39%)	**2 year** n = 34 (37%)	n = 29 (32%)	n = 2 (2.2%) 1 survived	n = 2 (2.2%) 2 survived	6 days	MOF (71%), septic shock (20%)
Wu 2010	n = 67 60.9%	n = 46 41.8%	n = 28 25.5%	**At 3 years** n = 9 8.2%	-	-	143h	Mediastinal Bleeding (n=8), cardiac failure

Table 4: Outcomes

PAPER	WEANED OFF ECMO	SURVIVAL TO DISCHARGE	SURVIVAL AT 1 YEAR	SURVIVAL AT 5 YEARS	RECEIVED CARDIAC TRANSPLANT	conversion to LVAD/other	mean duration of ECMO	most common COD
								(n=15), brain injury (n=6)
Li 2015	n = 69 56%	n = 42 34.1%	-	-	-	-	4.4 days	-
Slottosch 2013	n = 48 62%	**30d mortality** n = 54 (70.1%) i.e. 30d surv n = 23 (29.9%)	-	-	-	-	79h	-
Unosawa 2013	n = 29 60.7%	n = 14 29.8% 30d surv n = 16 (34%)	n = 14 29.8%	n = 10 20.1% **at 10y** n = 7 (17.6%)	0	0	63.5h	heart failure (n=7), MOF (n=5), brain death (n=4) bleeding (n=2)

Table 4: Outcomes

PAPER	WEANED OFF ECMO	SURVIVAL TO DISCHARGE	SURVIVAL AT 1 YEAR	SURVIVAL AT 5 YEARS	RECEIVED CARDIAC TRANSPLANT	conversion to LVAD/other	mean duration of ECMO	most common COD
Ko 2002	n = 46 60.5%	n = 20 26.3%	n= 18 at follow-up 33+/-22mo (all in NYHA-I-11) 23.4%	-	n = 2 2.6% 1 died at 3mo; other died at 21mo	n = 2 2.6% 1 survived after Tx 47d later; other died 7d later	-	MOF (n=16), bleeding (n=5)

Complications

Other secondary endpoints amongst studies included the collation of complications (summarized in table 5). This was more heterogeneously collated than survival, and thus more difficult to analyse across publications. For example, *'bleeding'* was not usually defined as how much blood loss warranted this to be recorded as a complication. It may have been a specific number of units of blood needing replacement, or it may have been the need for return to theatre. Even *'return to theatre'* was not sufficient to equate to *'bleeding'*, since those that returned to theatre may have done so purely for removal of cannulae (especially if central). Hence, there may not be much value in comparing these specific endpoints.

Similarly, sepsis and infection were recorded, and not qualified with any specific details. *'Infection'* may have included simple urinary tract infections, or qualified as full-blown sepsis, and this is not discussed. Yet *'sepsis'* too was not defined, and may have been simply pneumonia requiring intravenous antibiotics, or evidence of bacteraemia and the need for vasopressor infusions.

Limb ischaemia was reported in all but two publications. This was not consistently or clearly defined across papers, with some not giving a particular definition of what indicated limb ischaemia (rastan, khorsandi). Other studies reported limb ischaemia based upon incidence for return to theatre. Even this was inconsistent across papers, with some reporting thrombectomy, fasciotomy, and even amputation (33, 40).

Nonetheless, these complications have been collated and recorded to the author's best ability in the table below, but any comparison's across studies but comparison across studies cannot be performed due to disparity in reporting.

Table 5: Complications

	cardiac event	sepsis / infection	bleeding / RTT	limb ischaemia	CEREBROVASCULAR EVENT	gastrointestinal complication	AKI +/- renal replacement therapy
Elsharkawy 2010	-	n = 20 (8.6%)	-	-	n = 48 (20.6%)	n = 28 (12%)	n = 101 (43.3%)
Khorsandi 2016	-	n = 1 (3.7%)	n = 10 (37%)	n = 4 (14.8%)	n = 5 (18.5%)	-	n = 7 (25.9%)
Rastan 2010	n = 300 (58%)	-	n = 300 (58%)	n = 28/141 (20%)	n = 90 (17.4%)	n = 97 (18.8%)	n = 336 (65%)
Saxena 2015	n = 1 (2.2%)	n = 11 (24.4%)	n = 7 (15.6%)	n = 6 (13.3%)	n = 4 (10%)	n = 16 (35%)	n = 20 (44.4%)
Zhao 2015	n = 11 (45.8%) *CPR, Tamponade*	n = 11 (45.8%) '*infection*'	-	n = 2 (8.3%)	n = 2 (8.3%)	n = 5 (20.8%)	n = 7 (29.2%)
Hsu 2010	-	n = 11 (21.6%)	n = 33 (64.7%) '*GI/fem bleed*'	n = 3 (5.9%)	n = 3 (5.9%)	n = 13 (25%)	n = 38 (75%)
Bakhtiary 2008	-	n = 26 (58%) '*infection*'	n = 39 (87%) '*rethoracotomy*'	n = 3 (7%)	n = 4 (9%)	-	n = 39 (86.7%)
Doll 2003	-	n = 26 (27%)	n = 59 (62%)	n = 15 (16%)	n = 9 (9%)	-	n = 64 (67%)
Pokersnik 2012	-	-	n = 35 (71%)	-	n = 3 (6.1%)	-	n = 16 (32.6%)
Doll 2004	-	n = 52 (24%)	n = 136 (62%)	n = 16 (7.3%)	34 (16%)	-	n = 127 (58%)
Guihaire 2017	-	Pneumonia n = 48 (52%)	n = 18 (16.5%)	n = 9 (9.8%)	n = 3 (3.2%)	-	-
Wu 2010	-	n = 28 (25.5%)	n = 31 (28.2%)	n = 11 (10%)	n = 7 (6.4%)	n = 3 (2.7%)	n = 46 (41.8%)
Li 2015	-	n = 16 (13%)	n = 49 (39.8%)	n = 21 (17%)	n = 5 (4.1%)	-	n = 29 (23.6%)
Slottosch 2013		n = 19 (24.7%)	n = 23 (29.9%)	n = 16 (20.8%)	n = 17 (22.1%)	n = 17 (22.1%)	n = 53 (68.8%)
Unosawa 2013	-	n = 14 (29.8%)	n = 33 (70.2%)	n = 12 (25.5%)	n = 10 (21.3%)	-	n = 15 (31.9%)
Ko 2002	-	-	n = 35 (46%)	n = 3 (3.9%)	n = 9 (11.8%)	-	n = 38 (50%)

Pre-operative Risk Factors

Predictors of adverse events was evaluated by 15 of the 16 publications reviewed (table 6). Doll's 2003 paper was the only exception, although his later study published in 2004 did evaluate potential adverse predictors of outcome (29, 30). Advanced age was the most frequently described pre-operative risk factor for mortality, reported in 10 papers. What is just as important to note is what was *not* reported to be of significant risk to adverse outcomes, such as pre-morbid measurements including Euroscore (and its various forms), as well as pre-operative cardiac function (ejection fraction or NYHA status).

Age

9 studies described age as a statistically significant risk factor for mortality, and 1 paper (Khorsandi, 2016) reported that most survivors were under 60 years old, although without statistical significance. There was not absolute consensus on the threshold age defining an increased risk in mortality across papers, however. In Rastan's cohort of 517 patients, age over 70 years was found to increase mortality (OR 1.9; $p < 0.02$). Saxena's study of the elderly cohort came to the same conclusion, identifying age over 70 years to be a significant predictor of mortality ($p = 0.05$). Wu found that those over the age of 60 years were at increased risk ($p = 0.008$). Other publications, such as Pokersnik's and Li's identified advanced age as a significant risk factor for mortality, but did not define a threshold age. Rather, the age of survivors and non-survivors was significantly different (Pokersnik 59 vs 68yo [$p = 0.03$]; and Li 51 vs 59yo, respectively [$p < 0.001$]).

Diabetes

The second most frequently reported adverse predictor was diabetic status. Despite being the second-most reported, diabetes was only described in 4 of the 16 studies as a significant predictor of mortality. Elsharkawy described that a history of diabetes was present in 25.5% of non-survivors, but only 14.3% in survivors ($p = 0.052$). Rastan described diabetes to be of even more significance for mortality in his review of 517 patients (OR 2.61, $P < 0.001$). Similarly, Bakhtiary and Doll found absence of diabetes to be protective (28, 30, 31, 38).

Insulin dependence and associated end-organ disease were not specified, although it is important to note that chronic kidney injury - a complication reflective of diabetes control and progression - was not identified in any of these studies as an adverse risk factor.

Other pre-operative Risk Factors

Interestingly pre-operative cardiogenic shock was reported in Elsharkawy's cohort to be *protective* against adverse outcome (p = 0.005). This was not commented upon in other studies, however it may be described by a different mechanism of shock. Pre-operative cardiogenic shock in cardiac surgery is often related to myocardial stunning post infarction, and urgent revascularisation in coronary artery bypass graft surgery has been hypothesised to be of higher success than other causes of PCCS ECMO reported here (46).

Another aberrancy across the literature was of pre-operative cardiac function. All papers assessed this in one form or another (LVEF%, NYHA class, mild/mod/sev LV failure, history of CHF, etc), and the inconsistency of classifying this has already been mentioned to hinder comparing pre-morbid patient variables across studies. Nonetheless, only two studies reported cardiac function as a significant risk factor for adverse outcome, Guihaire and Hsu (32, 33). Guihaire reports that pre-operative LVEF% was significantly different between survivors and non-survivors, (52.5+/-13.9% vs 44.1+/-18.5%; p = 0.017). Despite this, there was no reported significant difference of NYHA or EuroSCORE II results in the same subset of patients. Hsu determined that a pre-op LVEF < 40% was predictive of a failure to wean ECMO (OR 12.34; 95% CI 3.01-72.02). Once again, heart failure status (CHF status C or D) was not predictive amongst the same sample of patients.

The variation in results is no better exemplified than with Hsu and Elsharkawy commenting on pre-operative albumin measurements. With both papers published in the same year, Hsu found that serum albumin was significantly higher in survivors than non-survivors (35 vs 28.9g/L, respectively; p <0.001). Yet, Elsharkawy found that survivors had a *lower* pre-operative albumin than non-survivors (31 vs 37mg/L, respectively; p = 0.004) (31, 33).

Procedure as a Risk Factor

All but 2 studies (Guihaire and Doll) found that procedure performed did *not* influence outcome. This may be counterintuitive given half the studies recorded whether redo-surgery was performed, and this did not seem to influence outcome in any of them. Similarly, emergency procedures - recorded in at least 6 publications - did not influence outcomes. Guihaire described that valvular surgery was the only procedure found to adversely affect outcome ($p = 0.029$). Although a p-value was not commented upon, Doll found that combined CABG and AVR was associated with higher mortality than any other procedure, with 20 of 21 patients dying (95%) (30, 32).

Rastan et al (2010) found in their multi-centre retrospective cohort study that significant tricuspid regurgitation, acute type A dissection, and combined aortic and mitral valve disease showed a strong *trend* towards worse outcome (TR 2+ 0.9% surv. 4.6% non-surv, $p = 0.1$; Type A dissection 0.9% surv. 4.9% non-surv, $p = 0.088$; AV/MV disease 0% surv, 2.3% non-surv, $p = 0.21$) (38). Interestingly, pre-operative emergency status, pre-operative MI, and active mechanical resuscitation were not significant factors for in-hospital death.

Post-operative Risk Factors

Renal Failure

5 studies reported renal failure, acute kidney injury (AKI), and the need for dialysis as significant factors for adverse outcome, whilst Zhao reported significant differences in peak creatinine and BUN between survivors and non-survivors after weaning from ECMO (31, 35, 38, 42, 43). Surprisingly, Zhao's publication did not note any impact of the need for dialysis upon survival. Rastan demonstrated that post-operative AKI was a highly significant risk factor for mortality (OR 4.3; $p < 0.001$) (38, 43).

Lactate

Elevated lactate levels, measured in different ways whether peak, mean, at 24 hours or otherwise, was noted to be of significance to mortality in 6 reports. As a marker of anaerobic metabolism, it reflects end-organ perfusion, and thus if it persists whilst on ECMO is suggestive of inadequacy of resuscitation, or late re-perfusion with end-organ damage. Rastan once again also reported on lactate, with peri-operative lactate levels > 4mmol/L and levels > 10mmol/L post-operatively identified as significant (OR 2.2 and 2.65, respectively; $p < 0.001$) (38).

Table 5: Complications

	cardiac event	sepsis / infection	bleeding / RTT	limb ischaemia	CEREBROVASCULAR EVENT	gastrointestinal complication	AKI +/- renal replacement therapy
Elsharkawy 2010	-	n = 20 (8.6%)	-	-	n = 48 (20.6%)	n = 28 (12%)	n = 101 (43.3%)
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Zhao 2015	n = 11 (45.8%) *CPR, Tamponade*	n = 11 (45.8%) '*infection*'	-	n = 2 (8.3%)	n = 2 (8.3%)	n = 5 (20.8%)	n = 7 (29.2%)
Hsu 2010	-	n = 11 (21.6%)	n = 33 (64.7%) '*GI/fem bleed*'	n = 3 (5.9%)	n = 3 (5.9%)	n = 13 (25%)	n = 38 (75%)
Bakhtiary 2008	-	n = 26 (58%) '*infection*'	n = 39 (87%) '*rethoracotomy*'	n = 3 (7%)	n = 4 (9%)	-	n = 39 (86.7%)
Doll 2003	-	n = 26 (27%)	n = 59 (62%)	n = 15 (16%)	n = 9 (9%)	-	n = 64 (67%)
Pokersnik 2012	-	-	n = 35 (71%)	-	n = 3 (6.1%)	-	n = 16 (32.6%)
Doll 2004	-	n = 52 (24%)	n = 136 (62%)	n = 16 (7.3%)	34 (16%)	-	n = 127 (58%)
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Wu 2010	-	n = 28 (25.5%)	n = 31 (28.2%)	n = 11 (10%)	n = 7 (6.4%)	n = 3 (2.7%)	n = 46 (41.8%)
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Ko 2002	-	-	n = 35 (46%)	n = 3 (3.9%)	n = 9 (11.8%)	-	n = 38 (50%)

Discussion

Extracorporeal membrane oxygenation is a suitable treatment modality for refractory post-cardiotomy cardiogenic shock. Although its rate of success is limited, with particularly high mortality rates in the short-term that seem to continue to affect long-term survival, the only alternative is death. Its indication is reasonably clear, although many centres describe differing parameters. Essentially, ECMO is indicated in cardiogenic shock that is refractory to chemical support and an intra-aortic balloon pump.

This literature review covers all the major and most up to date publications on the topic of ECMO-PCCS. Their indications, practices, and outcomes are all outlined as above, and neatly summated in the tables indexed. The main limitation encountered throughout this literature review is finding consistency of fields. From patient pre-morbid state (NYHA, EF, Euroscore, etc) to operations performed, and even to the survival timelines and complications, parameters were reported differently, making it almost impossible to compare endpoints.

The variation in collection of patient variables such as heart failure status, NYHA status, ejection fraction, EuroSCORE, and so on is a reflection in different practices across institutions. It also reflects the lack of standardisation both nationally and internationally, that would no doubt affect how guidelines can be made or adhered to on such a complex subject. Finally, this inconsistency of fields is emblematic of retrospectively collected data or performed studies, which essentially includes all the reviewed studies. To homogenise the data fields and allow adequate comparison, institutions - at least nationally - need to collate all data, or agree upon variables most important to record for their databases. Furthermore, prospectively collected data and prospectively performed trials needs to be performed, and would address the deficiencies in data collection described above.

Similarly, basic ECMO practice varies somewhat across institutions and countries and is worth standardising prior to performing these studies. Whether it be heparinisation practice, preference of central or peripheral cannulation, and clear indications for both establishing, weaning or withdrawal of ECMO. Only once these are firmly established is it possible to determine how a larger study with more statistical relevance can be performed.

Survival is essentially the primary outcome studied in all reviews, however of great interest is the variability of such results, as well as the significant decline from discharge to long-term survival. Likely attributable to the lack of standardisation of practice and data-collection across centres, no obvious factors were identifiable as to why some studies had a higher discharge than others.

Similarly with long-term survival, the only consistency across studies was a decline from the survival to discharge. Even at only 1 year, (of those that followed up) many studies had displayed a significant drop in survival (9, 18). And the few that followed up to 2, 3, 5, or 10 years displayed unexpectedly higher declines still (9, 10, 16, 17, 21). This ranged from 8.8% with Saxena, an admittedly older population, to 33% at 5 years in Guihaire's group, and even 17.6% at 10 years (Unosawa, 2013) (32, 41).

Despite the limitations in this literature review and the publications covered, there is a trend worth noting regarding pre-operative risk factors. Counter-intuitively, certain pre-operative conditions and presumed risk factors were not associated with adverse outcome for ECMO post-cardiotomy. Except for Rastan's study, no other cohort determined that Euroscore - or any of its subsidiary measurements - were associated with adverse outcome (38). Even Rastan's correlation seemed weak, with no p-value provided (OR of 1.8) and was only associated with adverse outcome amongst those that were weaned off ECMO in the first place. Similarly, although cardiac function was measured differently across studies, there was no correlation to adverse outcome. Finally, Zhao's study in 2015, which focused on patients that arrested post-cardiotomy (internal / external cardiac massage) and crashed onto ECMO had *no* identifiable differences in pre-operative state between survivors and non-survivors (43). Indeed, it is very worthwhile to note what is *not found* to be a statistically significant risk factor for adverse outcome in these studies, as it breaks many assumptions that may be made in the decision making process as to who is not a suitable candidate for ECMO.

Current practice should follow the guidelines of routine ECMO management, such as provided by the Extra-corporeal Life Support Organisation (ELSO) (47). The indication for ECMO post-cardiotomy should be determined by each unit according to an agreed-upon set of parameters, but generally is deemed suitable following failed chemical inotropic and balloon pump support in cardiogenic shock post-operatively. Finally, where possible, a team approach should be taken to make the decision for ECMO support, with the patient's wishes and best interest in mind. It may be appropriate to consider this decision pre-operatively in high-risk patients, where poor outcome may be of higher risk.

Finally, our recommendation for future studies is that they are preferably prospectively performed on a multi-centre, multinational basis. This would help determine institutional differences in practice and patient populations. Similarly, such a study would help determine better selection of patients, better allocation of resources, and better overall survival and prognosis for patients needing ECMO post-cardiotomy.

Addit: A Review Of A Meta-Analysis

In this literature review a meta-analysis on the topic of PCCS ECMO was found (27): *Extra-corporeal membrane oxygenation for refractory cardiogenic shock after adult cardiac surgery: a systematic review and meta-analysis,* by Khorsandi et al (published in 2017). Although search strategy was essentially the same, not all studies overlapped, likely based on differences in inclusion / exclusion criteria.

Methods

Unlike this literature review, the meta-analysis had no defined time-period, with included studies published as early as 1992, resulting in 8 more publications. Certain practices, experience and equipment has changed markedly in the use of ECMO, prompting our cut-off of studies performed after 2000. Oxygenators changed from predominantly silicone membrane to microporous polypropylene hollow fibre oxygenators gradually over this time period (48). Similarly, heparin-coated ECMO circuits have become standard (47), and has been suggested to have reduced contact-related activation of platelets and inflammatory cytokines, without impacting mortality (49).

Of note, although paediatric patients were excluded, transplant patients were neither excluded from the meta-analysis, nor were they independently evaluated in regards to their outcomes. This is significant in that indications, practice and outcomes of post-transplant ECMO are not identical to the described post-cardiotomy cardiogenic shock of non-transplant patients. ECMO post cardiac transplant is generally secondary to 'primary graft dysfunction' (PGD), a different pathological process to PCCS (50). As opposed to PCCS requiring mechanical circulatory support (MCS) - which has an incidence of 0.5-2% (27-43, 45) - PGD requiring MCS is reported to be from 2.3-28% (50). Takeda et al (2007) found that based upon similar criteria to that of PCCS-ECMO in their retrospective, single-centre study of 597 patients, PGD requiring MCS was 7.4% (50). Furthermore, they reported survival to discharge in heart transplant patients requiring VA-ECMO support post-operatively was 81.5% - significantly higher than non-transplant patients.

Khorsandi's meta-analysis was found to have a highly heterogenous dataset, reporting the *I2* to be 60%. *I2* represents the percentage of variability due to heterogeneity, and this result is deemed to be of at least moderate heterogeneity (51). This is very reflective of the cohort of cardiac surgical patients whom present for various procedures, yet may still require ECMO support post-operatively.

Results

Survival benefit was the primary outcome measured in Khorsandi's meta-analysis, whilst the secondary outcome was to measure the most commonly reported adverse prognostic indicators (APIs). The overall survival to discharge of the pooled 1926 patients (over 24 studies) was 30.8%. This is comparable to our review's finding of 31.9% mean survival to discharge.

Some of the most commonly reported APIs described in Khorsandi's trial were age (>70yo) and 'long' ECMO support. Importantly, as with our literature review, not all studies reported age as a predictor of poor outcome (29, 33-35, 41, 43). Although this meta-analysis describes 'long' ECMO support as an API, neither the publications reporting it, nor the length determined to be 'long' was described. Most importantly, on meta-regression analysis, neither age nor length of ECMO support was deemed statistically significant as a moderator. This also revealed that pre-ECMO IABP was not found to be statistically significant over the cohort of studies.

In this literature review, duration of ECMO has actually been reported as both a predictor of poor outcome, as well as protective for survival in conflicting studies. We feel that duration of ECMO is not an appropriate marker of prognosis as ECMO weaning and maintenance practices vary between institutions, and indeed between clinicians. Similarly, this may also be affected by whether a centre provides VAD and transplant services, as well as their 'culture' of palliation. Finally, termination of support varies patient to patient, according to progress. For example, early cessation of ECMO may be a result of poor initial outcomes and early complications, or excellent recovery. Similarly, late cessation may be confirmation of brain-death and withdrawal of care (often a protracted process), or a complex patient who has been deemed fit enough to tolerate multiple complications and insults. Hence duration of ECMO is not a reliable indicator of prognosis, either adverse or favourable.

Conclusion

Khorsandi's meta-analysis provides significant information regarding the outcomes of survival, as well as adverse prognostic indicators. As with our literature review, it seems a lack of consistency in measured patient variables across studies plays a significant role in the overall results, or lack thereof. However, despite this, there is value to be gained in determining what was nearly always reported, and not found to be of predictive value; namely - age, duration of ECMO, and pre-ECMO IABP. This reinforces the conclusion of this literature review - that numerical data presumed predictive of poor outcome such as age and pre-morbid status is *not* the reason behind successful or failed ECMO. In fact, it may suggest that with further refinement of ECMO practice, only then will support be optimised enough to determine the patient as the limiting factor. Hence, guidelines must

be set, and this cannot be performed without more thorough research. Furthermore, thorough studies will need larger sample sizes over more institutions that measure *the same* variables and practice similar ECMO strategies.

POST-CARDIOTOMY ECMO – THE AUSTRALIAN INSTITUTE OF HEALTH DATA

INTRODUCTION

As part of our investigation into post cardiotomy ECMO support, we wanted to gain an impression of the incidence of post cardiotomy ECMO in Australia. The main aim was to look at incidence and survival to hospital discharge.

METHODS

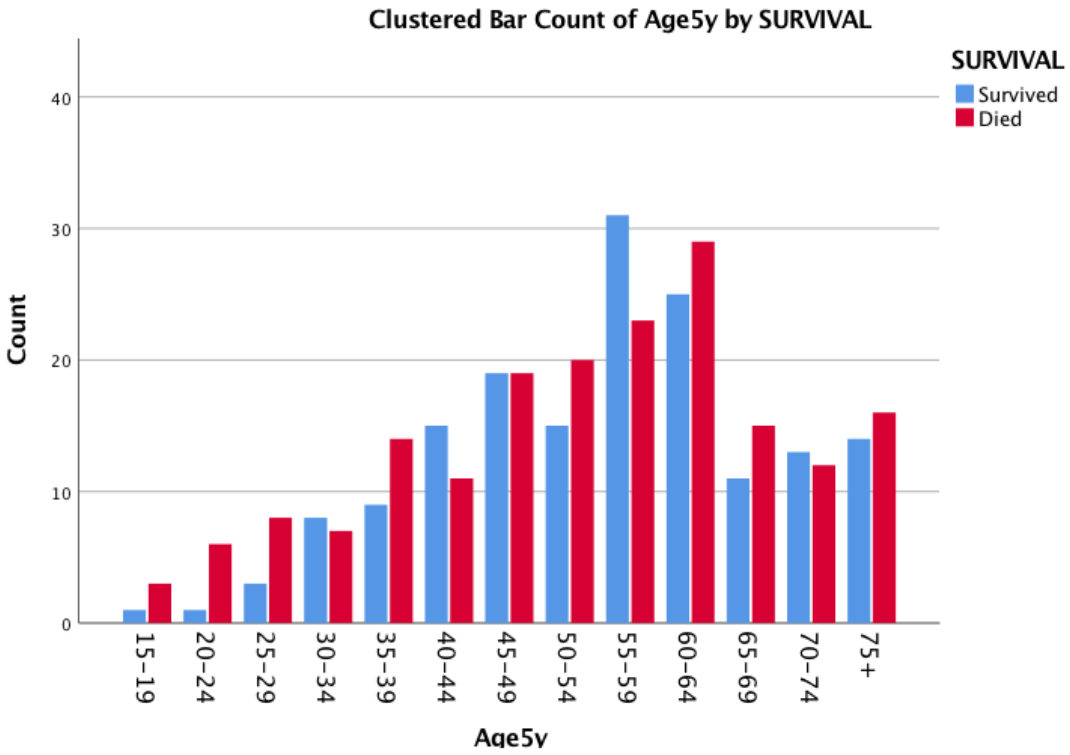
We applied to the Australian Institute of Health for an Australia wide dataset of all patients in the most recent five-year span of 2012 – 2017 who had been treated with post cardiotomy ECMO.

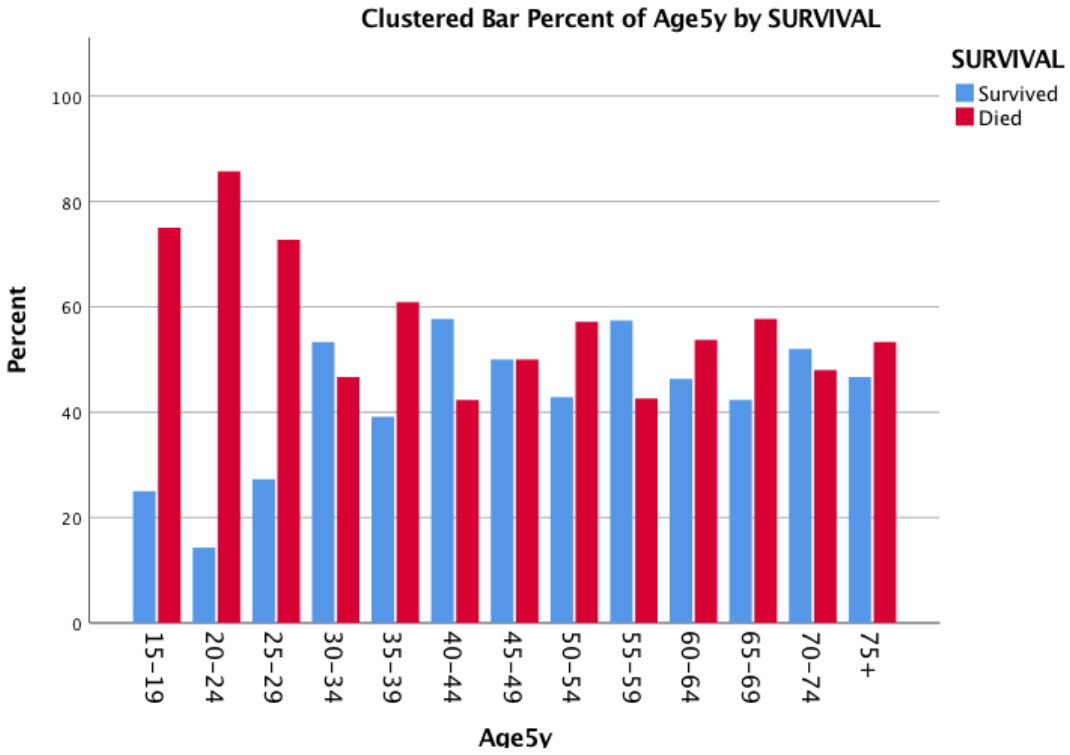
RESULTS

1513 patients were listed in the Australia wide database as having received ECMO over the 5 years. 435 paediatric patients (age less than 15 years) were excluded from further analysis. Patients who were identified as requiring ECMO post-transplant were excluded.

348 adult patients were found to have post-cardiotomy ECMO. Survival to discharge was 47.4% (n = 165). The relationship between age and survival is depicted in figures 1 and 2. Age was not predictive of survival in this analysis. Mean length of stay was significantly higher in those that survived than died (25.21 ±6.924 days vs 10.34 ±9.594 days; $p < 0.001$).

As surgical procedures were entered as MBS item codes in no particular order, there was no way to determine the impact of type of cardiac surgery on outcome.





DISCUSSION

Interestingly, age was not predictive of survival as with previous studies. However, age was provided in 5-year increments, and thus does not provide an accurate impression of its relationship with mortality. Length of stay was associated with greater survival most likely as a

result of death occurring early in the post-operative phase. Previous studies report median duration of stay in those that died was 10 days (35).

Data provided by the department of Health was purely survival status and MBS item codes, and very little further could be attained here. It was not clear at what stage ECMO was instituted in relation to the primary surgery. In cases of multiple cardiac surgeries, it was not clear which was the primary procedure. There was no data on pre-operative characteristics, intra-operative variables, nor post-operative outcomes apart from survival to discharge.

The limitations described above prompted us to pursue access to the ANZSCTS database to study this cohort in greater detail, including demographic and peri-/post-operative characteristics.

Post-Cardiotomy ECMO – the Australia and New Zealand Experience

INTRODUCTION

Over the last two decades, technological improvements in the delivery of extra corporeal membrane oxygenation (ECMO) have seen its use broaden. Latest generation membrane oxygenators, magnetically levitated pumps and heparin coated circuits have reduced equipment related complications, particularly thrombosis. Despite these improvements, survival after post cardiotomy ECMO remains poor, with survival to discharge figures ranging from 23 – 42% (28-43) (Table 1).

Post cardiotomy cardiogenic shock (PCCS) has been defined in the literature as cardiac failure that results in an inability to wean off cardiopulmonary bypass, or cardiac failure that occurs in the immediate post-operative period. More specific parameters include systolic blood pressure < 100mmHg, mean pulmonary artery pressure > 25mmHg, central venous pressure > 15mmHg, and cardiac index < 2.01 L/min/m2 (24). The aetiology is most commonly attributed to myocardial infarction, stunning, or poor myocardial preservation peri-operatively.

The incidence of PCCS has been shown to reach 3-5%, however use of inotropes and an intra-aortic balloon pump (IABP) is usually sufficient management to bridge to recovery (25). A smaller subset, approximately 1% of patients, require mechanical circulatory support beyond this. This is often provided in the form of VA-ECMO, although support devices such as bi- and left-ventricular assist devices (BiVAD, LVAD) have been utilised (34). These alternatives will not be considered in this study due to minimal use - often restricted to transplant centres only.

Use of ECMO for all indications is expanding, and has become a recent regulatory focus in Australia with the aim of identifying centres of excellence where ECMO can be centralized. Furthermore, it is anticipated that identifying and supporting high volume centres will aid in improving results. In terms of post cardiotomy ECMO, there is little agreement on specific prognostic indicators which could assist centres in identifying suitable patients for this level of support. Although most studies on this subject identify older age, there is no consensus on a cut-off (28-43). Ideally, identifying other prognostic indicators could assist in optimising patients and assist in patient selection, thus improving outcomes.

Our study aims to report on the Australian experience, with intent to contribute to the formation of guidelines.

METHODS

This study utilised the Australian and New Zealand Society of Cardiothoracic Surgeons (ANZSCTS) Database. Currently, 40 centres in Australia (23 public, 17 private) contribute to this database. 20 hospitals (19 private, 1 public) do not currently contribute to the registry. The database curates data prospectively collected in each contributing hospital, and patients have a choice to opt out. However, only their identifiable data is removed, whilst the de-identified procedural data is kept. As per the Australian Institute of Health and Welfare, the ANZSCTS database captures at least 60% of cardiac surgical data in Australia, annually.

Retrospective analysis of prospectively collected data was performed on patients from the ANZSCTS Database. Data was collected on patients who received ECMO post-cardiotomy from September 2016 - November 2017 inclusive (ECMO data was not accurately recorded prior to this). Over this period, ANZSCTS collected data on 16,605 adult patients (> 18 years old) who had cardiac surgery from contributing centres.

Post-cardiotomy ECMO was indicated in patients who were unable to be weaned off cardiopulmonary bypass or suffered cardiogenic shock in the immediate post-operative period, and in which inotropic and balloon pump support were insufficient.

Patients who received ECMO at any given point in their cardiac surgical stay were included in the study. This database is comprised of adult cardiac surgical centres, and thus paediatric patients were excluded. Patients supported on ECMO post transplant, or for cardiogenic shock secondary to cardiomyopathy (unrelated to post cardiotomy shock) were excluded from this analysis.

Institutional ethics approval from The Alfred and approval from the ANZSCTS Database Research Committee were obtained (approval number 175-18).

Statistical analysis

Data was initially assessed for normality. Group comparisons were performed using chi-square tests for equal proportion, student t-tests for normally distributed data and Wilcoxon rank sum tests otherwise, with results reported as frequencies (percentages), mean (standard deviation) or median (interquartile range) respectively.

To identify the strongest independent predictors of hospital mortality, a multivariable logistic regression was constructed using only variables that were statistically significant using both a stepwise selection and a backwards elimination selection procedure. All variables with a p-value < 0.10 at a univariable level were considered for model inclusion and the final model was assessed for

clinical and biological plausibility with results reported as odds ratios (95%CI). Variables identified using logistic regression were then included in a Cox-proportional hazards regression for time to death with results reported as Hazard Ratios (95%CI) and presented as survival curves reported using Kaplan Meier survival curves with a comparison using a log-rank test. Data was analysed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) and two-sided p-value of 0.05 was used to indicate statistical significance.

RESULTS

Of the 16,605 adult patients undergoing cardiac surgery in the 15 month period of the study, 87 patients required post-cardiotomy ECMO (0.52%).

Demographics of the patient group are outlined in Table 2. The average age of the entire cohort was 56 years. Demographics were compared between patients who died and survived, and significant differences found in age, history of hypertension and peripheral vascular disease, and baseline renal function (Table 2).

Operative variables are outlined in Table 3. Emergency or time critical nature of cardiac surgery was not significantly different between those who survived and those who died. Of the entire cohort, 42 (48%) patients underwent coronary artery bypass grafting, 39 (45%) underwent valve surgery, 42 (48%) underwent another cardiac procedure. Some patients underwent a combination of these procedures. In terms of mechanical support, 23 (26%) patients were supported for some part of their peri operative care with an intra aortic balloon pump. ECMO was commenced preoperatively in 17 (18%) patients, intraoperatively in 39 (45%) patients and post operatively in 31 (36%) patients. Timing of ECMO commencement was not significantly related to mortality (59% mortality if pre operative ECMO, 56% mortality for intraoperative commencement of ECMO, and 55% mortality for post operative commencement of ECMO; p=0.97). The only operative data shown to be significantly different between groups was the cross clamp time and the cardiopulmonary bypass time which were both longer in the patients who died (Table 3).

Overall survival to discharge was 43.7% (n = 38). Table 4 shows overall outcomes between patients who survived and died. Post operative cardiac arrest was significantly more common in the patient group who died, as was septicaemia and multi-system organ failure. All of the variables in tables 3 and 4 were considered for inclusion in the multivariable analysis. Multivariable logistic regression analysis demonstrated that three variables were significant predictors of in hospital mortality: multiorgan failure (MOF), age & cardiopulmonary bypass time. Patients with MOF were more than 5 times more likely to die [OddsRatio 5.74 (1.65-19.96) p=0.006] and risk of death increased by 7% for each year of age [OR 1.07 (1.02-1.11) p=0.002]. The odds of dying also increased by 60% for every additional hour of cardiopulmonary bypass time [OR 1.6 (1.11-2.31) p=0.012]. In a multivariate cox regression model for time to death, only 2 variables remained significant; multiorgan failure & age, with hazard ratios of 2.24 (1.23-4.08) p=0.007 and 1.03 (1.01-1.05) p=0.002 respectively.

Table 2. Patient demographics

	Total cohort (n=87)	Survived (n=38)	Died (n=49)	P value
Age (years) (mean ±SD)	56 ± 18	48 ± 19	62 ± 14	<0.0001
Male (sex)	53 (61%)	20 (53%)	33 (67%)	0.16
Current smoker	15 (42%)	7 (50%)	8 (36%)	0.42
Diabetic	20 (23%)	9 (24%)	11 (22%)	0.89
Hypercholesterolaemia	35 (40%)	10 (26%)	25 (51%)	0.02
Pre-op dialysis	7 (8%)	4 (11%)	3 (6%)	0.69
Hypertension	49 (56%)	14 (37%)	35 (71%)	0.001
Cerebrovascular disease	10 (12%)	3 (8%)	7 (14%)	0.35
Peripheral vascular disease	12 (14%)	1 (3%)	11 (22%)	0.008
Lung disease	21 (24%)	12 (32%)	9 (18%)	0.15
Pre-op Creatinine	89 [73-134]	81 [71-100]	111 [80-160]	0.01
Estimated GFR	69 [48-108]	94 [63-123]	57 [45-82]	0.001
Pre-op Haemoglobin	121 ± 29	121 ± 29	121 ± 28	0.99
Infective endocarditis	14 (14%)	5 (13%)	7 (14%)	0.88
Previous myocardial infarction	26 (30%)	8 (21%)	18 (37%)	0.11
Previous cardiac surgery	25 (29%)	11 (29%)	14 (29%)	0.97
CCS	0[0-2]	0[0-1]	0[0-2]	0.57
Congestive cardiac Failure history	33 (38%)	13 (34%)	20 (41%)	0.53
Ejection fraction (%)	46 ± 16	46 ± 18	47 ± 16	0.87
NYHA class	3[2-4]	3[2-4]	3[1-4]	0.25
IABP	23 (26%)	8 (21%)	15 (31%)	0.32
Elective admission	15 (17%)	7 (18%)	8 (16%)	2.8

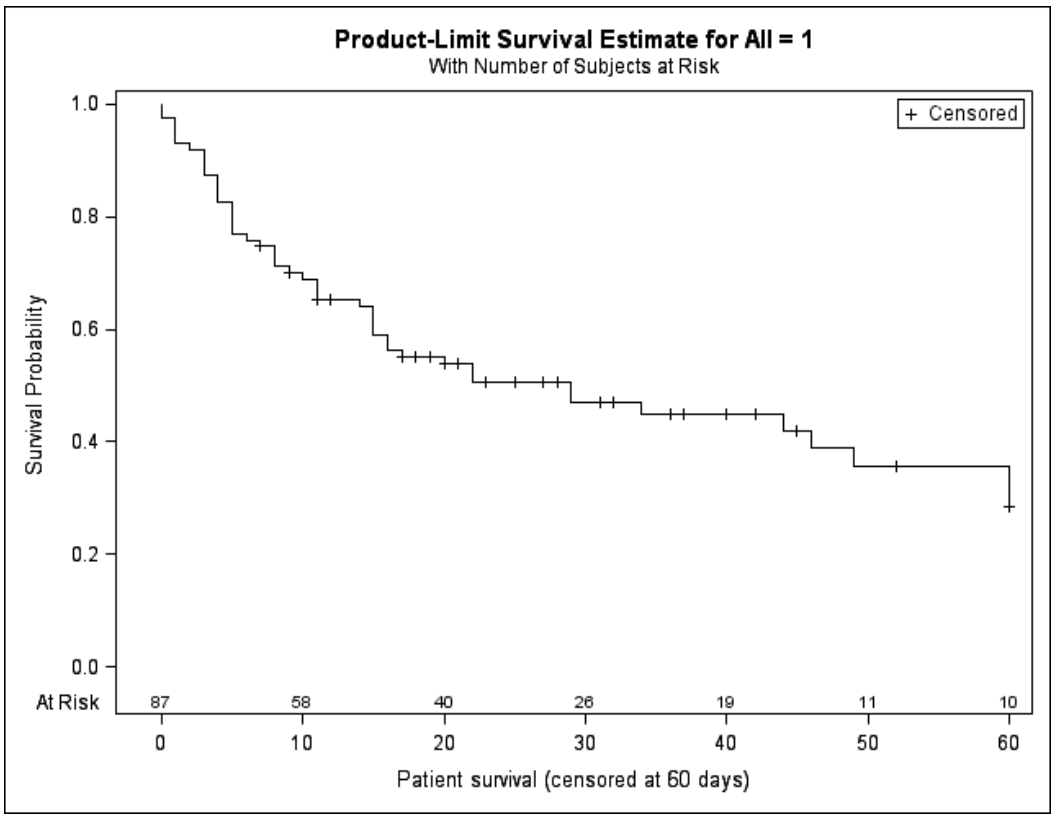
Table 3. Operative variables

	Survived (n=38)	**Died (n=49)**	**P value**
Direct transfer from cardiac catheterization laboratory	4 (10%)	3 (6%)	0.69
Coronary artery bypass grafting	14 (37%)	28 (57%)	0.06
Valve surgery	16 (42%)	23 (47%)	0.65
Aortic procedure	4 (11%)	12 (25%)	0.10
Other cardiac operation	19 (50%)	23 (47%)	0.78
Oral anticoagulants at time of operation	12 (32%)	18 (37%)	0.62
Inotropic support at time of operation	12 (32%)	15 (31%)	0.92
Cross clamp time (mins) (median[IQR])	74 [0-115]	125 [80-172]	0.002
Cardiopulmonary bypass time (mins) (mean ± SD)	199 ± 70	290 ± 131	0.001

Table 4. Post operative outcomes

	Survived (n=38)	**Died (n=49)**	**P value**
Intubation time (Hours) (median [IQR])	184 [60.3-325]	120 [25.6-197]	0.03
Length of stay days (median [IQR])	31 [20-45]	8 [4-16]	<0.0001
Intensive care unit stay (hours) (median [IQR])	334 [163-448]	100 [24-197]	<0.0001
ICU readmission	4 (11%)	1 (2%)	0.13
Reintubation	6 (16%)	3 (6%)	0.17
Drain tube losses first 4 hours (median [IQR])	405 [160-790]	228 [0-688]	0.12
Return to theatre for bleeding	13 (34%)	16 (33%)	0.88
New renal failure (doubling of creatinine and above 200 umol/L *or* need for dialysis); median [IQR]	14 (38%)	29 (60%)	0.03
Highest post-op Creatinine (median [IQR])	163 [124-334]	206 [138-274]	0.6
Peri-operative myocardial infarction	1 (2.6%)	5 (10.4%)	0.16
New arrhythmia	0 [0-1]	1 [0-1]	0.2
Cardiac arrest post-operatively	5 (13%)	18 (37%)	0.01
Permanent stroke	3 (8%)	6 (13%)	0.49
Transient stroke	1 (2.6%)	0 (0%)	0.44
Prolonged ventilation (>24h)	30 (79%)	32 (67%)	0.21
Pneumonia	10 (26%)	4 (8%)	0.02
Deep sternal wound infection	0 (0%)	1 (2.1%)	1.00
Septicaemia	0 (0%)	5 (10%)	0.06
Acute limb ischaemia	0 [0-0]	0 [0-0]	0.82
Anticoagulation complications	1 (2.6%)	8 (17%)	0.03
Gastrointestinal complications	10 (26%)	8 (17%)	0.28
Multi-system organ failure	9 (24%)	30 (63%)	<0.0001

Survival curves truncated at 60 days are shown in Figure 1, with raw data in Figure 1a and data stratified by MOF in Figure 1b.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With Number of Subjects at Risk
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Survival Probability
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At Risk
87
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50
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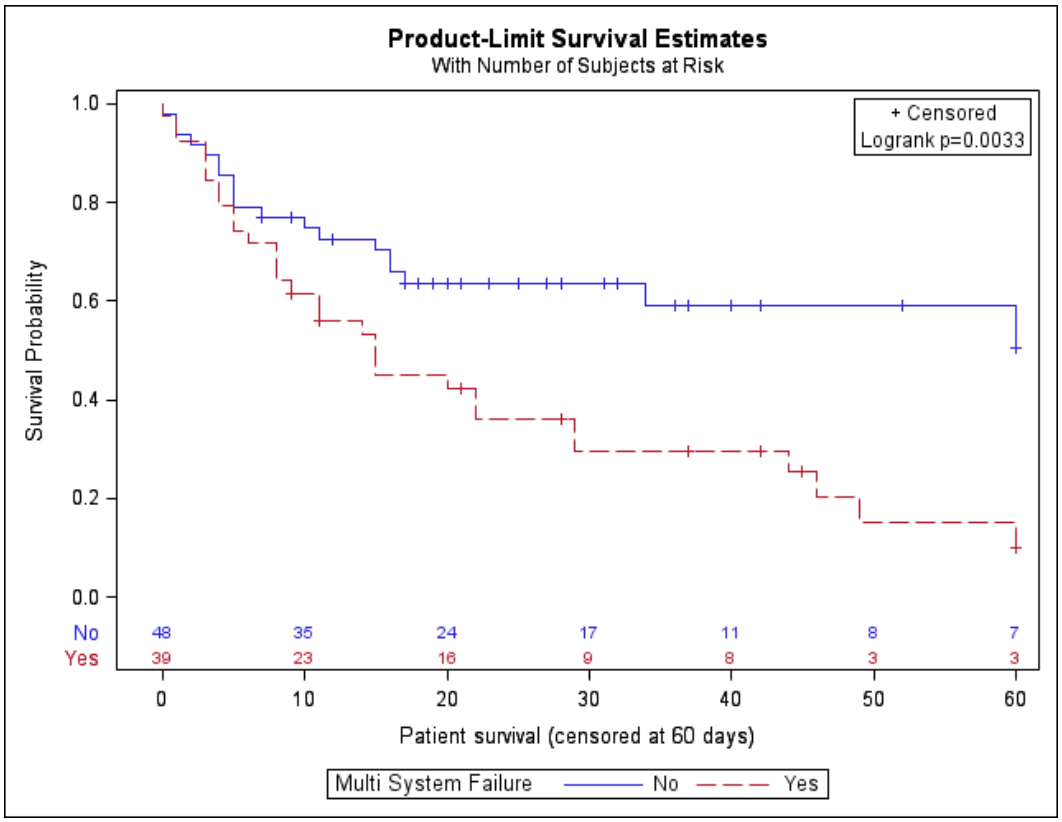
Patient survival (censored at 60 days)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With Number of Subjects at Risk
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Survival Probability
1.0
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Patient survival (censored at 60 days)
Multi System Failure
No
Yes

DISCUSSION

Cardiogenic shock is an uncommon complication of cardiac surgery, with the incidence of PCS-ECMO in our ANZSCTS database at 0.52%. This was somewhat lower than that reported in the literature, which ranges from 0.58% to 2.9% (31, 33). We specifically excluded patients whose primary procedure was cardiac / cardio-pulmonary transplantation, or ventricular assist device (VAD) insertion as these cases tend to have a different post operative course.

Although studies identify the failure of inotropes and IABP as an indication for VA-ECMO, there is likely vast differences between clinicians and centres as to how early ECMO is instituted. Lower inotropic thresholds may be reached before ECMO is instituted, and this is likely to be an indicator of better outcome. Unfortunately, our data was not able to determine time to ECMO from procedure. Duration between cardiotomy and ECMO-CPR has already been reported to be an independent risk factor for mortality (43), and we suspect delayed post-cardiotomy ECMO leads to worse outcomes secondary to multi-organ failure.

Multivariable logistic regression of our results found that multi-organ failure, age, and cardiopulmonary bypass time were significant predictors of mortality. This correlated with current literature, in particular with regards to age. In fact, the average age of our cohort was younger than many other reported groups (28-43). This may help to explain our better overall survival to discharge of 45.7%.

Cardiopulmonary bypass time is a known risk factor for poor outcome in cardiac surgery (33, 40). Rather than an inherent risk factor in itself, a longer cardiopulmonary bypass time is likely to indicate technical difficulties in the operation or inability to separate from cardiopulmonary bypass due to inadequate cardiac function.

Multi-system organ failure was three times more likely to occur in patients who died in our cohort. This end-organ dysfunction is most likely due to pre-ECMO malperfusion, as once a patient has good ECMO flows established with good oxygen flows, there should be no subsequent injury. What has been established in VA-ECMO management is that longer down-time leads to worse and more irreversible injury. This re-iterates our suspicion that earlier institution of ECMO is likely to improve outcomes. Although a different cohort, this has already been proven in the transplant population (50, 52).

Our results showed that vasculopaths had reduced survival, with hypertension and peripheral vascular disease being significant prognostic indicators on univariate analysis. This also explains the trend of poorer survival for patients undergoing CABG in our cohort. Post-operative pneumonia was higher in survivors, and this fits with our observation of survivors having longer post-operative ICU and hospital length of stay.

Data on longer term survival of patients is conflicting. Our data is censored at hospital discharge and so no long term data is available in this cohort. Previous publications have suggested that achieving hospital discharge could be the most important predictor of outcome, suggesting that survival remains good after discharge (53, 54). However, a recent meta-analysis of 20 observational studies contradicted that, reporting a pooled survival to hospital discharge of 34%, pooled 1 year survival of 24% and midterm survival of 18% (54).

Post-cardiotomy ECMO poses an ethical challenge. When should we limit intervention for an increasingly older, frailer, and higher-risk cardiac surgical cohort? Should limits exist, and what are the acceptable hospital and emotional expenses for an almost futile cause in some cases? It is not clear cut. The purpose of this study has been to identify and quantify what warrants significant risk for a poor outcome in a patient who has already been deemed suitable for cardiac surgery. With these results, the profession should aim to identify patients who are least suitable for this intervention, and potentially plan for it, by either intervening earlier or agreeing pre-operatively not to proceed to ECMO at all. Guidelines on the timing of institution would be of great benefit, with the earlier intervention potentially reducing the catastrophic sequelae before they are unmanageable.

In conclusion, this study provides us with a contemporary snapshot of post cardiotomy ECMO practice in Australia. Although the incidence of post cardiotomy ECMO is low, the overall numbers accrued in only 15 months are larger than many previously published series which span many years and often reflect changing practice over time.

Limitations

Although this cohort covers a comprehensive collection of public and private hospitals in Australia, it does not give us 100% coverage of all adult cardiac surgery centres. All public hospital cardiac units in Australia contribute to this database as the primary objective is a quality assurance program funded by the state governments. Fewer private hospitals submit data, possibly reflecting access to data managers which is a cost that private hospitals may struggle to cover.

The data was limited in that ECMO data was not collected as a separate variable prior to September 2016. Furthermore, the current dataset does not contain information on the site of cannulation (peripheral or central), exact timing of institution of ECMO or on duration of ECMO. No technical data on the running of the ECMO is collected such as flow rates, rotor speed, oxygenator thrombosis or exchange, cannulation strategies for lower limb perfusion or cannula sizes. Hopefully this study will serve to inform future data collection fields making the ECMO data more useful for further studies.

CONCOMITANT INTRA-AORTIC BALLOON PUMP AND ECMO USE

Concomitant use of Intra-Aortic Balloon Pump and ECMO – a Literature Review

VA-ECMO is becoming more widely used as a mainstay of treatment for refractory cardiogenic shock, and has superseded the intra-aortic balloon pump (IABP) as last-line therapy. However, although VA-ECMO can successfully support the cardiovascular system in delivering oxygenated blood to the patient's tissues, it is becoming increasingly clear that it may have a detrimental effect to myocardial recovery. Several mechanisms are thought to be involved including the increased left-ventricular afterload (in particular with femoral ECMO – the most frequently utilised configuration). Whether or not aortic regurgitation is present, the rise in afterload can significantly increase LV volumes resulting in pulmonary oedema, left ventricular distention, and LV thrombus formation from blood stasis (55). The LV distention in particular increases wall stress and potentially exacerbates myocardial ischaemia, reducing likelihood of recovery. LV distention occurs in 10-60% of patients on ECMO (56). Furthermore, the respiratory sequelae of increased pulmonary hydrostatic pressures are likely to lead to prolonged intubation. The use of the IABP is the most common device used available to attenuate LV distention. Other mechanisms are occasionally used, and are described earlier. Interestingly, the SHOCK-II trial (57) determined that use of intra-aortic balloon pump in patients undergoing early revascularization for myocardial infarction complicated by cardiogenic shock did not reduce mortality. Despite this, it remains a frequently used tool in some centres, justified to reduce LV afterload, and consequently improve myocardial recovery.

The literature is overall inconclusive as to whether there is benefit in the addition of a balloon pump to a peripherally configured ECMO circuit. Below are tables (table 1: human studies; table 2: laboratory studies) outlining the literature that has investigated the impact of concurrent IABP and ECMO use. 16 publications were identified (58-73), 10 of which were performed on humans (3 meta-analyses), the rest of which were experimental laboratory study. 3 of these experimental studies were performed on animals. A comprehensive review of the literature is tabulated below (table 1, 2), but the following is a summary of these results.

Table 1: HUMAN STUDIES

Paper	N	Study Design	Outcomes measured	Results	Comment / limitations
Petroni 2014	12	Prospective IABP stopped for 30 mins, measurements before/during/after	- Haemodynamics including PA Cath - TTE - Thenar eminence and brain tissue oxygenation - Side-stream dark-field (SDF) assessed sublingual microcirculation	On cessation of IABP: - Higher PA pressure: 19 vs 15mmHg; p=0.01) - Increased LVESD and LVEDD - Decreased pulse pressure (p=0.02) - Microcirculation not affected (SDF/O2)	- Although IABP ceased, still in-situ - Only measured on patients with minimal LVEF (LV-VTI < 5cm) - Did not assess outcomes of mortality / morbidity
Ma 2014	54	Retrospective analysis On post-cardiotomy patients	- Weaned - Mortality - Survival to DC - Complications	n = 34 (63%) weaned n = 21 (38.9%) survived to discharge - renal failure 7/54 - Infection 20/54 - Bleeding 18/54 - Neurological 7/54	- Does not assess impact of IABP / no control group
Lin 2016	529	Observational cohort study 227/529 ECMO alone 302/529 ECMO+IABP (IABP instituted <24h)	- All cause mortality at 2 weeks - Organ failure, vascular complication	Survival at 2 weeks no different: - ECMO 48.5% vs 47.7% combined (p=0.9) Patient selection showed statistically significant differences in: - age, gender, BMI, indication	- not randomised to ECMO+IABP or ECMO alone - Indication of IABP use was clinician dependant

Table 1: HUMAN STUDIES

Paper	N	Study Design	Outcomes measured	Results	Comment / limitations
			- LVEF and CVP measured at 1 week		- Mortality only assessed at 2 weeks (most patients wouldn't be discharged by this point) - Haemodynamic parameters were crude
Gass 2014	135	Retrospective cohort	- mortality - Complications - LOS	Overall in-hospital survival n=79 (57.8%) Cx: - bleeding at access site (n=19; 14.1%) - Stroke (n=15; 11.1%) - Vascular Cx requiring intervention (n=22; 16.3%) Pre-ECMO insertion of IABP associated with reduced mortality, CVA, Limb ischaemia (OR0.353; p=0.031)	- did not assess efficacy of IABP to survival - only timing of insertion - Did not establish limb Cx with access of ECMO or IABP side - needs to be determined - Not all fem VA ECMO had downstream cannula, likely confounding limb ischaemia (ie not attributed to IABP, but ECMO technique)

Table 1: HUMAN STUDIES

Paper	N	Study Design	Outcomes measured	Results	Comment / limitations
Madershahian 2009	6	Prospective study on CABG patients peri-operatively Emergency patients who had *fem-fem ECMO* + IABP	- haemodynamic parameters - *Venous* bypass graft flows (ml/min) via TTFM - pulsatility index	MAP: ECMO 63.6+-2.9mmHg vs ECMO+IABP 67.8+-2.9mmHg (p<0.0001) Graft flow: ECMO 46.8+-9.6ml/min ECMO+IABP 56.4+-12.1ml/min (p<0.005) (17% increase)	- unique study in that it assesses CAB- graft flows - All results and graft flows only assessed peri-operatively with an open chest
Yang 2014	12	Divided into 2 groups: - P: pulse-pressure >10mmHg - N: pulse-pressure <10mmHg Mean Cerebral blood flow (CBF) via doppler	Mean CBF in middle cerebral artery (MCA) via trans-cranial doppler +/- IABP	- IABP did *not* change mean CBF - Mean CBF higher *without* IABP than with in N group (257 vs 239ml/min; p <0.001) - Mean CBF higher *with* IABP than without in P group (261 vs 244ml/min; p<0.001)	- Demonstrates that IABP can be both beneficial or detrimental to flow according to different cardiac states (stunned or ejecting) - Does CBF correlate with stroke risk or end-organ perfusion morbidity? - Did not comment on neurological outcomes (eg CVA) or clinical neurology of patients

Table 1: HUMAN STUDIES

Paper	N	Study Design	Outcomes measured	Results	Comment / limitations
					- Unclear what flow of ECMO was pulsatility determined
Aso 2016	1650	retrospective cohort study of national database; propensity score matching (533 pairs)	Primary: all-cause mortality at 28 days / in-hospital mortality Secondary: proportion of patients weaned	(propensity score matched data): IABP+ECMO better outcome than ECMO alone - all-cause mortality (28 days): - 58.2% vs 48.4% p=0.001 in-hospital mortality: - 64.5% vs 55.9% p=0.004 Similarly weaned: - 82.6% vs 73.4% p<0.001 *Sub-Group analysis of those on CRRT, NOT S.S. difference if +/-IABP re mortality*	- Major limitation of study is generic overview of ECMO - Not specified which are subclavian and which are femoral ECMO - Cardiac arrest patients excluded from study - proportion of IHD 40%2 - known to be indicated for IABP earlier, more routinely, and may be more stable on induction of ECMO than those not initially indicated for IABP - Short VA-ECMO run - 2.2-2.5 days average

Table 1: HUMAN STUDIES

Paper	N	Study Design	Outcomes measured	Results	Comment / limitations
Cheng 2015	1517	Meta-analysis and systematic review 16 studies	Primary outcome: - survival to hospital discharge - Concomitant IABP + ECMO alone compared Secondary analyses on: - AMI - PCCS - Timing of IABP insertion	Survival no different: Comb 35.3% vs 37.5% ECMO Subgroup analysis showed no improvement in survival in AMI or PCS patients either Timing of IABP, nor routine IABP insertion did not improve survival	- Does not distinguish configuration of ECMO - Did not assess complications / morbidity - Very difficult to assimilate ECMO and IABP analyses to make any significant comparisons - studies all employed different methods and indications for IABP insertion - IABP timing analysis of great value - excluded significant heterogeneity across groups
Vallabhajosyula 2018	4653	Meta-analysis and systematic review 22 studies	Primary outcome - Short-term survival Sub-group analysis of: - Post-AMI cardiogenic shock - Post-Cardiotomy cardiogenic shock - Mixed cause cardiogenic shock	Survival not significantly different amongst total cohort: IABP/ECMO v ECMO alone (42.1% v 57.8; p = 0.30) - Post-AMI *was* significantly reduced by IABP (50.8% v 62.4%; p < 0.001) - Post-cardiotomy p = 0.22 - Mixed cause p = 0.47	- Didn't evaluate timing of ECMO and IABP insertion - Relation of timing of IABP as pre-/post- ECMO not described / evaluated - Timing of revascularisation in AMI not analysed - Did not report central / peripheral ECMO

Table 1: HUMAN STUDIES

Paper	N	Study Design	Outcomes measured	Results	Comment / limitations
Li 2019	4576 29 studies	Meta-analysis and systematic review	Primary outcome: In-hospital death Secondary outcome: neurological, gastro-intestinal, and limb-related complications	In all groups except myocarditis, ECMO/IABP combined had reduced mortality than ECMO alone Non-ECPR group: - RR 0.90; 95%CI 0.85-0.95; p < 0.0001 ECPR group: - RR 0.78; 95%CI 0.64-0.95; p = 0.01 PCS	- Timing and strategy of IABP insertion - Made note of other concomitant LV venting strategies including trans-septal, trans-aortic, pulmonary, and surgical venting but no evaluation of their individual impact on haemodynamics or outcomes - ECMO cannulation configuration not evaluated for outcome either

Table 1: HUMAN STUDIES

Paper	N	Study Design	Outcomes measured	Results	Comment / limitations
				- RR 0.91; 95%CI 0.85-0.98; p = 0.008) IHD - RR 0.83; 95%CI 0.73-0.96; p = 0.009 Myocarditis - RR 1.16; 95%CI 0.0-13.38; p = 0.90 Neurological / GI / limb-related Cx - IABP did not increase any of these complications	

Table 2: EXPERIMENTAL STUDIES

Paper	N	Subject	Study Design	Outcomes measured	Results	Comment
Miyamoto 1995	11	Canines	Prospective experimental Return cannula in Femoral artery perfusion (FAP) or Subclavian artery perfusion (SAP); central venous (RA); VAbypass flows 25, 50, 75, 85, 100% IABP concurrently	- aortic root pressure (AoP) - Coronary sinus blood flow - Mean SBP/DBP - LAP - CVP	At 75-85%VAB flows: - mSBP SAP > FAP At 50% or more VAB flows: - mDBP SAP > FAP - CSF SAP > FAP SAP > FAP in achieving diastolic augmentation with an IABP	- Subclavian arterial cannulation demonstrates better flows than femoral - VAB does not replicate ECMO (has reservoir, direct central venous access, controlled preload, etc) - This study does not evaluate effect of IABP upon ECMO; just cannulation site, (subclav vs fem)
Sauren 2007	7	Sheep	Prospective Experimental IABP + ECMO with either central cannulation (CC) or peripheral cannulation (PC)	- haemodynamic and cardiac function indices - Mean coronary artery flow (Qcor) - diastolic pressure time index (DPTI) - LV pressure volume area (PVA)	In both CC and PC ECMO+IABP - LV afterload reduced (0.02) - TTI reduced ($p<0.03$) - Qcor and DPTI increased ($p<0.05$) IABP augmented myocardial O2 supply/demand ratio	- Impaired haemodynamic profile in PC when low ECMO flow rate and low MAP - Ischaemic conditions replicated by LCx ligations NOT studied as not enough successful measurements - hence only *stable* and physiologically *normal* hearts

Table 2: EXPERIMENTAL STUDIES

Paper	N	Subject	Study Design	Outcomes measured	Results	Comment
				- Tension time index (TTI)	MAP, DPTI, PVA and Qcor significantly enhanced in CC > PC	studied (ie a fully ejecting heart) - not reflective of the clinical true indication and setting - Greatest benefit in CC > PC
Belohlavek 2012	11	Pigs	Prospective Experimental Cardiac arrest (CA) induced and ECMO at 5-10ml/kg/min —> 100ml/kg/min to compare low flow vs full flow ECMO Compared FemFem vs FemSubclav ECMO +/- IABP	Carotid blood flow (CaBF) and coronary blood flow (CoBF) measured by doppler flow wire Cerebral and peripheral oxygenation by near infrared spectroscopy Coronary perfusion pressure, myocardial oxygen demand and resuscitability also measured	CoBF 90% in FemFem ECMO only; addition of IABP 60.7% of baseline (p=0.004) FS ECMO +/-IABP not affected CaBF not affected significantly by ECMO or IABP config; similarly re O2 sats	Coronary blood flow found to be *reduced* with addition of IABP in FemFem-ECMO Arrest induced via 15min of VF; - the heart does eject (minimally) in most VA-ECMO patients so this is not a true replication of cardiac status in clinical experience - IABP set at 100/min; unclear benefit of IABP when there is no cardiac activity

Table 2: EXPERIMENTAL STUDIES

Paper	N	Subject	Study Design	Outcomes measured	Results	Comment
						No vasopressors used, and no mention of what HD parameters maintained
Geier 2017	0	Silicone aorta Model	Silicone aorta; VAD driven circulation + ECMO - formulated as central vs axillary vs femoral Left and right common carotid artery (LCCA/RCCA) flow and pressure measured	RCCA / LCCA flow and pressure measured	Flow in carotids influenced by cannulation site, whether LV ejecting, if ECMO pulsatile, and if IABP on - all significant FF-ECMO with IABP showed the lowest flows in carotids	- VAD may not accurately replicate cardiac ejection - pulsatile ECMO not utilised in most centres - Trend of lower flows in carotids w FF ECMO + IABP - Wide range of results; questionable reproducibility

Table 2: EXPERIMENTAL STUDIES

Paper	N	Subject	Study Design	Outcomes measured	Results	Comment
Carusso 2015	0	CFD	Computer modelled aorta from CT of 54yo male - healthy Ascending aorta cannula (outflow) Case A: total ECMO assistance Case B: partial ECMO assistance	Flows in arch vessels and descending aorta and Cannula Pressure waveforms in above Flow dynamics	Case A: drop in desc Ao flows on IABP inflation; rise in brachiocephalic vessels Case B: rise in flows in all vessels Flow dynamics case A: big vortices in asc ao and whirling in BC vessels Case B: chaotic flows in cannula on IABP inflation	- not replicative of a compliant human aorta - Ascending aortic cannula only; not assessing routine peripheral ECMO - Interestingly shows flow dynamics that may lead to thrombus formation or poor flow in epi-aortic vessels

Of the human studies, 7 had outcomes focused on overall mortality. Gass (2014) described a retrospective cohort study of 135 patients whom had concurrent ECMO and IABP support. They found that the use of IABP pre- ECMO had lower mortality than if instituted post ECMO implantation (63). This study, however, does no evaluate the additional benefit or harm of IABP as there was no control group, and hence no conclusion could be made upon the mortality benefit of a balloon pump. Rather, this may highlight that early mechanical cardiac support reduces improves survival outcome.

Aso et al (2016) reported on 1,650 patients from a national database and utilised propensity-score matching resulting in 533 pairs. They found that IABP in addition to ECMO had superior survival than ECMO alone (58.2% vs 48.4%, respectively; $p = 0.001$) (68). The secondary outcome measured of this cohort was of the proportion of patients weaned from ECMO successfully. Once again, concomitant IABP improved likelihood of weaning (82.6% vs 73.4%; $p < 0.001$). Of note, a sub-group analysis demonstrated that patients on continuous renal replacement therapy (CRRT) had no reduction in mortality with the use of an IABP (in-hospital mortality 72% vs 71.6%; $p = 0.944$). This suggests that established end-organ malperfusion negates any potential benefit of the additional mechanical support, and reiterates that timing and early implementation of circulatory support is far more efficacious at reducing mortality.

Lin (2016) compared ECMO alone and ECMO+IABP across 529 patients (70), and reported no difference in mortality at 2 weeks (48.5% vs 47.7%, respectively; $p = 0.90$). This finding was confirmed by Cheng et al (2015) whom performed a meta-analysis on 1,517 patients (67), determining no difference in survival to discharge (35.3% ECMO+IABP vs 37.5% ECMO alone). Lin's paper was the only study to report on morbidity (70). Although there was no difference in cerebral or renal events, more patients in the combined IABP/ECMO group received limb fasciotomy operations for vascular complications (2.6% vs 0.0%, $p = 0.012$). Hence, there was no reduction of morbidity with the use of IABP concurrently, and in fact limb ischaemia was significantly higher.

Vallabhajoysyula et al (2018) performed a systematic review and meta-analysis comparing the mortality outcomes of concomitant IABP and ECMO compared with ECMO alone (72). This meta-analysis covered 22 publications (a total of 4,653 patients) from 2000-2018, reviewing the adult population. Overall, they found no significant difference in short-term mortality (defined as 30-day, or hospital mortality depending upon study), of patients with and without IABP 42.1% vs 57.8% (risk ratio 0.80; 95%CI 0.52-1.22; $p = 0.30$). A sub-group analysis evaluated the indication for

ECMO into post- acute myocardial infarction (AMI), post-cardiotomy, and mixed-cause for cardiogenic shock. This revealed that post-AMI patients did, in-fact, show a significantly lower mortality with the concomitant use of IABP with ECMO compared to ECMO alone (50.8% vs 62.4%; $p < 0.001$). No significant reduction in mortality was observed in post-cardiotomy or mixed-cause cardiogenic shock, however. Interestingly, the heterogeneity was lowest in the post-AMI cohort (I^2 =0%) compared to the other sub-groups (post-cardiotomy cardiogenic shock I^2 = 93%; mixed cause cardiogenic shock I^2 = 70%). This suggests that the post-AMI shock cohort reflects the impact of IABP to a more accurate extent, and the concomitant use of ECMO and IABP may well be warranted. However, several factors were not evaluated, making the results of this meta-analysis difficult to interpret. In particular, Vallabhajoysyula reported that timing of IABP and ECMO insertion was not reported in most studies for the meta-analysis, and thus could not be analysed. It is well documented that early mechanical circulatory support, and in particular early post-AMI IABP insertion reduces mortality (74, 75) and that insertion of IABP pre-ECMO is shown to have reduced mortality than post -ECMO implantation (63). IABP implantation is a mainstay of treatment in the unstable myocardial infarction patient, and early insertion is far more likely. Furthermore, timing of revascularisation, other configurations of ECMO (often varied in the post-cardiotomy group) and other baseline data were also not reported.

Another meta-analysis by Li et al (2019) reported a survival benefit with concomitant IABP/ECMO than ECMO alone (73). This paper determined a favourable outcome for use of IABP with no increase in gastro-intestinal, neurological, or limb-related complications. Once again, timing of VA-ECMO and IABP were not evaluated. Furthermore, in none of the above studies or meta-analyses were other mechanisms of LV venting evaluated. Li et al reported that even when IABP was combined with ECMO, other venting strategies such as trans-septal (the most common), trans-aortic, surgical, and trans-pulmonary venting was utilised to decompress the left ventricle. Despite this, it's impact upon outcome was not determined.

Mortality is a relatively cumbersome measure of success when attempting to review the impact of a device that is inconsistently utilised both in indication and method, amongst a population of particularly ill patients. This is especially true when covering multiple centres, which will undoubtedly have differing practices and patient populations. This is well reflected in the conflicting results described above.

Haemodynamic parameters of flow and pressure to the heart and end-organs are more precise, and studied with greater scientific rigour. 8 studies reviewed the impact of a balloon pump - when ECMO was already instituted - upon haemodynamic parameters of flow and pressure.

Experimental non-living models were assessed, including a silicon aorta and a computational fluid dynamics (CFD) model (69, 71). Caruso's CFD model (69) was of particular interest, as it demonstrated the different effects of the IABP with varying haemodynamic conditions. They found that in partial assistance with a partially ejecting heart, the addition of IABP to ECMO led to a rise in blood flow through the brachiocephalic vessels and the descending aorta (figure 1). However, during total ECMO assistance (a non-ejecting heart), there was reduced descending aortic flow. A significant limitation of this study was that the arterial ECMO cannula was positioned in the ascending aorta, therefore not replicating the femoral ECMO set-up. Thus, the question remains if the inter-positioned IABP impedes or enhances flow to the heart and arch vessels.

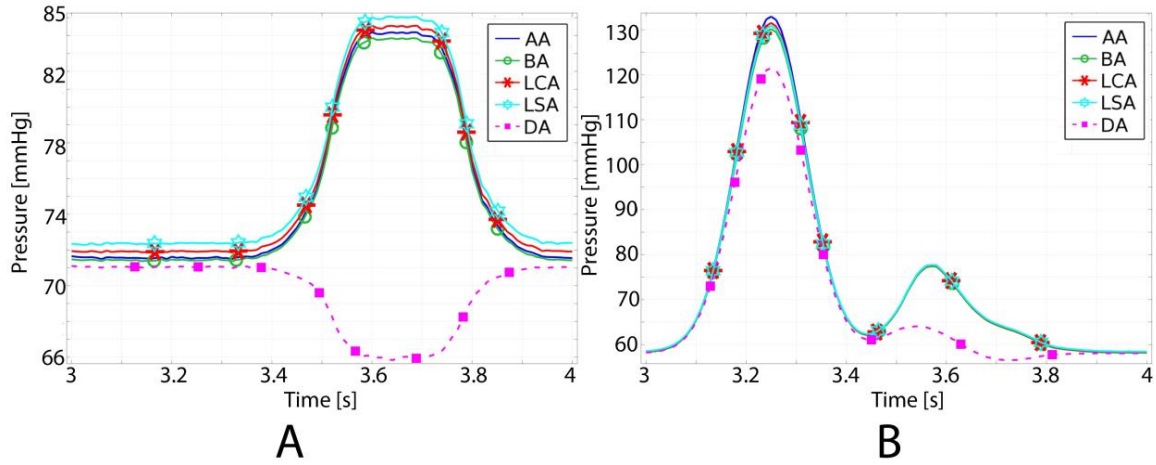


Figure 1 Pressure waveforms in ascending the aorta (AA), in the epiaortic vessels (BA, LCA and LSA), in the descending aorta (DA) and in the arterial cannula in case of total support (A) and partial one (B) during one cardiac cycle.

Geier et al (2017) evaluated carotid flows in a silicon aortic model, with various combinations of pulsatile / non-pulsatile ECMO, an ejecting / non-ejecting heart (replicated by a VAD), femoral / axillary / central arterial cannulation, and with / without IABP (71). They found that the combination of an IABP and femoral ECMO led to the lowest carotid flows ($p < 0.001$) (see figure 2). This study did not evaluate coronary pressures nor the changes that would occur at varying cardiac ejection fractions. Neither of the above studies reported on left ventricular pressures and dimensions – the primary indication for a concurrent intra-aortic balloon pump.

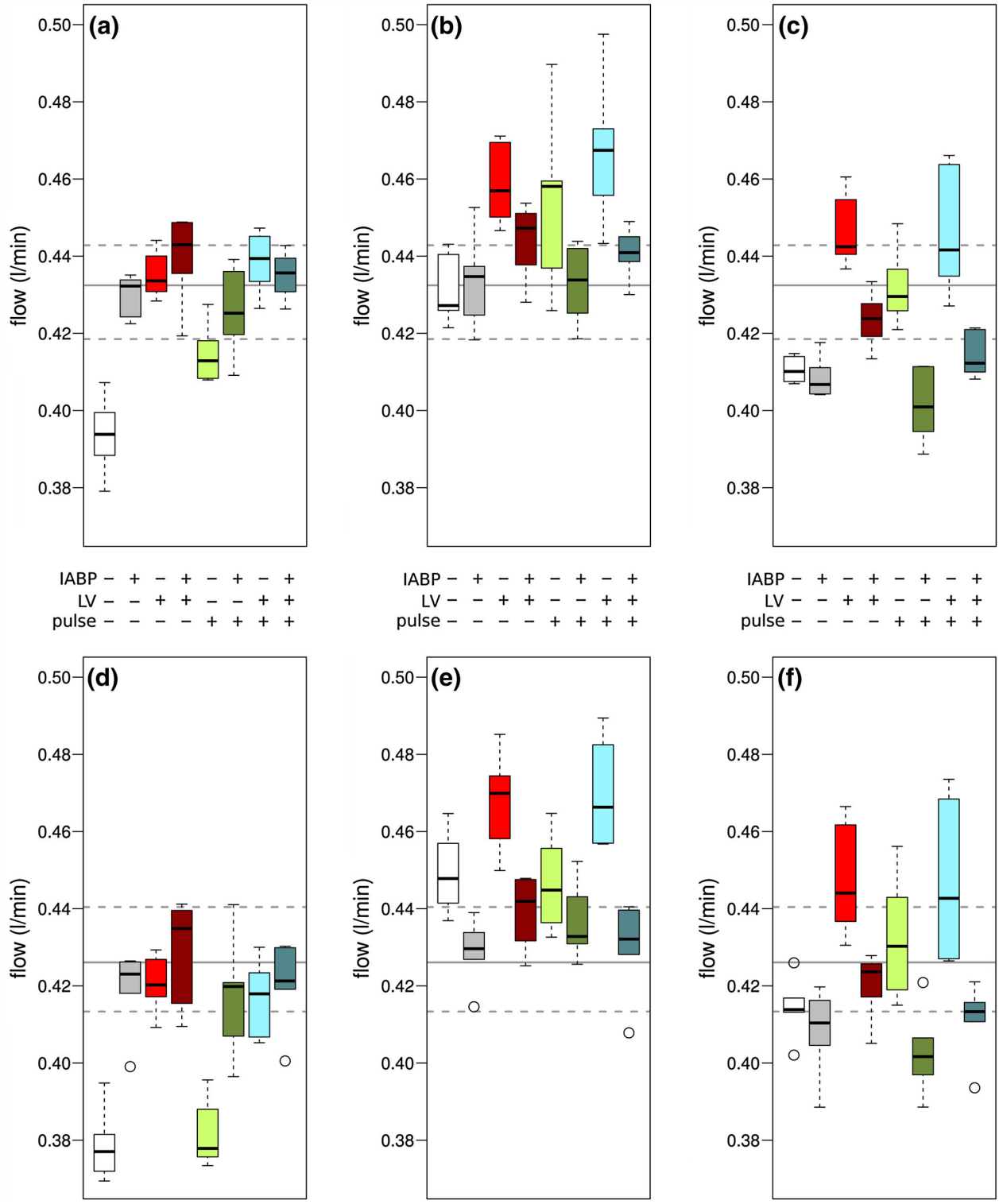


FIGURE 2 Effects of cannulation site on mean flow in the right (a–c) and left (d–f) common carotid arteries. (a, d) axillar cannulation; (b, e) central cannulation; (c, f) femoral cannulation. As a reference, the grey horizontal lines indicate median (solid) and 1st and 3rd quartiles (dashed) across all conditions measured in each vessel.

3 publications studied haemodynamic parameters upon humans (61, 65, 66). Outcomes varied as did results across these publications. Yang et al (2014) reported upon mean cerebral blood flow in 12 patients (66), divided into 2 groups (pulse pressure > 10mmHg [P], and <10mmHg [N]).

This division is significant in that the impact of IABP upon mean cerebral blood flow (CBF; measured via trans-cranial doppler) differed according to pulse pressure, and thus cardiac function. In the P group, the use of an IABP increased mean CBF, whilst in the N group it reduced mean CBF. This eloquently demonstrates that the impact of an IABP varies with changes in ventricular ejection, and should not be grossly labelled as beneficial or detrimental in ECMO.

Belohlavek et al (2012) reported a study on 11 pigs whom had cardiac arrest induced by ventricular fibrillation (62). During that time, they had standardised ECMO flow rates, configured femorally. Outcomes of coronary artery blood flow and carotid artery blood flow were compared with an IABP on or off. Interestingly, it was found that coronary blood flow was significantly reduced when an IABP was added than ECMO alone (60% of baseline vs 90%, respectively; $p = 0.004$). Additionally, carotid artery blood flows were not significantly affected by addition of an IABP. These subjects had no cardiac ejection, and thus the use of an IABP is likely to have occluded the retrograde femoral ECMO flow. Hence, early myocardial recovery may be compromised by the addition of a balloon pump, rather than assisted.

Sauren et al (2007) had performed a similar experiment on 7 sheep (60). They compared central and peripheral ECMO cannulation with a concurrent IABP. In both central and peripheral configurations, LV afterload was reduced ($p = 0.02$) and mean coronary artery flow (QCor) was increased ($p < 0.05$). It is important to note, however, that this study was performed on *normal* hearts. Despite trying to replicate low LVEF scenarios by ligating the left circumflex coronary artery, the sheep did not survive to testing, and only normally ejecting hearts were evaluated. The contrast between Sauren and Belohlavek's experimental results highlight the impact ventricular ejection has on the efficacy of a balloon pump. It may potentially be detrimental in a non-ejecting heart, occluding flows to the cerebral and coronary circulation, whilst doing the opposite and reducing afterload in the ejecting left ventricle. In fact, this dynamic result is supported by Yang's results described above, and may be the most consistent finding of all the studies reported.

These conflicting findings led to the formulation of our hypothesis that at varying ejection fractions of the heart, the impact of the retrograde counterpulsion from the IABP would change. More specifically, with no ejection from the heart, the counterpulsion would occlude the retrograde flow from the femoral ECMO cannula, and therefore reduce flow to the coronaries and cerebral circulation. But as the heart begins to eject more and pressurise the aortic root and arch, the inflation of the IABP would improve coronary and cerebral blood flow. Evaluating these changes would explain the discrepancies across studies, and potentially support a weaning regimen for use of the IABP in an improving heart.

STUDY PROPOSAL

We propose an experimental study that covers the following outcomes to determine the usefulness of IABP and ECMO, and the impact of timing:

Protocol

A mechanical loop will simulate both the systemic and pulmonary systems, as well as all four chambers of the heart, including valves. An air compressor programmed to deliver controlled ejections, will mimic the ventricle at various contractile strengths. The resistance, compliance, and volumes throughout the loop are all adjustable via various valves and reservoirs. These are all centrally controlled by a computer programmed to reflect the expected physiologic changes in a patient.

This loop will be attached to an ECMO pump and oxygenator, imitating arterial cannulation via the femoral artery (i.e. tip ending in the descending thoracic aorta), and venous cannulation of the femoral vein (with the tip in the right atrium). An intra-aortic balloon pump will be attached also via the femoral artery, with its tip positioned at the end of the aortic arch, as per routine in the clinical setting.

Flow meters, doppler probes, and pressure monitors are placed at various points, most important of which are:

- Cerebral circulation
- Coronary arteries
- Aortic root / arch
- Chambers of the heart

Pressure, flow, and doppler wave-form data are then gathered at all measured points and at varying ejection fractions.

ECMO flows will be adjusted to match MAP 65mmHg

- As LVEF increases, ECMO flow will be reduced as in the clinical setting

- In low SVR cases, ECMO flows will need to be higher to maintain MAP, mimicking cardiogenic shock complicated by end-organ failure syndrome

In simulating VF, both ventricles will not eject any volume and a heart rate of 0 can be set as an alternative. Pulmonary pressures should passively reflect the simulated left and right heart conditions, and need not be altered.

Below are several tables describing the various parameters to be changed and assessed. The series below will be replicated at the following ejection fractions:

- 0% (VF)
- 10%
- 20%
- 30%
- 40%

Baseline non-ejecting Left heart

Run 1-1

LVEF	0%
IABP	OFF
ECMO flows	5 l/min
SVR	Normal
RHF	Normal
HR	100

Run 1-2

LVEF	0%
IABP	100/min
ECMO flows	5 l/min
SVR	Normal
RHF	Normal
HR	100

Low SVR

Run 1-3

LVEF	0%
IABP	0 (OFF)
ECMO flows	5 l/min
SVR	Low
RHF	Normal

Run 1-3

HR	100

Run 1-4

LVEF	0%
IABP	100/min
ECMO flows	5 l/min
SVR	Low
RHF	Normal
HR	100

Severe Right Heart Failure

Run 1-5

LVEF	0%
IABP	OFF
ECMO flows	5 l/min
SVR	Normal
RHF	Severe (15%)
HR	100

Run 1-6

LVEF	0%

Run 1-6

IABP	100/min
ECMO flows	5 l/min
SVR	Low
RHF	Severe (<15%)
HR	100

- **VF**

Run 1-7

LVEF	0%
IABP	OFF
ECMO flows	5 l/min
SVR	Normal
RHF	Severe (15%)
HR	VF

Run 1-8

LVEF	0%
IABP	80/min Automatic
ECMO flows	5 l/min
SVR	Normal
RHF	Severe (15%)

Run 1-8

HR	VF

Below is a manuscript currently in submission for publication on concomitant IABP and ECMO use, based upon the above protocol.

Concomitant Intra-Aortic Balloon Pump and ECMO – A Mock Loop Study

Introduction

Intra-aortic balloon pumps (IABPs) have been utilised in cardiogenic shock to assist in myocardial recovery following ischaemic events, to varying success (76, 77). Theoretically, the inflation of the balloon pump during diastole increases coronary and pulsatile flow, whilst reducing afterload during deflation in the systole phase; in essence, increasing myocardial oxygen supply and reducing demand. Its use in conjunction with veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is quite widespread, with proponents suggesting it improves flow to coronary grafts or native arteries, reduces afterload, and assists in weaning. However, as much evidence exists to the contrary, suggesting there is no benefit to the use of IABP and ECMO in conjunction. Similarly, non-clinical / experimental studies show contradictory results, including in the evaluation of coronary and carotid arterial flows.

Several gaps still exist in current knowledge, possibly contributing to the contradictory nature of the results. Configuration of the ECMO circuit is a large confounder, with peripheral arterial cannulation not consistently studied in both clinical and experimental publications. Similarly end-points and outcomes measured are inconsistent also, and the timing of ECMO and IABP not tailored to the various haemodynamic states more reflective of clinical experience. In fact, the inconsistency of evidence may relate primarily to this - that at various times in the recovery of cardiac function, the IABP may have either beneficial, ineffective, or adverse effect.

We hypothesised that with variations of left ventricular failure on peripheral VA-ECMO, addition of IABP would have differing effects upon coronary and cerebral flows, as well as venting and afterload reduction the heart.

Methods

A standardised mock circulatory loop (MCL) was connected to a VA-ECMO circuit, configured to replicate peripheral cannulation. Support with ECMO alone was compared with support with the addition of a 40cc IABP and measured in different pathological conditions, simulating:

- Biventricular failure with different stages of LV recovery

- Isolated left ventricular failure
- Biventricular standstill

End-points measured included:

- Coronary flow (CorQ)
- Left ventricular ejection fraction (LVEF)
- Markers of left ventricular distention
    - Left ventricular end-diastolic pressure (LVEDP)
    - Left ventricular end-diastolic volume (LVEDV)
    - Left atrial pressure (LAP)
- Right ventricular systolic pressure (RVSP)
- Right atrial pressure (RAP)
- Peripheral perfusion
    - Total systemic flow
    - Distal flow
    - Mean arterial pressure (MAP)
    - Cerebral perfusion (CerQ)

Results were recorded for each end-point with the pathological conditions alone as baseline, then ECMO support, followed by the addition of the IABP to ECMO support. ECMO flows were adjusted to maintain a MAP of 65mmHg, as per routine in the clinical setting. Ten seconds of steady state data were recorded for each experimental run. Left ventricular pressure was used to trigger the inflation and deflation of the balloon. The balloon was set to inflate with the onset of diastole, and deflate at the onset of systole, at a 1:1 support ratio.

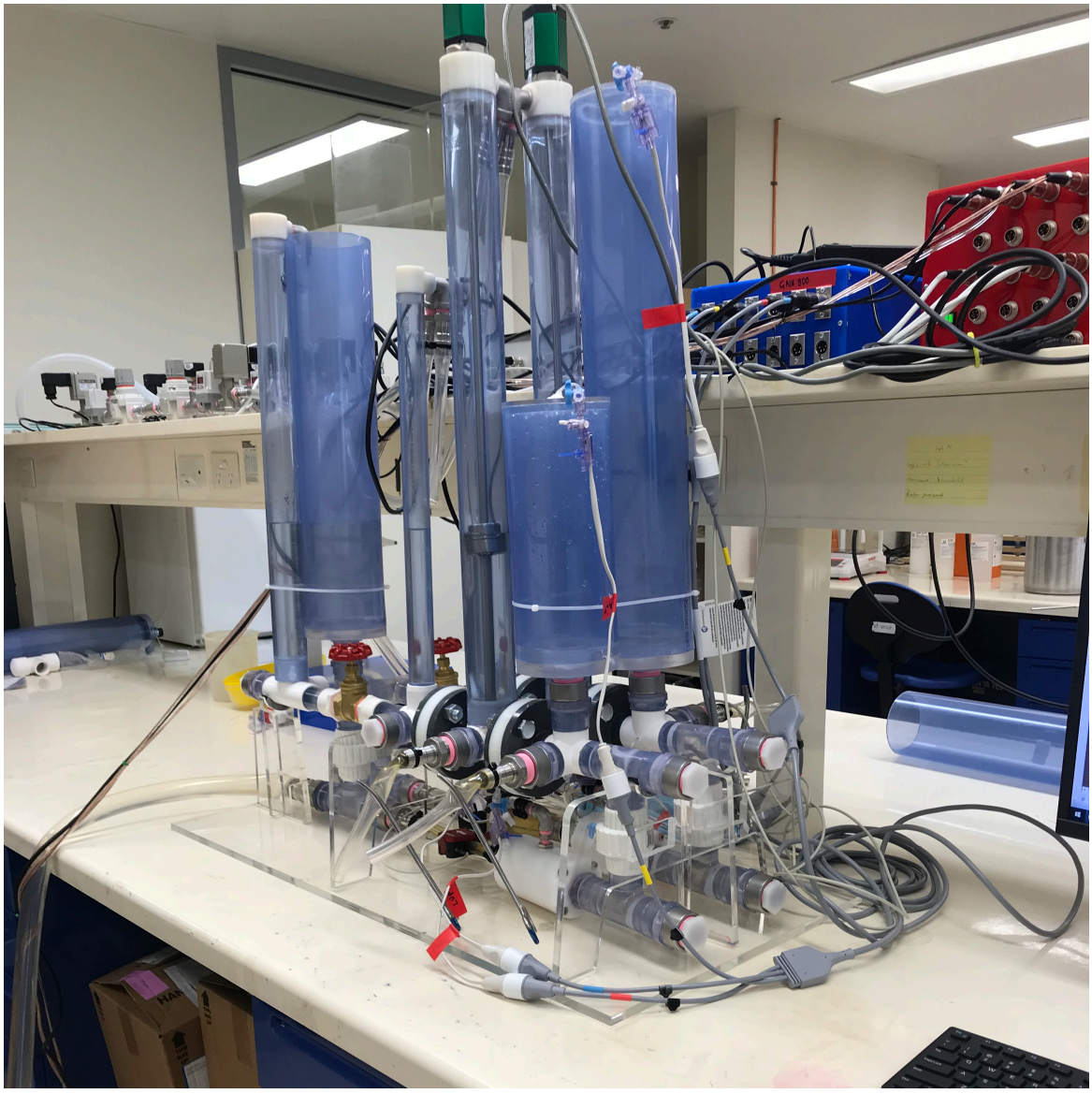
As stroke volume – and thus ejection fraction – was dependant upon flows and conditions imposed by the circuit, left and right ventricular contractility was adjusted according to their respective end-systolic pressure volume relationship (LVESPVR, RVESPVR). Contractility was thus controlled as 0, 15, 30, 45, and 100% of normal.

The patient conditions simulated were as follows:

- Biventricular failure with graduated LV improvement
    - RV contractility 40%; LV contractility 15%

    - RV contractility 40%; LV contractility 30%
    - RV contractility 40%; LV contractility 45%
- Isolated LV failure
    - RV contractility 100%; LV contractility 15%
- Biventricular standstill (ventricular fibrillation)
    - RV contractility 0%; LV contractility 0%

Kolmogorov Smirnov test (k-test) showed that the data extracted from the MCL were not normally distributed, hence, a non-parametric tool was required to analyse the experimental data. Wilcoxon rank sum test was used to test the statistical differences between ECMO only and the ECMP + IABP configuration.



Results

Based on the Wilcoxon Rank sum Test performed on the indicated hemodynamic parameters, the result showed statically significant differences ($p < 0.05$) between the ECMO only and the ECMO plus IABP configuration.

Table 1 demonstrates the results of the condition, ECMO support, and ECMO+IABP support. Statistical significance was found in all comparisons of results between ECMO and ECMO+IABP support, as the results were highly replicable in the MCL.

LV Venting

There was a reduction in LVEDV by up to 6-10ml in all circumstances of biventricular failure. The reduction was less pronounced in isolated LV failure (4ml) and no reduction at all in biventricular standstill. LVEDP reduction was overall negligible, with a maximum of 1mmHg reduction with IABP addition for a biventricular failure state. This was similar for LAP and RVSP with a maximum of 1mmHg drop in pressure in the one state. Figures 1-4 below demonstrate the overall increase in LV volume and pressure with addition of femoral ECMO to resuscitate, but also the venting effect with the addition of the IABP.

EF

Ejection fraction increased with the addition of the IABP in the biventricular failure group - most pronounced in the more recovered LV function by 5%. In isolated severe LV failure and biventricular standstill there was no notable impact.

Coronary flows

There were 2 models of coronary flow measured – coronary flow with an autoregulation model programmed to normal physiology (CorQ-ON), and coronary

perfusion with the autoregulation *off* (CorQ-OFF). With autoregulation ON, coronary perfusion dropped with the addition of IABP to ECMO in biventricular failure models (up to 12ml/min). However, with autoregulation OFF, coronary perfusion increased. This was most pronounced in the most severely impaired left ventricle, by 20ml/min (6.9%). Similarly with the isolated LV failure, coronary perfusion (with autoregulation) was minimally impaired by IABP (dropped by 3ml/min), yet increased significantly by 17ml/min (5.4%) with autoregulation off.

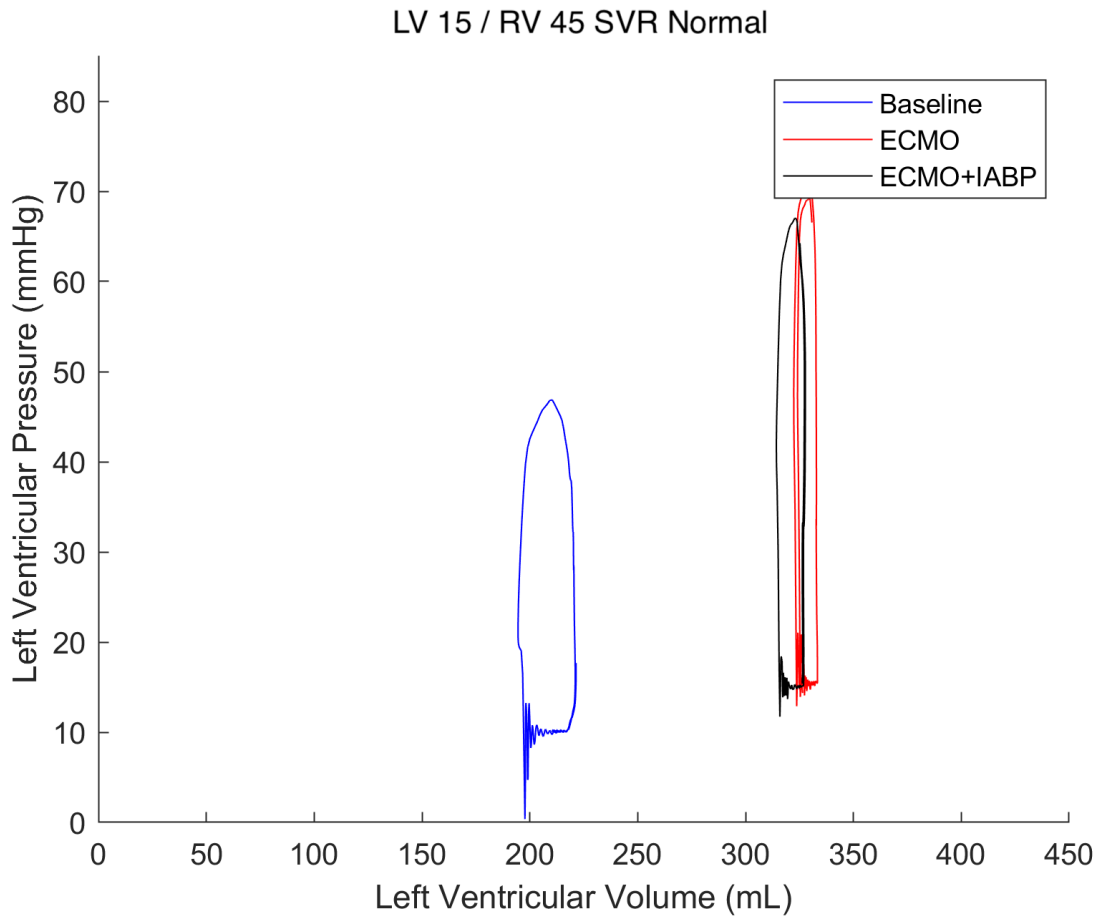
Cerebral flows

Cerebral perfusion was improved by up to 29ml/min (5.2%) with additive IABP in biventricular failure models, but this margin dropped as left ventricular function improved. A similar improvement was noted in isolated LV failure (25ml/min), and in biventricular standstill it improved once again by 13ml/min.

Systemic flows and pressures

MAP improved by 2-4mmHg in all models with the addition of an IABP. Total systemic flow improved by 10-50ml/min, whilst flow distal to the IABP was much the same.

	EF (%)	MAP (mmHg)	CorQ-ON (ml/min)	CorQ-OFF (ml/min)	CerQ (ml/min)	LVEDP (mmHg)	LAP (mmHg)	RVSP (mmHg)	RAP (mmHg)	LVEDV (ml)	Systemic flow (l/min)	Distal flow (l/min)
LV15RV45	8	35	79	138	223	11	12	13	9	219	1.44	1.14
ECMO	2	64	172	305	561	16	16	15	6	332	2.21	1.48
ECMO + IABP	3	68	166	325	590	16	16	15	6	328	2.23	1.48
LV30V45	19	54	138	229	467	8	8	13	10	144	1.93	1.32
ECMO	16	65	173	291	566	9	9	13	9	164	2.18	1.44
ECMO + IABP	19	69	162	307	591	8	8	13	10	154	2.19	1.44
LV45RV45	27	57	142	244	500	7	7	12	10	118	2.12	1.48
ECMO	24	65	167	286	564	7	7	13	10	127	2.24	1.51
ECMO + IABP	29	67	155	298	582	7	7	12	10	119	2.22	1.49
LV15RV100	6	41	124	185	321	18	18	21	6	344	1.59	1.14
ECMO	1	65	200	315	564	19	19	19	4	396	2.15	1.39
ECMO + IABP	2	68	197	332	589	19	19	18	5	392	2.20	1.42
LV0RV0	0	11	26	0	5	11	11	11	10	233	0.11	0.08
ECMO	0	65	47	290	563	13	13	8	9	278	2.10	1.49
ECMO + IABP	0	67	47	298	576	13	13	9	9	278	2.07	1.44


LV 15 / RV 45 SVR Normal
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ECMO
ECMO+IABP
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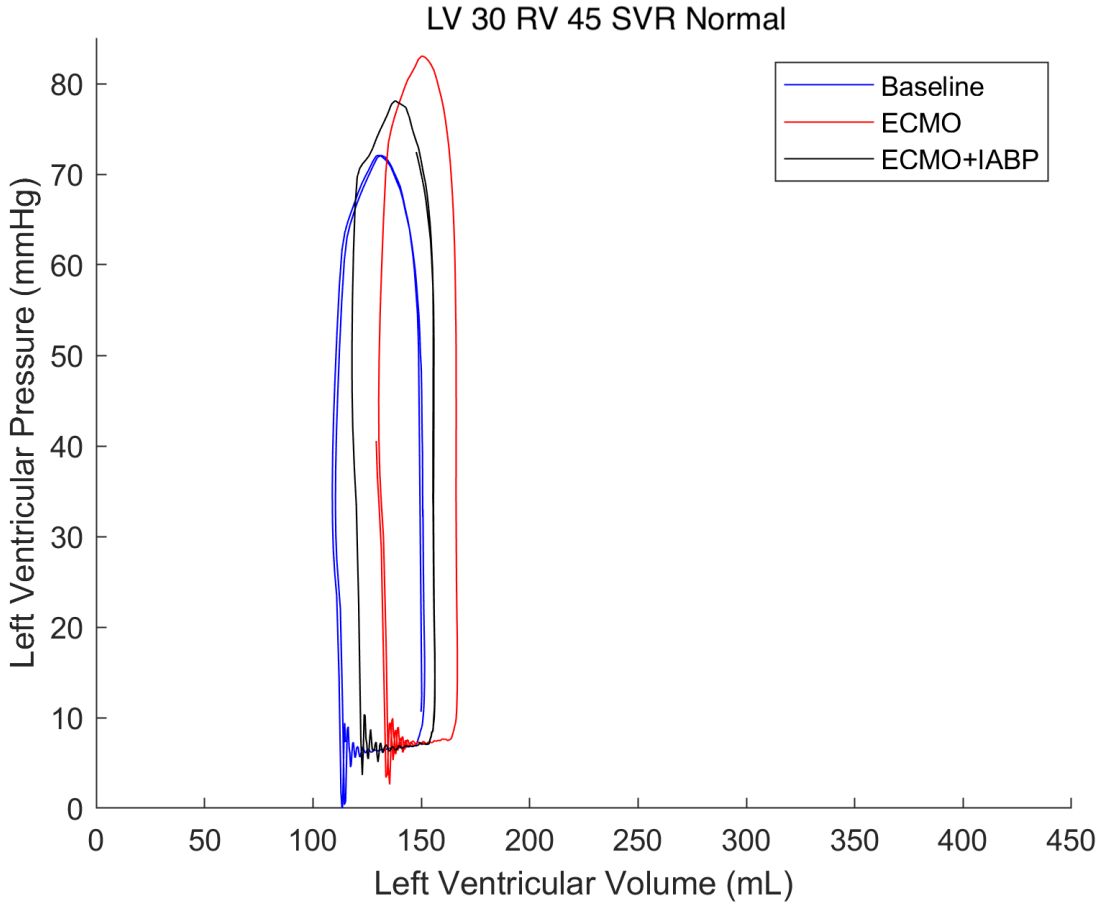
LV 30 RV 45 SVR Normal
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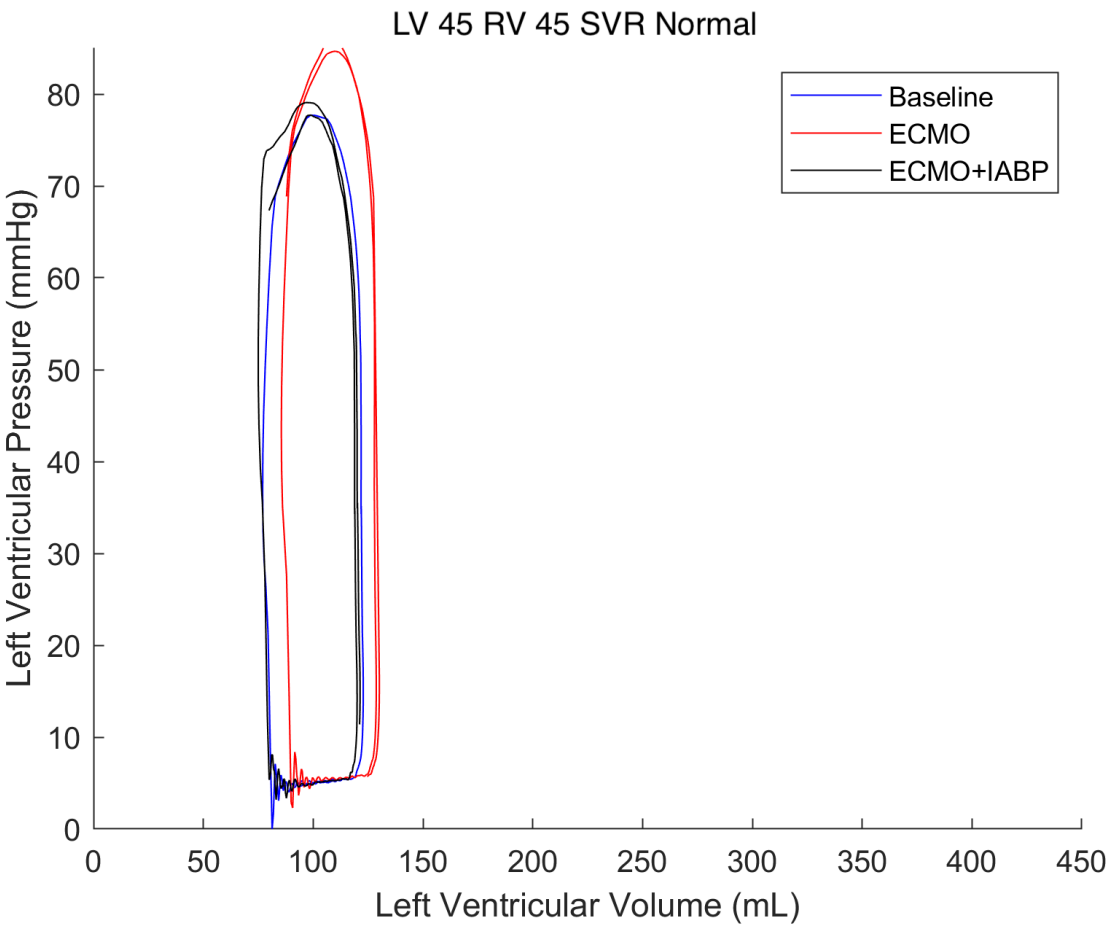
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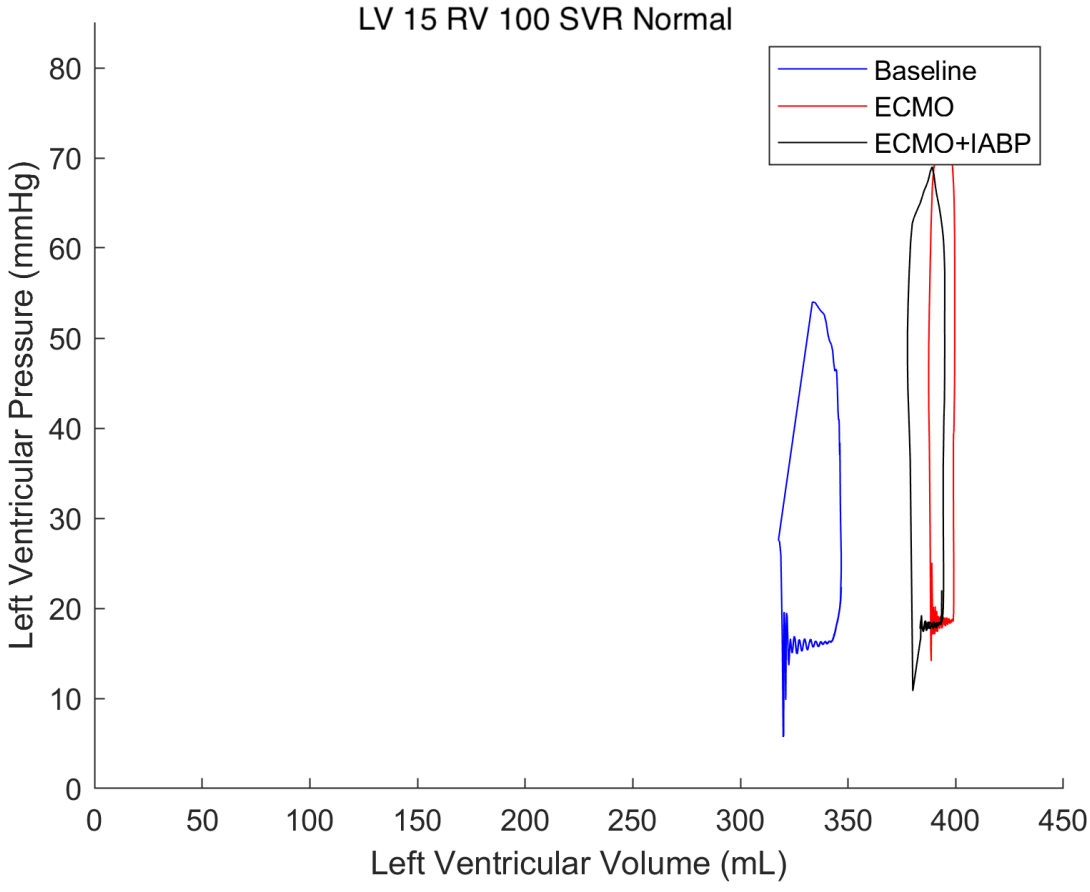
LV 15 RV 100 SVR Normal
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Discussion

VA-ECMO – most commonly configured femorally – is known to cause left ventricular dilatation, with the resultant distention potentially increasing risk of ischaemia and reduced myocardial recovery. In the poorly ejecting heart, this can be pronounced and the stasis can lead to LV thrombus formation. There is a variety of practices across centres, with some routinely employing IABP to vent the heart when on femoral VA-ECMO, whilst other centres avoid concomitant use altogether to avert peripheral vascular sequelae. So far, the evidence has been mixed with regards to survival, LV venting, and the flows to the coronary and cerebral circulations. Our study aimed to delineate whether addition of an IABP affected flows and pressures, to what degree, and how changes to haemodynamics impacted these end-points.

We demonstrated an overall improvement in LV venting with the addition of IABP. It was most pronounced with severe biventricular failure, and became less pronounced as left ventricular function improved. The reduction in LV strain is consistent with existing literature. Petroni et al reported in 2014 prospectively on 12 patients, where a pulmonary artery catheter and trans-thoracic echocardiography were utilised to determine effects of IABP for patients on femoral VA-ECMO for severe cardiogenic shock (65). They found that LV end-diastolic and end-systolic dimension (LVEDD, LVESD) were both significantly reduced with the addition of an IABP, as was pulmonary artery occlusion pressure. These results are consistent with successful LV venting with concomitant IABP/ECMO in the clinical setting. Although our MCL measured LV volumes and pressure rather than dimensions, the PV loops (figure 1-4, above) demonstrated a likely clinically significant reduction in LV distension. Additional to any literature currently available, we were able to demonstrate that this improvement varied with LV function, and thus can be rationalised to the severely impaired Left / biventricular failure.

Coronary flow was measured with an autoregulation model, with the intention to replicate normal physiologic responses to flows. Interestingly, with autoregulation on, the coronary flow was paradoxically reduced with the addition of an IABP. However, with the autoregulation model excluded, a significant increase in coronary flow was observed. We believe that with coronary autoregulation off, this replicates what is most likely the flow to be

delivered to the coronary ostia, as well as there being no suggestion of normal coronary physiology in such pathological states with retrograde ECMO flows. The maximal effect of coronary flow improvement was found with the addition of IABP in severe biventricular failure, with an increase of 7% (20ml/min). The least significant improvement in coronary flow was in biventricular standstill, with only 8ml/min increase with concomitant IABP (2.7%). These improvements once again correlate with existing literature. Madershahian et al assessed coronary venous bypass graft perfusion in 6 patients who were on ECMO and IABP for severe post-cardiotomy cardiogenic shock (61). They used a transit-time flow meter (TTFM) to determine venous graft flows and pulsatility index. Impressively, they found the IABP augmentation led to a 17% increase ($p < 0.001$) in graft flow, and no significant impact on the pulsatility index. Sauren et al reported on 7 sheep who were placed on ECMO and the effects of concomitant IABP were measured on coronary flow and LV afterload (60). Both coronary flow and diastolic pressure time index (DPTI) – a measure for diastolic coronary perfusion – were significantly improved with concomitant IABP. Importantly, the sheep in this study had normal cardiac function when placed on ECMO, as attempted simulations of heart failure were not sustainable with life long enough to examine. Belohlavek reported on 11 pigs in 2012 whom had cardiac arrest induced by VF for 15 minutes (62). They reported the opposite effect, with coronary blood flow reduced with concomitant IABP and femoral ECMO. One of the main hypotheses against the use of concomitant IABP with femoral ECMO is the concern of occlusion of the retrograde flows from the arterial return cannula during balloon inflation. These contradicting studies may demonstrate that the flows are most reduced with a non-ejecting heart (correlating with Belohlavek's study inducing VF), but potentially *augmenting* flow in the ejecting heart. Overall, our results demonstrate once again that early implementation of the IABP, or selection at least to severe biventricular impairment is a worthwhile endeavour, whilst in the non-ejecting or the recovering heart, the benefits may not be as pronounced.

Cerebral perfusion has been studied in various human and experimental models to determine if concomitant IABP has a beneficial impact. In our study, there was improvement in carotid flow across all simulations, but most profoundly in severe biventricular failure, with a 5.2% increase (29ml/min). The significance of this increased flow is difficult to ascertain. Yang et al reported on 12 patients with femoral VA-ECMO and measured the impact of IABP with trans-cranial doppler measuring flow in the middle cerebral artery. The mean cerebral flow was significantly improved by 17ml/min (6.9%) in patients who had pulsatility (>

10mmHg pulse pressure on ECMO), whilst those who were non-pulsatile (< 10mmHg pulse pressure) had significantly *reduced* cerebral flow (by 6.2%). A similar subset of patients studied by Petroni found no difference in cerebral saturations (via a near infra-red spectroscopy (NIRS) probe) with the addition of IABP. The clinical impact of these changes to flow are difficult to ascertain, but our study shows that additive IABP impacts cerebral perfusion most positively in low biventricular output states.

Clinical studies evaluating the impact of concomitant IABP and VA-ECMO on mortality have shown mixed results. A meta-analysis by Cheng et al (2015) reviewed 16 studies covering 1,517 patients (67). They found no survival benefit with the addition of IABP. Aso et al reported on a retrospective cohort study of 1,650 patients from a national database, and similarly evaluated concomitant IABP and VA-ECMO outcomes. Amongst 512 propensity-score matched pairs, they found an improvement in all-cause mortality with the use of IABP (58.2% vs 48.4%, $p = 0.001$), as well as a greater success of weaning off ECMO (82.6% vs 73.4%, $p < 0.001$). The contrast in results demonstrates that optimisation of concurrent IABP use may significantly improve outcomes, whilst inadequate selection of patients may confer no benefit and expose patients to unnecessary device-related risks. Our study aimed to demonstrate that the different cardiac failure states result in varied impacts from the IABP augmentation. We have shown that the greatest support provided by concomitant IABP use is for severe biventricular failure, whilst the non-ejecting heart and the recovering left ventricle have lesser impacts on LV venting and coronary and cerebral perfusion. With this in mind, more focused animal and human studies can evaluate the clinical implications of concurrent IABP use and delineate at what threshold of ventricular functions an IABP is best utilised.

Right Heart Failure in Left Ventricular Assist Devices

Introduction

Left ventricular assist devices (LVADs) are utilised in refractory end-stage heart failure. These devices are used as a bridge to transplant, destination therapy, and occasionally as a bridge to recovery (78). Right heart failure (RHF) is a frequent complication with significant mortality and morbidity (79).

Definition of RHF in LVAD Patients

Right ventricular failure (RVF) leads to poor filling of the left ventricle (LV), and thus insufficient flow to the left ventricular assist device. This subsequently leads to inadequate flow from the LVAD itself, and the patient will suffer from the sequelae of both right and left heart failure, culminating in end-organ malperfusion and central venous congestion.

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) defines right heart failure as signs and symptoms of persistent right ventricular dysfunction following LVAD insertion. This is stratified into mild, moderate, and severe according to inotrope therapy duration (≤7, 8-14, and >14 days, respectively) (80). However, this definition is limited to patients left unsupported mechanically post-procedure, and is retrospective in nature. In patients with severe RVF following LVAD insertion, it may indeed be fatal to leave them without definitive mechanical support.

Potapov et al developed a criteria for the diagnosis of right heart failure post LVAD insertion in 2009 (81). RHF is diagnosed by:

- Death
- Inability to wean from cardiopulmonary bypass CPB

OR any 2 of the following (sustained for 15 minutes after complete withdrawal of CPB):

- LV flow rate index ≤ 2.0l/min/m2
- Administration of ≥ 20 inotropic equivalents (IE)
- Mean arterial pressure (MAP) ≤ 55mmHg
- Central venous pressure (CVP) ≥ 16mmHg
- SvO2 ≤ 55%

Right heart failure signs in patients fitted with an LVAD reflect the physiologic sequelae expected. These include elevated right atrial pressures with a relatively low left atrial pressure, poor LVAD filling, and low systemic blood pressure. It is important to note that high left atrial pressures in conjunction with high right atrial pressure and low cardiac index may suggest LVAD inflow obstruction, which may be due to thrombosis of the inflow cannula, and should not be confused with RVF. This is often found in conjunction with increased LVAD power output. The physiological changes of RVF can all be determined by pulmonary artery catheter measurements. Echocardiographic findings will demonstrate poor right ventricular ejection, whilst also demonstrating whether the LVAD inflow is obstructed (82).

Decision of LVAD vs BiVAD

The indications for ventricular assist devices are not diagnosis-specific, and are rather determined by the degree of heart failure, responsiveness to medical therapy, and the intermediate- to long-term plan. Thus, patients are divided into:

- bridge to transplant (BTT)
- Bridge to decision (upon transplant) (BTD)
- Bridge to recovery (BTR)
- Destination therapy (DT)

INTERMACS lists profiles of patients receiving mechanical assist devices, from which outcomes of therapy are evaluated on a regular basis. The INTERMACS classes are listed below:

1) Critical cardiogenic shock
2) Progressive decline on inotrope support
3) Stable but inotrope dependent (in- or out-patient)
4) Resting HF symptoms (home on oral therapy)
5) Exertion intolerant
6) Exertion limited
7) Advanced NYHA class III symptoms

Biventricular assist devices (BiVADs) are utilised where an LVAD alone would be insufficient therapy due to the significance of the right heart failure. This configuration is simply a permanent right ventricular assist device (pRVAD) inserted in conjunction with an LVAD. However, this must be weighed against the significantly higher morbidity and mortality of BiVADs when compared with LVADs. In fact, Kirklin's review of the INTERMACS database published in 2008 found that BiVADs had twice the mortality rate of LVADs (81). Similarly, in the 7th INTERMACS annual report, it was

found that BiVAD recipients had a 50% survival at 12 months compared with 80% in LVADs (83). Although this may be a reflection of an overall more unwell pre-operative condition of the patient rather than the device itself, Cleveland found that BiVAD recipients had a significantly higher rate of infection, bleeding, and device failure than LVAD recipients (84).

Yet, a planned permanent RVAD has been proven to be of greater benefit than delayed placement of an RVAD in LVAD recipients. Fitzpatrick et al (2009) found that in a cohort of 99 LVAD recipients, planned RVADs had a superior survival to delayed RVADs, and a trend towards improved bridging to transplantation. However, the two groups had no significant pre-operative differences that would help differentiate them (85). This reiterates the difficulty in the choice of LVADs and BiVADs. The single device - LVAD alone - has better survival, less morbidity, and improved quality of life; yet a failure to implant the more complex device early - a planned BiVAD - has significant negative consequences.

Pathogenesis of Right Ventricular Failure in Setting of An LVAD

In patients with an LVAD, there are a multitude of haemodynamic and anatomical changes that occur which have potential to affect the right ventricle. In the pre-operatively impaired right ventricle, there is potential that these changes cause systemic cardiovascular compromise. These changes by the LVAD can be grouped into effect on right ventricular preload, afterload, and anatomical function (82, 86-88).

Preload

With the insertion of an LVAD in a previously failed heart, there is a sudden increase in the volume ejected into the systemic circulation. This is followed by an increase in venous return from the end-organs to the right atrium, and thus an increase in preload. Hence, the workload upon the right heart has increased rapidly between pre- and post-LVAD implant phases.

Afterload

In an otherwise normal pulmonary vascular system, the unloading of the left ventricle should subsequently unload the pulmonary vasculature. Hence, any pre-existing passive pulmonary hypertension secondary to left heart failure would be alleviated, and right ventricular afterload would decrease. However, in a pulmonary vasculature compromised by obstructive disease (atherosclerosis or emboli) this would have the opposite effect. The increase in preload to the right ventricle previously described would further elevate pulmonary pressures that are not unloaded by the LVAD, as the pulmonary hypertension is not secondary to left heart failure.

Anatomical and Functional Changes

Ventricular interdependence has been described by Santamore et al (1998) as *'the forces that are transmitted from one ventricle to the other through the myocardium and pericardium, independent of neural, humoral, or haemodynamic changes'* (89). This concept has been studied in animal and other laboratory experiments, concluding that reduction in left ventricular output led to 20-40% reduction in RV systolic pressure and output (90-92). The mechanism behind this is believed to be related to the orientation of muscle fibres in the right ventricle (non-concentric), and the assistance the septum provides - essentially as an anchor - against which it contracts.

Interventricular septal deviation to the left occurs with LVAD placement (Figures 1 and 2). This is due to the volume being unloaded by the device and displaced directly into the ascending aorta via the conduit. This has been shown in various studies utilising ultrasonic crystals and echocardiography (82). Although this shift may lead to better compliance, it also impacts the contractility of the right ventricle. The unnatural leftward bending of the septum has consequent pathologic compression of myocardial fibres on the RV side of the septum (93). Hence, an LVAD will subsequently have a detrimental effect on right ventricular ejection.

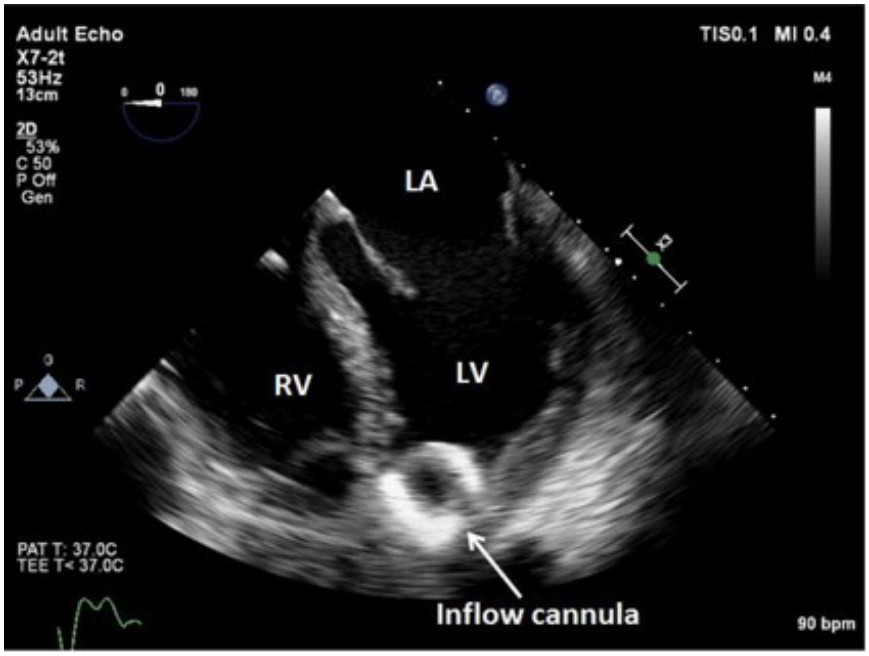


Figure 1 Trans-esophageal echocardiography showing movement of interventricular septum to the left with inflow cannula of LVAD in situ (94).

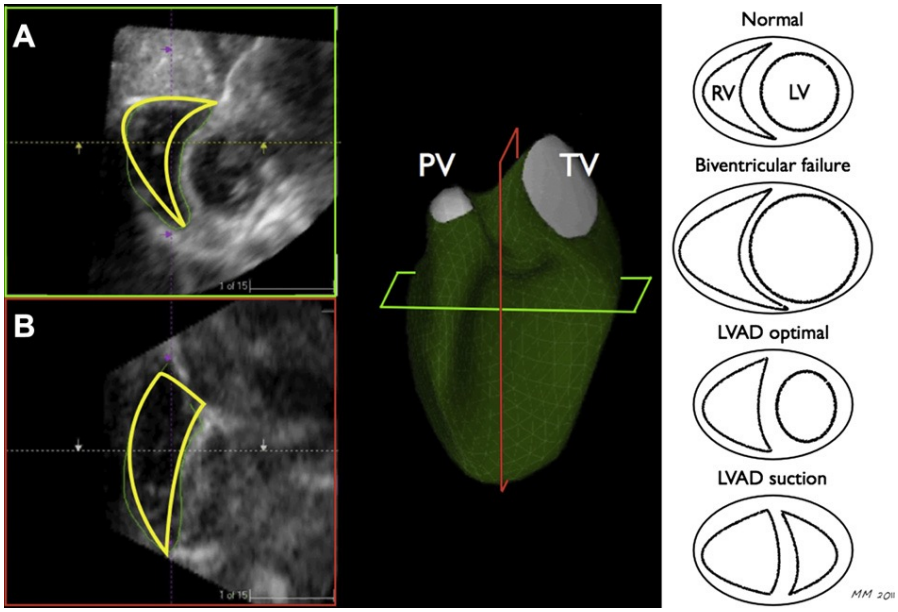


Figure 2 Midpapillary (A) and long axis (B) biventricular imaging demonstrating optimal shape of RV in the LVAD patient (95).

In summary, in patients with an LVAD, unloading of the left ventricle alters the size and shape of the right ventricle (in particular the interventricular septum) as well as affecting the haemodynamic flow before and after the RV. Hence, an increase in workload and distortion of anatomy and functionality of the right ventricle is thought to be a major contributor in unexpected RV failure with LVAD implantation (82, 86-88). Certain pre-operative characteristics of right ventricular dysfunction may provide clues as to which patients cannot compensate for these changes.

Incidence and Aetiology of RHF in LVAD Population

Although infrequent in all cardiac surgical procedures with an incidence of 0.04-0.1%, acute refractory right ventricular failure occurs in 20-50% of LVAD insertions (92, 96, 97). This complication is becoming increasingly more frequent with more marginal candidates having LVADs implanted, and the device being utilised more frequently (98).

The aetiology of the RHF is likely a combination of:

1) The original insult to the left ventricle
2) The acute or chronic increase in afterload contributed by the left heart failing, and
3) The mechanical effects described above, once the LVAD is inserted

Outcomes of RHF in LVADs

RHF post-LVAD has a significant post-operative mortality. Dang et al reported a more than 3 fold early mortality (≤30 days) in LVAD patients who were complicated with RHF than those who were not (19% vs 6.2%; p = 0.037) (79). Kormos et al (2010) also reported that survival to transplant was significantly lower in patients suffering RHF post LVAD insertion) (78). Survival to transplant, recovery, or ongoing device support at 180 days was 71% in those with RHF, compared with 89% in those without (p < 0.001) (78). Similarly, there is a known increase in overall morbidity. Delayed rehabilitation, increased transfusion requirements, and delayed or failed restoration of end-organ function have been associated with RVF post-LVAD insertion (99).

Predictors of RHF

Independent assessments of right heart function, such as RV ejection fraction, CVP, and TAPSE are not alone adequate to distinguish right heart failure (98, 99). As preload is reduced with left heart failure, right ventricular dysfunction can be masked, and is often more obvious once the LVAD is inserted. The LVAD insertion also significantly impacts upon ventricular interdependence as described previously, exacerbating an impaired right ventricle.

Several features have been identified as risk factors for right heart failure post-LVAD insertion including end-organ dysfunction, non-ischaemic cardiomyopathy, and severe TR (95). More complex scoring systems have been developed and analysed to predict right ventricular failure following LVAD implantation. These scoring systems were developed in retrospective cohort studies utilising logistic regression scoring of blood, echocardiographic, and right heart catheter results. Some of the more common scoring systems will be discussed below (99-102).

Matthews' Score

Published in 2008, Matthews et al used multivariate logistic regression on a sample of 197 patients whom underwent LVAD implantation (99).

RHF was defined as the post-operative need for:

1) Intravenous inotrope therapy > 14 days,
2) Inhaled nitric oxide ≥ 48 hours,
3) Right-sided circulatory support (ECMO or RVAD), or
4) Hospital discharge with an intravenous inotrope

68 patients suffered right heart failure, and the pre-operative findings were analysed to determine significant risk factors. A vasopressor requirement, elevated ALT, bilirubin and creatinine were all independent predictors of RHF. Furthermore, a scoring system was formulated to determine an

odds-ratio for RV failure. Below is the scoring allocation as well as the scoring system (Table 1 and Table 2).

Table 1 Scoring allocation.

Predictor	p-value	Points
Vasopressor requirement	<0.005	4
Aspartate Aminotransaminase (AST) ≥ 80 IU/l	0.001	2
Bilirubin ≥ 2.0mg/dl	<0.005	2.5
Creatinine ≥ 2.3mg/dl	<0.005	3

Table 2 RVF risk (Matthews') score.

Score	OR	95% CI	180 day survival	p-value
≤3	0.49	0.37-0.64	90±3%	0.0045
4-5	2.8	1.4-5.9	80±8%	
≥5.5	7.6	3.4-17.1	66±9%	

Fitzpatrick's Score

Fitzpatrick et al (2008) reviewed 266 patients whom underwent LVAD implantation at the University of Pennsylvania from 1995-2007 (100). Multivariate logistic regression identified that the most significant predictors for RVAD were:

- Low cardiac index (CI) (≤ 2.2l/min/m2)
- Low RV stroke work index (RVSWI) (≤ 0.25mmHg/l/m2)
- Severe pre-op RV dysfunction
- High Pre-operative creatinine (≥1.9mg/dl)
- Previous cardiac surgery
- Low systolic blood pressure (SBP)(≤96mmHg)

If a patient fulfilled one of the above criteria, it was assigned a 1; and if they did not meet a criterion, it was assigned a 0 in the following equation:

18x(CI) + 18x(RVSWI) + 17x(creatinine) + 16x(previous cardiac surgery) + 16x(severe RV dysfunction) + 13x(SBP)

Thus, the maximum number a patient could acquire was 98 and minimum was 0. A threshold of 50 points was utilised by this study; delineating:

- < 50 predictive of successful LVAD
- ≥ 50 predictive of need for BiVAD

Based upon the above, the sensitivity and specificity of these scores was 83% and 80%, respectively. 96% of patients that scored < 30 underwent successful LVADs, whilst 89% of patients scoring ≥ 65 required BiVADs.

Atluri's (CRITT) Score

Atluri et al (2013) developed a scoring system to predict right ventricular failure following insertion of continuous flow LVADs (102). They evaluated 218 patients operated on in their centre between 2003-2011, with the intent of identifying independent risk factors of right heart failure, and to develop a tool to predict this outcome pre-operatively. They used univariate analysis and multivariable logistic regression, and identified the following:

A score of 2 or more provided a sensitivity of 84%, specificity of 63%, and negative predictive value of 93%. That is, a score less than 2 predicted successful isolated LVAD therapy in 93%.

The above scoring systems have some limitations. Cardiac index and RVSWI require invasive tests such as a right heart catheter - not readily performed in the acutely unwell patient. Furthermore, a patient on ECMO may not project accurate right ventricular and tricuspid function on echocardiography (Table 3).

Table 3 Atluri's (CRITT) score.

Predictor (pre-op)	OR	95% CI	p-value
CVP > 15mmHg	2.0	0.9-4.2	0.089
Severe RV dysfunction	3.7	1.7-8.1	0.001
Pre-operative Intubation	4.3	1.9-9.6	<0.001
Severe tricuspid regurgitation (TR)	4.1	1.4-12.4	0.011

Predictor (pre-op)	OR	95% CI	p-value
Tachycardia (>100bpm)	2.0	0.9-4.3	0.086

These scoring systems have been shown in their publications to be highly sensitive, yet not all are particularly specific and thus it can be difficult to justify the expense, morbidity and mortality associated with a second VAD. None of them have been validated in prospective studies. Finally, these scoring systems do not determine which patients will be sufficiently managed with a temporary device compared with permanent support. The sensitivies and specificities of each scoring system are outlined in Table 4.

Table 4 Comparison of scoring systems.

SCORING SYSTEM	SENSITIVITY	SPECIFICITY
Matthews, 2008 [22]	35%	-
Fitzpatrick, 2008 [24]	83%	80%
Atluri, 2013 [26]	84%	63%

Management

Prevention

The management of RHF following LVAD insertion can begin pre-operatively, with the intent of prevention. Pre-operative management is aimed at reducing large volume shifts, particularly with the use of blood products which may cause volume strain. Monitoring of right ventricular function pre-operatively is suggested in those who are deemed high risk (95). A pulmonary artery catheter can provide accurate assessment of RV function and pulmonary vascular resistance (PVR) and allow titration of inotropes and pulmonary vascular dilators. Dobutamine and milrinone are agents commonly used for right heart optimization. These inodilator agents are often used in conjunction with other pulmonary vascular dilators such as iloprost and inhaled nitric oxide (NO). Norepinephrine is also a useful adjunct to maintain perfusion pressure to the right coronary artery, as well as end organs. Aggressive diuresis assists in lowering central venous pressure, reducing end organ venous hypertension, reducing right ventricular strain and normalizing right ventricular geometry.

A large double blinded, randomised control trial encompassing centres in Germany and the US investigated whether inhaled nitric oxide (NO) was of benefit in the LVAD population (81). Unfortunately, it did not prevent RV failure post-operatively, despite decreasing mean pulmonary artery pressures (mPAP) and increasing LVAD flows. Several small studies have evaluated the use of milrinone, inhaled nitric oxide, and phosphodiesterase inhibitors in optimizing right heart function

(103, 104). Although these studies demonstrate reduction in pulmonary artery pressures and improved RV echocardiography findings, they are small sample sizes and do not exclusively evaluate use of these agents in the pre-operative period.

Peri-Operative Management

Good peri-operative technique with the intent of reducing unnecessary blood loss, reducing CPB time, and good myocardial protection are all vital in protecting against post-operative RVF. Maintaining perfusion pressure peri-operatively, avoiding air embolism down the right coronary artery, and not expecting the right heart to deliver high flows immediately are useful protective strategies. Several publications have reported the outcome of concomitant tricuspid valve surgery (TVS) for severe TR at the time of LVAD implantation. Tricuspid regurgitation (TR) is often secondary to RV and TV annular dilatation in LVAD recipients, reflective of the chronicity of their heart failure. Furthermore, the geometric changes to the septum by the LVAD are thought to contribute to worsened TR (105). Significant TR has been found to be associated with right heart failure following LVAD implantation (106). Hence, the reasoning for TV repair or replacement to prevent post-LVAD RVF has been reported in several publications. A systematic review and meta-analysis on concomitant TVS by Dunlay et al was published in 2015 (107). They reviewed 6 papers comparing the outcomes of LVAD+TVS versus LVAD alone. No paper found any difference in mortality. Additionally, pooled analysis found no difference in need for RVAD, whether concomitant TVS was performed or not. A subset analysis evaluated the 3 publications which selected patients with moderate and severe TR only, and no difference in need for RVAD post-operatively was re-affirmed. Although a link exists between significant TR and post-operative RVF in LVAD recipients, tricuspid valve surgery may not be enough to prevent the need for mechanical right-sided support.

Post-Operative Management

Inotrope therapy is most commonly used for post-LVAD RHF, and success of this will be determined by end-organ function and LVAD flows. If these are compromised, and echocardiographic findings confirm RV failure with the aforementioned consequences, mechanical therapy needs to be instituted. Chemical therapies proven to be of benefit in RHF include:

- Inhaled Nitric Oxide (see above)
- Dobutamine - increases cardiac index and stroke volume, whilst maintaining preload
- Dopamine - of benefit in hypotensive patients
- Milrinone - agent of choice if tachyarrhythmic patient

Phosphodiesterase inhibitors including milrinone and iloprost have been shown to improve right heart function in the peri-operative period. Hamdan et al reported on the use of sildenafil in 8 of 16 patients with RVF and pulmonary hypertension receiving LVADs. Patients also received nitric oxide. This small population was shown to have significantly improved PVR, pulmonary artery pressure, trans-pulmonary gradient (TPG), cardiac index, and other measurements of right heart function (104).

Once again, the use of multi-modal therapy with careful monitoring is likely to be most beneficial.

Pulmonary artery balloon pumps have been utilised for short periods of time, although with limited success (81). The main mechanical options are a temporary right ventricular assist device (tRVAD) and permanent RVAD. It is important to note that there is no specific mechanical right ventricular device - all permanent RVADs utilised are off-label use of devices designed as LVADs.

Temporary RVAD (tRVAD)

Various tRVADs exist on the market currently, or are used as such.

CENTRIMAG™

LoForte et al describes the use of a CentriMag™ device as a temporary right ventricular device (108), whilst Aissaoui reports on both Thoratec PVAD and CentriMag™ at different times for temporary right ventricular support (109). The CentriMag™ is a magnetically levitated radial pump, and is utilised as a temporary device for either left or right ventricular support. It has been approved for use up to 30 days in either position. In its form as a tRVAD, the inflow cannula lies in the right atrium, whilst the outflow cannula is in the main pulmonary artery (110).

IMPELLA™

The Impella RP™ device has recently been described for use as a temporary RVAD by Anderson et al (2015) in the prospective RECOVER RIGHT study (111). The Impella RP™ is a 22Fr catheter-based percutaneous micro-axial pump mounted on an 11Fr catheter. The catheter is advanced via the femoral vein into the pulmonary artery, with the pump traversing the tricuspid and pulmonary valves. The pump's inflow is positioned in the IVC and the outflow in the PA, able to expel blood up to 4l/min. Its intended use is up to 14 days. In the 2015 non-randomised trial, 30 patients were recruited and divided into 2 cohorts: patients suffering RHF post LVAD insertion (n = 18; cohort A) and patients who had RHF post-cardiotomy or post myocardial infarction (n = 12, cohort B). Anderson reported a 70% survival to discharge of both cohorts combined, and although not statistically significant, a higher survival to discharge in cohort A (77.8% vs 53.8% in cohort B). In 2018, Anderson reported on sixty patients in a prospective study dividing patients into the same two cohorts as the 2015 study (111). Cohort A (RVF post-LVAD) had 31 patients, and Cohort B (post-

cardiotomy RVF and post myocardial infarction RVF) had 29 patients. Once again, survival to discharge or at 30 days (whichever was longer) was 77.4% in Cohort A, and 73.3% overall. In short, the Impella RP is a novel method for right heart support and appears to be a useful support strategy for LVAD patients with post implant RHF.

TANDEMHEART™

The TandemHeart is a ventricular assist device that has been proposed for use in left heart failure. However its use has been proposed by Schmack et al (2016) as a right ventricular assist device in conjunction with an LVAD (112). They proposed that the cannula is placed via the right internal jugular vein via a Seldinger technique over a previously inserted Swann-Ganz catheter. The outer cannula (29Fr) is positioned in the RA (under TOE guidance) and the inner cannula (16Fr) in the pulmonary trunk. There are no clinical reports of this device's use as a temporary RVAD as yet.

CENTRIFUGAL PUMP AS AN RVAD

An alternative temporary support consists of a modified ECMO circuit, with the oxygenator removed. Temporary RVAD support is provided by a Biomedicus centrifugal pump (Figure 3). A 21 French inflow cannula is inserted via the femoral vein, with the tip of the cannula in the proximal IVC or right atrium. The return cannula is via an 8mm Dacron graft sewn end-to-side to the main pulmonary artery. This is tunnelled from the thorax to exit the anterior abdominal wall (113).

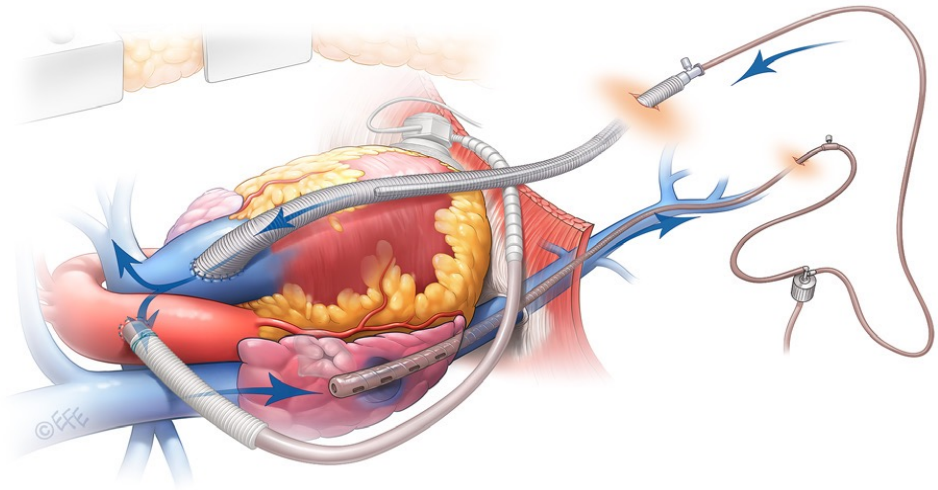


Figure 3 Centrifugal pump as an RVAD Saxena, 2015 (114)

Weaning of the tRVAD is performed in the intensive care unit, where LVAD flows and haemodynamic and echocardiographic parameters were monitored. A patient is deemed suitable for decannulation if weaning studies are successful, then placed back on full flow until decannulation. Decannulation can be performed in either the ICU or operating room depending on whether return to the operating room is necessary for other reasons, such as evacuation of mediastinal clot. The access femoral cannula is removed and manual pressure applied. The return line is decommissioned by removing

the 21Fr cannula, withdrawing the Dacron graft sufficiently to expose a sterile portion, clamping, dividing and oversewing the graft and letting it retract back into the chest (113, 114) (Figure 4).

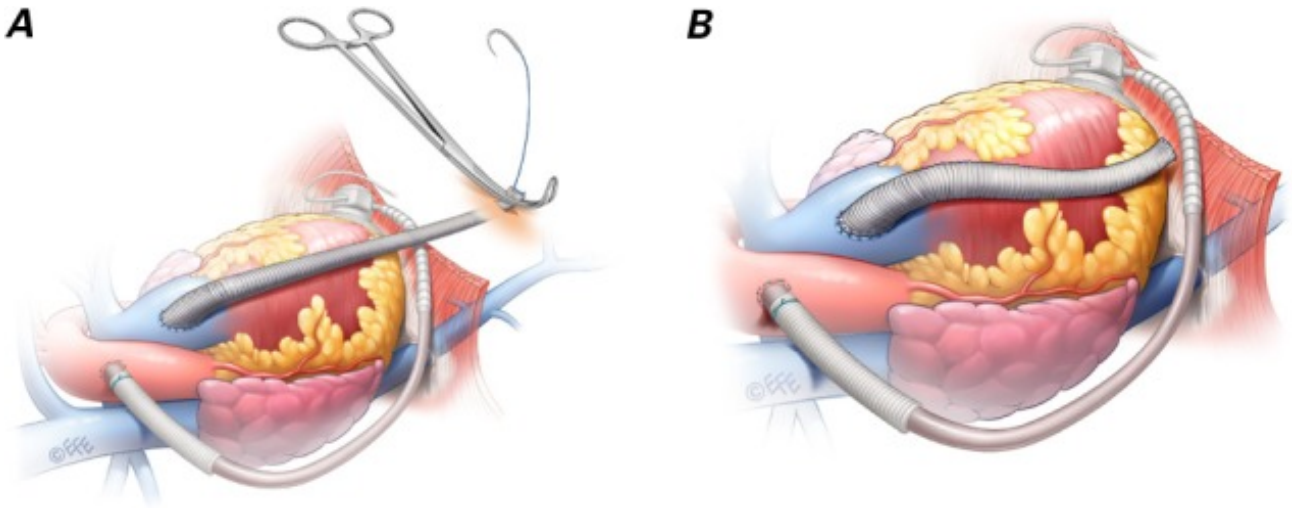


Figure 4 Centrifugal pump as an RVAD. Saxena, 2015 (114).

8.5 Permanent RVAD

An alternative to temporary RV support with an LVAD, is the insertion of a permanent RVAD. In this case, a patient would be discharged with a BiVAD (two permanent devices) as opposed to an LVAD, alone. As mentioned previously, early permanent RVAD insertion has been shown to have lesser mortality, morbidity, and successful bridging to transplant than if implanted secondarily - i.e. following failure of temporary support.

Comparisons of Temporary and Permanent RVADs

Clear guidelines as to the institution of tRVAD or pRVAD at the time of LVAD insertion are lacking, and thus the decision making is inconsistent across centres and surgeons. Temporary RVAD is preferred as a single device on discharge has lesser morbidity and mortality (81), whilst the cost of biventricular permanent devices is significant. Yet readmissions for heart failure and complication rates suggest that this cost-saving decision may be flawed. Similarly, a tRVAD may not in fact have a lower mortality and morbidity compared with a pRVAD (108, 115), and a planned insertion of a pRVAD has superior survival and reduced morbidity than an unplanned insertion (85).

Loforte et al reported in 2013 on 77 patients whom received an LVAD in combination with a right ventricular device (108). They divided their groups as follows:

- A1: temporary RVAD implemented primarily (ie concurrently with the LVAD)
- A2: temporary RVAD implemented secondarily (Delayed up to 48 hours post LVAD insertion)
- B: BIVAD or total artificial heart (TAH)

The patients were all deemed to have a high risk of RV failure post LVAD insertion according to 3 different scoring systems: the Matthews', Fitzpatrick's, and Berlin scores. Furthermore, there was no significant difference in the scores between those whom received temporary or permanent RV devices. The only significant difference between group A and B was the presence of an IABP (76% vs 55%, respectively; p = 0.05), whilst all other demographic and pre-operative data were similar.
Interestingly, the stratification of patients for BiVAD or tempRVAD/LVAD was determined by the patients. All 46 patients in group A were worked up and planned for BiVADs, but were given the option of temporary RVAD support when they refused. Hence, patient preference distinguished which device was utilised.

Loforte found that survival to discharge was the same across the two major groups (56.5% vs 54.8%; p = 0.56). Similarly, 90 day and 6 month survival were no different. In fact, the most distinct findings in the study were between planned and unplanned temporary RV support (group A1 vs A2). Survival to discharge was better in the planned group (A1 57.1%, A2 45.4%; p = 0.04). A higher number of patients died whilst on support when tRVADs were delayed (A1 20%, A2 45.4%; p = 0.04), and were less likely to be weaned from their RV support device (A1 71.4%, A2 45.4%; p = 0.02).
Aissaoui et al performed a retrospective study on 173 patients from 2000-2011 whom received LVADs with a right ventricular device (115). Amongst this group, 84 received BIVADs and 87 had LVAD with therapy for RV failure. Of these, 57 had LVAD combined with tRVAD, and 32 had LVAD with medical therapy for RHF. RV failure was defined as the need for a temporary RVAD, or inotropic therapy for more than 14 days post-LVAD insertion. The only differences across the groups were that BiVAD patients were younger than those who received medical therapy or temporary RVADs (50 vs 54yo; p = 0.011), as well as having a higher pre-operative CVP (15.8 vs 11.1mmHg; p = 0.005).

Mortality was seen to be significantly higher in the BiVAD group within 48 hours of surgery (8% vs 0%; p = 0.005). However, as with Loforte's findings, 6 month survival was no different between the BiVAD and non-BiVAD groups (52% vs 43%; p = 0.71). Importantly, survival to discharge was not reported.

Other differences were readmission for device related infections (26% BiVAD; 15% LVAD with RVF) and overall neurological complications (BiVAD 37%, LVAD with RVF 20%; p = 0.002).
Finally, readmissions for heart failure were significantly lower in the BiVAD group compared to the LVAD with RVF group (1% vs 11%; p = 0.02). Yet it is important to make note of how these groups were analysed. In this study, the grouping of LVAD with RVF was:

- LVAD + tempRVAD, or

- LVAD + medical therapy only

Unfortunately, there was no direct comparison of temporary and permanent RVADs in this case, with medical therapy grouped along with the temporary devices when comparing outcomes.
The current literature does not outline which patients would benefit from temporary over permanent RV mechanical support, and how to differentiate them. This is an area of ongoing research, and clear guidelines are lacking.

Right Heart Failure and Cardiac Transplantation

Right heart failure has been recognised as an independent risk factor of poor outcome pre- and post-heart transplantation.
The presence of an RVAD in conjunction with an LVAD has been found to be a risk factor for reduced survival to transplantation. Ochiai et al reported in 2002 on 245 LVAD-recipients (116). 9% of the cohort necessitated a permanent RVAD, although no comment was made upon RVF post-LVAD insertion that did not require a permanent RVAD. Nevertheless, survival to transplant was significantly less in patients who had a RVAD (17% vs 74%, $p < 0.001$).
Baumwol reported in 2011 on 40 LVAD recipients and their survival to transplant (117). They noted that survival to transplant was significantly impacted by LVAD recipients complicated by post-operative right heart failure 54.5% vs 90.9% ($p = 0.027$). Of the 13 patients who had post-LVAD RVF, only 3 received mechanical support in the form of a temporary RVAD. No comment was made on whether patients had a permanent RVAD inserted thereafter.
Ravis et al retrospectively analysed 221 patients in their centre on the waiting list for heart transplantation (118). Initially categorised HE1 (highly-emergent category 1) - patients transpanted within 8 days of listing) patients were excluded in order to identify patients on a waiting list. This study reported that 47 candidates died whilst still on the waiting list (21.3%). Multivariate analysis determined that the only independent risk factors associated with waiting-list mortality was an LVEF<30% (HR 3.76, 95%CI 1.38-10.24; $p = 0.01$) and severe right ventricular failure (HR 2.89, 95%CI 1.41-5.92; $p = 0.004$). Once again, severe RVF (pre-operatively) was identified as an independent risk factor for post-transplant mortality on multivariate analysis (HR 5.38, 95%CI 1.38-10.24; $p = 0.02$). Importantly, only 19 patients had an LVAD pre-transplant (8.6%).
The literature clearly demonstrates that the need for a permanent RVAD and/or the presence of RV failure significantly impairs survival to transplant and even post-transplant outcomes. More data needs to be gathered to identify whether permanent or a temporary device will impact survival differently.

Summary

Right ventricular failure is a common complication, to some degree, following LVAD insertion and is a major cause of morbidity and mortality. It has also been found to reduce survival to transplant. The pathophysiology is complex, and, as such, the indication for a concomitant RVAD is not always clear. Several scoring systems exist that aim to predict RVF in hope of preventing the poor outcomes of a late RVAD insertion. These have yet to be validated in prospective cohort studies. Furthermore, they often require comprehensive assessment utilising right heart catheterisation and echocardiography – not always possible or accurate in the acutely unwell patient on ECMO. The role of temporary RVADs has been utilised more frequently in its various forms in more recent times. Its use has been driven by the desire to reduce morbidity and improve survival to transplant by avoiding biventricular devices. Although survival in the short-term has been comparable between permanent or temporary RVADs (amongst LVAD-recipients), overall morbidity and survival to transplant has not yet been shown to be advantageous. Further research needs to be performed to assist in guidelines to clarify guidelines for temporary versus permanent mechanical support in the LVAD-recipient.

Comparison of Outcomes Between Temporary and Permanent Right Ventricular Assist Devices Following LVAD Implantation

INTRODUCTION

Right heart failure (RHF) affects 20-30% of left ventricular assist device (LVAD) recipients (79), and is a major cause of morbidity and mortality (88, 119).

The aetiology of RHF has been ascribed in part to the unloading effect of the LVAD, which alters the size and shape of the right ventricle (in particular the interventricular septum). The LVAD similarly impacts upon right heart preload and afterload, whilst the underlying cardiomyopathy may also contribute to right heart failure. Hence, an increase in workload and distortion of anatomy and functionality of the right ventricle is thought to be a major contributor in unexpected RHF post LVAD implantation (86, 88).

Several scoring systems are available to help identify patients at risk of RHF following LVAD insertion, including the CRITT score and Michigan score (99-102). A high risk according to any one of these scoring systems may indicate the need for mechanical right heart support. However, identifying whether a temporary or permanent RV assist device (tRVAD or pRVAD, respectively) is the best modality is yet to be determined.

Clear guidelines as to the institution of tRVAD or pRVAD at the time of LVAD insertion are lacking, and thus the decision making is inconsistent across centres and surgeons. Temporary RVAD is preferred as a single device on discharge has lesser morbidity and mortality (81), whilst the cost of biventricular permanent devices is significant. Yet readmissions for heart failure and complication rates suggest that this cost-saving decision may be flawed. Similarly, a tRVAD may not in fact have a lower mortality and morbidity compared with a pRVAD (108, 115), and a planned insertion of a pRVAD has superior survival and reduced morbidity than an unplanned insertion (85).

We hypothesized that the benefits of tRVADs may be overestimated, and insertion of a planned pRVAD may have better survival, reduced morbidity, and reduced re-admission rates. Thus, the aim of this study was to compare outcomes in LVAD patients who had tRVAD versus pRVAD insertion.

METHODS

Retrospective analysis was performed on 116 consecutive patients undergoing LVAD insertion at The Alfred Hospital between 2011 to 2018. Of these 116 patients, 32 received some form of right ventricular mechanical support, in the form of either a temporary or permanent right ventricular device (tRVAD or pRVAD, respectively) and these patients form the cohort analysed for this study. 22 patients received temporary RVAD support and 10 patients received a permanent RVAD at the time of LVAD implantation.

Pre-operative and intra-operative assessments were utilised to determine whether a temporary or permanent RVAD was to be implanted. This was based upon echocardiographic, angiographic, hemodynamic and clinical findings (119).

Heartware (HeartWare Inc, Framingham, MA, USA), HeartMate II (Thoratec, Pleasanton, CA, USA) and HeartMate III (Thoratec, Pleasanton, CA, USA) left ventricular assist devices were implanted. Permanent right ventricular assist devices were either Heartware HVAD or HeartMate III and all were inserted into the right atrium as previously described (120, 121).

Temporary RVAD support was provided by a Biomedicus centrifugal pump. A 21 French inflow cannula was inserted via the femoral vein, with the tip of the cannula in the proximal IVC or right atrium. The return cannula was via an 8mm Dacron graft sewn end-to-side to the main pulmonary artery. This was tunnelled from the thorax to exit the anterior abdominal wall (113).

Weaning of the tRVAD was performed in the intensive care unit, where LVAD flows and haemodynamic and echocardiographic parameters were monitored. A patient was deemed suitable for decannulation if weaning studies were successful, then placed back on full flow until decannulation. Decannulation was performed in either the ICU or operating room depending on whether return to the OR was necessary for other reasons, such as evacuation of mediastinal clot. The access femoral cannula was removed and manual pressure applied. The return line was decommissioned by removing the 21Fr cannula, withdrawing the Dacron graft sufficiently to expose a sterile portion, clamping, dividing and oversewing the graft and letting it retract back into the chest (113, 114).

Data was collected retrospectively from the institution's electronic medical records and ventricular assist database, and the Australia and New Zealand Society of CardioThoracic Surgeons (ANZSCTS) database. Institutional ethics and ANZSCTS approval were given (approval ID 175/18). Census date of last review was 22nd August 2018.

RESULTS

Patient demographics and pre-operative findings are recorded in table 1. Patients were well matched in terms of preoperative characteristics although RVF severity based on echocardiographic parameters was worse in the pRVAD group. The incidence of pulmonary hypertension was higher in the tRVAD group, as was pulmonary vascular resistance, based on right heart catheterization data (Table 2).

Of the 116 consecutive LVAD patients, 32 (28.4%) required either temporary or permanent RVAD (tRVAD or pRVAD, respectively). Outcomes were analysed according to the primary device implanted – either a temporary or permanent RVAD. Of the 22 patients who received a temporary device primarily, 9 were not able to be weaned. Four died, and 5 (22.7%) were converted to a permanent device. Five (50%) of the pRVAD and 8 (36.4%) of the tRVAD patients were bridged from ECMO to LVAD implant (p = 0.47).

Table 1: Demographics and Pre-Operative Characteristics

Variable	pRVAD (n = 10)	tRVAD (n = 22)	p-value
Age (mean±SD)	41.5 ±13.1	45.5 ±15.4	0.49
Male (n)	77.3% (17)	90% (9)	0.39
Aetiology - **IDCM** - **Ischaemic** - **Other***	 50% (5) 10% (1) 40% (4)	 54.5% (12) 18.2% (4) 27.2% (6)	0.95
Intended Treatment - **BTT** - **BTD** - **BTR** - **Destination**	 70% (7) 20% (2) 10% (1) 0% (0)	 68.2% (15) 22.7% (5) 4.5% (1) 4.5% (1)	0.94
LVEF%	14.8± 6.91	15.4 ±6.16	0.81
Bridged from ECMO	50% (5)	36.4% (8)	0.47

Table 1: Demographics and Pre-Operative Characteristics

Variable	pRVAD (n = 10)	tRVAD (n = 22)	p-value
RV failure severity - **None** - **Mild** - **Moderate** - **Mod-severe** - **Severe**	 10% (1) 0% (0) 0% (0) 20% (2) 70% (7)	 0% (0) 18.2% (4) 31.8% (7) 27.3% (6) 22.7% (5)	**0.022**
RV Base (mm)	51.6 ±13.6	47 ±10.7	0.41
TR	100% (10)	77.3% (17)	0.12
MR	80% (8)	95.5% (21)	0.13
RVSP (mmHg)	42.6 ±13	49.2 ±15.8	0.34
TAPSE (cm)	1.15 ±0.33	1.5 ±0.487	0.08
TRV (cm/s)	2.5 ±0.698	2.16 ±1.07	0.57
Pulmonary Hypertension	71.4% (5)	100% (13)	**0.042**
ALT (U/l)	50 [30-71]	30 [19-66]	0.25
Billirubin (μmol/l)	23.5 [18-41]	26 [21-48]	0.63
Creatinine (μmol/l)	118 ±52.9	108 ±38.4	0.54
Renal Replacement Therapy	25% (2)	23.8% (5)	0.95
INR	1.3 ±0.156	1.65 ±0.717	0.14
Platelet count (x10^9/l)	162 ±66.1	163 ±65.9	0.95
Haemoglobin (g/l)	97.7 ±37.9	110 ±25.3	0.3
Lactate (mmol/l)	1.45 [1.3-1.6]	1.55 [1.3-2.4]	0.53
Intubated	100% (8)	90% (18)	0.35

Table 2: Right Heart Catheter Findings

Variable	pRVAD (n = 10)	tRVAD (n = 22)	p-value
mPAP (mmHg)	33.8 ±7.22 (n = 7)	37.5 ±11.1 (n = 12)	0.48
mRAp (mmHg)	15.1 ±4.85 (n = 9)	13.6 ±5.98 (n = 19)	0.53
CI (l/min/m2)	1.9 ±0.494 (n = 7)	1.58 ±0.528 (n = 12)	0.23
CO (l/min)	3.64 ±1.28 (n = 7)	3.04 ±0.885 (n = 12)	0.26
RVSWI (g-m/beat)	464 ±331 (n = 6)	526 ±257 (n = 10)	0.69
PCWP (mmHg)	26.5 ±3.33 (n = 7)	24.5 ±8.34 (n = 12)	0.58
PVR (PRU)	2.1 [1.8-2.8] (n = 8)	3.8 [3.2-5.8] (n = 13)	**0.001**
TPG (mmHg)	7.67 ±5.43 (n = 8)	12.6 ±6.79 (n = 12)	0.14

Abbreviations: IDCM, Idiopathic Dilated Cardiomyopathy; BTT, Bridge to transplant; BTD, Bridge to decision; BTR, bridge to recovery; LVEF, left ventricular ejection fraction; RV, right ventricle; TR, Tricusipid regurgitation; MR, mitral regurgitation; RVSP, right ventricular systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TRV, tricuspid regurgitation velocity; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; CI, cardiac index; CO, cardiac output; RVSWI, right ventricular stroke work index; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; TPG, trans-pulmonary gradient; pulm htn, pulmonary hypertension; ALT, alanine transaminase; RRT, renal replacement therapy; INR, international normalised ratio

***other causes of cardiomyopathy:**

- Familial dilated cardiomyopathy (n = 2)
- Haemochromatosis (n = 2)
- Drug-induced cardiomyopathy (n = 3)
- Transplant rejection (n = 1)

- Post-partum cardiomyopathy (n = 1)
- Lymphocytic cardiomyopathy (n = 1)

Table 3: Outcomes

Variable	pRVAD (n = 10)	tRVAD (n = 22)	p-value
Survival to Discharge	90% (9)	81.8% (18)	0.56
Mean Length of Stay post-op (days)	64.30 ±50.5	56.73 ±30.4	0.342
Post-op RRT	10% (1)	50% (11)	0.044
Drain output first 4h (ml)	435 [340-560]	463 [240-960]	0.87
Total Ventilation time (hours)	69.9 [44.5-108]	86.2 [32.3-314]	0.45
Total ICU hours	333 [155-539]	451 [314-788]	0.21
Return to theatre	60% (6)	54.5% (12)	0.77
Peak ALT (U/l)	64 [35-111]	46.5 [22-90]	0.23
Peak Bilirubin (μmol/l)	48.1 ±30.9	57.5 ±38.5	0.51
Peak Creatinine (μmol/l)	156 ±94.2	151 ±91.6	0.91
Peak lactate (<24h) (mmol/l)	1.55 [1.4-2]	2.4 [1.9-3.2]	0.031
Duration of RV support (days)	339 [98-815]	10.5 [9-14]	<0.0001
Time to Transplant (days)	546 [104-1329]	208 [131-567]	0.699

Abbreviations: RRT, renal replacement therapy; ICU, intensive care unit; ALT, alanine transaminase; RV, right ventricle

Survival

There was no significant difference in survival to discharge whether a permanent or temporary RVAD was primarily implanted (pRVAD 90%, tRVAD 81.8%; p = 0.56). All patients were followed up until last review in clinic or inpatient hospital visit. Survival was no different across groups who had

temporary versus permanent right ventricular support, whether inserted primarily or secondarily (p = 0.21 and 0.62, respectively).

At the time of census date, 25 patients were alive - 13 having been transplanted, 10 awaiting transplant, and 2 with explanted devices not requiring transplant listing. Seven patients died, 5 prior to discharge. Causes of death were sepsis in 2, cerebrovascular event in one and multiorgan failure in four.

Morbidity and other Outcomes

Patients who received a tRVAD were more likely to need post-operative renal replacement therapy than pRVAD recipients (50% vs 11.1%, respectively; p = 0.044). Total ICU hours, ventilation hours, and return to theatre were similar across the two groups (Table 3). Peak lactate within 24 hours of operation was found to be higher in tRVAD than pRVAD patients but other post-operative pathology results, including liver function tests, were not found to be significantly different (Table 3). On discharge, the dose of frusemide trended towards being higher in those discharged without any mechanical RV support, compared with those discharged with a pRVAD (40mg [95%CI 0 -120] vs 0mg 95%CI 0 - 0], respectively; p = 0.06). Amongst the successfully weaned tRVAD group, right heart failure severity (based upon TTE findings) did not improve significantly between admission and discharge, with 21.7% having severe RVF before LVAD with tRVAD implantation and after tRVAD explantation (p = 0.971). Of the 13 patients discharged with an LVAD, pre-transplant central venous pressure was a median of 9mmHg. Only one of these patients was discharged on an inotrope infusion (milrinone) and this was ceased prior to transplant. Another patient had a milrinone infusion commenced post-discharge, and this was continued until cardiac transplantation.

Time to transplant was no different across permanent or temporary RV devices, whether inserted primarily (546 days [104-1329] vs 208 days [131-567]; p = 0.69) or secondarily (975 days [546-1398] vs 185 [162-208]; p = 0.166).

Readmissions

Table 4 shows the comparison of readmissions for patients based on device on discharge. Patients who were discharged following a successful tRVAD wean – that is no right-side device on discharge - had more readmission days for heart failure, compared with those discharged with a pRVAD (0.5 days [95%CI 0 - 10] vs 0 days [95%CI 0 - 0], respectively; p = 0.014). Otherwise, duration of readmission for other complications was no different, whether discharged with a BiVAD or simply an LVAD.

The most common cause for readmission was bleeding (gastro-intestinal, dental, other) followed by sepsis unrelated to the ventricular assist device. These were no different across the groups.

Table 4: Outcomes of Device on Discharge

Variable	BiVAD (n = 14)	LVAD (n = 13)	p-value
Survival at census date	78.6% (11)	76.9% (10)	0.974
Readmission for complication (days)	17 [11-24]	13.5 [7-23]	0.44
readmission for heart failure (days)	0 [0-0]	0.5 [0-10]	**0.014**
Discharge frusemide dose (mg)	0 [0-40]	40 [40-120]	0.06
Time to transplant (days)	970 [546-1398]	185 [162-208]	0.166

DISCUSSION

RVF remains a common complication of LVAD insertion, and has a particularly high morbidity and mortality, as it signals the patient is on a rapid downhill trajectory. The decision to place mechanical circulatory support on the right side is often a difficult one and varies widely between centres. Multiple scoring systems have been proposed to guide this decision making (99-102). We have previously used these scoring systems in our own patient population with varying success (119).

Even more difficult is the decision to place a permanent or temporary RVAD. Existing scoring systems do not indicate which device should be utilised (108). Although the tRVAD is associated with much lower cost and allows the patient to be discharged with a single (left-sided) permanent device, we were concerned that these patients seemed to have prolonged ICU stays, and persisting heart failure. This prompted our study assessing the outcomes of temporary and permanent right ventricular devices.

In our centre, the indications for a tRVAD mirrored that of other studies and institutions that utilise this technique - that is, a temporary device was implanted where RV failure was diagnosed on LVAD insertion, and recovery was expected following a period of right ventricular accommodation. Patients placed on a tRVAD had an overall lower severity of RV failure on echocardiographic assessment, which confirmed the decision to proceed to a temporary device.

Our results showed that survival to discharge was no different whether a temporary or permanent RVAD was inserted. However, morbidity appeared to be worse for temporary RV support compared with a planned permanent device. Patients who received a temporary RVAD had a significantly higher incidence of post-operative renal replacement therapy than BiVAD recipients. This was despite no difference in renal replacement therapy or creatinine pre-operatively between groups.

Furthermore, readmission for heart failure was higher in the temporary RVAD group. Additionally, RV failure severity did not improve after temporary RVAD support. Hence, the perception that LV unloading (with an LVAD), and a tRVAD allows recovery of RV function is not fully supported by this study. This is quite a significant finding, considering that it has been the main indication for a temporary RVAD in clinical practice.

BiVAD support has been identified as being associated with lower survival than LVAD alone at 1 year (83). However, that report does not distinguish between LVAD alone and LVAD complicated by RHF. Patients discharged following successful temporary RV support are not comparable to patients with uncomplicated LVAD implantation. Consequently, it is likely incorrect to assume that discharge

with an LVAD complicated by RV failure is any less morbid than a BiVAD. Furthermore, several studies have shown that a delayed permanent RVAD (including those who failed tRVAD) had significantly worse outcomes than patients receiving a BiVAD (85, 108).

There are several other publications that have compared outcomes of the temporary and permanent RVAD for management of RV failure following LVAD implantation. LoForte et al reported in 2013 on 77 patients, and similarly found no difference in survival at discharge, 90 days, and 6 months (108). This was despite there being no difference in indication or risk score between the temporary and permanent RVAD. The only distinction between the two groups pre-operatively was that patients who refused to have a permanent device and needed RV support were given a tRVAD. Finally, they made no comment on morbidity or post-operative readmissions, and thus concluded that the temporary RVAD was a suitable alternative to a permanent device. Our study aimed to determine whether an appropriately indicated tRVAD conferred survival or morbidity benefit over a BiVAD.

Aissaoui et al reported in 2014 on 173 patients stratified into 3 groups – BiVAD, LVAD and temporary RVAD, and LVAD with inotropic support for RV failure (115). Their results showed no difference in survival at 6 months whether the patient had a BiVAD or LVAD on discharge. This study also identified that readmission for heart failure was significantly higher in the group discharged with a single device compared to a BiVAD (11% vs 1%; $p = 0.02$).

Several publications have reported the outcome of concomitant tricuspid valve surgery (TVS) for severe TR at the time of LVAD implantation. Tricuspid regurgitation (TR) is often secondary to RV and TV annular dilatation in LVAD recipients, reflective of their heart failure. Furthermore, the geometric changes to the septum by the LVAD are thought to contribute to worsened TR (105). Significant TR has been found to be associated with right heart failure following LVAD implantation (106). Hence, the reasoning for TV repair or replacement to prevent post-LVAD RVF has been reported in several publications. A systematic review and meta-analysis on concomitant TVS by Dunlay et al was published in 2015 (107). They reviewed 6 papers comparing the outcomes of LVAD+TVS versus LVAD alone. No paper found any difference in mortality. Additionally, pooled analysis found no difference in need for RVAD, whether concomitant TVS was performed or not. A subset analysis evaluated the 3 publications which selected patients with moderate and severe TR only, and no difference in need for RVAD post-operatively was re-affirmed. Although a link exists between significant TR and post-operative RVF in LVAD recipients, tricuspid valve surgery may not be enough to prevent the need for mechanical right-sided support. In our program, tricuspid valve surgery was performed if the patient was expected to be discharged with a single device and had significant TR. Amongst our group of tRVAD recipients only 1 patient received TVS, in the form of a

repair. There does not seem to be any other surgical technique described that would avoid the need for an RVAD.

Our study had several limitations, including relatively short follow-up (median follow up 13.5 months), a small sample size, and being a single centre retrospective study. Despite this, we demonstrated clearly significant differences in post-operative morbidity, particularly heart failure admissions.

These results re-iterate the need for guidelines upon the indications for temporary RV support, and the need to reconsider any aversion to a permanent device where doubt exists. Similarly, the potential cost-benefit of avoiding a permanent device is unlikely to be significant in consideration of these results.

A Real Life Experience With HeartMate III

Introduction

The HeartMate 3 (HM3) left ventricular assist device (VAD) (Abbott, Chicago, IL, USA), is a relatively new bearingless magnetically levitated centrifugal VAD which supersedes the axial flow HeartMate II VAD. The benefits of the HM3 are that it is a smaller compact pump designed to sit within the pericardium. It has a modular driveline designed to make the exchange of a damaged driveline easier. An artificial pulse has been built into the software, aimed at washing the rotor surfaces and eliminating stasis. The pump itself has wider gaps in the blood contact surfaces to reduce shear stress and thereby reduce thrombosis.

The first in man study of 50 patients in 10 centres across Europe, Kazakhstan, Canada and Australia demonstrated excellent results up to 12 months with no haemolysis, pump thrombosis or pump failure (122-124). Survival was 92% at 6 months and 81% at 12 months.

More recently a review of 27 patients receiving the HM3 LVAD, outside of a clinical trial setting, also demonstrated excellent results with 6 month survival of 85.2% (125) and 1 year survival of 85.2% (126). Both those publications, of the same cohort of patients followed up at 6 months (125) and 1 year (126), reported no pump thrombosis or stroke events at either time point. However, that study did not reflect a ‘real-life’ experience with the pump as patients with biventricular support, other types of assist devices such as extra corporeal membrane oxygenation (ECMO), VAD exchanges or reoperative procedures were excluded. Furthermore, eight of the included patients were in the HM3 CE Mark trial.

The aim of our study was to present an uncensored consecutive experience with the HM3 LVAD in our institution.

Materials and methods

We conducted a retrospective review of prospectively collected data. All patients who underwent HM3 LVAD implantation at The Alfred Hospital, Melbourne, Australia between November 2014 and October 2018 were included. There were no planned 'Destination Therapy' patients as this is not a funded indication in Australia. All patients were implanted with either a 'Bridge to Transplant' or 'Bridge to Candidacy' aim. Patients with pre-operative ECMO, right sided mechanical support, redo sternotomy, concomitant procedures and pump exchanges were all included.

All HM3 VADs were implanted via median sternotomy and on cardiopulmonary bypass support using standard techniques. Post operatively heparin infusion was commenced at 12 hours provided there was no untoward bleeding issues. Warfarin (aiming for an international normalized ratio (INR) of 2.0-3.0, and aspirin (100mg.day) were commenced once the patient had started oral intake. Pump speed on the left side was maintained within operating parameters of 5400 to 6000 rpm aiming for a mean blood pressure of 65-75mmHg. Regular echocardiographic assessment was used to adjust flows to ensure aortic valve opening.

Right sided support was provided by a temporary centrifugal circuit or by off label use of the HM3 VAD (114). Our operative technique for temporary (127) and permanent (120) RVAD implantation has been previously published. In brief, temporary RVAD support is provided by anastomosing an 8 mm Dacron graft to the main pulmonary artery and tunneling it through the anterior abdominal wall to the subcostal area where it is cannulated with a 21F or 23F wire-reinforced arterial cannula (Maquet Cardiovascular, LLC; Wayne, NJ). A 23F or 25F wire-reinforced venous cannula (Maquet) is placed percutaneously or through a cutdown over the right femoral vein, with its tip in the mid-right atrium. Both of the cannulae are connected to a Rotaflow centrifugal pump (Maquet) without an oxygenator. Flows are adjusted to maintain adequate filling of the LVAD and are monitored by echocardiographic assessment of interventricular septal position and ventricular cavitary size.

Permanent RVAD support has utilised the off-label application of the HM3 pump which we have inserted into the right atrium using multiple layers of Teflon felt as a 'standoff' over the inflow cannula. Thus only about 10mm of inflow cannula is within the right atrium, and the pump sits away from the atrial wall, usually in the right pleural cavity. The outflow conduit is not banded but is kept fairly long by bringing it down along the diaphragm and then over the right ventricle beneath the left hemisternum and then anastomosed to the main pulmonary artery.

Use of ECMO to bridge patients to permanent VAD can stabilize patients in cardiogenic shock, improve end organ function and allow time for further assessment of suitability for VAD therapy. All ECMO patients in this series were supported by peripheral ECMO prior to VAD implantation. Peripheral cannulation of the femoral vasculature by Seldinger technique under ultrasound guidance is typically performed. A distal perfusion catheter is placed percutaneously in the limb with arterial cannulation to provide antegrade limb perfusion in all cases. Support is provided by a centrifugal pump, Biomedicus Carmeda coated cannulae (Medtronic Inc., Minneapolis, MN, USA) and a Quadrox D membrane oxygenator (Maquet Cardiovascular LLC, San Jose, CA, USA). Patients are anti-coagulated with intravenous heparin in the absence of bleeding complications, aiming for an Activated Partial Thromboplastin Time of 55-75 seconds. Patients who were not able to wean went on to have VAD implantation, and are included in this study.

Statistical analysis

This data was analysed using SAS® Version 9.3 [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 numbers (%). Patient survival was analysed using Cox proportional hazards regression models, reported as hazard ratios (95% CI) and presented using a Kaplan Meier curve. A two-sided p-value of 0.05 was considered to be statistically significant.

Results

Between November 2014 and October 2018, 71 LVADs were implanted at The Alfred Hospital, Melbourne, Australia. Of these, 33 were HM3 LVADs and the remainder were Heartware HVADs (Heartware Inc., Framingham MA, USA). Only one patient (the first implant) was part of a study (the CE Mark trial) (122-124). The remainder were implanted under the Australian Special Access Scheme and then after Therapeutic Goods Administration (TGA) approval (April 2018).

Demographics and pre operative characteristics of the patient group are outlined in Table I. Peri-operative data is outlined in Table 2.

The census date was 28th December 2018. Six patients were bridged from ECMO to HM3 LVAD support. 14 patients required temporary mechanical RVAD support and seven patients required permanent HM3 RVAD support. Of the seven HM3 RVAD implants, five were performed at the time of the LVAD implant due to severe right heart failure considered not to be reversible by the treating surgeon and cardiology team. Two patients supported by a temporary RVAD failed weaning and were converted to a HM3 RVAD; one at 11 days and one at 21 days post LVAD implant. The remaining 12 temporary RVAD patients successfully weaned from the RVAD and had it removed.

There was one LVAD exchange in the study cohort in a patient who had a HMII implanted 22 months earlier. Due to short to shield issues, he suffered a pump stop and had the HMII exchanged for a HM3. Two patients, (both with known internal jugular or superior vena cava thrombus) suffered clot ingestion into the right sided HM3. One required a pump exchange at seven months post implant and one was successfully treated with heparinization. After three days of anticoagulation, that HM3 RVAD spontaneously recommenced operation without any obvious sequelae. The patient had remained stable without significant right heart failure during the period of RVAD pump stop. Overall 41 HM3 devices were implanted in 33 patients.

The duration of HM3 support at the time of census was a median of 196 (IQR118-386) days. This represents the equivalent of over 23.8 years of HM3 support analysed in the left position. The analysis also includes 1767 days (4.8 years) of support in the right atrial position. The longest supported (LVAD) patient is also the first implanted patient and has been supported for 1469 days (over 4 years) at the time of census (and remains supported at the time of submission).

Eleven patients have been transplanted. A competing risks analysis is shown in Figure 1 and Kaplan Maier survival in figure 2. Two patients died in the post operative period. One died on day 3 post operatively from a large embolic stroke which was thought to have occurred intraoperatively from left

ventricular cavitary thrombus ingestion. The second death occurred on day 12 post operatively from multi organ failure and sepsis, despite a temporary RVAD implanted at the time of the LVAD.

Table 1. Preoperative and demographic data

Data presented as n (%); mean (SD); or median (IQR)

Variable	HM3 patients (n=33)
Male/Female n(%)	31/2 (94/6%)
Age (years) mean (SD)	50 (13)
Height (cm) mean (SD)	177 (7)
Weight (kg) mean (SD)	79 (15)
Body Mass Index mean (SD)	25.7(4.2)
Diagnosis	
Dilated Idiopathic cardiomyopathy	16 (49%)
Ischaemic cardiomyopathy	9 (27%)
Other	8 (24%)
Pre operative status	
Pre operative invasive ventilation	4 (13%)
Pre operative ECMO support	6(18%)
Pre operative renal replacement therapy	2 (6%)
Preoperative hemodynamics*	
LVEF (%)	17 (6)
Cardiac Index (L.min.m^2)	2.2 (0.7)
Heart rate (bpm)	85 [70-100]
LVEDD (mm)	72 (10)
Mean right atrial pressure (mmHg)	11 (6)
Mean pulmonary artery pressure (mmHg)	25 (5)
Right ventricular stroke work index	707 (352)
Pulmonary capillary wedge pressure (mmHg)	25 (5)
Pulmonary vascular resistance (Woods units)	3.8 (2.2)
Transpulmonary gradient	13.4 (7.5)
Pre operative biochemistry results	
ALT Uunits)	36 [21-58]
Bilirubin	25.9 (13.2)
Creatinine	115 (46)
Estimated glomerular filtration rate	81 (26)
International Normalised Ratio	1.3 [1.2-1.6]
Activated Partial Thromboplastin Time	34 [30-46]
Platelets	175 (66)

Preoperative echocardiography results	**HM3 patients (n=33)**
Right ventricular systolic pressure	54 (19)
TAPSE	1.6 (0.5)
Right ventricular failure severity	
None	2(6%)
Mild	8(18%)
Moderate	16 (49%)
Severe	9 (27%)
Preoperative Tricuspid regurgitation	
None	5(15%)
Mild	5(45%)
Moderate	11(33%)
Severe	2(6%)
Pre operative mitral regurgitation	
None	0
Mild	10(30%)
Moderate	11(33%)
Severe	12(36%)

Table 2. Operative data

Variable	HM3 (n=33)
ECMO support at time of HM3 implant	6 (18%)
Redo sternotomy	5 (15%)
Aortic Valve replacement	6 (18%)
PFO closure	2 (6%)
Temporary RVAD insertion	14 (42%)
Permanent RVAD insertion	7 (21%)
Cardiopulmonary bypass time (mins)(n=33)	100 (40)
Aortic cross clamp time (mins) (n=6)	36 (15)
Blood loss first four hours (mls)	350 (233-1700)
Return to theatre post sternotomy bleeding	12 (36%)
Intensive care unit stay (hours)	254(158 – 1323)
Invasive ventilatory support (hours)	71 (27-768)
Cerebrovascular accident – permanent	1 (3%)
Cerebrovascular accident – temporary	1 (3%)
Haemofiltration – new renal failure	8 (24%)

Data presented as n (%); mean (SD); or median (IQR).

ECMO (extra corporeal membrane oxygenation); HM3 (HeartMate 3); PFO (patent foramen ovale); RVAD (right ventricular assist device).

HM3 = HeartMate III; ECMO = extra corporeal membrane oxygenation

Table 3. VAD operating parameters

LVAD	**Discharge (n=28)**	**3 months (n=27)**	**6 months (n=16)**	**12 months (n=9)**
Pump speed rpm mean (SD)	5639 (386)	5663 (401)	5669 (353)	5733 (283)
Pump power watts mean (SD)	4.3 (0.6)	4.5 (0.6)	4.4 (0.5)	4.6 (0.5)
Pulsatility index mean (SD)	4.7 (0.7)	4.8 (0.7)	4.7 (0.8)	4.8 (0.8)
RVAD	**Discharge (n=7)**	**3 months (n=7)**	**6 months (n=4)**	**12 months (n=2)**
Pump speed rpm mean (SD)	4867 (455)	5071 (482)	4900 (356)	5100 (283)
Pump power watts mean (SD)	3.2 (0.6)	3.5 (0.5)	3.3 (0.5)	3.7 (0.4)
Pulsatility index mean (SD)	3.7 (1.2)	4.4 (0.7)	4.4 (1.1)	4.9 (0.8)

Table 4. Biochemical data at follow up

	Pre-operative (n=33)	**Post operative peak (n=33)**	**Discharge (n=30)**	**3 months (n=29)**	**6 months (n=23)**	**12 months (n=15)**
Lactate dehydrogenase (U/L)		534 (417-703)	307 (66)	277 (240-304)	252 (48)	263 (46)
Creatinine (μmol/L)	115 (46)	131 (93-200)	72 (59-91)	88 (68-105)	97 (66-115)	105 (53)
Bilirubin (μmol/L)	26 (13)	45 (31-65)	10 (8-16)	10 (8-15)	15 (8)	15 (12)
Alanine transaminase (U/L)	36 (21-58)	51 (36-98)	30 (20-44)	24 (14-37)	28 (16)	28 (22)

Figure 1. Competing risks curve for the HM3 LVAD patient series.

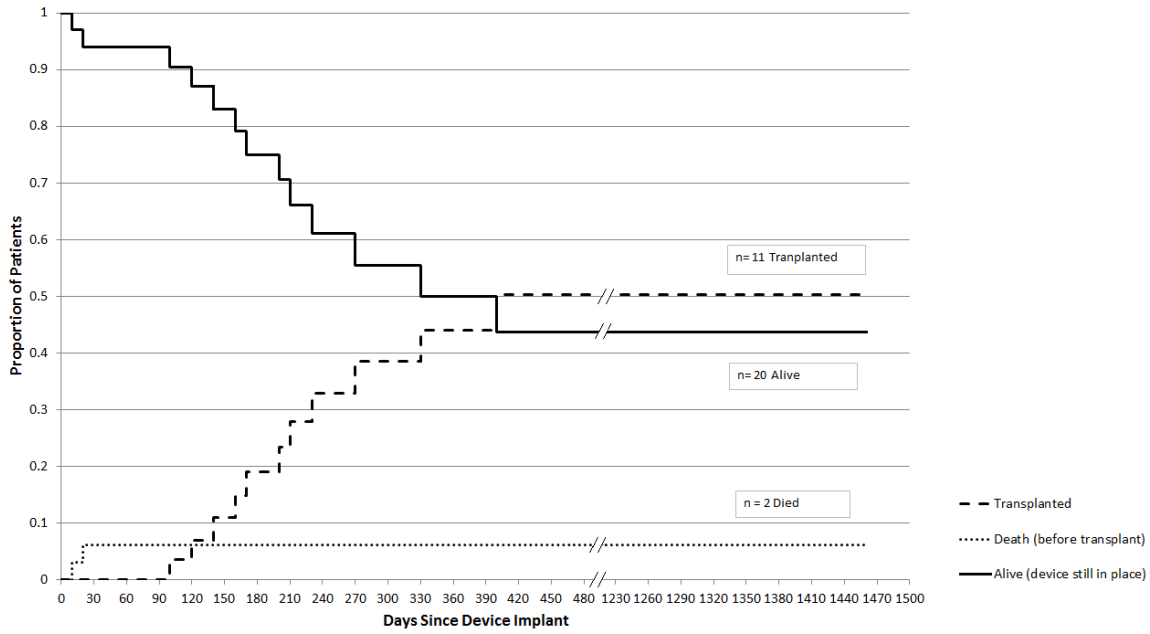
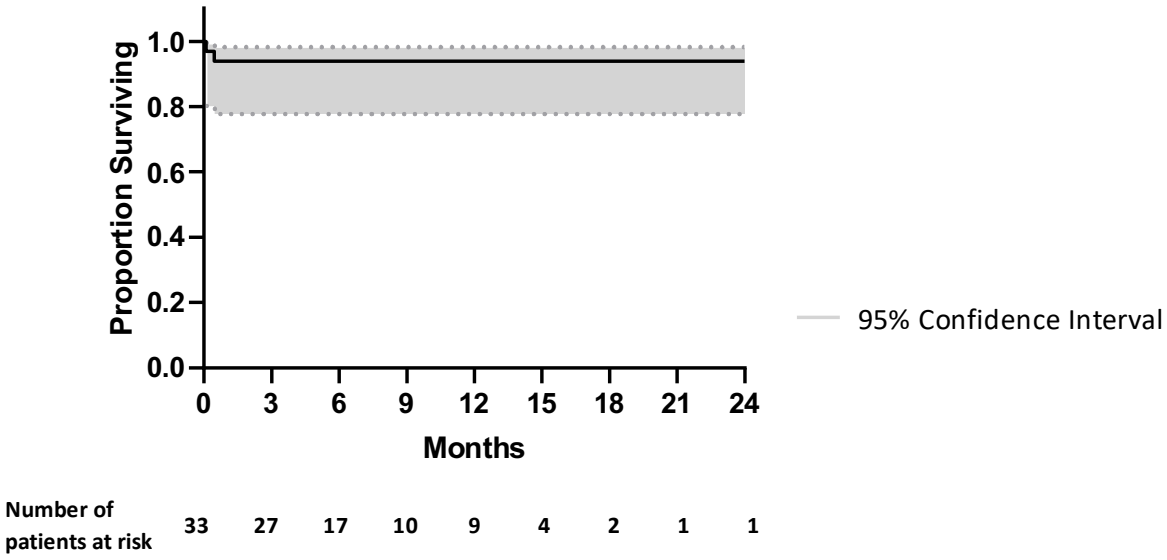


Figure 2. Kaplan Meier Survival



Bleeding complications were prominent. Twelve patients required return to the operating room for bleeding. These events tended to occur within the first few days after VAD implant. Five patients had gastrointestinal tract bleeding, all occurring in the first three months post implant, and seven patients had recurrent epistaxis. One patient developed persistent intra-abdominal bleeding in the early post-operative period requiring repeat laparotomies, eventually recovering.

Two patients required revision of their outflow graft in the early post-operative period, for kinking. One patient required resternotomy two years after LVAD implant with erosion of the outflow graft from the drive line within the pericardium. One patient required a pleurodesis for recurrent effusions.

In terms of infective complications, eight patients had driveline infections requiring localized treatment. One patient developed a deep sternal wound infection requiring multiple debridements and eventual closure.

Discussion

In this series of 33 consecutive HM3 patients, we have presented a truly 'real world' consecutive unfiltered experience. Previous reports have excluded many high risk patients in accounts of their HM3 experience and have included significant numbers of patients enrolled as part of the European CE Mark trial (125, 126). Those reports excluded patients requiring concomitant procedures, mechanical right sided support, pre VAD mechanical support such as ECMO and redo sternotomies. All of these conditions are well known to increase mortality and morbidity in VAD recipients (128, 129). A recent report from Germany found that redo sternotomy increased the risk of mortality, blood product transfusion, hepatic and renal dysfunction and ischaemic stroke after VAD implant compared to patients with no previous sternotomy (129). In a separate publication, the same authors found preoperative ECMO to be associated with worse survival, increased right heart failure, respiratory failure and renal failure (128). In our series, 5 (15%) patients were redo sternotomies, and 6 (18%) were supported on ECMO leading up to the VAD implant. This significantly increases the potential perioperative risk of our cohort according to those previously published studies. However, we have previously analysed our own results for patients supported to VAD implant by ECMO, and found no significant reduction in survival (130). Indeed, all six of the patients bridged to VAD by ECMO in this current series were alive at the census date, as were all five patients who had redo sternotomies.

More recently, the ELEVATE registry data has been released, describing results in a prospective observational multinational registry of 463 consecutive HM3 implants after commercial approval in Europe and Kazakhstan (131). In that cohort, 12% of patients had pre operative mechanical circulatory support and 17% had previous sternotomy. These premorbid conditions are more in line with the cohort we have presented. However, the follow up in that study is short with a survival of 90% reported at 30 days, improving to 95% if only primary implant patients were included. In contrast our uncensored median follow-up of 6 months demonstrated a survival of 95%.

The CE Mark study and the ELEVATE registry did not identify any pump thromboses (122-124, 131). The much larger MOMENTUM study which compared the HM3 to the axial flow HMII, identified only 7 cases of suspected or confirmed pump thrombosis in 516 patients implanted (132). This contrasted significantly with 70 suspected or confirmed cases of pump thrombosis in the 512 patients implanted with the axial flow device. This appears to be an important benefit of the HM3 in comparison to previous generation VADs. Other case reports of HM3 thrombosis do exist, with one occurring as early as day 2. In that report no identifiable kink or technical reason and no manufacturer fault was identified (133). The proposed mechanism was inadequate anticoagulation soon after surgery and multiple low flow events. Another pump thrombus occurring at day 8 has been reported, a possible mechanism in that instance being an off-pump implantation (134). At reoperation, left ventricular clot

was identified and removed and the pump exchanged but clot ingestion into the second pump and subsequent thrombosis again occurred. A third report, of a patient who died of multi-organ failure at day 229 post implant confirmed layered thrombus of differing age on the rotor of the explanted HM3 (135). It is evident, from all the reports thus far, that the thrombosis event rate in the HM3 is low compared to previous VADs. However, it is possible that the pump thrombosis rate is under reported. Reports of clot ingestion, as opposed to in situ thrombosis are almost always assumed and difficult to prove unless the VAD is explanted.

The design features of the HM3 were aimed specifically at reducing hematological complications and it appears at this stage that they have been successful in that endeavor. Specifically, the larger rotor gaps aim at reducing shear stresses on blood cells which are implicated in the acquired von Willebrand syndrome seen in almost all patients with implanted continuous flow LVADs. A recent study comparing the multimeric structure of vWF between patients with a HM3 and HVAD found less reduction of high molecular weight multimers and a higher concentration of factor VIII in the HM3 patients indicating less shear stress to blood components in those patients (135). The authors proposed that better flow characteristics due to larger blood flow paths and extended gaps between rotating elements were responsible for the higher stability of vWF multimers and lower platelet activation seen in the HM3 patients. This is a likely proposed mechanism for the lower thrombotic events being seen with this device in studies to date as outlined above.

Further support of the lower tendency to thrombotic events in the HM3 is the significantly lower stroke event rate seen over the longer term (181 – 730 days) in the 2 year pre specified ‘as treated’ secondary analysis of the MOMENTUM 3 (136). Although no difference in stroke events was found between the HM3 and HMII arms in the first 180 days post implant, the longer term follow up revealed a 3.3 times lower event rate in the HM3 patients.

Conclusions

Although we have presented a single centre retrospective cohort of patients, it is completely uncensored, with all patients receiving a HM3 device in our institution being included for analysis. The study shows excellent survival and very low thrombosis rates in a real world setting, confirming the findings in the more restricted enrolment environment of the landmark trials.

CONCLUSION – MECHANICAL CIRCULATORY SUPPORT

Mechanical circulatory support is an ever-changing field. New technology has brought increasing device developments. Our understanding of the capabilities of these devices has also broadened our application of them, with an ever-increasing list of indications.

However, with the increasing use of ECMO and ventricular assist devices has come a greater understanding of the limitations and complexities they add to patient care. From the challenge of pressure-care for patients on devices, to concomitant IABP and ECMO use, this field is evolving in its practice. The fluidity afforded by individual centres' practices has demonstrated that finesse and nuance are key contributors to patient outcomes. Indeed, identifying and optimising these factors can be the difference between life and death for patients on mechanical circulatory support. This has been the purpose of this thesis: to identify the most influential factors on patient outcomes, and give rationale behind tailored practice. With this, guidelines can be formed to ensure outcomes can universally be optimal with the application of these medical technologies.

Finally, although mechanical circulatory support has brought great advancement in the field of medicine and surgery, it has also come with a multitude of ethical dilemmas (137). Post-cardiotomy ECMO practices and outcomes have revealed that the indication for life-saving cardiac surgery is not necessarily an appropriate indication for resuscitative mechanical support when catastrophes arise. Similarly, some of the rationale for the use of temporary right ventricular devices in LVAD recipients is a cost-saving one, and may demonstrate worse outcomes than previously thought. The focus on the key ethical principle of non-maleficence needs to be balanced against heroics, whilst maintaining dignity for patients and their family.

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PUBLICATIONS

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Review

Right Heart Failure in Left Ventricular Assist Device Patients

James Farag [1, 2, †], Silvana Marasco [1, 2, †, *]

1. Department of Cardiothoracic Surgery, The Alfred Hospital, Melbourne. Victoria, Australia; E-Mail: s.marasco@alfred.org.au
2. Department of Surgery, Monash University, Clayton. Victoria, Australia; E-Mail: faragjames@gmail.com

† These authors contributed equally to this work.

* **Correspondence:** Silvana Marasco; E-Mail: s.marasco@alfred.org.au

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Abstract

Left ventricular assist devices (LVADs) improve quality of life in end-stage heart failure patients but a frequent complication is Right heart failure (RHF) causing significant morbidity and mortality. This review article discusses key issues that need to be considered in the assessment and clinical management of RHF in LVAD patients including the use of Right Ventricle (RV) support devices and off-label LVADs as temporary or permanent RV support.

Keywords

Right ventricular failure; ventricular assist device; end-stage heart failure

1. Introduction

Left ventricular assist devices (LVADs) are utilised in refractory end-stage heart failure. These devices are used as a bridge to transplant, destination therapy, and occasionally as a bridge to recovery [1]. Right heart failure (RHF) is a frequent complication with significant mortality and morbidity [2].

2. Definition of RHF in LVAD Patients

Right ventricular failure (RVF) leads to poor filling of the left ventricle (LV), and thus insufficient flow to the left ventricular assist device. This subsequently leads to inadequate flow from the LVAD itself, and the patient will suffer from the sequelae of both right and left heart failure, culminating in end-organ malperfusion and central venous congestion.

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) defines right heart failure as signs and symptoms of persistent right ventricular dysfunction following LVAD insertion. This is stratified into mild, moderate, and severe according to inotrope therapy duration (≤7, 8-14, and >14 days, respectively) [3]. However, this definition is limited to patients left unsupported mechanically post-procedure, and is retrospective in nature. In patients with severe RVF following LVAD insertion, it may indeed be fatal to leave them without definitive mechanical support.

Potapov et al developed a criteria for the diagnosis of right heart failure post LVAD insertion in 2009 [4]. RHF is diagnosed by:

- Death
- Inability to wean from cardiopulmonary bypass CPB

OR any 2 of the following (sustained for 15 minutes after complete withdrawal of CPB):

- LV flow rate index ≤ 2.0l/min/m2
- Administration of ≥ 20 inotropic equivalents (IE)
- Mean arterial pressure (MAP) ≤ 55mmHg
- Central venous pressure (CVP) ≥ 16mmHg
- SvO2 ≤ 55%

Right heart failure signs in patients fitted with an LVAD reflect the physiologic sequelae expected. These include elevated right atrial pressures with a relatively low left atrial pressure, poor LVAD filling, and low systemic blood pressure. It is important to note that high left atrial pressures in conjunction with high right atrial pressure and low cardiac index may suggest LVAD inflow obstruction, which may be due to thrombosis of the inflow cannula, and should not be confused with RVF. This is often found in conjunction with increased LVAD power output. The physiological changes of RVF can all be determined by pulmonary artery catheter measurements. Echocardiographic findings will demonstrate poor right ventricular ejection, whilst also demonstrating whether the LVAD inflow is obstructed [5].

3. Decision of LVAD vs BiVAD

The indications for ventricular assist devices are not diagnosis-specific, and are rather determined by the degree of heart failure, responsiveness to medical therapy, and the intermediate- to long-term plan. Thus, patients are divided into:

- bridge to transplant (BTT)
- Bridge to decision (upon transplant) (BTD)
- Bridge to recovery (BTR)
- Destination therapy (DT)

INTERMACS lists profiles of patients receiving mechanical assist devices, from which outcomes of therapy are evaluated on a regular basis. The INTERMACS classes are listed below:

1) Critical cardiogenic shock
2) Progressive decline on inotrope support
3) Stable but inotrope dependent (in- or out-patient)
4) Resting HF symptoms (home on oral therapy)
5) Exertion intolerant
6) Exertion limited
7) Advanced NYHA class III symptoms

Biventricular assist devices (BiVADs) are utilised where an LVAD alone would be insufficient therapy due to the significance of the right heart failure. This configuration is simply a permanent right ventricular assist device (pRVAD) inserted in conjunction with an LVAD. However, this must be weighed against the significantly higher morbidity and mortality of BiVADs when compared with LVADs. In fact, Kirklin's review of the INTERMACS database published in 2008 found that BiVADs had twice the mortality rate of LVADs [4]. Similarly, in the 7th INTERMACS annual report, it was found that BiVAD recipients had a 50% survival at 12 months compared with 80% in LVADs [6]. Although this may be a reflection of an overall more unwell pre-operative condition of the patient rather than the device itself, Cleveland found that BiVAD recipients had a significantly higher rate of infection, bleeding, and device failure than LVAD recipients [7].

Yet, a planned permanent RVAD has been proven to be of greater benefit than delayed placement of an RVAD in LVAD recipients. Fitzpatrick et al (2009) found that in a cohort of 99 LVAD recipients, planned RVADs had a superior survival to delayed RVADs, and a trend towards improved bridging to transplantation. However, the two groups had no significant pre-operative differences that would help differentiate them [8]. This reiterates the difficulty in the choice of LVADs and BiVADs. The single device - LVAD alone - has better survival, less morbidity, and improved quality of life; yet a failure to implant the more complex device early - a planned BiVAD - has significant negative consequences.

4. Pathogenesis of Right Ventricular Failure in Setting of An LVAD

In patients with an LVAD, there are a multitude of haemodynamic and anatomical changes that occur which have potential to affect the right ventricle. In the pre-operatively impaired right ventricle, there is potential that these changes cause systemic cardiovascular compromise. These changes by the LVAD can be grouped into effect on right ventricular preload, afterload, and anatomical function [5, 9-11].

4.1 Preload

With the insertion of an LVAD in a previously failed heart, there is a sudden increase in the volume ejected into the systemic circulation. This is followed by an increase in venous return from

the end-organs to the right atrium, and thus an increase in preload. Hence, the workload upon the right heart has increased rapidly between pre- and post-LVAD implant phases.

4.2 Afterload

In an otherwise normal pulmonary vascular system, the unloading of the left ventricle should subsequently unload the pulmonary vasculature. Hence, any pre-existing passive pulmonary hypertension secondary to left heart failure would be alleviated, and right ventricular afterload would decrease. However, in a pulmonary vasculature compromised by obstructive disease (atherosclerosis or emboli) this would have the opposite effect. The increase in preload to the right ventricle previously described would further elevate pulmonary pressures that are not unloaded by the LVAD, as the pulmonary hypertension is not secondary to left heart failure.

4.3 Anatomical and Functional Changes

Ventricular interdependence has been described by Santamore et al (1998) as *'the forces that are transmitted from one ventricle to the other through the myocardium and pericardium, independent of neural, humoral, or haemodynamic changes'* [12]. This concept has been studied in animal and other laboratory experiments, concluding that reduction in left ventricular output led to 20-40% reduction in RV systolic pressure and output [13-15]. The mechanism behind this is believed to be related to the orientation of muscle fibres in the right ventricle (non-concentric), and the assistance the septum provides - essentially as an anchor - against which it contracts.

Interventricular septal deviation to the left occurs with LVAD placement (Figures 1 and 2). This is due to the volume being unloaded by the device and displaced directly into the ascending aorta via the conduit. This has been shown in various studies utilising ultrasonic crystals and echocardiography [5]. Although this shift may lead to better compliance, it also impacts the contractility of the right ventricle. The unnatural leftward bending of the septum has consequent pathologic compression of myocardial fibres on the RV side of the septum [16]. Hence, an LVAD will subsequently have a detrimental effect on right ventricular ejection.

In summary, in patients with an LVAD, unloading of the left ventricle alters the size and shape of the right ventricle (in particular the interventricular septum) as well as affecting the haemodynamic flow before and after the RV. Hence, an increase in workload and distortion of anatomy and functionality of the right ventricle is thought to be a major contributor in unexpected RV failure with LVAD implantation [5, 9-11]. Certain pre-operative characteristics of right ventricular dysfunction may provide clues as to which patients cannot compensate for these changes.

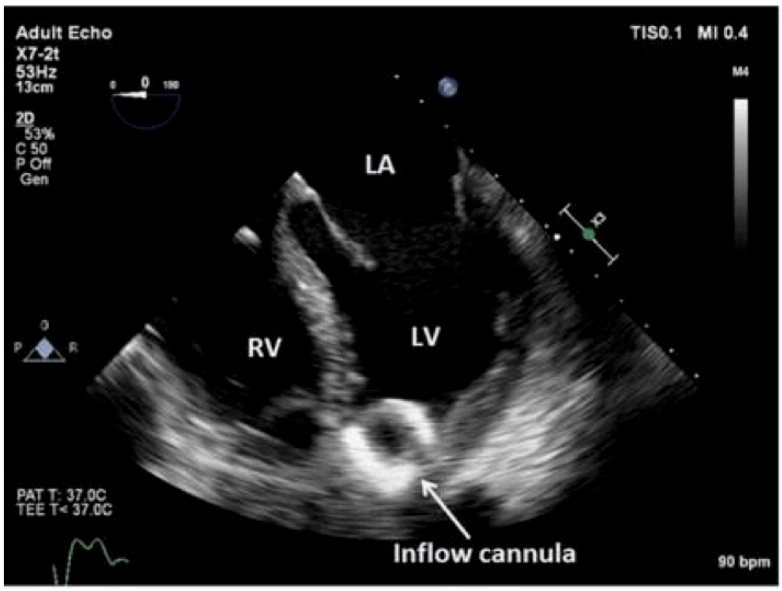

Figure 1 Trans-esophageal echocardiography showing movement of interventricular septum to the left with inflow cannula of LVAD in situ [17].

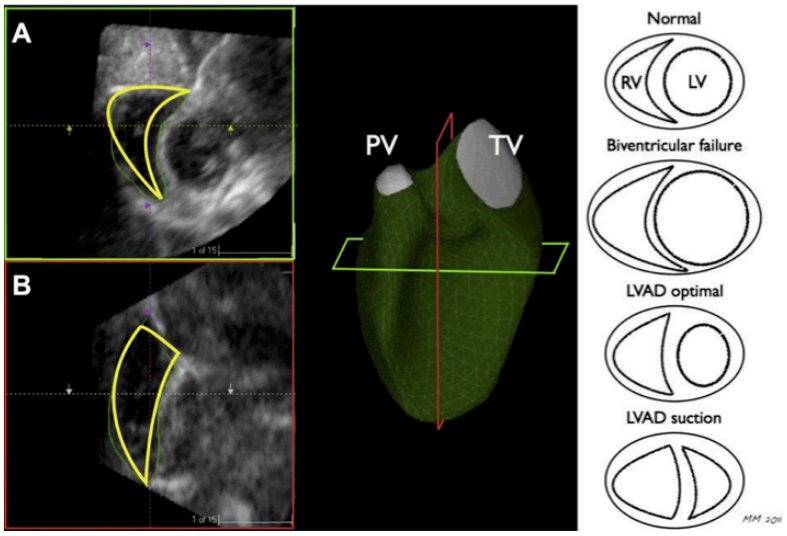

Figure 2 Midpapillary (A) and long axis (B) biventricular imaging demonstrating optimal shape of RV in the LVAD patient [18].

5. Incidence and Aetiology of RHF in LVAD Population

Although infrequent in all cardiac surgical procedures with an incidence of 0.04-0.1%, acute refractory right ventricular failure occurs in 20-50% of LVAD insertions [15, 19, 20]. This complication is becoming increasingly more frequent with more marginal candidates having LVADs implanted, and the device being utilised more frequently [21].

The aetiology of the RHF is likely a combination of:

1) The original insult to the left ventricle
2) The acute or chronic increase in afterload contributed by the left heart failing, and
3) The mechanical effects described above, once the LVAD is inserted

6. Outcomes of RHF in LVADs

RHF post-LVAD has a significant post-operative mortality. Dang et al reported a more than 3 fold early mortality (≤30 days) in LVAD patients who were complicated with RHF than those who were not (19% vs 6.2%; p = 0.037) [2]. Kormos et al (2010) also reported that survival to transplant was significantly lower in patients suffering RHF post LVAD insertion) [1]. Survival to transplant, recovery, or ongoing device support at 180 days was 71% in those with RHF, compared with 89% in those without (p < 0.001) [1]. Similarly, there is a known increase in overall morbidity. Delayed rehabilitation, increased transfusion requirements, and delayed or failed restoration of end-organ function have been associated with RVF post-LVAD insertion [22].

7. Predictors of RHF

Independent assessments of right heart function, such as RV ejection fraction, CVP, and TAPSE are not alone adequate to distinguish right heart failure [22-24]. As preload is reduced with left heart failure, right ventricular dysfunction can be masked, and is often more obvious once the LVAD is inserted. The LVAD insertion also significantly impacts upon ventricular interdependence as described previously, exacerbating an impaired right ventricle.

Several features have been identified as risk factors for right heart failure post-LVAD insertion including end-organ dysfunction, non-ischaemic cardiomyopathy, and severe TR [23]. More complex scoring systems have been developed and analysed to predict right ventricular failure following LVAD implantation. These scoring systems were developed in retrospective cohort studies utilising logistic regression scoring of blood, echocardiographic, and right heart catheter results. Some of the more common scoring systems will be discussed below [22, 24-26].

7.1 Matthews' Score

Published in 2008, Matthews et al used multivariate logistic regression on a sample of 197 patients whom underwent LVAD implantation [22].

RHF was defined as the post-operative need for:

1) Intravenous inotrope therapy > 14 days,
2) Inhaled nitric oxide ≥ 48 hours,
3) Right-sided circulatory support (ECMO or RVAD), or
4) Hospital discharge with an intravenous inotrope

68 patients suffered right heart failure, and the pre-operative findings were analysed to determine significant risk factors. A vasopressor requirement, elevated ALT, bilirubin and creatinine were all independent predictors of RHF. Furthermore, a scoring system was formulated to determine an odds-ratio for RV failure. Below is the scoring allocation as well as the scoring system (Table 1 and Table 2).

Table 1 Scoring allocation.

Predictor	p-value	Points
Vasopressor requirement	<0.005	4
Aspartate Aminotransaminase (AST) ≥ 80 IU/l	0.001	2
Bilirubin ≥ 2.0mg/dl	<0.005	2.5
Creatinine ≥ 2.3mg/dl	<0.005	3

Table 2 RVF risk (Matthews') score.

Score	OR	95% CI	180 day survival	p-value
≤3	0.49	0.37-0.64	90±3%	0.0045
4-5	2.8	1.4-5.9	80±8%	
≥5.5	7.6	3.4-17.1	66±9%	

7.2 Fitzpatrick's Score

Fitzpatrick et al (2008) reviewed 266 patients whom underwent LVAD implantation at the University of Pennsylvania from 1995-2007 [23]. Multivariate logistic regression identified that the most significant predictors for RVAD were:

- Low cardiac index (CI) (≤ 2.2l/min/m2)
- Low RV stroke work index (RVSWI) (≤ 0.25mmHg/l/m2)
- Severe pre-op RV dysfunction
- High Pre-operative creatinine (≥1.9mg/dl)
- Previous cardiac surgery
- Low systolic blood pressure (SBP) (≤96mmHg)

If a patient fulfilled one of the above criteria, it was assigned a 1; and if they did not meet a criterion, it was assigned a 0 in the following equation:

18x(CI) + 18x(RVSWI) + 17x(creatinine) + 16x(previous cardiac surgery) + 16x(severe RV dysfunction) + 13x(SBP)

Thus, the maximum number a patient could acquire was 98 and minimum was 0. A threshold of 50 points was utilised by this study; delineating:

- < 50 predictive of successful LVAD
- ≥ 50 predictive of need for BiVAD

Based upon the above, the sensitivity and specificity of these scores was 83% and 80%, respectively. 96% of patients that scored < 30 underwent successful LVADs, whilst 89% of patients scoring ≥ 65 required BiVADs.

7.3 Atluri's (CRITT) Score

Atluri et al (2013) developed a scoring system to predict right ventricular failure following insertion of continuous flow LVADs [25]. They evaluated 218 patients operated on in their centre between 2003-2011, with the intent of identifying independent risk factors of right heart failure, and to develop a tool to predict this outcome pre-operatively. They used univariate analysis and multivariable logistic regression, and identified the following:

A score of 2 or more provided a sensitivity of 84%, specificity of 63%, and negative predictive value of 93%. That is, a score less than 2 predicted successful isolated LVAD therapy in 93%.

The above scoring systems have some limitations. Cardiac index and RVSWI require invasive tests such as a right heart catheter - not readily performed in the acutely unwell patient. Furthermore, a patient on ECMO may not project accurate right ventricular and tricuspid function on echocardiography (Table 3).

Table 3 Atluri's (CRITT) score.

Predictor (pre-op)	OR	95% CI	p-value
CVP > 15mmHg	2.0	0.9-4.2	0.089
Severe RV dysfunction	3.7	1.7-8.1	0.001
Pre-operative Intubation	4.3	1.9-9.6	<0.001
Severe tricuspid regurgitation (TR)	4.1	1.4-12.4	0.011
Tachycardia (>100bpm)	2.0	0.9-4.3	0.086

These scoring systems have been shown in their publications to be highly sensitive, yet not all are particularly specific and thus it can be difficult to justify the expense, morbidity and mortality associated with a second VAD. None of them have been validated in prospective studies. Finally, these scoring systems do not determine which patients will be sufficiently managed with a temporary device compared with permanent support. The sensitivies and specificities of each scoring system are outlined in Table 4.

Table 4 Comparison of scoring systems.

SCORING SYSTEM	SENSITIVITY	SPECIFICITY
Matthews, 2008 [22]	35%	-
Fitzpatrick, 2008 [24]	83%	80%
Atluri, 2013 [26]	84%	63%

8. Management

8.1 Prevention

The management of RHF following LVAD insertion can begin pre-operatively, with the intent of prevention. Pre-operative management is aimed at reducing large volume shifts, particularly with the use of blood products which may cause volume strain. Monitoring of right ventricular function pre-operatively is suggested in those who are deemed high risk [18]. A pulmonary artery catheter can provide accurate assessment of RV function and pulmonary vascular resistance (PVR) and allow titration of inotropes and pulmonary vascular dilators. Dobutamine and milrinone are agents commonly used for right heart optimization. These inodilator agents are often used in conjunction with other pulmonary vascular dilators such as iloprost and inhaled nitric oxide (NO). Norepinephrine is also a useful adjunct to maintain perfusion pressure to the right coronary artery, as well as end organs. Aggressive diuresis assists in lowering central venous pressure, reducing end organ venous hypertension, reducing right ventricular strain and normalizing right ventricular geometry.

A large double blinded, randomised control trial encompassing centres in Germany and the US investigated whether inhaled nitric oxide (NO) was of benefit in the LVAD population [4]. Unfortunately, it did not prevent RV failure post-operatively, despite decreasing mean pulmonary artery pressures (mPAP) and increasing LVAD flows. Several small studies have evaluated the use of milrinone, inhaled nitric oxide, and phosphodiesterase inhibitors in optimizing right heart function [27, 28]. Although these studies demonstrate reduction in pulmonary artery pressures and improved RV echocardiography findings, they are small sample sizes and do not exclusively evaluate use of these agents in the pre-operative period.

8.2 Peri-Operative Management

Good peri-operative technique with the intent of reducing unnecessary blood loss, reducing CPB time, and good myocardial protection are all vital in protecting against post-operative RVF. Maintaining perfusion pressure peri-operatively, avoiding air embolism down the right coronary artery, and not expecting the right heart to deliver high flows immediately are useful protective strategies. Several publications have reported the outcome of concomitant tricuspid valve surgery (TVS) for severe TR at the time of LVAD implantation. Tricuspid regurgitation (TR) is often secondary to RV and TV annular dilatation in LVAD recipients, reflective of the chronicity of their heart failure. Furthermore, the geometric changes to the septum by the LVAD are thought to contribute to worsened TR [29]. Significant TR has been found to be associated with right heart failure following LVAD implantation [30]. Hence, the reasoning for TV repair or replacement to prevent post-LVAD RVF has been reported in several publications. A systematic review and meta-analysis on concomitant TVS by Dunlay et al was published in 2015 [31]. They reviewed 6 papers comparing the outcomes of LVAD+TVS versus LVAD alone. No paper found any difference in mortality. Additionally, pooled analysis found no difference in need for RVAD, whether concomitant TVS was performed or not. A subset analysis evaluated the 3 publications which selected patients with moderate and severe TR only, and no difference in need for RVAD post-operatively was re-affirmed. Although a link exists between significant TR and post-operative RVF

in LVAD recipients, tricuspid valve surgery may not be enough to prevent the need for mechanical right-sided support.

8.3 Post-Operative Management

Inotrope therapy is most commonly used for post-LVAD RHF, and success of this will be determined by end-organ function and LVAD flows. If these are compromised, and echocardiographic findings confirm RV failure with the aforementioned consequences, mechanical therapy needs to be instituted. Chemical therapies proven to be of benefit in RHF include:

- Inhaled Nitric Oxide (see above)
- Dobutamine - increases cardiac index and stroke volume, whilst maintaining preload
- Dopamine - of benefit in hypotensive patients
- Milrinone - agent of choice if tachyarrhythmic patient

Phosphodiesterase inhibitors including milrinone and iloprost have been shown to improve right heart function in the peri-operative period. Hamdan et al reported on the use of sildenafil in 8 of 16 patients with RVF and pulmonary hypertension receiving LVADs. Patients also received nitric oxide. This small population was shown to have significantly improved PVR, pulmonary artery pressure, trans-pulmonary gradient (TPG), cardiac index, and other measurements of right heart function [28].

Once again, the use of multi-modal therapy with careful monitoring is likely to be most beneficial.

Pulmonary artery balloon pumps have been utilised for short periods of time, although with limited success [4]. The main mechanical options are a temporary right ventricular assist device (tRVAD) and permanent RVAD. It is important to note that there is no specific mechanical right ventricular device - all permanent RVADs utilised are off-label use of devices designed as LVADs.

8.4 Temporary RVAD (tRVAD)

Various tRVADs exist on the market currently, or are used as such.

8.4.1 CENTRIMAG™

LoForte et al describes the use of a CentriMag™ device as a temporary right ventricular device [29], whilst Aissaoui reports on both Thoratec PVAD and CentriMag™ at different times for temporary right ventricular support [32]. The CentriMag™ is a magnetically levitated radial pump, and is utilised as a temporary device for either left or right ventricular support. It has been approved for use up to 30 days in either position. In its form as a tRVAD, the inflow cannula lies in the right atrium, whilst the outflow cannula is in the main pulmonary artery [33].

8.4.2 IMPELLA™

The Impella RP™ device has recently been described for use as a temporary RVAD by Anderson et al (2015) in the prospective RECOVER RIGHT study [31]. The Impella RP™ is a 22Fr catheter-based percutaneous micro-axial pump mounted on an 11Fr catheter. The catheter is advanced via the femoral vein into the pulmonary artery, with the pump traversing the tricuspid and pulmonary valves. The pump's inflow is positioned in the IVC and the outflow in the PA, able to expel blood

up to 4l/min. Its intended use is up to 14 days. In the 2015 non-randomised trial, 30 patients were recruited and divided into 2 cohorts: patients suffering RHF post LVAD insertion (n = 18; cohort A) and patients who had RHF post-cardiotomy or post myocardial infarction (n = 12, cohort B). Anderson reported a 70% survival to discharge of both cohorts combined, and although not statistically significant, a higher survival to discharge in cohort A (77.8% vs 53.8% in cohort B). In 2018, Anderson reported on sixty patients in a prospective study dividing patients into the same two cohorts as the 2015 study [34]. Cohort A (RVF post-LVAD) had 31 patients, and Cohort B (post-cardiotomy RVF and post myocardial infarction RVF) had 29 patients. Once again, survival to discharge or at 30 days (whichever was longer) was 77.4% in Cohort A, and 73.3% overall. In short, the Impella RP is a novel method for right heart support and appears to be a useful support strategy for LVAD patients with post implant RHF.

8.4.3 TANDEMHEART™

The TandemHeart is a ventricular assist device that has been proposed for use in left heart failure. However its use has been proposed by Schmack et al (2016) as a right ventricular assist device in conjunction with an LVAD [35]. They proposed that the cannula is placed via the right internal jugular vein via a Seldinger technique over a previously inserted Swann-Ganz catheter. The outer cannula (29Fr) is positioned in the RA (under TOE guidance) and the inner cannula (16Fr) in the pulmonary trunk. There are no clinical reports of this device's use as a temporary RVAD as yet.

8.4.4 CENTRIFUGAL PUMP AS AN RVAD

An alternative temporary support consists of a modified ECMO circuit, with the oxygenator removed. Temporary RVAD support is provided by a Biomedicus centrifugal pump (Figure 3). A 21 French inflow cannula is inserted via the femoral vein, with the tip of the cannula in the proximal IVC or right atrium. The return cannula is via an 8mm Dacron graft sewn end-to-side to the main pulmonary artery. This is tunnelled from the thorax to exit the anterior abdominal wall [36].

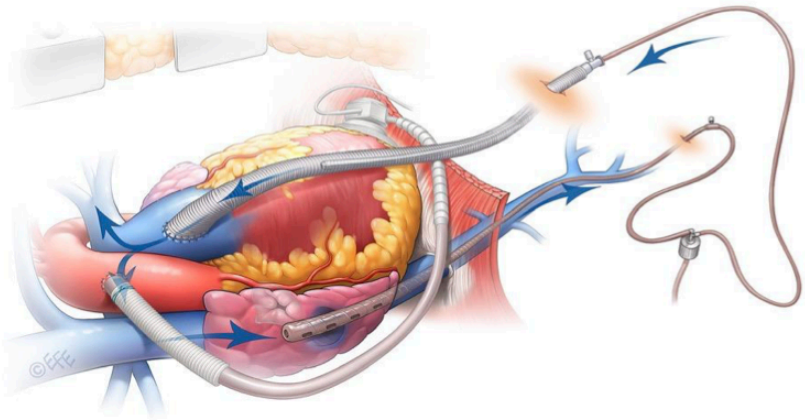

Figure 3 Centrifugal pump as an RVAD Saxena, 2015 [37]

Weaning of the tRVAD is performed in the intensive care unit, where LVAD flows and haemodynamic and echocardiographic parameters were monitored. A patient is deemed suitable for decannulation if weaning studies are successful, then placed back on full flow until decannulation. Decannulation can be performed in either the ICU or operating room depending on whether return to the operating room is necessary for other reasons, such as evacuation of mediastinal clot. The access femoral cannula is removed and manual pressure applied. The return line is decommissioned by removing the 21Fr cannula, withdrawing the Dacron graft sufficiently to expose a sterile portion, clamping, dividing and oversewing the graft and letting it retract back into the chest [36, 37] (Figure 4).

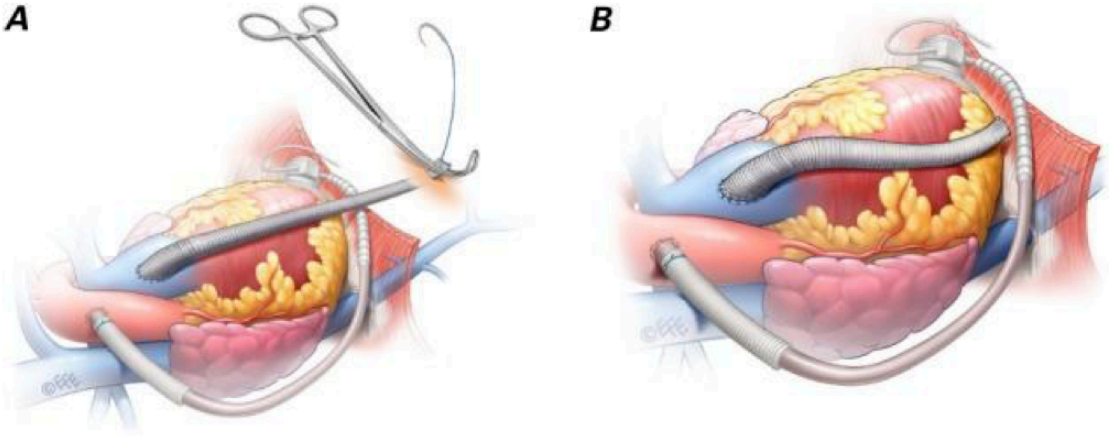

Figure 4 Centrifugal pump as an RVAD. Saxena, 2015 [37].

8.5 Permanent RVAD

An alternative to temporary RV support with an LVAD, is the insertion of a permanent RVAD. In this case, a patient would be discharged with a BiVAD (two permanent devices) as opposed to an LVAD, alone. As mentioned previously, early permanent RVAD insertion has been shown to have lesser mortality, morbidity, and successful bridging to transplant than if implanted secondarily - i.e. following failure of temporary support.

9. Comparisons of Temporary and Permanent RVADs

Clear guidelines as to the institution of tRVAD or pRVAD at the time of LVAD insertion are lacking, and thus the decision making is inconsistent across centres and surgeons. Temporary RVAD is preferred as a single device on discharge has lesser morbidity and mortality [4], whilst the cost of biventricular permanent devices is significant. Yet readmissions for heart failure and complication rates suggest that this cost-saving decision may be flawed. Similarly, a tRVAD may not in fact have a lower mortality and morbidity compared with a pRVAD [35, 38], and a planned insertion of a pRVAD has superior survival and reduced morbidity than an unplanned insertion [8].

Loforte et al reported in 2013 on 77 patients whom received an LVAD in combination with a right ventricular device [35]. They divided their groups as follows:

- A1: temporary RVAD implemented primarily (ie concurrently with the LVAD)

- A2: temporary RVAD implemented secondarily (Delayed up to 48 hours post LVAD insertion)
- B: BIVAD or total artificial heart (TAH)

The patients were all deemed to have a high risk of RV failure post LVAD insertion according to 3 different scoring systems: the Matthews', Fitzpatrick's, and Berlin scores. Furthermore, there was no significant difference in the scores between those whom received temporary or permanent RV devices. The only significant difference between group A and B was the presence of an IABP (76% vs 55%, respectively; p = 0.05), whilst all other demographic and pre-operative data were similar.

Interestingly, the stratification of patients for BiVAD or tempRVAD/LVAD was determined by the patients. All 46 patients in group A were worked up and planned for BiVADs, but were given the option of temporary RVAD support when they refused. Hence, patient preference distinguished which device was utilised.

Loforte found that survival to discharge was the same across the two major groups (56.5% vs 54.8%; p = 0.56). Similarly, 90 day and 6 month survival were no different. In fact, the most distinct findings in the study were between planned and unplanned temporary RV support (group A1 vs A2). Survival to discharge was better in the planned group (A1 57.1%, A2 45.4%; p = 0.04). A higher number of patients died whilst on support when tRVADs were delayed (A1 20%, A2 45.4%; p = 0.04), and were less likely to be weaned from their RV support device (A1 71.4%, A2 45.4%; p = 0.02).

Aissaoui et al performed a retrospective study on 173 patients from 2000-2011 whom received LVADs with a right ventricular device [39]. Amongst this group, 84 received BIVADs and 87 had LVAD with therapy for RV failure. Of these, 57 had LVAD combined with tRVAD, and 32 had LVAD with medical therapy for RHF. RV failure was defined as the need for a temporary RVAD, or inotropic therapy for more than 14 days post-LVAD insertion. The only differences across the groups were that BiVAD patients were younger than those who received medical therapy or temporary RVADs (50 vs 54yo; p = 0.011), as well as having a higher pre-operative CVP (15.8 vs 11.1mmHg; p = 0.005).

Mortality was seen to be significantly higher in the BiVAD group within 48 hours of surgery (8% vs 0%; p = 0.005). However, as with Loforte's findings, 6 month survival was no different between the BiVAD and non-BiVAD groups (52% vs 43%; p = 0.71). Importantly, survival to discharge was not reported.

Other differences were readmission for device related infections (26% BiVAD; 15% LVAD with RVF) and overall neurological complications (BiVAD 37%, LVAD with RVF 20%; p = 0.002).

Finally, readmissions for heart failure were significantly lower in the BiVAD group compared to the LVAD with RVF group (1% vs 11%; p = 0.02). Yet it is important to make note of how these groups were analysed. In this study, the grouping of LVAD with RVF was:

- LVAD + tempRVAD, or
- LVAD + medical therapy only

Unfortunately, there was no direct comparison of temporary and permanent RVADs in this case, with medical therapy grouped along with the temporary devices when comparing outcomes.

The current literature does not outline which patients would benefit from temporary over permanent RV mechanical support, and how to differentiate them. This is an area of ongoing research, and clear guidelines are lacking.

10. Right Heart Failure and Cardiac Transplantation

Right heart failure has been recognised as an independent risk factor of poor outcome pre- and post- heart transplantation.

The presence of an RVAD in conjunction with an LVAD has been found to be a risk factor for reduced survival to transplantation. Ochiai et al reported in 2002 on 245 LVAD-recipients [23]. 9% of the cohort necessitated a permanent RVAD, although no comment was made upon RVF post-LVAD insertion that did not require a permanent RVAD. Nevertheless, survival to transplant was significantly less in patients who had a RVAD (17% vs 74%, $p < 0.001$).

Baumwol reported in 2011 on 40 LVAD recipients and their survival to transplant [40]. They noted that survival to transplant was significantly impacted by LVAD recipients complicated by post-operative right heart failure 54.5% vs 90.9% ($p = 0.027$). Of the 13 patients who had post-LVAD RVF, only 3 received mechanical support in the form of a temporary RVAD. No comment was made on whether patients had a permanent RVAD inserted thereafter.

Ravis et al retrospectively analysed 221 patients in their centre on the waiting list for heart transplantation [41]. Initially categorised HE1 (highly-emergent category 1) - patients transpanted within 8 days of listing) patients were excluded in order to identify patients on a waiting list. This study reported that 47 candidates died whilst still on the waiting list (21.3%). Multivariate analysis determined that the only independent risk factors associated with waiting-list mortality was an LVEF<30% (HR 3.76, 95%CI 1.38-10.24; $p = 0.01$) and severe right ventricular failure (HR 2.89, 95%CI 1.41-5.92; $p = 0.004$). Once again, severe RVF (pre-operatively) was identified as an independent risk factor for post-transplant mortality on multivariate analysis (HR 5.38, 95%CI 1.38-10.24; $p = 0.02$). Importantly, only 19 patients had an LVAD pre-transplant (8.6%).

The literature clearly demonstrates that the need for a permanent RVAD and/or the presence of RV failure significantly impairs survival to transplant and even post-transplant outcomes. More data needs to be gathered to identify whether permanent or a temporary device will impact survival differently.

11. Summary

Right ventricular failure is a common complication, to some degree, following LVAD insertion and is a major cause of morbidity and mortality. It has also been found to reduce survival to transplant. The pathophysiology is complex, and, as such, the indication for a concomitant RVAD is not always clear. Several scoring systems exist that aim to predict RVF in hope of preventing the poor outcomes of a late RVAD insertion. These have yet to be validated in prospective cohort studies. Furthermore, they often require comprehensive assessment utilising right heart catheterisation and echocardiography – not always possible or accurate in the acutely unwell patient on ECMO. The role of temporary RVADs has been utilised more frequently in its various forms in more recent times. Its use has been driven by the desire to reduce morbidity and improve survival to transplant by avoiding biventricular devices. Although survival in the short-term has been comparable between permanent or temporary RVADs (amongst LVAD-recipients), overall morbidity and survival to transplant has not yet been shown to be advantageous. Further research needs to be performed to assist in guidelines to clarify guidelines for temporary versus permanent mechanical support in the LVAD-recipient.

Author Contributions

Both authors contributed equally to this work.

Competing Interests

The authors have declared that no competing interests exist.

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ORIGINAL ARTICLE

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A real-life experience with HeartMate III

Silvana F. Marasco MBBS,PhD, FRACS[1,2] | James Farag MBBS[1,2] | Christina Kure PhD[1,3] | Robyn Summerhayes BSc[1] | Michael Bailey PhD[4] | David McGiffin MBBS, FRACS[1,2]

[1]Department of Cardiothoracic Surgery, The Alfred Hospital, Melbourne, Victoria, Australia

[2]Department of Surgery, Monash University, Melbourne, Victoria, Australia

[3]Department of Medicine, Central Clinical School, Monash University, Melbourne, Victoria, Australia

[4]Department of Epidemiology, Monash University, Melbourne, Victoria, Australia

Correspondence
Prof Silvana Marasco, Department of Cardiothoracic Surgery, The Alfred Hospital, Commercial Rd, Prahran, Melbourne, VIC 3181, Australia.
Email: s.marasco@alfred.org.au

Abstract

Background: The HeartMate III (HM3) left ventricular assist device (LVAD) is the most recent LVAD to receive CE Mark and the Food and Drug Administration approval. It is a fully magnetically levitated pump with no reported haemolysis, pump thrombosis or pump failure in the first in-man study (a previous stody). It has now received market approval in the European Union, United States of America, and Australia. We reviewed our real-life experience with the device, to assess outcomes over the medium term.

Methods: We conducted a retrospective review of prospectively collected data for 33 consecutive patients implanted with a HM3 LVAD between November 2014 and October 2018 at The Alfred Hospital, Melbourne, Australia.

Results: Of the 33 patients, 31 remained alive at the census date, with only two early deaths and 11 patients transplanted. There were no pump thromboses, but there were three cases of clot ingestion (two on the right and one on the left). Seven patients required permanent biventricular assist device support. The duration of HM3 support at the time of census was a median of 196 (interquartile range, 118-386) days.

Conclusion: This series demonstrates excellent results of the HM3 LVAD in an uncensored, real-life, consecutive group of patients in a single institution.

KEYWORDS

HeartMate III, left ventricular assist device (LVAD), ventricular assist device (VAD)

1 | INTRODUCTION

The HeartMate III (HM3) left ventricular assist device (LVAD; Abbott, Chicago, IL), is a relatively new bearingless, magnetically levitated centrifugal VAD, which supersedes the axial flow HeartMate II VAD. The benefits of the HM3 are that it is a smaller, more compact pump designed to sit within the pericardium. It has a modular driveline designed to make the exchange of a damaged driveline easier and an artificial pulse built into the software, aimed at washing the rotor surfaces and eliminating stasis. The pump itself has wider gaps in the blood-contact surfaces to reduce shear stress, and thereby reduce thrombosis.

The first, in-man study of 50 patients, conducted in 10 centres across Europe, Kazakhstan, Canada, and Australia, demonstrated excellent results up to 12 months with no haemolysis, pump thrombosis, or pump failure.[1-3] Survival was 92% at 6 months and 81% at 12 months.

More recently a review of 27 patients receiving the HM3 LVAD, outside of a clinical trial setting, also demonstrated excellent results with 6-month survival of 85.2%,[4] 1-year survival of 85.2%,[5] and the absence of pump thrombosis or stroke events at either time point.[4,5] Although purporting to be a "real-life" experience with the pump, the study excluded patients with biventricular support, other types of assist devices such as extra corporeal membrane oxygenation (ECMO), VAD exchanges, and reoperative procedures. Furthermore, eight of the included patients were participants in the HM3 CE Mark trial.

The aim of our study was to present an uncensored, consecutive experience with the HM3 LVAD in our institution.

2 | MATERIALS AND METHODS

We conducted a retrospective review of prospectively collected data. All patients who underwent HM3 LVAD implantation at The Alfred Hospital, Melbourne, Australia between November 2014 and October 2018 were included in the analysis. There were no planned "destination therapy" patients as this indication is not funded in Australia. All patients were implanted with either a "bridge to transplant" or "bridge to candidacy" aim. Patients with Preoperative ECMO, right-sided mechanical support, redo sternotomy, concomitant procedures, and pump exchanges were all included. The census date was 28 December 2018.

All HM3 VADs were implanted via median sternotomy and on cardiopulmonary bypass support using standard techniques. Postoperatively, heparin infusion was commenced at 12 hours provided there was no untoward-bleeding risk. Warfarin (targeted international normalized ratio [INR] of 2.0-3.0, and aspirin 100 mg/d) were commenced once the patient had started oral intake. Pump speed on the left side was maintained within operating parameters of 5400 to 6000 rpm aimed for a mean blood pressure of 65-75 mm Hg. Regular echocardiographic assessment was used to adjust flows to ensure aortic valve opening.

Right-sided support was provided by a temporary centrifugal circuit or by off label use of the HM3 VAD.[6] Our operative technique for temporary[7] and permanent[8] RVAD implantation has been previously published. In brief, temporary RVAD support is provided by anastomosing an 8 mm Dacron graft to the main pulmonary artery and tunneling it through the anterior abdominal wall to the subcostal area where it is cannulated with a 21 or 23-F wire-reinforced arterial cannula (Maquet Cardiovascular, LLC; Wayne, NJ). A 23 or 25-F wire-reinforced venous cannula (Maquet) is placed percutaneously or through a cutdown over the right femoral vein, with its tip in the mid-right atrium. Both of the cannulae are connected to a Rotaflow centrifugal pump (Maquet) without an oxygenator. Flows are adjusted to maintain adequate filling of the LVAD and are monitored by echocardiographic assessment of interventricular septal position and ventricular cavitary size.

Permanent RVAD support has utilised the off label application of the HM3 pump, which we insert into the right atrium using multiple layers of Teflon felt as a "standoff" over the inflow cannula. Thus, only about 10 mm of inflow cannula is within the right atrium, and the pump sits away from the atrial wall, usually in the right pleural cavity. The outflow conduit is not banded but is kept fairly long by bringing it down along the diaphragm and then over the right ventricle beneath the left hemisternum and then anastomosed to the main pulmonary artery.

Use of ECMO to bridge patients to permanent VAD can stabilize patients in cardiogenic shock, improve end-organ function, and allow time for further assessment of suitability for VAD therapy. All ECMO patients in this series were supported by peripheral ECMO before VAD implantation. Peripheral cannulation of the femoral vasculature by Seldinger technique under ultrasound guidance is typically performed. A distal perfusion catheter is placed percutaneously in the limb with arterial cannulation to provide antegrade limb perfusion in all cases. Support is provided by a centrifugal pump, Biomedicus Carmeda-coated cannulae (Medtronic Inc, Minneapolis, MN) and a Quadrox D membrane oxygenator (Maquet Cardiovascular LLC, San Jose, CA). Patients are anticoagulated with intravenous heparin in the absence of bleeding complications, aiming for an activated partial thromboplastin time of 55 to 75 seconds. Patients who were not able to wean went on to have VAD implantation and are included in this study.

2.1 | Statistical analysis

This data was analysed using SPSS software version 25. Data was initially assessed for normality. Parametric data is reported as mean (standard deviation), nonparametric data is presented as median with an interquartile range, and categorical data presented as frequencies and percentages. Patient survival is reported as hazard ratios (95% confidence interval) and presented using a Kaplan-Meier curve. Biochemical variables were assessed for normality and as all were found to be well approximated by a log-normal distribution they were log-transformed before analysis. Differences between time points were determined using post hoc pairwise comparisons after fitting a main effect for time with each patient treated as a random effect. Results are presented as geometric means and ratios, both with 95% confidence intervals. To account for multiple comparisons, a reduced *P* value of .01 (or maybe even .001) was used to reduce the chance of a type I error.

3 | RESULTS

Between November 2014 and October 2018, 71 VADs were implanted at The Alfred Hospital, Melbourne, Australia. Of these, 33 were HM3 LVADs and the remainder were Heartware HVADs (Heartware Inc, Framingham MA). Only one patient (the first implant) was part of a study (the CE Mark trial).[1-3] The remainder were implanted under the Australian Special Access Scheme and with Therapeutic Goods Administration (TGA) approval from April 2018.

Demographics and preoperative characteristics of the patient group are outlined in Table 1. Perioperative data is outlined in Table 2.

Six patients were bridged from ECMO to HM3 LVAD support. Fourteen patients required temporary mechanical RVAD support and seven patients required permanent HM3 RVAD support. Of the seven HM3 RVAD implants, five were performed at the time of the LVAD implant due to severe right heart failure considered not to be reversible by the treating surgeon and cardiology team. Two patients supported by a temporary RVAD failed weaning and were converted to a HM3 RVAD; one at 11 days and one at 21 days post LVAD implant. The remaining 12 temporary RVAD patients were successfully weaned from the RVAD and had it removed.

TABLE 1 Preoperative and demographic data

Variable	HM3 (n = 33)
Male/Female, n (%)	31/2 (94/6)
Age, y	50 (13)
Height, cm	177 (7)
Weight, kg	79 (15)
Body mass index	25.7 (4.2)
Diagnosis	
Dilated Idiopathic cardiomyopathy	16 (49%)
Ischaemic cardiomyopathy	9 (27%)
Other	8 (24%)
Preoperative status	
Preoperative invasive ventilation	4 (13%)
Preoperative ECMO support	6 (18%)
Preoperative renal replacement therapy	2 (6%)
Preoperative hemodynamics	
LVEF, %	17 (6)
Cardiac index, $L \cdot min^{-1} \cdot m^{-2}$	2.2 (0.7)
Heart rate, bpm	85 [70-100]
LVEDD, mm	72 (10)
Mean right atrial pressure, mm Hg	11 (6)
Mean pulmonary artery pressure, mm Hg	25 (5)
Right ventricular stroke work index	707 (352)
Pulmonary capillary wedge pressure, mm Hg	25 (5)
Pulmonary vascular resistance (Woods units)	3.8 (2.2)
Transpulmonary gradient	13.4 (7.5)
Preoperative biochemistry results	
Estimated glomerular filtration rate	81 (26)
International normalised ratio	1.3 [1.2-1.6]
Activated partial thromboplastin time	34 [30–46]
Platelets	175 (66)
Preoperative echocardiography results	
Right ventricular systolic pressure	54 (19)
TAPSE	1.6 (0.5)
Right ventricular failure severity, n (%)	
None	2 (6%)
Mild	8 (18%)
Moderate	16 (49%)
Severe	9 (27%)
Preoperative tricuspid regurgitation, n (%)	
None	5 (15%)
Mild	5 (45%)
Moderate	11 (33%)
Severe	2 (6%)
Preoperative mitral regurgitation	
None	0
Mild	10 (30%)
Moderate	11 (33%)
Severe	12 (36%)

Note: Data presented as n (%); mean (SD); or median [IQR].
Abbreviations: ECMO, extra corporeal membrane oxygenation; HM3, HeartMate 3; IQR, interquartile range; LVEDD, left ventricular end diastolic diameter, mm; LVEF, left ventricular ejection fraction; TAPSE, Tricuspid Annular Plane Systolic Excursion.

TABLE 2 Perioperative data

Variable	HM3 (n = 33)
ECMO support at time of HM3 implant	6 (18%)
Redo sternotomy	5 (15%)
Aortic valve replacement	6 (18%)
PFO closure	2 (6%)
Temporary RVAD insertion	14 (42%)
Permanent RVAD insertion	7 (21%)
Cardiopulmonary bypass time (n = 33), min	100 (40)
Aortic cross clamp time (n = 6), min	36 (15)
Blood loss first 4 h, mL	350 (233-1700)
Return to theatre post sternotomy bleeding	12 (36%)
Intensive care unit stay, h	254 (158-1323)
Invasive ventilatory support, h	71 (27-768)
Cerebrovascular accident—permanent	1 (3%)
Cerebrovascular accident—temporary	1 (3%)
Hemofiltration—new renal failure	8 (24%)

Note: Data presented as n (%), mean (SD), or median (IQR).
Abbreviations: ECMO, extra corporeal membrane oxygenation; HM3, HeartMate 3; IQR, interquartile range; PFO, patent foramen ovale; RVAD, right ventricular assist device.

There was one LVAD exchange in the study cohort in a patient who had a HMII implanted 22 months earlier. Due to short-to-shield issues, the patient suffered a pump stop, and had the HMII exchanged for a HM3. Two patients, (both with known internal jugular or superior vena cava thrombus) suffered clot ingestion into the right-sided HM3. One required a pump exchange at 7 months post implant and one was successfully treated with heparinization. After 3 days of anticoagulation, that HM3 RVAD spontaneously recommenced operation without any obvious sequelae. The patient had remained stable without significant right heart failure during the period of RVAD pump stop. Overall, 41 HM3 devices were implanted in 33 patients. VAD operating parameters at discharge and follow-up visits are outlined in Table 3. Biochemical parameters preoperatively and postoperatively are outlined in Figure 1. Repeated measures of analysis of variance performed on log-transformed data demonstrated significant differences only between the peak postoperative values of alanine transferase, creatinine, bilirubin, and lactate dehydrogenase, and their measurements made at all other time points ($P < .001$). Otherwise the measurements did not significantly differ over time.

The duration of HM3 support at the time of census was a median of 196 (IQR, 118-386) days. This represents the equivalent of over 23.8 years of HM3 support analyzed in the left position. The analysis also includes 1767 days (4.8 years) of support in the right atrial position. The longest supported (LVAD) patient is also the first implanted patient and has been supported for 1469 days (over 4 years) at the time of census (and remains supported at the time of submission).

Eleven patients have been transplanted. A competing risks analysis is shown in Figure 2 and Kaplan-Meier survival in Figure 3. Two patients died in the postoperative period. One died on day 3 postoperatively from a large embolic stroke which was thought to have occurred intraoperatively from left ventricular cavitary thrombus ingestion. The second death occurred on day 12 postoperatively from multi-organ failure and sepsis, despite a temporary RVAD implanted at the time of the LVAD.

TABLE 3 VAD operating parameters

LVAD	Discharge (n = 28)	3 mo (n = 27)	6 mo (n = 16)	12 mo (n = 9)
Pump speed, rpm	5639 (386)	5663 (401)	5669 (353)	5733 (283)
Pump power, watts	4.3 (0.6)	4.5 (0.6)	4.4 (0.5)	4.6 (0.5)
Pulsatility index	4.7 (0.7)	4.8 (0.7)	4.7 (0.8)	4.8 (0.8)
RVAD	Discharge (n = 7)	3 mo (n = 7)	6 mo (n = 4)	12 mo (n = 2)
Pump speed, rpm	4867 (455)	5071 (482)	4900 (356)	5100 (283)
Pump power, watts	3.2 (0.6)	3.5 (0.5)	3.3 (0.5)	3.7 (0.4)
Pulsatility index	3.7 (1.2)	4.4 (0.7)	4.4 (1.1)	4.9 (0.8)

Note: Data presented as mean (SD)
Abbreviations: LVAD, left ventricular assist device; RVAD, right ventricular assist device.

Bleeding complications were prominent. Twelve patients required return to the operating room for bleeding. These events tended to occur within the first few days after VAD implant. Five patients had gastrointestinal tract bleeding, all occurring in the first 3 months post implant, and seven patients experienced recurrent epistaxis. One patient developed persistent intraabdominal bleeding in the early postoperative period requiring repeat laparotomies, before eventually recovering.

Two patients required revision of their outflow graft in the early postoperative period, for kinking. One patient required resternotomy 2 years after LVAD implant with erosion of the outflow graft from the driveline within the pericardium. One patient required a pleurodesis for recurrent effusions.

In terms of infective complications, eight patients had driveline infections requiring localized treatment. One patient developed a deep sternal wound infection requiring multiple debridements and eventual closure.

4 | DISCUSSION

In this series of 33 consecutive HM3 patients, we have presented a truly "real-world" consecutive unfiltered experience. Previous reports have excluded many high-risk patients in accounts of their HM3 experience and have included significant numbers of patients

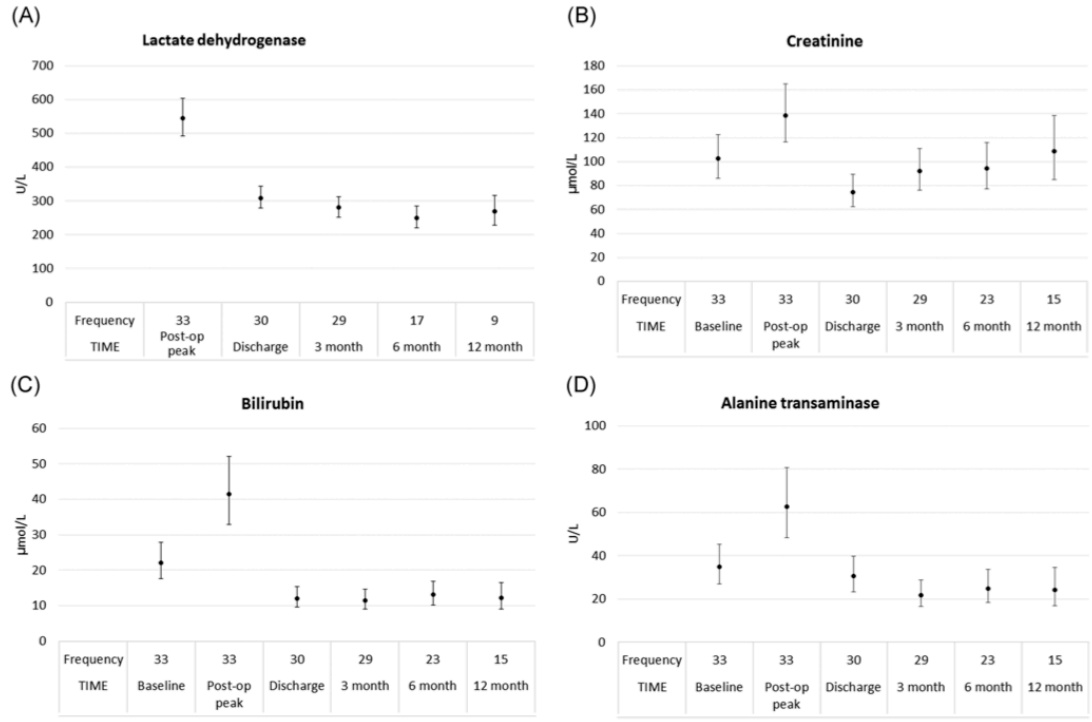

FIGURE 1 Biochemical results preoperatively, postoperatively, at discharge, and 3, 6, and 12 months post HM3 implantation, presented as geometric means and 95% confidence interval. A, Lactate dehydrogenase (U/L); B, creatinine (µmol/L); C, bilirubin (µmol/L); and D, alanine transaminase (U/L)

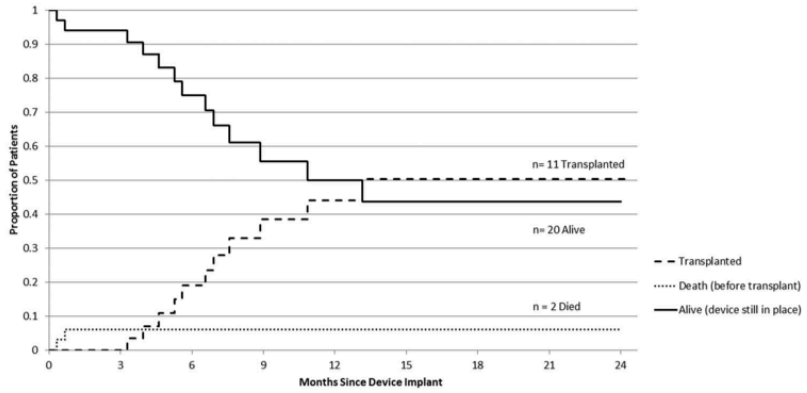

FIGURE 2 Competing risks curve for the HM3 LVAD (HeartMate III left ventricular assist device) patient series

enrolled as part of the European CE Mark trial.[4,5] Those reports excluded patients requiring concomitant procedures, mechanical right-sided support, pre-VAD mechanical support such as ECMO and redo sternotomies. All of these conditions are well known to increase mortality and morbidity in VAD recipients.[9,10] A recent report from Germany found that redo sternotomy increased the risk of mortality, blood product transfusion, hepatic and renal dysfunction, and ischaemic stroke after VAD implant compared to patients with no previous sternotomy.[9] In a separate publication, the same authors found preoperative ECMO to be associated with worse survival, increased right heart failure, respiratory failure and renal failure.[10] In our series, five (15%) patients were redo sternotomies, and six (18%) were supported on ECMO leading up to the VAD implant. This significantly increases the potential perioperative risk of our cohort according to those previously published studies. However, we have previously analyzed our own results for patients supported to VAD implant by ECMO, and found no significant reduction in survival.[11] Indeed, all six of the patients bridged to VAD by ECMO in this current series were alive at the census date, as were all five patients who had redo sternotomies.

More recently, the ELEVATE registry data has been released, describing results in a prospective observational multinational registry of 463 consecutive HM3 implants after commercial approval in Europe and Kazakhstan.[12] In that cohort, 12% of patients had

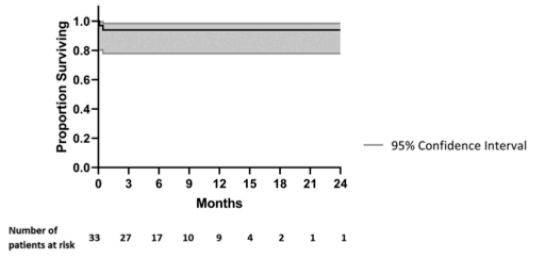

FIGURE 3 Kaplan-Meier survival curve for the time to all-cause mortality in patients who had a HM3 (HeartMate III) implant

preoperative mechanical circulatory support and 17% had previous sternotomy. These premorbid conditions are more in line with the cohort we have presented. However, the follow-up period in that study was brief with a survival of 90% reported at 30 days, improving to 95% if only primary implant patients were included. In contrast, our uncensored median follow-up of 6 months demonstrated a survival of 95%.

The CE Mark study and the ELEVATE registry did not identify any pump thromboses.[1-3,12] The much larger MOMENTUM study which compared the HM3 to the axial flow HMII, identified only seven cases of suspected or confirmed pump thrombosis in 516 patients implanted.[13] This contrasted significantly with 70 suspected or confirmed cases of pump thrombosis in the 512 patients implanted with the axial flow device. This appears to be an important benefit of the HM3 in comparison to previous generation VADs. Other case reports of HM3 thrombosis do exist, with one occurring as early as day 2. In that report, no identifiable kink or technical reason and no manufacturer fault was identified.[14] The proposed mechanism was inadequate anticoagulation soon after surgery and multiple low-flow events. Another pump thrombus occurring at day 8 has been reported, a possible mechanism in that instance being an off pump implantation.[15] At reoperation, a left ventricular clot was identified and removed and the pump exchanged but clot ingestion into the second pump and subsequent thrombosis again occurred. A third report, of a patient who died of multiorgan failure at day 229 post implant confirmed layered thrombus of differing age on the rotor of the explanted HM3.[16] It is evident, from all the reports thus far, that the thrombosis event rate in the HM3 is low compared to previous VADs. However, it is possible that the pump thrombosis rate is under reported. Reports of clot ingestion, as opposed to in situ thrombosis are almost always assumed and difficult to prove unless the VAD is explanted.

The design features of the HM3 were aimed specifically at reducing hematological complications and it appears at this stage that they have been successful in that endeavor. Specifically, the larger rotor gaps aim at reducing shear stresses on blood cells which are implicated in the acquired von Willebrand syndrome seen in almost all patients with

implanted continuous flow LVADs. A recent study comparing the multimeric structure of von Willebrand factor (vWF) between patients with a HM3 and HVAD found less reduction of high molecular weight multimers and a higher concentration of factor VIII in the HM3 patients indicating less shear stress to blood components in those patients.[17] The authors proposed that better flow characteristics due to larger blood flow paths and extended gaps between rotating elements were responsible for the higher stability of vWF multimers and lower platelet activation seen in the HM3 patients. This is a likely mechanism proposed for the lower thrombotic events being seen with this device in studies to date as outlined above.

Further support of the lower tendency to thrombotic events in the HM3 is the significantly lower stroke event rate seen over the longer term (181-730 days) in the 2-year, prespecified "as treated," secondary analysis of the MOMENTUM 3.[18] Although no difference in stroke events was found between the HM3 and HMII arms in the first 180 days post implant, the longer term follow-up revealed a 3.3 times lower event rate for the HM3 patients.

5 | CONCLUSIONS

Although we have presented a single-centre retrospective cohort of patients, it is completely uncensored, with all patients receiving a HM3 device in our institution being included for analysis. The study shows excellent survival and very low thrombosis rates in a real-world setting, confirming the findings in the more restricted enrolment environment of the landmark trials.

CONFLICT OF INTERESTS

With the exception for Prof McGiffin, who declares himself as a Proctor for implantation of Heartmate III, the remaining authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Concept/design: SM and JF; data analysis/interpretation: SM, JF, and MB; drafting article: JF; critical revision of article: SM and DMcG; approval of article: SM and DMcG; statistics: MB; Data collection: JF; other: RS and CK.

ORCID

Silvana F. Marasco http://orcid.org/0000-0001-7826-0986
David McGiffin http://orcid.org/0000-0003-4894-2518

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