MONASH University

Extracorporeal and Mechanical Circulatory Therapy for Patients with Advanced Heart and Lung Disease

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Abstract

International guidelines recommend the use of extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VADs) for patients with severe cardiac and respiratory failure who do not respond to less invasive treatments. Over the last two decades, improvements in device biocompatibility, coupled with a deficiency of cardiac and lung transplant donors, has led to widespread increase in use. However ECMO and VADs remain complex, high-risk and costly interventions, and many guidelines are based on low-quality evidence and expert opinion. There is a pressing need to improve the evidence base to inform the appropriate use of ECMO and VADs.

The aims of the research presented in this thesis were to 1) review the outcome measures and complications reported in the ECMO literature, 2) investigate the patient's pathophysiological response to ECMO, 3) review the cannulation technique in venovenous ECMO, 4) describe the complications of ECMO and VADs, 5) investigate a model of the inter-hospital transport of patients on ECMO, 6) investigate the long-term survival of patients after venoarterial (V-A) ECMO, and 7) investigate the utility of invasive investigations in patients with left ventricle assist devices.

To address these aims, the research followed the patient journey from initiation, complications, to long-term outcomes. Its first component was a systematic review of the outcome measures and definitions of complications being used in V-A ECMO research. In the second, in a prospective observational study, the impact of ECMO on the patient's immune-inflammatory response was investigated. The third was a review of cannulation techniques used to initiate ECMO. Fourth, a descriptive review of common complications in patients during ECMO and VADs. Fifth was a retrospective observational study of a model of inter-hospital transport of patients in ECMO. Sixth, a retrospective cohort study of the long term outcomes after ECMO. The final component was a prospective observational study of haemodynamic changes during long-term VAD support.

This research investigated many of the current methods and techniques used in ECMO and VADs, described the anti-inflammatory effect of ECMO, and highlighted the long-term outcomes for patients supported using these devices. It also highlighted the lack of high-quality evidence to inform ECMO practice globally. Through ongoing national ECMO research projects and the ECMONet consortium, this work will form the basis of a new international consensus on outcome and data definitions, the development of a new registry database, and a network of ECMO providers who will perform a large multi-centre randomised controlled trial.

General Declaration

Declaration for thesis based or partially based on conjointly published or unpublished work. In accordance with Monash University Doctorate Regulation, the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes six original manuscripts published in peer-reviewed journals (and a seventh manuscript currently under review). The core theme of the thesis is mechanical cardiac and respiratory supports in advanced heart and respiratory failure. The ideas, development and writing up of all the papers in the thesis were the principal responsibility of myself, the candidate, working within the Alfred Hospital and Monash Universities School of Epidemiology and Preventative medicine under the supervision of Professors Jamie Cooper and David Kaye.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

My contribution to the work, with the support of my supervisors, Professors Jamie Cooper and David Kaye, included developing the key aims and hypotheses of this thesis. Using both my literature review and clinical experience as an intensive care specialist with specific interests in advanced heart and respiratory failure, I was responsible for ethics applications, subject recruitment, data acquisition, data analysis and manuscript production for all studies, and I am the first author on all papers included in this thesis.

Declaration of Contribution

Thesis Chapter	Publication Title	Status	Nature and % of student contribution	Co-author name(s) Nature and % of contribution*	Co-author(s), Monash student
2	Venoarterial Extracorporeal Membrane Oxygenation: A Systematic Review of Selection Criteria, Outcome Measures and Definitions of Complications	Under Review	50%. Concept, development of search process, writing of the protocol and drafting and critical revision of the manuscript	V Bennett (5%) A Serra (5%) V Pellegrino (2.5%) L Romero (2.5%) E Fan (5%) D Brodie (5%) DJ Cooper (5%) D Kaye (5%) J Fraser (5%) C Hodgson (10%)	No
3	The Impact of Venovenous Extracorporeal Membrane Oxygenation on Cytokine Levels in Patients with Severe Acute Respiratory Distress Syndrome: A Prospective, Observational Study	Published	60%. Concept, development of search process, writing of the protocol and drafting and critical revision of the manuscript	M Lubnow (5%) T Enger (2.5%) V Nanjayya (5%) A Philipp (5%) M Malfertheiner (2.5%) D Lunz (2.5%) T Bein (2.5%) V Pellegrino (5%) T Müller (10%)	No
4	Cannulation Technique: Femoro-femoral	Published	75%. Concept, development of search process, writing of the protocol and drafting and critical revision of the manuscript	J Ihle (5%) V Pellegrino (5%) J Sheldrake (5%) P Nixon (10%)	No
5	Complications of Mechanical and Respiratory Support	Published	80%. Concept, development of search process, writing of the protocol and drafting and critical revision of the manuscript	B Salamonsen (5%) D Murphy (15%)	No
6	Retrieval of Adult Patients on Extracorporeal Membrane Oxygenation by an Intensive Care Physician Model	Published	75%. Concept, development of search process, writing of the protocol and drafting and critical revision of the manuscript	D Pilcher (10%) V Pellegrino (5%) S Bernard (10%)	No
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8	Clinical Utility of Invasive Exercise Hemodynamic	Published	60%. Concept, development of search process, writing of the	CHayward (10%) J Mariani (5%) A Leet (5%)	No

	Evaluation in LVAD Patients		protocol and drafting and critical revision of the manuscript	D Kaye (20%)	

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

Student signature [redacted] **Date:** 10-1-19

The undersigned 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 signature: [redacted] **Date:** 14-1-19

Acknowledgements

This thesis has spanned six years of my life. During this time I have completed my ICU examinations and fellowship, seen my one year old son Felix grow up and start school, shared the birth of my daughter Antonia with my wife, and began working as an ICU consultant. This thesis has been a witness to all of these life events, and now, as I complete it, it has become a life event in and of itself.

I would like start by thanking my supervisors. Professor Cooper knew when and how to help when it counted. He knew when to nudge me, when to support me and when to challenge me. He is made a huge contribution to ICU research in ANZ, and I'm extremely grateful to have had the opportunity to work with him and be his student.

Professor Kaye has been an outstanding support. This thesis grew out of my time working as a fellow in heart failure, where Professor Kaye's seamless integration of clinical work and research inspired me to pursue a career as a clinician researcher. His "door has always been open", be it for quick feedback, to help refine my ideas or provide sage advice.

My father has been an inspiration and a tireless support throughout my career. He has never told me how to do things (despite the many mistakes I've made!) – rather he always let me come to him. My mother's stubborn persistence "how is the PhD going?" constantly pushed me not to lose sight of the bigger picture and what is important.

I would like to thank all my co-authors, the researchers at the ANZICS RC, the cardiology research fellows, and the team in Regensburg who have all taught me the methods required to answer research questions, and the power of collaboration. I would also like to thank Dr Campbell Aitken who provided professional editing services in accordance with the Institute of Professional Editors' Guidelines for editing research theses.

The heart foundation provided me with very much needed financial support. And I would like to thank all the patients and their families who have agreed to be part of the research in this thesis, and for willing to submit to the proposition that studying things now will improve things in the future.

Finally I would like to thank my wife, who has put up with so much, the late nights, the weekends, the deadlines. She should be a recipient of this award as well.

Table of Contents

List of Figures

Note: Figures and tables in published articles and manuscripts submitted for publication are not listed here.

List of Tables

Acronyms and Abbreviations

AMI	Acute myocardial infarction
ANZICS	Australian and New Zealand Intensive Care Society
ARDS	Adult Respiratory Distress Syndrome
BLENDER	Blend to limit oxygen in ECMO trial
CI	Confidence interval
ECMO	Extracorporeal Membrane Oxygenation
ECMONet	Extracorporeal Membrane Oxygenation Network
ECOR	Extra Corporeal Carbon Dioxide Removal
ECPR	Extracorporeal cardiopulmonary resuscitation
ELSO	Extracorporeal Life Support Organization
EXCEL Registry	A collaborative approach to improve outcomes of Australian patients with acute heart failure and cardiac arrest requiring extracorporeal life support
FiO_2	fractional inspired oxygen
HFO	High-frequency ventilator oscillation
IABP	Intraortic Balloon Pump
ICU	Intensive care unit
INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support
LV	Left ventricular
LVAD	Left ventricular assist device
MCRCT	Multicentre randomised controlled trial

MRI	Magnetic resonance imaging
NHMRC	National Health and Medical Research Council
NICE	National Institute for Health and Care Excellence
NNT	Number needed to treat
PaO_2	Arterial oxygen partial pressure
PaO_2/FiO_2	Ratio of arterial oxygen partial pressure to fractional inspired oxygen
PEEP	Positive end expiratory pressure
RBC	Red blood cell
RCT	Randomised controlled trial
RIFLE	Risk, Injury, Failure, Loss, and End-stage kidney failure
RR	Relative risk
RRT	Renal replacement therapy
SaO_2	Arterial saturations
TMCS	Temporary mechanical heart supports
V-A	Venoarterial
VAD	Ventricular assist device
VILI	Ventilator induced lung injury
V-V	Venovenous

Publications, Conference Abstracts and Awards

Peer-reviewed publications arising from this thesis

Burrell AJC, Ihle J, Pellegrino VA, Sheldrake J, Nixon PT. Cannulation technique: femoro-femoral. *J Thorac Dis 2018*;10(S5):S616–23

Burrell AJC, Lubnow M, Enger TB, et al. The impact of venovenous extracorporeal membrane oxygenation on cytokine levels in patients with severe acute respiratory distress syndrome: a prospective, observational study. *Crit Care Resusc* 2017;19(Suppl 1):37–44.

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Invited national and international presentations arising from this thesis

2018 **Burrell A,** Blend to limit oxygen in ECMO: a randomised controlled trial (BLENDER trial). Noosa ANZICS Clinical Trials Group. Noosa, Queensland, Australia.

2018 **Burrell A,** V-A ECMO. Outcome measures and definitions of complications. ECMO Network (ECMONet) annual meeting, Rome, Italy

2018 **Burrell A,** BLENDER Trial. ECMO Network (ECMONet) annual meeting, Rome, Italy

2018 **Burrell A,** SCOPE Project – Core Outcomes in ECMO. ECMO Network (ECMONet) annual meeting, Rome, Italy

2017 **Burrell A,** Current Indications for V-A, V-V and ECPR. 27th Annual Congress of the Association of Thoracic and Cardiothoracic Surgeons of Asia. Melbourne. 2017.

2017 **Burrell A,** Techniques for ECMO Cannulation. 27th Annual Congress of the Association of Thoracic and Cardiothoracic Surgeons of Asia. Melbourne. 2017.

2017 **Burrell A,** Neuromuscular blockade in ARDS: "To paralyse or perish?" Alfred Advanced Mechanical Ventilation Conference (AAMVC), Melbourne, Australia July 2017

2017 **Burrell A,** E-DATM Early results, ECMO Network (ECMONet) annual meeting, Barcelona, Spain

2016 **Burrell A,** Patient selection for V-V ECMO. Reanimate ECMO training conference https://reanimateconference.com, San Diego, USA

2016 **Burrell A,** Indications for ECMO. ANZICS Annual Scientific Meeting, Perth, Australia

2016 **Burrell A,** Role of ECOR, Panel discussion, ANZICS Annual Scientific Meeting, Perth, Australia

2016 **Burrell A,** Long term outcomes session, Chair of session, Alfred Advanced Mechanical Ventilation Conference (AAMVC), Melbourne, Australia

2015 **Burrell A,** Right heart failure for the Intensivist. Victorian Intensive Care Network Meeting, Melbourne, Australia

2015 **Burrell A,** Optimizing your non-clinical time: a trainee's reflections. Victorian Intensive Care Network Meeting, Melbourne, Australia

Grants, scholarships and awards during doctoral candidature

2018 EXCEL Registry: A collaborative approach to improve outcomes of Australian patients with acute heart failure and cardiac arrest requiring extracorporeal life support. **NHMRC GNT1152793. Partnership Project.** CIs: Hodgson C, Cooper DJ, Bailey M, Fraser J, Pilcher D, Bernard S, Gattas D, Pellegrino V, Stub D, Higgins A. AIs: D. Brodie, H Buhr, **A Burrell**, E. Fan, S. Huckson, E. Litton, P. Nair. Orford, A. Udy. 2018-2021. **$692,657**

2018 Best New Presentation, BLENDER Trial. ANZICS Clinical Trials Group. **A Burrell** Noosa, Queensland, Australia.

2017 BLENDER Trial: Blend to Limit Oxygen in ECMO: A Randomised Controlled Registry Trial. **NHMRC GNT1152270. MRFF** Clinical Trials and Registries. CIs: Pilcher D, Hodgson C, Fraser J, Cooper DJ, **Burrell A**, Pellegrino V, Udy A, Gattas D, Bailey M, Higgins A. AIs: Hilton A, MacIsaac C, Litton E, Eastwood G, Buscher H, Ziegenfuss M, Orford N, Forrest P, Nair P, Bellomo R. 2018-2022. **$726,004**

2015 Alfred Hospital Senior Medical Staff Scholarship. **A. Burrell.** Presentation at the European meeting of ECMO (EuroELSO), Regensburg, Germany. $2500

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2015 Alfred Hospital Small Project Grant. Ivabradine in Sepsis for Heart Rate, Benefits and Disadvantages trial (IS-HR-BAD): an open-label Phase-II feasibility study. T Rozen, O Roodenburg, L Roberts, **A Burrell**, J Hare, A Udy **$10000**

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This chapter provides an introduction to advanced cardiac and respiratory diseases, the use of extracorporeal membrane oxygenation (ECMO) and ventricular assist devices (VADs), and the need to improve the evidence base for mechanical assist devices.

1.1 Overview of advanced cardiac and respiratory failure – definitions, epidemiology, severity, pathophysiology, and management

Definitions and epidemiology

Advanced cardiac and respiratory diseases have severe symptoms, are progressive and/or irreversible, and often require invasive treatments [1]. Cardiogenic shock is at the most extreme and acute end of the advanced heart failure spectrum. It is defined as hypotension (systolic blood pressure <90mmHg) causing a state of critical end-organ hypoperfusion due to reduced cardiac output [2].

The incidence of cardiogenic shock is approximately 6% of all admissions to intensive care units (ICUs), accounting for approximately 40 000 to 50 000 patients per year in the United States and 60 000 to 70 000 in Europe [3,4]. Acute myocardial infarction is the commonest cause of cardiogenic shock, accounting for 80% of all cases [5]. Other causes of cardiogenic shock are listed in Table 1.

Table 1. Common causes of severe cardiac and respiratory failure

Cardiac failure	Respiratory failure
Acute myocardial infarction	Adult respiratory distress syndrome
Acute on chronic heart failure	Pneumonia
Arrthymias	Extra-pulmonary sepsis
Fulminant myocarditis	Aspiration
Primary graft failure post heart transplant	Asthma
Post-cardiotomy (e.g., coronary bypass surgery, valve surgery etc.)	Chronic lung disease (e.g., cystic fibrosis, Pulmonary fibrosis)
Pulmonary embolus	Primary graft failure post-lung transplant

Respiratory failure is defined by an inability to maintain normal oxygen and carbon dioxide levels. It may be acute or chronic, and be characterised as either type 1, when it is primarily hypoxic respiratory failure (usually defined as SaO_2 <90% or PaO_2 <60 mmHg), or as type 2, when inadequate ventilation results in elevated carbon dioxide levels (>45mmHg). The commonest cause of hypoxic respiratory failure in the critical care setting is the adult respiratory distress syndrome (ARDS), which accounts for

approximately 10% of all ICU admissions [6]. The causes of severe respiratory failure are listed in Table 1.

Severity classifications

Advanced heart failure is classified into multiple stages (called Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS] stages) [7] (see Figure 1). Stages 1–3 define progressive stages of cardiogenic shock, with stage 1 – severe hemodynamic instability despite increasing doses of inotropes – being the most severe. These stages correlate with mortality, so that patients with INTERMACS stage 1 have mortality rates of 40–50%, while those with stage 3 have mortality rates of 20–30%

Table 13.2 INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) stages for classifying patients with advanced heart failure

INTERMACS level	NYHA Class	Description	Device	1y survival with LVAD therapy
1. Cardiogenic shock "Crash and burn"	IV	Haemodynamic instability in spite of increasing doses of catecholamines and/or mechanical circulatory support with critical hypoperfusion of target organs (severe cardiogenic shock).	ECLS, ECMO, percutaneous support devices	52.6±5.6%
2. Progressive decline despite inotropic support "Sliding on inotropes"	IV	Intravenous inotropic support with acceptable blood pressure but rapid deterioration of renal function, nutritional state, or signs of congestion.	ECLS, ECMO, LVAD	63.1±3.1%
3. Stable but inotrope dependent "Dependent stability"	IV	Haemodynamic stability with low or intermediate doses of inotropics, but necessary due to hypotension, worsening of symptoms, or progressive renal failure.	LVAD	78.4±2.5%
4. Resting symptoms "Frequent flyer"	IV ambulatory	Temporary cessation of inotropic treatment is possible, but patient presents with frequent symptom recurrences and typically with fluid overload.	LVAD	78.7±3.0%
5. Exertion intolerant "Housebound"	IV ambulatory	Complete cessation of physical activity, stable at rest, but frequently with moderate fluid retention and some level of renal dysfunction.	LVAD	93.0±3.9%[a]
6. Exertion limited "Walking wounded"	III	Minor limitation on physical activity and absence of congestion while at rest. Easily fatigued by light activity.	LVAD / Discuss LVAD as option	-
7. "Placeholder"	III	Patient in NYHA Class III with no current or recent unstable fluid balance.	Discuss LVAD as option	-

ECLS = extracorporeal life support; ECMO = extracorporeal membrane oxygenation; INTERMACS = Interagency Registry for Mechanically Assisted Circulatory Support; LVAD = left ventricular assist device; NYHA = New York Heart Association.
[a]Kaplan-Meier estimates with standard error of the mean for 1 year survival with LVAD therapy. Patients were censored at time of last contact, recovery or heart transplantation. Due to small numbers outcomes for INTERMACS levels 5, 6, 7 were combined[610].

Figure 1. European Society of Cardiology ESC 2016 Heart Failure Guidelines [8]

The severity of acute respiratory failure is most commonly defined using the 2012 Berlin definition of ARDS [9]. These criteria use three categories (mild/moderate/severe) based on the ratio of arterial oxygen partial pressure to fractional inspired oxygen (PaO_2/FiO_2 ratio). These categories have been shown to correlate with mortality, with severe respiratory failure having a mortality rate of 45%. A fourth category of $PaO_2/FiO_2<60$ – very severe respiratory failure – is also used clinically, though is not validated [10].

Table 2. Severity classification of respiratory failure in ARDS and mortality. ARDS Definition Taskforce [9]

ARDS Severity	PaO_2/FiO_2	Mortality
Mild	200–300	27%
Moderate	100–200	32%
Severe	<100	45%

Pathophysiology of cardiac and respiratory failure

Following an initial cardiac or respiratory insult (e.g., low cardiac output secondary to an acute myocardial infarction, or pneumonia with severe hypoxia and lung injury), a cascade of events occurs, including worsening local tissue damage and hypoxia, progressive system wide inflammatory mediator and cytokine release, multi organ failure and eventually death [11]. The cellular injury results from the initial cellular hypoxic injury, the resulting inflammatory cascade which leads to further hypotension [12] and accumulation of protein rich fluid in alveoli, damaging endothelium and alveolar lining leading to hypoxia and poor ventilation [13], and the treatments themselves, which are required to sustain life, such as high-dose vasopressors and inotropes, and mechanical ventilation leading to ventilator induced lung injury (VILI) [13].

If the process can be reversed early, before the onset of organ failures, the subsequent inevitable deterioration can be stopped and the patient can recover. Once organ failure becomes established, however, the process becomes irreversible despite treatments, and there is progression of multiorgan failure, and often death (see Figure 2).

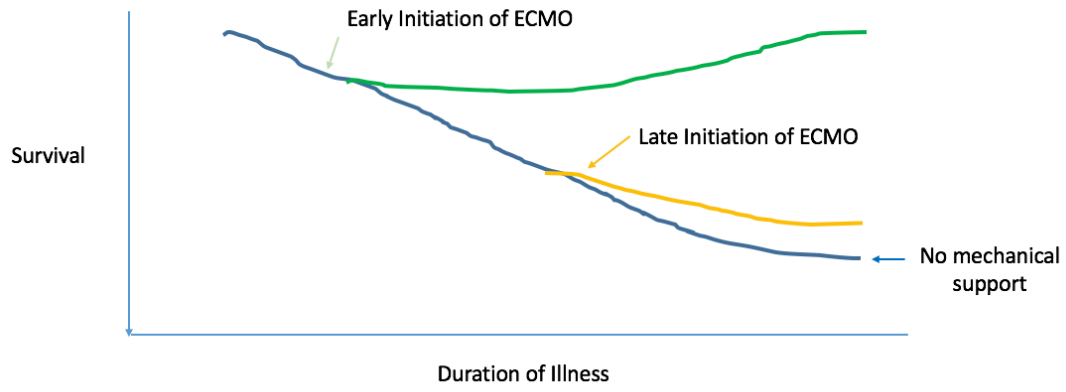


Figure 2. Stopping the descent into multiorgan failure and death: A proposed schematic

Medical management of advanced heart failure and cardiogenic shock

The overall goal of management of severe heart failure is to improve cardiac output and end organ perfusion, while also unloading the heart to allow cardiac rest and recovery. International guidelines recommend a combination of diuretics, intravenous fluid therapy, vasodilators, inotropes and vasopressors [8,14]. Patients refractory to pharmacological therapy often require intubation with positive pressure ventilation (which further unloads the heart) and/or renal replacement therapy. Concurrently with these supportive measures, patients are moved to the ICU for close monitoring, and reversible causes such as blocked coronary arteries are diagnosed and treated [15,16].

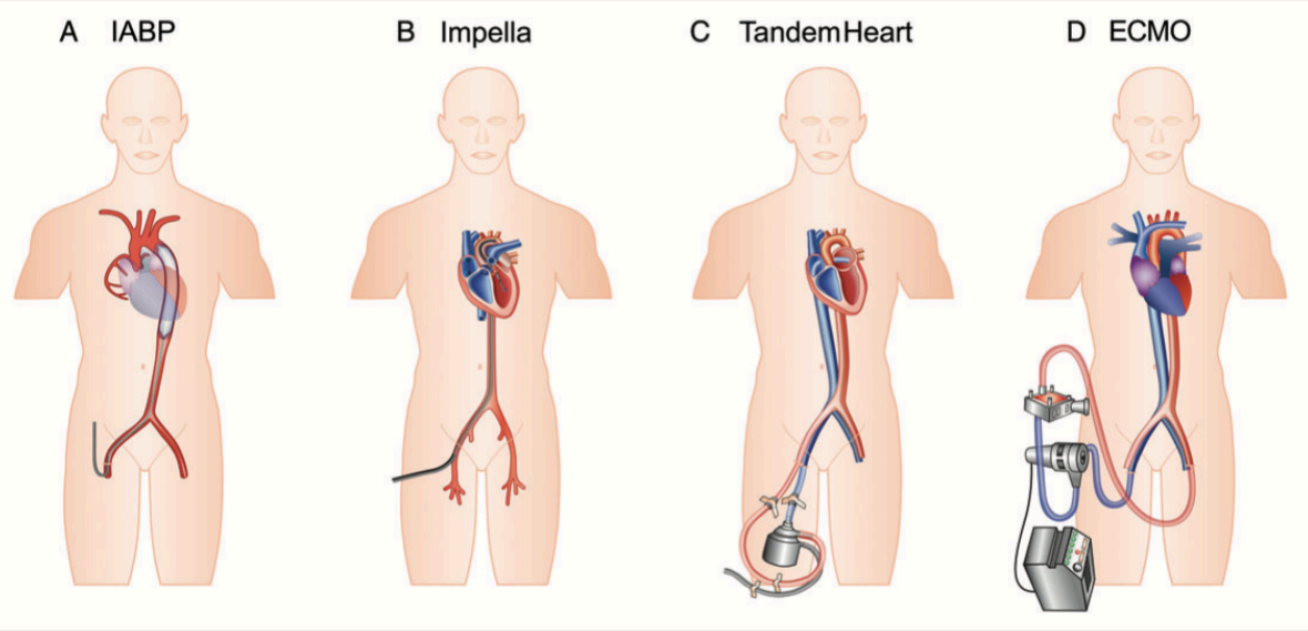


Figure 3. Percutaneous mechanical heart supports available to treat cardiogenic shock [17]

Types of mechanical cardiac supports

For patients with refractory heart failure or cardiogenic shock despite medical therapy, mechanical heart supports can be used to improve haemodynamic and end organ perfusion support. The intraortic balloon pump (IABP) was the first mechanical support to be widely available, and has been used since the 1960s [18]. A small (25-50cc) balloon is placed in the aorta, and through diastolic inflation and rapid systolic deflation, it can reduce myocardial afterload, increase diastolic pressure and improve coronary perfusion, although its ability to increase cardiac output is limited [4]. The IABP SHOCK II trial, published in 2012, compared a strategy of IABP insertion to standard medical treatment in patients with cardiogenic shock complicating acute myocardial infarction; there was no difference in the primary outcome of 30-day

mortality, or in any of the secondary outcomes. Following IABP SHOCK II publication, recommendations for IABP use were downgraded from class I to class IIIa in 2014 [19] and its use for cardiogenic shock has declined[20].

Several other types of mechanical cardiac assist devices are available, including the Impella® and the TandemHeart™ (see Figure 3). These devices have been shown to increase cardiac output and improve left ventricular unloading when compared to the IABP [21], but no mortality advantage has been demonstrated [22]. Both modalities are limited by the complexity of insertion (including the need for femoral arterial surgical cut down) and cost.

For longer-term support, the gold standard for advanced heart failure is cardiac transplantation. Cardiac transplantation has been shown to give improved duration and quality of life, however it is limited by donor availability, and is generally not used as an acute intervention in cardiogenic shock due to the high risk of failure (although some countries, such as France, use it for this indication).

Management of severe respiratory failure

The treatment of severe respiratory failure focuses on maintaining adequate oxygen and carbon dioxide gas exchange while preventing VILI [23]. Clinical practice guidelines recommend the use of lung protective ventilation strategies, which include low tidal volume and airway pressures, application of positive end expiratory pressure (PEEP), and increased respiratory rate to maintain adequate carbon dioxide removal [24]. Additional rescue therapies, including avoiding excessive fluids [25], use of neuromuscular blockade infusion [26] and prone positioning during mechanical ventilation [27], have been found to reduce mortality in patients with moderate to severe ARDS.

High-frequency ventilator oscillation (HFO) is a type of mechanical ventilator support that has been used in the past. Two large trials in 2013 showed no benefit and potential harm [28,29], and the use of HFO devices has since been decreasing.

Lung transplantation is reserved for patients with severe and irreversible lung disease. Similar to heart transplant programs, small numbers of donors mean very strict criteria must be applied, and patients with acute severe respiratory failure are usually ineligible.

Extracorporeal membrane oxygenation and VADs are primarily mechanical pumps that circulate blood. In addition to this, ECMO devices have an oxygenator to add oxygen and remove carbon dioxide from the blood. They may be within the body, directly attached to the heart (intracorporeal), or attached to major blood vessels with large tubes and circuits (extracorporeal). The ECMO system has similar components to a cardiac bypass machine, but differs in its intent and allows longer-term support

(days to weeks) [30]. It consists of a drainage cannula in the venous system, a centrifugal pump, and a membrane oxygenator. Blood is returned into the aorta for venoarterial (V-A) ECMO to support the failing heart, and is returned to the right atrium in venovenous (V-V) ECMO for severe respiratory failure. It can be initiated quickly by trained skilled intensivists at the bedside, without the need of advanced surgical skills or theatre time.

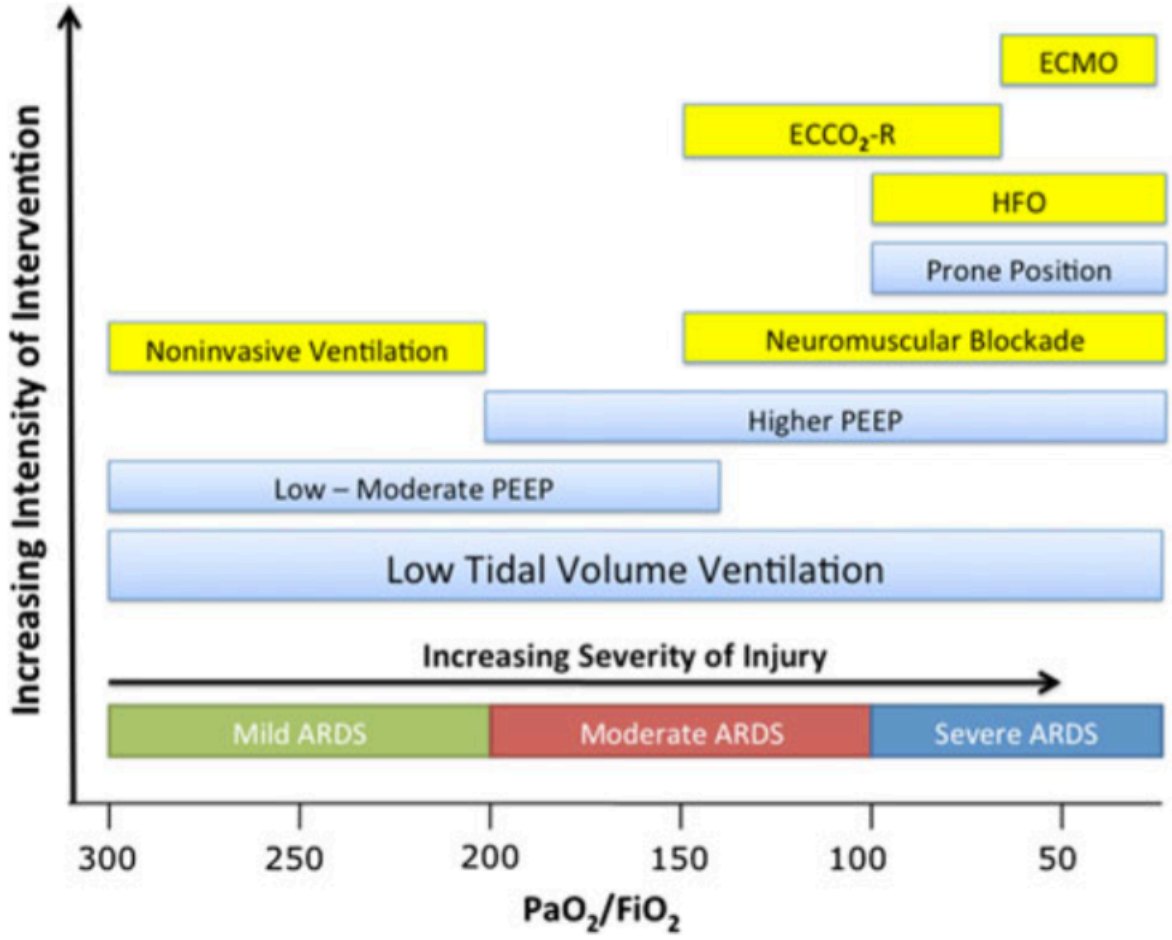


Figure 4. A schematic representation of the treatment options in the management of severe respiratory failure and ARDS patients [31]

1.2 Introduction to extracorporeal membrane oxygenation and ventricular assist devices

Ventricular assist devices draw blood from the apex of the left ventricle (LV), pass it through the pump, and deliver it to the ascending aorta via an outflow graft. These are surgically implanted devices which require journeys to the operating theatre and a sternotomy incision. They have a drive line which leaves the device and percutaneously exits the body to the power source. They can provide long-term

support, sometimes for many years. They are most often used as a bridge to transplant, although VAD destination programs are available in some countries [32].

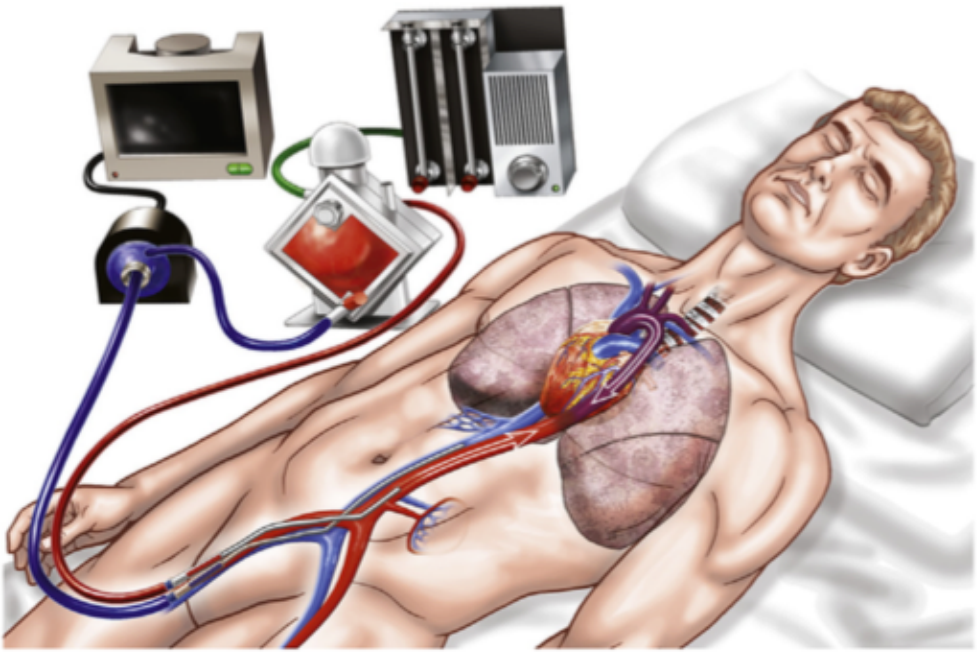


Figure 5. Fem-femoral venoarterial extracorporeal membrane oxygenation. Note return cannula is femoral artery [33].

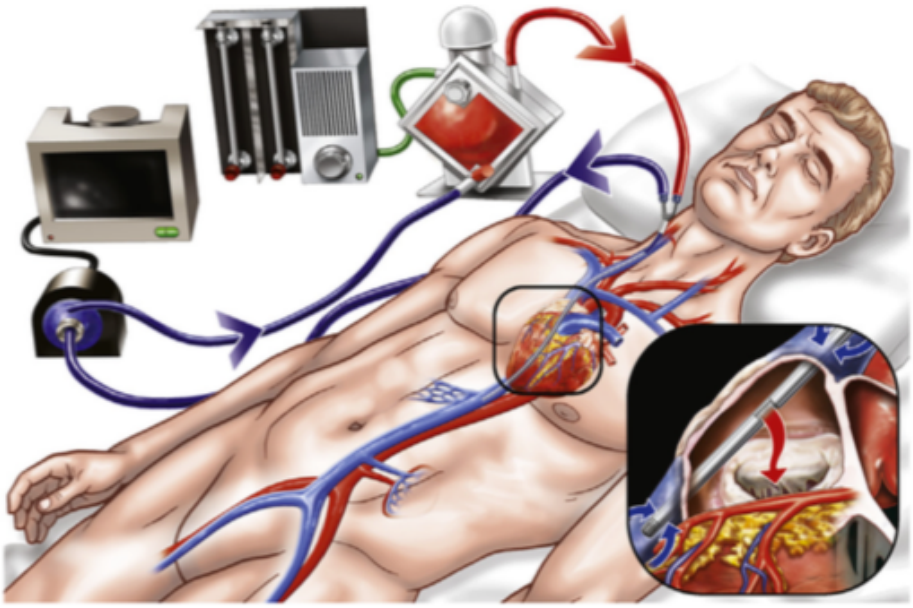


Figure 6. Single-site venovenous extracorporeal membrane oxygenation. Note both access and return cannulae enter via the internal jugular vein [33].

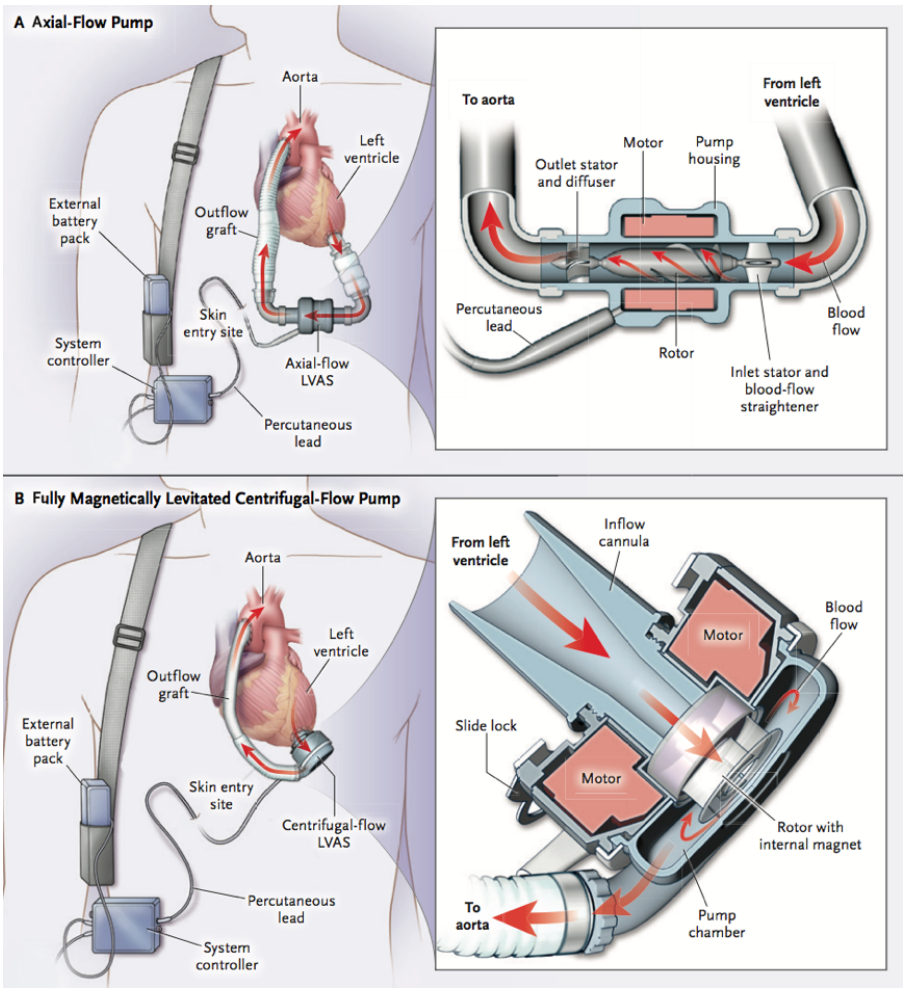


Figure 7. (A) HeartMate II pump – a continuous, axial pump that is inserted into the preperitoneal space. (B) A HeartMate III – a continuous, centrifugal pump that is inserted directly into the left ventricular apex and remains within the pericardial space *[34].*

1.3 Epidemiology and costs

In parallel with improvements in device design, the use of ECMO and VADs for adults with severe cardiac and respiratory failure has rapidly increased over the last decade [35,36]. The Extracorporeal Life Support Organization's (ELSO) international summary shows there were approximately 250 adult cases/year globally in 2009, while in 2015 there were over 2000 [37]. In Germany, which has a larger but otherwise similar health care system to Australia, the use of V-A ECMO for cardiac failure increased from 96 cases/year in 2007 to 2873 cases/year in 2014, representing an almost 2900% increase [38]. V-V ECMO cases in Germany similarly increased from approximately 800 cases/year in 2007 to 1944 cases in 2014. The global INTERMACS report shows large increases in the numbers of VADs being inserted, with now over 2500 cases/year [39].

The drivers of this increase in use include the publication of the IABP-SHOCK II trial in 2012, which demonstrated no benefit of IABPs for the treatment of cardiogenic shock [40]. In addition, in 2009, the H1N1 influenza epidemic [41,42] and the publication of the CESAR trial [43] resulted in an increased use of V-V ECMO for acute severe respiratory failure. Furthermore, the use of VADs has also increased following publication of two large trials, the REMATCH [44] and HeartMate II [44] trials, which showed more contemporary devices reduced complications and were superior to medical management.

The high costs of ECMO for severe acute cardiac and respiratory failure places it in the top three most expensive diagnosis-related groups in Australia, costing $243 929 per admission and a total cost of AUD$50 million per year [45,46]. In a recent study, the average cost of a VAD for a patiant in Australia was more than double that of a cardiac transplant, costing over $400 000 for the first 12 months [47].

1.4 Physiology and pathophysiology

Venoarterial ECMO provides support in severe cardiac failure via several mechanisms. It improves organ perfusion and coronary blood flow by returning pressurised and oxygenated blood into the arterial system [17]. It also supports the heart by draining blood from the right side of the circulation, reducing preload to the right and left ventricles.

A potential limitation of V-A ECMO is that it can increase LV afterload, which leads to an increase in wall stress, increase in left ventricular end diastolic pressure, and can lead to increases in oxygen demand which impede recovery [48]. Several strategies have been proposed to improve LV unloading during ECMO, including percutaneous and surgical LV venting, concurrent IABP use [49], and the addition of an Impella® [50]. The large arterial cannulas may also cause lower limb ischaemia, bleeding and infection, making it difficult to support patients on V-A ECMO beyond 2-3 weeks [51].

Ventricular assist devices drain the LV directly through the LV inflow cannula. They reduce preload and cardiac filling pressures, LV wall stress and oxygen consumption. Pressurised blood from the pump enters the aorta and maintains organ and coronary perfusion, [52]. Frazier et al have shown that left ventricular assist devices (LVADs) can improve LV function, including reducing the size of the LV (6.8cm->5.3cm), improve the ejection fraction (11%->22%) and lower pulmonary capillary pressure [53]. In some patients, these improvements can even allow the explantation of the LVAD [54].

Venovenous ECMO partially supports the respiratory system by oxygenating and removing carbon dioxide from the blood. This allows a more protective lung ventilation strategy via the ventilator and a reduction in VILI. This was shown in the recent

randomised EOLIA randomised trial of V-V ECMO for severe ARDS, where ECMO patients had lower peak pressures, lower PEEPs, and lower driving pressures than the control patients [55]. It is still unclear what the optimal ventilator settings are during V-V ECMO [56], although high driving pressures have been shown to be associated with worse outcomes [57].

1.5 History and development of extracorporeal membrane oxygenation and ventricular assist devices

The history of mechanical cardiac and respiratory support dates back to the initial discovery of bypass surgery in the operating room in the 1950s. Since then, mechanical supports have moved into the ICU, between hospitals with ECMO retrieval, and now to durable VADs, making it possible to support the patients to return to their homes, often as a bridge to transplantation.

Table 3. Key historical moments and landmark trials in V-A and V-V ECMO

1950s	1950–60s	1970	1980	1990s–2000s	2018
1953 – first clinical bypass machine	Improvements in oxygenator enabled longer ECMO support	1971 – first patient managed with ECMO (V-V ECMO post trauma) [58] 1972 – first V-A ECMO for transposition [59] 1972 – first newborn ECMO[60] 1979 – first RCT in V-V ECMO [61]	1984 – first RCT in paediatrics 1989 – second RCT in paediatrics	2008/9 – H1N1 outbreak 2009 – CESAR RCT	ECMO for ARDS EOLIA Trial

The cardiac bypass machine was the first means of mechanical cardiac and respiratory support. In 1953, John Gibbons developed the machine to provide a bloodless operating field during the closure of a large atrioseptal defect in the operating theatre [62]. Following this success, the whole field of cardiac surgery using cardiac bypass developed rapidly. However, the limitations of cardiac bypass soon became clear – those patients who could not be weaned off quickly would die within a few hours [63].

A problem for the early bypass and ECMO circuits was the oxygenator and the damage it caused to the blood. Initial oxygenators used direct gas exposure to oxygenate the blood (e.g., bubble or film oxygenators) [64]. These damaged the blood,

leading to significant haemolysis, bleeding and thromboembolism, and carried the risk of air embolism.

The technique improved following the development of the first (silicone) membrane oxygenators, which mimicked the alveolar membrane in the lung (with blood on one side and air/oxygen on the other). Oxygen, carbon dioxide and nitrogen could be exchanged across the membrane, whilst fluid was kept out. The membrane oxygenators were found to be less traumatic to the blood, which reduced complications and enabled longer duration of support. Animal models supported with these new oxygenators and circuits could be kept alive for up to four days [65]. These changes, along with a simplified circuit, allowed ECMO to move from the operating room to the ICU.

However the first membrane oxygenators still caused significant problems, including platelet adhesion, cytokine and factor release leading to inflammation and thrombosis, necessitating systemic anticoagulation [60,65]. More modern oxygenators are now made of polymethylpentine membrane. These oxygenator membranes are also now made of many small tubes ("hollow fibres"); gas runs through the fibres and blood runs over the outside. The microporous membrane has become extremely thin (<0.5mm), enabling the efficient diffusion of gas, but not blood, across the membrane. They are more biocompatible, with less platelet and plasma protein consumption and therefore fewer complications. They are coated with a thromboresistant coating which requires less anticoagulation and causes fewer associated complications [66]. They are also much smaller than early models, and have much less resistance to flow, which has reduced the amount of blood trauma. Ongoing issues with oxygenators include the amount of anticoagulation that is required, which must be balanced against bleeding complications, the impact of the hyperoxygenation of the blood, and concern around inflammation.

Pump technology developed alongside oxygenators. The first pumps were roller pumps, which were associated with minimal haemolysis. A key problem was however was the risk of circuit rupture if a clamp was placed on the outflow side. Centrifugal pumps have now replaced roller pumps; they are pressure limited, so a clamp will not lead to a circuit rupture. They also don't require a reservoir, which has enabled simplification and miniaturisation of design. They may also be associated with reduced blood trauma, haemolysis, and inflammation[67].

The circuit tubing has also evolved, and now is most commonly made of polyvinylchloride tubing. A recent development has seen them being bonded with substances such as heparin, which make them more biocompatible, reduce platelet adhesion and induce less inflammatory reaction [68]. These circuits may also enable less anticoagulation, which will lead to fewer and less severe bleeding complications. A further development has been the miniaturisation of both oxygenators and pumps,

which has made it possible to integrate the oxygenator and pump within one system, such as with the Cardiohelp®, making it ideal for ECMO-supported transportation [69].
Table 4. Key historical moments and landmark trials in ventricular assist devices *[70]*

1960s	1970s	1980s	1990s	2000s	2010s
1963 – first pneumatic LVAD pump inserted	1978 – LVAD used as a bridge to transplant	1984 – first electrically driven LVAD	Further electric pulsatile pumps developed	2001 – REMATCH trial – the first pulsatile VAD RCT [71] Development of continuous flow pumps [72]	2009 – HeartMate II DT 2010 – Intrapericardial pumps 2012 – ADVANCE Trial 2017 – MOMENTUM 3 pulsatile pumps

Despite these developments in ECMO technology, there remained an unmet need for more durable support in patients whose hearts didn't recover. Problems such as bleeding and infection become more common the longer ECMO support continues. Furthermore, the large percutaneous cannulas often translated into prolonged sedation and bed rest for the patient, which led to rapid muscle loss and clinical deconditioning, and ineligibility for transplantation. What was required was long-term support which would allow patients to wake up, mobilise, and potentially leave the ICU.

The first of these long-term cardiac specific devices were developed in the 1980s. These were large, extracorporeal, pneumatically driven pulsatile pumps. The pumps lived outside the patient, so large cannulas traversed the skin, and patients remained confined to bed.

In the 1990s the Thoratec XVE pump was developed. This was a smaller, electric pulsatile pump that could be fully implanted into the body, usually into an abdominal preperitoneal space called a pump pocket. This pump was much improved over earlier versions: it stopped the problem of large cannulas traversing the skin and sitting outside the body. The design was simplified, leading to improved durability and a reduced need to reoperate to repair broken pumps. Since the power source was electric, the pumps could now be driven by batteries which enabled improved patient mobility. The main problems that persisted were ongoing device failure, bleeding and sepsis [71].

In the 2000s, electric pulsatile pumps were replaced by continuous flow devices, such as the HeartMate II continuous flow axial pump (see Figure 7). These pumps used a rapidly spinning turbine to generate flow through the pump head. Patients with these devices no longer had a pulse but instead had a mean arterial pressure that could be measured by doppler ultrasound machines. These pumps were first trialled in patients awaiting cardiac transplantation and were shown to have lower complication rates than pulsatile pumps [72]. The lower rate of complications ultimately paved the way for expansion of LVAD programs, and to destination programs in which long-term LVAD support was a viable competitor to cardiac transplantation.

In the late 2000s centrifugal pumps (for example, HeartWare) began to challenge the traditional axial design. Centrifugal pumps have a rotating impeller, and can be made much smaller than axial devices, enabling direct implantation into the LV, permitting it to remain within the intrapericardial space. The pump pocket, which was a potential space for infection, was no longer required. Although not clearly shown to have a survival benefit or reduced complications over axial pumps [73], centrifugal VADs were desirable due to their simpler and smaller design.

The latest-generation pump, the HeartMate III, has been available since 2014. This uses a centrifugal mechanism, and is fully implanted into the pericardial space. Where it differs from previous LVADs is that its impeller is fully levitated via a magnetic current [34]. It is also significantly smaller, and has a regular fluctuating speed which induces some pulsatility (which may reduce thrombosis).

Despite all the progress, several key challenges remain for VADs. In the short term, bleeding and right heart failure are major early postimplantation problems. Later drive line infections can lead to major complicaitons, including sepsis and device infection, which are difficult to treat. Longer-term issues, such as aortic valve disease and pump failure, are also important as destination programs become more common and VAD patients are living longer.

1.6 Key trials in extracorporeal membrane oxygenation and ventricular assist devices

Table 5. Pivotal randomised controlled trials of adult ECMO and mechanical cardiac supports

Trial, Author, Year, Journal	Type	Study Design	Population	Intervention	Control	Primary Outcome
ECMO						
Zapol, 1979, *JAMA* [61]	V-A	MCRCT in 9 US centres	Severe respiratory failure	V-A ECMO	"ICU treatments" (not specified)	Hospital survival 5/42 (9.5%) vs 5/48 (8.3%) p=NS
Several paediatric trials followed, including Bartlet [74], [75] and [76]						
Morris, 1994, *American Journal of Respiratory and Critical Care Medicine* [77]	V-V	Single-centre RCT	40 Severe ARDS patients	Pressure controlled inverse ratio ventilation and ECMO	Protocolised mechanical ventilation	Primary Outcome Survival at 30 days: ECMO 33% vs control 42% p=0.8
CESAR Peek, 2009 *Lancet* [43]	V-V	MCRCT, 103 centres in UK	Severe ARDS	Protocol of transport and consideration of V-V ECMO in a specialist centre	No specific mechanical ventilation protocol	Death or disability at 6 months 57/90 63% ECMO allocation survived vs 41/87 (47%) conventional RR 0.69 0.05-0.97
EOLIA, Combes, 2018 *NEJM* [55] 2018	V-V	MCRCT in 64 centres in France and internationally	Severe ARDS	V-V ECMO	Protocolised lung protective ventilation, including	60 day mortality 44/124 (35%) vs 57/125 (46%) RR 0.76 P 0.09.

					NMB and proning	
Ventricular Assist Device						
REMATCH, Rose, 2009, *NEJM* [71]	VAD	MCRCT in 20 experienced cardiac transplantation centres in US	129 end stage heart failure patients not eligible for cardiac transplant	Pulsatile Thoratec HeartMate XVE	Optimal medical management	Death from any cause RR, 0.52 (0.34 to 0.78 P=0.001
HeartMate II DT (Destination therapy), Slaughter, 2009, *NEJM* [44]	VAD	MCRCT in 38 centres in US	200 Patients with advanced heart failure who were ineligible for transplantation	Continuous HeartMate II (axial)	Pulsatile HeartMate XVE	Survival at 2 y free of disabling stroke or reoperation for device repair or replacement 46% with HeartMate II vs 11% with HeartMate XVE *P*<0.001
MOMENTUM, Mehra, 2017, *NEJM* [34]	VAD	MCRCT in 69 US centres	294 Advanced heart failure patients (BTT or DT)	HeartMate III magnetically elevated centrifugal pump	HeartMate II axial pump	Survival free of disabling stroke or survival free of reoperation to replace or remove the device at 6 months HMIII 86% vs HMII 76% P<0.001 for noninferiority

MCRCT = multicentre randomised controlled trial

Table 6. Summary of international guideline recommendations for the use of ECMO and VADs

	ESC2016[8]	**AHA 2013** [14]	**ESC revasc 2014** [19]	**2015 SCAI/ACC/HFSA/STS Clinical Expert Consensus Statement** [52]	**ECMONet**	**ELSO**
V-A ECMO	"Temporary mechanical heart supports cannot be recommended as a proven or efficacious treatment for acute cardiogenic shock. In selected patients it may serve as a bridge to definite therapy"	IIa Level B	IIb Class C	"Early TMCS may be considered in those who fail to stabilize or show signs of improvement quickly after initial interventions" "Severe biventricular failure may require use of both right- and left-sided percutaneous MCS or veno-arterial ECMO" "When oxygenation remains impaired, adding an oxygenator to a TandemHeart circuit or use of ECMO should be considered"	No clear recommendation. "There is an ongoing need for controlled clinical trials and other high-level evidence to clarify the appropriate use of ECMO in severe refractory cardiogenic shock and other cardiac indications" [78]	"ECLS is considered in patients with a 50% mortality risk, ECLS is indicated in most circumstances at 80% mortality risk" [30]
V-V ECMO	-	-	-	-	No clear recommendation "Although some evidence suggests that ECMO may be life-saving in severe ARF, the risk-to-benefit ratio of ECMO in this setting has yet to be fully elucidated" [79]	In hypoxic respiratory failure due to any cause (primary or secondary) ECLS should be considered when the risk of mortality is 50% or greater, and is indicated when the risk of mortality is 80% or greater [80]
VAD	IIa Level C BTT IIa Level B DT	Class IIa Level B	IIa	-	-	-

IIa = "Moderate strength. Reasonable, can be useful/effective, probably recommended over alternatives". Benefit >> Risk

IIb = "weak, may be reasonable, may be considered, usefulness is unknown, unclear or not well established". Benefit≥Risk
Level C = RCT or observational or registry data with limitations in design
MCS = mechanical circulatory support
TMCS = temporary mechanical circulatory support

Although ECMO has been available for some centres since the 1950s and VADs since the 1980s, there is a scarcity of high-quality evidence to guide clinical practice. Furthermore, as the technology has changed rapidly, many of the older trials cannot be directly applied to contemporary conditions. Nevertheless, a review of the major trials, evidence base and guidelines in ECMO and VADs informs our current understanding and guides the best direction forward (see Tables 5 and 6).

Evidence and guidelines for ECMO for cardiac failure

There are currently no published randomised controlled trials (RCTs) comparing V-A ECMO with alternative treatments for the treatment of cardiogenic shock. Several observational studies suggest possible benefit. In a single centre before-and-after study, 219 patients with cardiogenic shock following acute myocardial infarction were treated with ECMO between 2002 and 2009 [81]. These were compared to a historical control group of 115 patients treated between 1993 and 2002 without ECMO. 30-day survival in the ECMO group was 60%, compared with 35% in the non-ECMO group ($p = 0.003$). A 2016 systematic review of observational studies suggested improved 30-day survival when compared to IABP, although no difference compared to TandemHeart/Impella [82].

Current international guidelines do not have consensus for the use of V-A ECMO in cardiogenic shock (see Table 6). The 2013 AHA guideline gave a IIA Class C recommendation, and the 2014 European guidelines recommended IIB level C recommendation. ELSO suggests “extracorporeal life support should be considered when the expected mortality rate is >50% and it “is indicated in most circumstances at 80% mortality risk”[30]. The guidelines in Table 6 emphasise the importance of individual hospital experience and careful patient selection, rather than the routine application of ECMO [83].

Evidence and guidelines for ECMO for respiratory failure

There have been four major RCTs in ECMO for adult respiratory failure during the last four decades. The first trial was published by [61]. ECMO was used to treat patients with severe acute respiratory failure. Hospital survival was 5/42 (9.5%) vs 5/48 (8.3%; no significant difference). The shortcomings of this trial were that V-A ECMO was used to treat the respiratory failure, which is no longer considered optimal, and ECMO was initiated on average 7–9 days after initiation of mechanical ventilation, when the disease had often become irreversible. In addition, older generations of ECMO support were at higher risk of thrombosis and bleeding.

In the second major ECMO trial, published in 1994, patients with severe respiratory failure underwent a strategy of V-V ECMO plus pressure-controlled inverse ratio ventilation compared to protocolised mechanical ventilation [77]. Survival at 30 days was lower in the ECMO group than in the mechanical ventilation group (33% vs 42%, $p=0.8$). Limitations of this trial include it being a single-centre trial, and was stopped early at 40 out of 60 planned patients due to lower survival in the ECMO group. Neither

of these first two trials is relevant to modern ECMO, because case selection, ventilation strategies and disease management were completely different from modern protocols, and circuit design has vastly improved [84].

The CESAR trial was published in 2009. Patients in the UK with severe potentially reversible respiratory failure were randomised to either transfer to a specialist centre for consideration for ECMO treatment, or to continue conventional ventilation in the original hospital. This trial reported improvement in survival at six months without disability after randomisation in the ECMO group compared to the conventional ventilation group (63% vs. 47%, relative risk [RR] 0.69; 95% confidence interval [CI] 0.05–0.97, p = 0.03, number needed to treat [NNT] 7). Limitations of this trial include that only 65/90 (75%) actually received ECMO in the intervention arm, so it may have been the specialist centre that provided the benefit, and the treatments in the control arm were not standardised.

The EOLIA trial, published in May 2018, randomised patients with severe ARDS to receive either V-V ECMO or standard protocolised mechanical ventilation strategy. The trial included current evidence-based practices, such as continuous use of neuromuscular blockade, and proning. The trial was stopped early due to a prespecified stopping rule, and was therefore underpowered to answer the primary outcome of day 60 mortality (35% vs 46%, RR 0.76, 95% CI 0.55-1.04, p=0.09). In addition to being underpowered, 28% of control patients crossed over and had rescue ECMO, making the interpretation of the result challenging. The interpretation of this trial has been controversial, but many have argued that the data in aggregate suggest a clinical benefit from ECMO over standard care, especially if initiated early rather than late[85].

The trials reviewed above highlight the many challenges in conducting clinical ECMO research. The low patient numbers that present to hospitals, the severity of illness, and the complexity of the intervention make completing RCTs very difficult. While there have been only a few trials, many other observational studies of ECMO for respiratory failure have been performed [86]. Many show potential benefit but are limited by their non-controlled design, lack of blinding, and considerable potential for bias. ELSO recommends *considering* ECMO when the risk of mortality is 50% or greater, and that it is *indicated* when the risk of mortality is 80% or greater. This definition can be difficult to apply in practice. The American Thoracic Society guideline for mechanical ventilation in ARDS [24], as well as the ECMONet guideline for respiratory failure [79], recommend *caution*, and that ongoing trials are needed to clarity the exact role of ECMO in the treatment of severe respiratory failure.

Evidence and guidelines for ventricular assist devices

Three major trials have assessed the role of VADs in the management of advanced heart failure. The first was the REMATCH trial [71]. This trial demonstrated that, in

patients with end-stage heart failure who were ineligible for transplantation, a pulsatile LVAD decreased the risk of death compared to best medical treatment (RR 0.52, 95%CI 0.34 to 0.78, p=0.001). The device used was an early model pulsatile Thoratec device, and there was a high rate of infection, bleeding and device malfunction. The next trial was the HeartMate II DT trial, published in 2009 [44]. This trial randomised 200 patients who were ineligible for cardiac transplantation, and compared a newer generation HeartMate II continuous flow axial device with an older HeartMate XVE pulsatile device. The primary composite end point of 2-year survival free from disabling stroke and reoperation to repair or replace the device was more common with the newer HeartMate II device than the older device (62 of 134 [46%] vs. 7 of 66 [11%], p<0.001, hazard ratio 0.38, 95% CI 0.27 to 0.54, p<0.001), suggesting both survival benefits and a reduction in VAD-related morbidity. The third trial was the recent MOMENTUM trial, which randomised 294 patients with end-stage heart failure (bridge to transplant or destination therapy patients) to either a newer HeartMate III (with magnetically elevated centrifugal pump and "pulsatility") or an older continuous Axial HeartMate II pump [34]. This trial reported improved patient survival, and an increase in patients free from disabling stroke or need for reoperation to replace or remove the device at 6 months (86.2% vs 76.8%, p<0.001).

Taken together, these trials, in highly selected trial populations, support the use of VADs over medical therapy, and also suggest that the newer miniaturised continuous flow devices have fewer complications than older models. The 2016 European Society of Cardiology guideline states that VADs should be considered in patients who have end-stage heart failure despite optimal medical and device therapy in order to improve symptoms, reduce the risk of heart failure-related hospitalisation and the risk of premature death, and to reduce the risk of premature death in those who are not eligible for transplantation (i.e. destination therapy) [8]. Likewise, the 2013 American College of Cardiology guidelines suggest the use of durable mechanical cardiac supports is reasonable to prolong survival for *carefully selected patients* with severe refractory heart failure [14].

In summary, high-level evidence to guide the use of ECMO and VADs is scarce, and is often limited to observational studies and expert opinion. Many older studies are no longer relevant to today's practice. Further high-quality evidence is needed to address these gaps in the future.

1.7 Patient selection – inclusion/exclusion criteria and timing

Inclusion and exclusion criteria

The decision for clinicians to initiate ECMO and VADs is complex. It involves weighing up multiple individual factors so that ideally only patients who will benefit are selected, whilst patients with irreversible disease, a high risk of death or no destination are excluded. Important factors that impact survival include the age of the patient, the

extent and number of chronic comorbidities, the cause and reversibility of the disease, the number of acute organ failures, acute physiological disturbance and the wishes of the patient. The decision to start ECMO must often be done quickly in a rapidly deteriorating patient, and therefore is often made without all information being available. Systems factors are also important and include the location of the patient and whether the patient needs to be transported, and the availability of resources (see Table 7).

In addition to the above factors, initiating VADs must be considered carefully since VAD support usually continues after hospital into the outpatient setting. Patients with unresolved psychological issues, drug or alcohol problems, or concerns around compliance are all relative contraindications to starting a VAD [87].

Table 7. Indications, absolute and relative contraindications for mechanical supports

	V-A ECMO	V-V ECMO	VADs
Indications	Post-AMI [88,89]	Severe ARDS [43]	Established heart failure
	Dilated cardiomyopathy (with an exit strategy)	Pneumonia and acute lung injury	Unable to wean inotropes
	Myocarditis [90]	Influenza [91]	
	Cardiac arrest		
	Post-drug overdose [92]	Aspiration	
	Post-cardiotomy [93]	Asthma	
	Primary graft dysfunction post cardiac transplant [94]	Chronic lung disease with an exit strategy	
	Massive pulmonary embolus [95]	Primary graft dysfunction post lung transplant [96]	
	Refractory arrythmias	ECMO as a bridge to lung transplantation	
	Sepsis associated cardiomyopathy		
Absolute Contraindications	>Mild aortic regurgitation	Chronic/terminal lung disease and no exit strategy	Sepsis
	Aortic dissection	Mechanical ventilation > 7 days	≥2 Major end organ failures
	Chronic heart failure with no exit strategy	Liver cirrhosis ≥CHILD B	Severe haemodynamic instability
	Severe peripheral vascular disease		Need for prolonged mechanical ventilation
			Uncertain neurological status
Relative Contraindications	Older age >65	Older age >70	Right heart failure
	Chronic organ failures	Immunosuppression [97]	Potentially reversible end organ failure
	Mechanical ventilation >7days	VILI prior to ECMO	Uncertain neurological status
	Severe coagulopathy	≥2 organ failures	Psychological issues [87]
			Drug or alcohol issues
			Compliance concerns

Timing of insertion

A key decision for initiating mechanical cardiac and respiratory support is what triggers to use and when to begin. Initiating ECMO or a VAD too early in the time course of the disease results in patients being exposed to the risk of the devices when they

ultimately would have recovered without them. However, initiating support too late, (known as rescue ECMO, or inserting a VAD at INTERMACS stage 1), when organ (renal or liver failure) are present, or following cardiac arrest, is associated with large increases in mortality [98],[99]. Table 8 shows commonly used triggers for initiating V-A ECMO, V-V ECMO and VAD supports.

Table 8. Commonly used triggers for initiating V-A ECMO, V-V ECMO and VAD supports

Venoarterial ECMO	**Venovenous ECMO**	**Ventricular assist devices** [8]
Increasing lactate or malperfusion despite: - inotropes - mechanical ventilation	Worsening oxygenation or CO_2 removal despite: - mechanical ventilation - high PEEP/FiO_2 - proning - nitric oxide	LVEF<25% and VO_2 <12Kg/min Unable to wean inotropes ≥3heart failure admissions/year without obvious precipitating cause Progressive organ dysfunction

Various scoring systems have been developed to improve decision-making around patient selection. These include the SAVE score [98] for V-A ECMO, the ENCOURAGE score for patients on V-A ECMO post-AMI [89], the RESP score for V-V ECMO [100] and the ECMONet score for H1N1 influenza requiring V-V ECMO [100,101]. The INTERMACS score has been used to predict outcomes post-VAD insertion [102]. Scoring systems can predict outcomes better than individual clinicians, as they can weigh each variable in the model more objectively and help with prognostication [103]. Limitations of scoring systems, however, are that they only include patients who are already on ECMO or have a VAD (and don't include patients who are excluded), and many models have not been validated to work on an individual patient level, but work on a population level only. Team-based decision-making is another important factor used to reduce individual bias and improve outcomes. Selection of patients and timing remains a major challenge, and future studies are need to define the optimal patients and timing for the initiation of ECMO and VADs.

1.8 Organisation of ECMO and VAD services

Centre volumes
Extracorporeal membrane oxygenation and VAD use has traditionally been limited to high-volume centres with considerable expertise. Benefits of this include the concentration of expertise, knowledge sharing, financial efficiencies and opportunities for research. In addition, ECMO should be managed at centres that can both initiate and provide long-term support therapies, such as VADs and transplant [83]. A relationship between ECMO patient volume and outcome has been shown [104]. Likewise, the organisation of VAD services is ideally limited to only centres with cardiac surgeons, theatres and perfusionists. It requires sternotomy, access to operating rooms, transoesophageal echocardiography, and specialist anaesthetists, heart failure services and VAD coordinators, and often is linked with transplant services.

Patient retrieval
Patients with severe cardiac or respiratory failure may present to any hospital, including smaller peripheral hospitals without advanced mechanical cardiac or respiratory support programs. However transportation of such patients with conventional supports is extremely dangerous and has been associated with significant morbidity [43]. Therefore, ECMO retrieval teams/services have been developed, staffed from the ECMO centre, to enable the safe initiation and transportation of patients from the peripheral hospital to specialist ECMO and VAD centres. The optimal way to organise this service has not been determined.

1.9 Outcomes after hospital

To date, much research for ECMO and VADs has focused on short-term outcomes, including in-hospital morbidity and mortality, and costs [105]. But as hospital survival increases following ECMO and VADs and intensive care, understanding the long-term survival and morbidity of these patients is becoming more important. Programs such as destination programs in VADs, which are real alternatives to cardiac transplants, need to be evaluated in the post-hospital period, but relatively little emphasis has been placed on these factors in research so far.

1.10 Summary of introduction

- Advanced cardiac and respiratory failure are life-threatening conditions with mortalities in excess of 40%.
- ECMO and VADs provide temporary circulatory and oxygenation support, enabling time for other treatments and recovery to occur.
- ECMO and VAD use has increased greatly over the last 20 years.

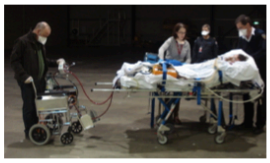
- Major developments have occurred in ECMO and VAD equipment over the last 50 years, including improved biocompatibility and miniaturisation.
- ECMO is indicated to treat cardiogenic shock or severe respiratory failure when failing conventional treatments.
- The costs of ECMO and VADs remains extremely high, therefore good patient selection remains essential.
- VADs are used for long-term cardiac support in those patients who don't recover.
- Although our understanding of the way these devices work and their complication rate has improved, there remains little evidence to guide much of their use.

Given this summary, the aims of the research presented in this thesis were to:

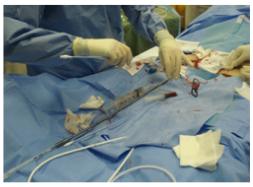
1) review the current reporting and definitions of outcomes and complications in V-A ECMO literature;
2) investigate the immune-inflammatory response to ECMO;
3) review the cannulation technique in V-V ECMO;
4) describe the complications of ECMO and VADs;
5) review a critical care physician-led system of ECMO retrieval;
6) investigate the long-term survival of patients after V-A ECMO; and
7) investigate the utility of invasive investigations in patients with LVADs.

1.11 Thesis structure

Chpt 5. Complications



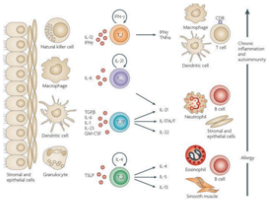
Chpt 6. Retrieval



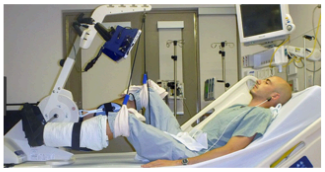
Chpt 4. Cannulation

Chpt 2. Definitions and Evidence Base

Chpt 7. Long Term Survival



Chpt 3. Inflammation



Chpt 8. Exercise Physiology

Chapter 2: Venoarterial extracorporeal membrane oxygenation

This chapter consists of a systematic review of the current reporting, outcomes and definitions used in V-A ECMO research. Studies were selected for study quality based on having ≥100 V-A ECMO patients and patient-centred outcomes measures. The aim of the study was to appraise the selection criteria, outcome measures, and definitions of complications used in current V-A ECMO studies. This work related to thesis aim 1.

Venoarterial Extracorporeal Membrane Oxygenation: A Systematic Review of Selection Criteria, Outcome Measures and Definitions of Complications

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Venoarterial Extracorporeal Membrane Oxygenation: A Systematic Review of Selection Criteria, Outcome Measures and Definitions of Complications

Abstract

Purpose:

The purpose of this study was to systematically investigate the reporting of selection criteria and outcome measures, and to examine definitions of complications used in venoarterial extracorporeal membrane oxygenation studies (VA-ECMO).

Materials and methods:

Medline, EMBASE and the Cochrane central register were searched from January 2005 to July 2017. We included all adult VA-ECMO studies. We excluded studies >12 years old, studies with ≤99 patients, and studies without patient centered outcomes. Two reviewers independently assessed search results and undertook data extraction.

Results:

Forty-six studies met the inclusion criteria, and all were retrospective, observational studies. Inconsistent reporting of selection criteria and outcome measures was common. In-hospital mortality was the most common primary outcome (41% of studies), followed by 30-day mortality (11%). Bleeding was the most frequent complication reported, most commonly defined as "bleeding requiring transfusion" (median ≥2 Units/day). Significant variation in reporting and definitions was also evident for other vascular, neurological and renal complications.

Conclusion:

This systematic review provides clinicians with the most commonly reported selection critieeria, outcome measures and complications used in ECMO practice. However non-

standardized definitions and inconsistent reporting limits their ability to inform practice. New consensus driven definitions of complications and patient centred outcomes are urgently needed.

Highlights

- This review highlights the commonly reported selection criteria, outcomes and complications used in VA-ECMO research.
- We found inconsistent reporting and significant variation of definitions used for complications.
- These findings highlight the problems aggregating and interpreting current VA-ECMO research.
- New consensus driven definitions of complications and patient centered outcomes are needed to address this.

Keywords Venoarterial; Extracorporeal Membrane Oxygenation; Heart Failure; Outcomes; Definitions

Abbreviations

Venoarterial (VA)

Extracorporeal Membrane Oxygenation (ECMO)

Venovenous (VV)

Extracorporeal cardiopulmonary resuscitation (ECPR)

Cardiac Index (CI) $L/min/m^2$

Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)

Computerised topography (CT)

Magnetic resonance imaging (MRI)

Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) Classification

Renal replacement therapy (RRT)

National Institute for Health and Care Excellence (NICE)

Extracorporeal Life Support Organization (ELSO)

Red Blood Cells (RBCs)

Introduction

As venoarterial extracorporeal membrane oxygenation (VA-ECMO) for cardiac failure becomes more widespread, high quality robust evidence is crucial to inform its appropriate use[1,2]. However, performing VA-ECMO research is challenging. It is a complex intervention with substantial inter-center variation in technique. Complications result from both the ECMO support and the patients' underlying illness. Furthermore, VA-ECMO for cardiac failure is uncommon, making it challenging to perform prospective trials with adequate power.

For clinicians, rigorous appraisal and understanding of the available data is essential to assist their clinical decision-making and delivery of care. High quality research methods, standardized outcome measures, and consensus driven definitions and complications are essential to facilitate ECMO research, which will in turn lead to better outcomes[3,4].

There has been little appraisal of the methodology and reporting used in current ECMO studies. Although several international guidelines exist, which include various definitions of ECMO and its complications, it is not clear how these have been adopted into practice[5-7]. The aims of this study were to systematically investigate the reporting of selection criteria and outcome measures, and to examine the common definitions of complications used in current VA-ECMO studies.

Methods

The protocol for this review was prospectively registered with PROSPERO (International prospective register of systematic reviews; (CRD42015030031). We adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for reporting this review[8].

Search Strategy

MEDLINE, EMBASE, and Cochrane central register of controlled trials (CENTRAL) were searched up to June 2017 for relevant studies. We manually searched systematic reviews and searched references of relevant studies.

Inclusion and exclusion criteria

We included interventional and observational studies of ECMO for cardiac and respiratory failure in English language (see search strategy in Supplemental Digital Content). Studies were excluded if they were pathophysiological studies without patient-centred outcomes, if they had ≤99 patients, if there were co-interventions where the focus was not ECMO, all nonhuman studies, and paediatric studies (age less than 18 years). Studies that were over 12 years old were excluded to account for the rapidly changing nature of the ECMO field. Studies that had a mixture of modes were excluded if the predominant type of ECMO was venovenous (VV) or extracorporeal cardiopulmonary resuscitation (ECPR).

Study Selection and data extraction

All screening and data extraction was completed using Covidence software[10]. Titles and abstracts of all identified studies were screened by two of three authors (AB, AS, VB), with discrepancies resolved by consensus. Full text review of eligibility was conducted by three authors independently (AB, VB, AS) and relevant data was extracted in duplicate from included studies. Discrepancies were resolved by discussion and adjudication by a fourth author (CH).

Outcomes

The primary focus was the reporting of patient selection (inclusion, exclusion, and diagnostic groups), ECMO management, primary and secondary outcomes, and definitions of complications.

Analysis

The comparison between the number of patients in single centre versus multicentre studies was performed using chi square test (SPSS (Version 24 SPSS Inc, Chicago, IL, USA). No formal meta-analysis was performed on this descriptive systematic review.

Results

Selected studies

The initial search yielded 2885 articles, of which 2309 were excluded through title and abstract review, leaving 575 potentially meeting our inclusion criteria. After a complete text analysis, 529 were excluded, leaving 46 studies, encompassing 20375 patients (Figure 1 and Supplemental Digital Content - Tables 1 and 2).

Description of studies

Of the 46 studies evaluated, all were observational and retrospective in design, with no randomized controlled trials. Thirty-seven (80%) were single centre studies, while nine (20%) were multicentre. There were no single centre cohort studies, and only 3 multicentre cohort studies. The ECMO modality was mixed (e.g VA plus VV or ECPR) in 13/46 (28%). Multicentre studies had larger median numbers of patients compared to single centre studies (322 vs 154; P≤0.01). However there were no differences in the number of prospective studies, interventional studies or in the use of multivariate analyses (See Supplemental Digital Content - Table 2).

Patient selection (Table 1).

An indication for ECMO was reported in forty-three (94%) studies, with the most common indication being "cardiogenic shock" and "refractory heart failure". Several terms, such as "heart failure refractory to treatment" were also used interchangeably. Thirty-three (72%) studies had specific physiological criteria (e.g., cardiac index [CI]) for initiating ECMO. The threshold for initiating ECMO for the 10 studies which reported a cardiac index was variable, with a median CI ≤2.0 L/min/m^2 (range ≤1.5-2.4 L/min/m^2) and a median for systolic blood pressure ≤80 mmHg (range 60-90 mmHg). Forty-three (94%) studies reported diagnostic groups, with the commonest being post-cardiac surgery (57%), followed by ECMO post-cardiac or respiratory transplantation (28%) and ECMO post-acute myocardial infarction (26%). Only 16 (37%) studies reported any exclusion criteria. A median age cut off of ≤80 years old was reported in 3 studies (range 65-80).

ECMO Management (Table 2)

The details of the ECMO pump were specified in 27 (59%) studies. Ten (22%) studies reported routinely using 2 or more brands of pumps, and Rotaflow® (Maquet), Capiox®

(Terumo) and Cardiohelp® (Marquet) were the most commonly reported. The type of oxygenator was reported in 23 (50%) studies, with Quadrox® and Affinity® (Medtronic) being the most common. A heparin anticoagulation strategy was reported in 24 (52%). The ECMO cannulation site was the most commonly reported information on cannulation 32 (69%). Sixteen (35%) studies reported the use of backflow cannulas with 9 (20%) performing these routinely, and 5 (11%) performing these on a selective basis.

Complications (Table 3)

Bleeding was the most commonly reported complication in 28 (61%) of studies. Twenty four (52%) of these studies defined bleeding more specifically. The most common definition was "bleeding requiring RBCs/transfusion". Two or more units was the most common threshold (4 studies), with studies ranging from ≥1 units to five units[11]. The time period used to define the amount of bleeding was rarely reported – but ranged from less than 6 hours[12] to 30 days[13]. "Bleeding requiring surgery" (eg surgical revision of a cannula or gastroenterological endoscopy) or "bleeding from cannulation or surgery" were the next most common definitions. Several studies used definitions from Extracorporeal Life Support Organization (ELSO), European coronary artery bypass graft (ECABG) bleeding definition, or the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) bleeding definitions (Supplemental Digital Content: Definitions Used in Studies).

Vascular complications were reported in 26 (57%) studies and 23 (38%) studies defined this in more detail. Ischaemia or thromboembolism were the commonest definitions: ischaemia (45%) was defined in several studies as "pallor, pulselessness, gangrene"[14] or diagnosed "clinically and corroborated by 2D ultrasound"[12]. No studies defined thromboembolism. In one study, compartment syndrome was defined as compartment pressure >30 mmHg[12],

fasciotomy was defined as "fasciotomy for compartment syndrome", and amputation rates were also reported. "Vascular injury requiring surgical repair" in 17 (37%) studies was defined in one study as "vascular injury requiring surgery, but not repair on removal"[15]. Neurological injury was reported in 25 (54%) studies, with many studies reporting the incidence of stroke or intracranial haemorrhage (ICH). However the method of diagnosis was only reported in 5 (11%) studies mostly commonly as "evidence of ischaemia or blood on computerised topography (CT) or magnetic resonance imaging (MRI) scans"[15-19].

Renal failure was reported in 24 (52%) studies. Acute kidney injury requiring renal replacement therapy (RRT) was the most common definition, followed by the Risk, Injury, Failure, Loss, and End-stage Kidney (RIFLE) classification (Supplemental Digital Content). Whether the RRT was initiated before or during the ECMO was not specified. Infection or sepsis was reported in 19 (40%) studies, but the majority had no stated criteria or definitions. Other less commonly reported complications included: cannula infection in 8 (17%) studies and equipment failure in 9 (20%) studies. Equipment failure was most commonly described as a circuit change in 5 (11%) studies, but also included oxygenator change and circuit thrombosis.

Outcomes measures (Figure 2)

A single primary outcome was reported in 21 (46%) of studies. The most common was in-hospital mortality in 19 (41%), followed by 30-day mortality in 5 (11%). In 23 (50%) studies there were multiple primary outcomes, and these were most commonly assessing mortality across multiple time points. A non-mortality primary outcome was the focus of 9 other studies, including vascular complications in 4 (9%)[12,20-22], bleeding events in 2

(4%)[23,24], central nervous system (CNS) complications in 2 (4%)[17,18] and infection in one (2%)[25] study.

Discussion

This systematic review describes the most commonly reported patient selection criteria, ECMO management strategies, and outcome measures used in VA-ECMO studies and clinical practice. We found the reporting of these domains was highly variable and inconsistent. We found substantial variability in the definitions used for complications. These findings have significant implications for the interpretation of current VA-ECMO research.

Similar to previous systematic reviews of VA ECMO [26,27], the vast majority of ECMO studies were single centre, retrospective, observational studies with a high potential for bias, and there were no randomized controlled trials. This reflects an overall low quality of evidence to guide practice[28].

In our study, we found the selection criteria for commencing ECMO was highly variable. For example, reporting of upper limits for age, number of organ failures, duration of mechanical ventilation and the type of disease process differed between studies. In one study, the threshold to commence ECMO was a cardiac index of <1.5 $L/min/m^2$ for entry[29], while another only required an index of <2.2 $L/min/m^2$[25]. These factors have been shown in published predictive models to have an important impact on overall outcomes [30]. Many studies also combined venovenous and extracorporeal cardiopulmonary resuscitation patients with VA-ECMO patients. The overall result is that very different patient populations enter

into each study, which in turn limits the ability to compare studies or draw firm conclusions [31].

We found the daily management of ECMO was poorly reported, with approximately 50% or fewer of studies including information on equipment or technique. ECMO is a complex intervention, and many individual aspects can impact outcomes. Poor description of the technique can limit the ability to reproduce and generalise to other systems, as well as limits the ability to compare across studies, as was recently observed in a meta-analysis of backflow cannulas[32]. The reporting was most detailed for cannulation site, type of ECMO pump, anticoagulation use, and weaning protocols.

The primary outcome reported in the studies was also highly variable, and most had a short-term focus. Short term outcomes can be insensitive to the effect of interventions[33] and maynot be as important to the patient or their family. As survival rates continue to improve in intensive care, functional outcomes, morbidity and long term survival are becoming more important measures of an intervention. This is reflected in the recent NICE guidelines for heart failure which recommend a combination of mortality and functional outcomes[34]. In our study, 50% of studies also had multiple primary outcomes, which can lead to reporting bias, as multiple outcomes increase the chance of false positive results, especially when not defined a priori.

The reporting of complications in the studies was also inconsistent, and few utilized standardized definitions, such as the Extracorporeal Life Support Organization (ELSO) or the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) definitions. A bleeding event was defined in some studies as “bleeding requiring

RBC's/transfusion", while in others a specific threshold was chosen, such as the number of units of RBC transfused per day. The time period used to define the event was also variable – from 6 hours up to 30 days. Descriptors such as "bleeding requiring surgery" were common but are subjective and are difficult to interpret between studies. Poor descriptions and subjectivity were also common in descriptions of ischaemia, thrombosis, acute kidney injury, stroke or intracranial haemorrhage, infection and cannula related infections. Selective reporting of complications can also lead to important other complications being missed[16]. For example, only reporting bleeding rates from femoral cannulation may miss other consequences such as lower limb ischaemia or amputation.

As ECMO becomes more common, ECMO research needs to move from smaller, single center studies to well-designed prospective trials, using consensus-based selection criteria, standardized definitions and patient-centered outcome measures. The result of the inconsistent reporting and the lack of standardization of definitions of complications described in this systematic review is that it reduce the capacity of metaanalyses to derive meaningful conclusions to inform clinical practice[35][17]. This review highlights the problems aggregating and interpreting current VA-ECMO research, and highlights the need for future development of consensus driven definitions of complications and patient centered outcomes

This review has a number of strengths. It was conducted using high quality systematic review methodology. A highly sensitive search strategy was developed which was independently reviewed by an information specialist in order to comprehensively cover the literature. In order to keep the studies current, the search was restricted to the last 12 years.

There are several limitations of this study. Studies with ≤99 patients were excluded as per this previous systematic review [9], however this may have excluded some lower volume centers. We also focused on studies with patient related clinical outcomes, which meant excluding certain pathophysiological studies.

Conclusion

This systematic review provides clinicians with the most commonly reported selection criteria, complications and outcome measures used in VA-ECMO studies and clinical practice. Clinicians need to be aware of the overall low quality of VA-ECMO studies, the inconsistent reporting of selection criteria and outcomes, and the lack of standardized definitions of complications. Consensus-based definitions and longer term outcomes are urgently needed to address this issue.

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Ethics approval and consent to participate:

All data presented has been previously published and referenced, and no patient or participants were contacted as part of the study.

Consent for publication:

All authors have given final approval of the manuscript.

Availability of data and material:

All data presented has been previously published and referenced.

Competing interests:

The authors declare that they have no competing interests.

Authors contributions:

Authors contributed in the following way: Conception or design of the work (AB, VB, AS, EF, DB, JF, CH), Data collection (AB, VB, AS, CH), Data analysis and interpretation (AB, VB, AS, EF, DB, VP, JF, DK, JC, CH), Drafting the article (AB, VP, JF, JC, DK, CH), and critical revision of the article and final approval of the version to be published (AB, VB, AS,

VP, LR, EF, DB, JC, DK, JF, CH).

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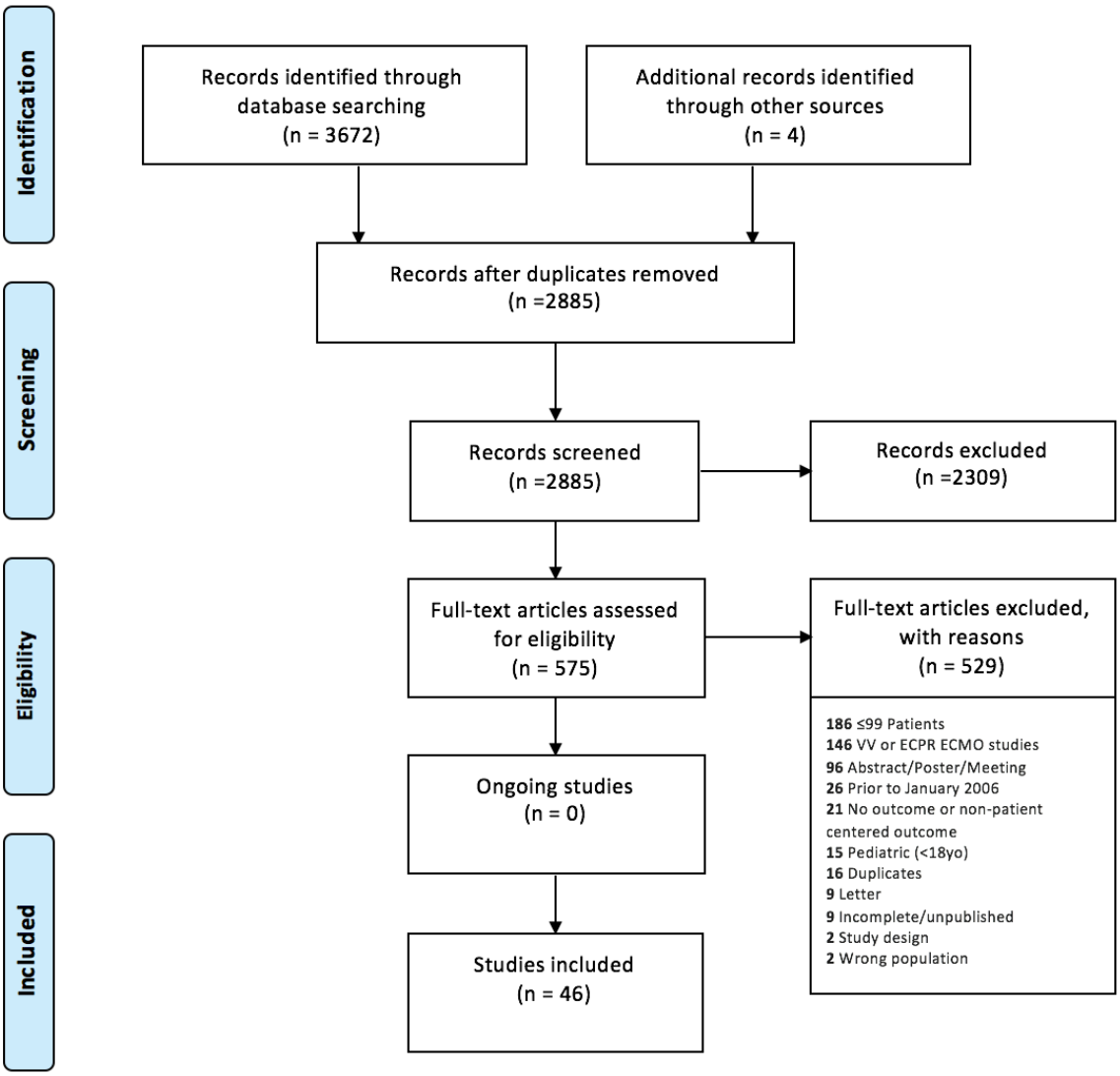

Figure 1: Venoarterial ECMO flow diagram 2006-2017

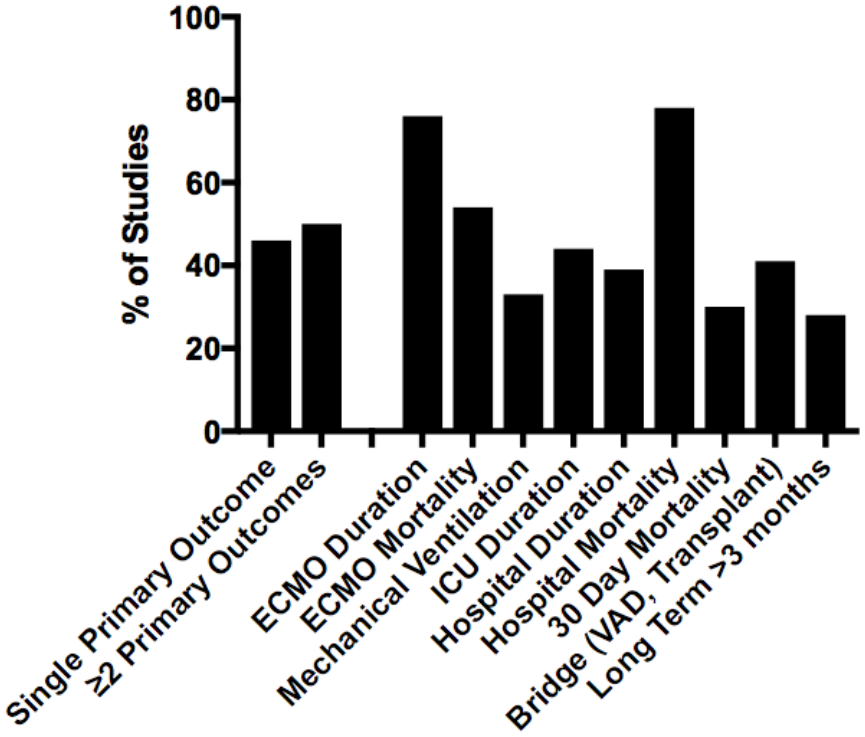

Figure 2: Studies reporting outcome measures

Table 1: All Studies Reporting Patient Selection Criteria for VA-ECMO

Selection Criteria	Specific or Defined Criteria	Total studies no, (%)
Indications	Cardiogenic shock/refractory cardiac failure	29/46 (63%)
	Post cardiotomy cardiogenic shock	18/46 (39%)
	Cardiac arrest	12/46 (26%)
	Failure to wean from bypass	6/46 (13%)
	Any indications reported	43/46 (94%)
Specific Physiological Criteria	Presence of or refractory to inotropes	19/46 (41%)
	Cardiac index (median ≤ 2.0 L/min/m^2, range 1.5-2.2)	10/46 (22%)
	SBP (median ≤80mmHg, range 60-90)	10/46 (22%)
	Presence of IABP[#]	19/46 (41%)
	Lactate (median ≥ 4 mmol, range 3-4)	3/46 (7%)
	Any specific physiological criteria	33/46 (72%)
Diagnostic Category	Post cardiac surgery	26/46 (57%)
	Post transplantation surgery (cardiac and/or respiratory)	13/46 (28%)
	Post acute myocardial infarction	12/46 (26%)
	Cardiomyopathy	12/46 (26%)
	Myocarditis	6/46 (13%)
	Acute decompensated heart failure	4/46 (9%)
	Any diagnostic category reported	43/46 (94%)
Exclusions	Malignancy	4/46 (9%)
	Age (Median ≥80, Range 65-80)	3/46 (7%)
	Irreversible organ damage	3/46 (7%)
	Death expected within 24hours	3/46 (7%)
	Multiple runs of ECMO	2/46 (4%)
	Irreversible neurological damage	2/46 (4%)
	Mechanical ventilation ≥7 days	1/46 (2%)
	Not for resuscitation order	1/46 (2%)
	Any exclusions reported	17/46 (37%)

ECMO - Extracorporeal membrane oxygenation; *SBP - Systolic blood pressure; [#] IABP – Intra-aortic Balloon Pump

Table 2: Studies reporting ECMO Management

Management	Details Reported	Total Studies n, (%)
Equipment	Type of ECMO pump	27/46 (59%)
	Type of oxygenator	23/46 (50%)
	IABP use	19/46 (41%)
Methodology	Anticoagulation use	24/46 (52%)
	Routine heparin administration	16/46 (35%)
	Bolus plus routine heparin administration	8/46 (17%)
	ECMO Weaning Protocol	20/46 (43%)
	Left ventricular venting	5/46 (11%)
Cannulation	Any Site	32/46 (69%)
	Femoral-femoral	31/46 (67%)
	Femoral-axillary	9/46 (20%)
	Central	18/46 (39%)
	Method of cannulation	25/46 (54%)
	Percutaneous	22/46 (48%)
	Open/Surgical	11/46 (24%)
	Backflow indication	16/46 (35%)
	Routine	11/46 (24%)
	Selective	5/46 (11%)

ECMO - Extracorporeal membrane oxygenation; IABP – Intra-aortic Balloon Pump

Table 3: Reporting and Definitions of ECMO Complications

Complication	Reported	Common definitions used	Total Studies n, (%)
Bleeding	28/46 (61%)	Bleeding requiring RBC's/transfusion (median ≥2 units, range 1-5U)	7/46 (15%)
		≥1Unit	4/46 (9%)
		≥2Units	1/46 (2%)
		≥3Units	1/46 (2%)
		≥4Units	1/46 (2%)
		≥5Units	1/46 (2%)
		Bleeding requiring surgical intervention	4/46 (9%)
		Bleeding from cannulation or surgery	3/46 (7%)
		ELSO[1] or ECABG[2] or INTERMACS[3] definitions	3/46 (7%)
		Any bleeding definition	24/46 (52%)
Vascular Complications	26/46 (57%)	Ischaemia or thromboembolism	21/46 (46%)
		Vascular injury requiring surgical repair	17/46 (37%)
		Compartment syndrome	3/46 (7%)
		Fasciotomy	3/46 (7%)
		Amputation	3/46 (7%)
		Any vascular complications defined	23/46 (50%)
CNS Injury	25/46 (54%)	CVA or ICH (not further defined)	8/46 (17%)
		Blood or ischaemia on CT/MRI	5/46 (11%)
		INTERMACS or ICD-9 or CPC scale definitions	3/46 (7%)
		Any CNS injury definition	23/46 (50%)
Renal Failure	24/46 (52%)	AKI requiring renal replacement therapy #	10/46 (22%)
		RIFLE classification	3/46 (7%)
		KDIGO[6], AKIN or ICD9 codes each	3/46 (7%)
		Any renal failure definition	21/46 (46%)
Infection/ Sepsis	19/46 (41%)	Sepsis (not defined)	4/46 (9%)
		CDC[6] or INTERMACS[7] definitions each	4/46 (9%)
		Positive sputum or blood cultures	2/46 (4%)
		Any Infection/sepsis definition	17/46 (37%)
Cannula Infection	9/46 (20%)	Local cannula site infection	4/46 (9%)
		Positive cultures	2/46 (4%)
		CLABSI or CRI criteria	2/46 (4%)
		Any cannula infection definition	8/46 (17%)
Equipment Failure	9/46 (20%)	Circuit change	5/46 (11%)
		Oxygenator change	4/46 (9%)
		Circuit thrombosis	2/46 (4%)
		Equipment failure defined	9/46 (20%)

ECMO - Extracorporeal membrane oxygenation; ELSO – Extracorporeal life support organization; CNS – central nervous system; ICH – Intracranial haemorrhage; CVA – Cerebrovascular accident; RIFLE - Risk, Injury, Failure, Loss, and End-stage Kidney definition; RRT – Renal replacement therapy; RBCs – Red blood cells; CT – Computerized Tomography; MRI – Magnetic resonance imaging; INTERMACS - Interagency Registry for Mechanically Assisted Circulatory Support; CDC – Centers for Disease Control; CLABSI - Central Line Associated Blood Stream Infection ICD-9 – International classification of diseases. ECABG – European coronary artery bypass graft bleeding definition; CPC – Cerebral performance category; KDIGO – Kidney disease: improving global outcomes definition;

Chapter 3: The impact of venovenous extracorporeal membrane oxygenation on cytokine levels in patients with severe acute respiratory distress syndrome

This chapter describes a single-centre observational study, conducted in Regensburg, Germany, of the interaction between V-V ECMO and the immune-inflammatory response of patients undergoing V-V ECMO for severe ARDS (the primary aim). Secondary aims were to investigate the impact of mechanical ventilation and mortality has on inflammation. This work related to thesis aim 2.

The impact of venovenous extracorporeal membrane oxygenation on cytokine levels in patients with severe acute respiratory distress syndrome: a prospective, observational study

A J C Burrell, M Lubnow, T B Enger, V B Nanjayya, A Philipp, M V Malfertheiner, D Lunz, T Bein, V A Pellegrino and T Müller

The inflammatory response is central to the pathogenesis of acute respiratory distress syndrome (ARDS), and if severe or unchecked, can lead to endothelial injury, end organ failure and death.[1] Venovenous (VV) extracorporeal membrane oxygenation (ECMO) has been shown to reduce mortality in patients with severe ARDS.[2,3] Little is known about the associated inflammatory/cytokine response of these patients on the commencement of ECMO, and what impact this has on overall outcomes.

Currently, conflicting data exist on whether ECMO is overall pro- or anti-inflammatory.[4] Exposure of blood to non-endothelialised surfaces has been shown to activate pro-inflammatory cytokines.[1,5-7] However, ECMO also restores oxygen supply to hypoxic tissue and enables ultraprotective lung ventilation (eg, tidal volumes of 3–5 mL/kg), which may reduce ongoing ventilator-induced lung injury (VILI) and organ failure.[8]

Understanding the inflammatory response of patients with ARDS who undergo VV ECMO is important. Many current therapeutic strategies are focused on influencing it, such as reducing VILI through lung-protective ventilation.[2,3,9] Cytokine removal has been discussed as a therapeutic target to control excessive inflammation. Inflammatory mediators may also enable better prognostication and improved patient selection.[5,10]

Our primary aim was to examine the immuno-inflammatory response in patients undergoing VV ECMO for severe ARDS.

Methods

Population and setting

From January 2009 to August 2015, all consecutive adult patients with ARDS who underwent VV ECMO in the University Hospital Regensburg (UKR), were included in the study. The UKR is a tertiary referral hospital in Germany which operates a regional ECMO referral service and performs over 100 ECMO runs per year. Patients were excluded if they had incomplete data on their cytokine levels, or if they did not have ARDS (eg, patients with chronic fibrotic diseases who were being bridged to lung transplantation, or patients who had had a near-drowning).

ABSTRACT

Objective: The immunoinflammatory response is central to the pathogenesis of acute respiratory distress syndrome (ARDS). However, little is known how this is affected by venovenous (VV) extracorporeal membrane oxygenation (ECMO). Our objective was to investigate the factors that influence the inflammatory response of patients with ARDS undergoing VV ECMO, and to analyse the impact of this response on hospital mortality.

Design and setting: A prospective observational study of all consecutive patients with severe ARDS who had VV ECMO at a tertiary German ECMO centre from 2009 to 2015. Patients without complete datasets were excluded. Cytokines (interleukin [IL]6, IL8 and tissue necrosis factor [TNF]〈) and inflammatory markers (white cell count and C-reactive protein) were assessed before ECMO initiation and on Days 1, 5 and 10, before explantation and at explantation.

Results: A total of 262 adult patients undergoing VV ECMO were analysed. Their median Sequential Organ Failure Assessment score was 12, Pa_{O_2}/Fi_{O_2} ratio was 64 mmHg, and overall in-hospital mortality was 34%. Cytokine levels fell quickly within 24 hours and fell further over the first 5 days. Extra-pulmonary ARDS was associated with higher IL6 and IL8 levels compared with pulmonary ARDS. Mechanical ventilation with positive end-expiratory pressure > 15 cmH_2O before ECMO was associated with higher IL6, IL8 and TNF〈 levels. Driving pressures above 19 cmH_2O before ECMO were associated with higher IL8 levels. Non-survivors had higher IL6 and IL8 levels for the duration of ECMO.

Conclusion: Cytokine levels, on average, fall rapidly after initiation of VV ECMO, which may be related to the reduction of invasiveness of mechanical ventilation. Higher cytokine levels are associated with extra-pulmonary causes of ARDS, more aggressive mechanical ventilation before VV ECMO, and mortality.

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ECMO indication and support

ECMO was initiated in patients with severe, potentially reversible respiratory failure, with a Pa_{O_2}/Fi_{O_2} ratio of < 80 mmHg on a positive end-expiratory pressure (PEEP) of ≥ 15 cmH_2O, and/or refractory respiratory acidosis (pH < 7.25), despite optimisation of conventional therapy. The ECMO circuit consisted of a centrifugal pump and a coated polymethylpentene oxygenator. Cannulation was performed percutaneously with the Seldinger technique. In most cases, a single-lumen access cannula (21-23Fr) was inserted into the inferior vena cava via the femoral vein, and a short return cannula (15-19Fr) was inserted into the right internal jugular vein. Mechanical ventilation was initiated according to the institution's standard protocol, and included an open-lung strategy with protective lung settings according to published guidelines.[11] Specifically, for mechanical ventilation during ECMO, tidal volume was rapidly de-escalated to an ultra-low volume (3–5 mL/kg) while the PEEP level was titrated individually to prevent atelectasis. Information on ECMO settings, manufacturers and the institutional protocol for patient management has been described previously[12] and is in the Appendix (online at cicm.org.au/Resources/Publications/Journal).

Data collection

De-identified information relating to pre-ECMO, procedural and post-ECMO characteristics was registered prospectively in the UKR ECMO database. The database contained patient demographic data and information on cardiorespiratory and laboratory parameters, duration of stay and complications. All patients were followed up until in-hospital death (non-survivors) or hospital discharge (survivors). The study was approved by the local ethics committee of the UKR, which waived the requirement for individual patient consent.

Laboratory data

Blood samples were collected daily from all patients. An extended laboratory investigation (including plasma levels of interleukin [IL]6, IL8 and tissue necrosis factor [TNF]〈) was done before ECMO initiation, on Days 1, 5 and 10, before explantation and at explantation. The samples were transported to the laboratory immediately after drawing. IL6 levels were measured straight away and IL8 and TNF〈 levels were frozen and analysed weekly. The IL6 level was analysed using electrochemiluminescence (Cobas e411, Roche Diagnostics), and IL8 and TNF〈 levels were analysed by chemiluminescence (Immulite 1000, Siemens Healthcare Diagnostics), according to the manufacturer's specifications.

Study endpoints and definitions

The primary endpoint of our study was to analyse the pattern of immunoinflammatory biomarkers over time in patients with ARDS receiving ECMO. Three subgroup analyses were performed. The first compared the inflammatory response between patients with ARDS of pulmonary origin (primary lung failure) and patients with ARDS of extra-pulmonary origin (secondary lung injury). Pulmonary ARDS included bacterial, viral or aspiration pneumonia; extra-pulmonary ARDS included lung failure secondary to sepsis or multitrauma.

The second analysis assessed the association of ventilator settings and cytokine levels. Ventilator settings before ECMO initiation were divided into above-median and below-median values, and the associated interleukin levels for each group were compared over the first 5 days. The third subgroup analysis compared the cytokine patterns between survivors and non-survivors.

Statistical analysis

We show continuous variables as medians with interquartile ranges (IQRs), owing to their non-normal distribution. Categorical data are shown as frequencies with percentages. Differences in plasma concentrations of immunoinflammatory mediators across diagnostic groups were assessed using the χ^2, Mann–Whitney *U* or Kruskal–Wallis tests, as appropriate, for categorical, 2-group continuous and multiple-group continuous variables. The cytokine level changes over time were analysed using multilevel models that account for repeated measures on the same individual. For more detailed information see Appendix E1. The repeated-measures analysis was performed using Stata, version 11.2 (StataCorp). All other statistical analyses were performed using SPSS, version 22.0 (SPSS) and SigmaPlot, version 12.0 (Systat).

Results

During the study period, 426 patients underwent VV ECMO for severe respiratory failure. A total of 114 patients with incomplete data and 50 patients requiring ECMO for non-ARDS were excluded, leaving 262 patients in the study population. The median age was 49 years (IQR, 37–60 years), the median SOFA score was 12 (IQR, 8–15), and the median duration of ECMO was 8 days (IQR, 5–14 days). Overall hospital mortality was 90/262 (34%).

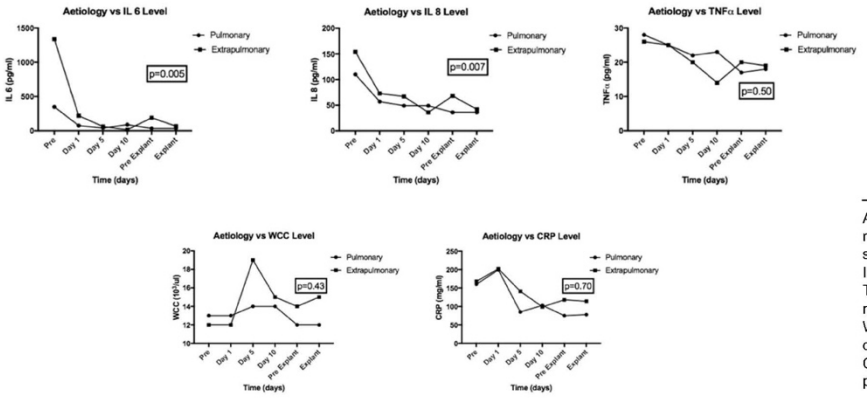
Patients with extra-pulmonary ARDS had higher pre-ECMO lactate levels, higher SOFA scores, and longer durations of pre-ECMO mechanical ventilation, compared with patients with pulmonary ARDS (Table 1). Ventilation settings before ECMO initiation were similar between groups. Mortality on ECMO (30% v 18%), hospital duration (37 days [IQR, 18–60 days] v 25 days [IQR, 14–40 days]), and in-hospital mortality (40% v 32%) were higher for extra-pulmonary ARDS. In contrast, patients with extra-pulmonary ARDS had shorter durations of ECMO support (7 days [IQR, 4–10 days] v 10 days [IQR, 6–16 days]).

Table 1. Characteristics of patients with pulmonary v extra-pulmonary ARDS

Characteristic	Total population (*n* = 262)	Pulmonary ARDS (*n* = 159)	Extra-pulmonary ARDS (*n* = 103)
Median age, years (IQR)	49 (37–60)	51 (39–60)	46 (30–58)
Women, *n* (%)	76 (28%)	51 (32%)	25 (24%)
Median duration of pre-ECMO ventilation, days (IQR)	1 (1–5)	1 (1–3)	3 (1–7)
Median pre-ECMO illness severity (IQR)			
PaO_2/FiO_2 ratio (mmHg)	64 (52–85)	64 (52–86)	62 (52–82)
$PaCO_2$ (mmHg)	64 (53–79)	67 (54–83)	60 (50–71)
Norepinephrine dosage (mg/h)	1.7 (0.6–3.3)	1.5 (0.5–3.0)	2.0 (1.0–4.0)
Arterial pH	7.22 (7.15–7.32)	7.23 (7.15–7.32)	7.21 (7.16–7.32)
Serum lactate (mmol/L)	2.2 (1.2–4.7)	1.8 (1.1–3.3)	2.9 (1.4–6.7)
SOFA score	12 (8–15)	11 (8–14)	13 (11–16)
Median pre-ECMO ventilation parameter (IQR)			
Tidal volume/kg PBW (mL/Kg)	7.0 (6.0–8.2)	7.1 (6.0–8.3)	7.0 (6.1–8.1)
Driving pressure (cmH_2O)	19 (16–22)	20 (16–22)	18 (16–22)
PEEP (cmH_2O)	15 (13–18)	15 (12–18)	15 (13–18)
Peak Pressure (cmH_2O)	35 (30–38)	35 (30–38)	35 (31–40)
Median hospital support duration, days (IQR)			
ECMO	8 (5–14)	10 (6–16)	7 (4–10)
Mechanical ventilation	12 (7–19)	12 (8–22)	11 (7–16)
Intensive care	26 (16–40)	23 (15–37)	30 (17–42)
Hospital	29 (16–48)	25 (14–40)	37 (18–60)
Mortality on ECMO, *n* (%)	59 (22)	28 (18)	31 (30)
In-hospital mortality, *n* (%)	89 (34)	48 (32)	41 (40)

ARDS = acute respiratory distress syndrome. IQR = interquartile range. ECMO = extracorporeal membrane oxygenation. SOFA = Sequential Organ Failure Assessment score. PBW = predicted body weight. PEEP = positive end-expiratory pressure.

Figure 1. Cytokine changes according to cause of ARDS



ARDS = acute respiratory distress syndrome.
IL = interleukin.
TNF = tumour necrosis factor.
WCC = white cell count.
CRP = C-reactive protein.

Pulmonary and extra-pulmonary ARDS

Figure 1 shows the trajectories of cytokine levels during the study period. The baseline cytokine level was significantly higher in patients with extra-pulmonary ARDS compared with patients with pulmonary ARDS. Patients with extra-pulmonary ARDS had higher pre-ECMO IL6 levels (1338 pg/mL [IQR, 214–8120 pg/mL] v 349 pg/mL [IQR, 79–3111 pg/mL]; $P < 0.01$), and IL8 levels (154 pg/mL [IQR, 55–223 pg/

Table 2. Estimated associations between type of ARDS, survival status and cytokine levels during the study period, from multilevel models

	Pulmonary v non-pulmonary ARDS*			In-hospital survivors v non-survivors*		
Variable	% Change†	95% CI	*P*	% Change†	95% CI	*P*
IL6	–59.9%	–78.73 to –24.29	0.01	–70.4%	–84.42 to –43.92	< 0.01
IL8	–52.7%	–72.59 to –18.39	0.01	–76.8%	–86.37 to –60.40	< 0.01
TNF(	–6.7%	–24.57 to 15.33	0.52	–23.2%	–38.02 to –4.85	0.02
WCC	9.77%	–12.95 to 38.41	0.43	53.6%	22.03 to 93.36	< 0.01
CRP	–5.16%	–27.70 to 24.41	0.70	17.7%	–10.62 to 54.93	0.25

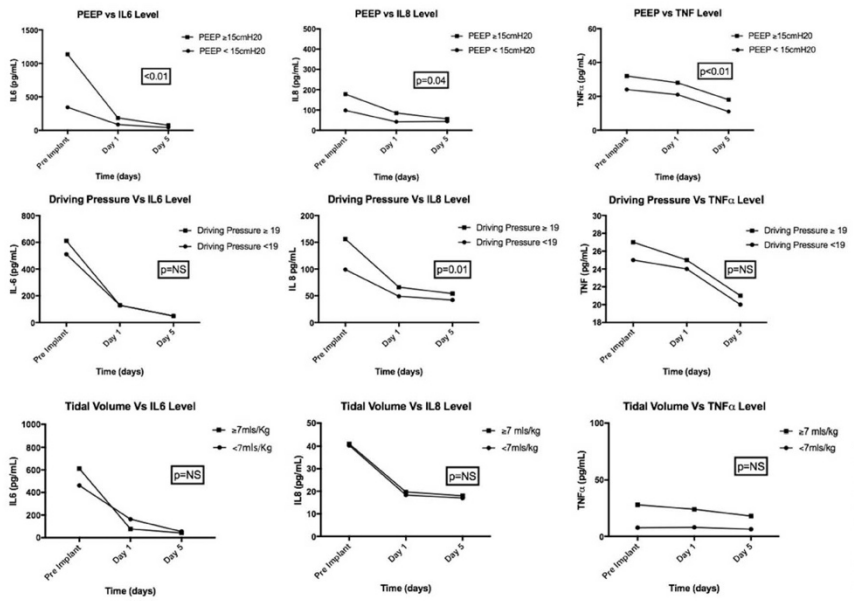
ARDS = acute respiratory distress syndrome. CI = confidence interval. IL = interleukin. TNF = tumour necrosis factor. WCC = white cell count. CRP = C-reactive protein. * Reference category in the comparison groups. † Per cent change of geometric mean of the cytokine level in the comparison group (pulmonary ARDS or in-hospital survivors) compared with the reference group (non-pulmonary ARDS or non-survivors).

mL] v 110 pg/mL [IQR, 36–338 pg/mL]; *P* = 0.02). The multilevel model (Table 2) showed that in the extra-pulmonary ARDS group, the geometric mean of the IL6 level was 59.9% higher compared with the pulmonary ARDS group (95% CI, 24.29–78.73%; *P* = 0.01). Similarly, the IL8 level was higher in the extra-pulmonary ARDS group (difference in geometric means, 52.7%; 95% CI, 18.39–72.59%; *P* = 0.01). The IL6 and IL8 levels dropped rapidly after ECMO initiation, particularly over the first 5 days, and then remained stable. TNF(levels were not different between groups with different causes of ARDS. In contrast, the white cell count (WCC) was only mildly elevated before ECMO, and increased in the extra-pulmonary ARDS group in Days 1–5. C-reactive protein (CRP) also increased from pre-ECMO to Day 1, then fell in the next 10 days.

Pre-ECMO mechanical ventilation

The associations between the cytokine levels in three different sub-groups, based on their pre-ECMO ventilation status, are shown in Figure 2. The top three graphs in

Figure 2. Cytokine changes according to ventilation settings (PEEP, driving pressure and tidal volume)



PEEP = positive end-expiratory pressure.
IL = interleukin.
TNF = tumour necrosis factor.
NS = not significant.

Figure 2 compare the trajectory of cytokine levels in the group who received PEEP ≥ 15 cmH_2O with those who received PEEP < 15 cmH_2O. The IL6, IL8 and TNF〈 levels were higher in patients who had PEEP ≥ 15 cmH_2O (Table 3). The bottom three graphs in Figure 2 show the trajectories of cytokines in patients who had tidal volumes of < 7 mL/kg v those with tidal volumes > 7 mL/kg. The multilevel modelling showed that the level of cytokines did not differ significantly between the two groups over the duration of the study (Table 3). Similarly, the cytokine level variation over time was compared between patients who received mechanical ventilation with driving pressure < 19 cmH_2O and > 19 cmH_2O (Figure 2, middle three graphs). The multilevel modelling showed higher IL8 levels in patients who had a driving pressure ≥ 19 cmH_2O. There was no difference in IL6 or TNF〈 levels.

In-hospital survival

Figure 3 shows the differences in IL6, IL8 and TNF〈 levels between in-hospital survivors and non-survivors. ECMO non-survivors had higher pre-ECMO median IL6 levels than survivors (1237 pg/dL [IQR, 148–17 246 pg/dL] v 400 pg/dL [IQR, 89–2850 pg/dL]) and higher median IL8 levels (260 pg/dL [IQR, 76–1786 pg/dL] v 83 pg/dL [33–326 pg/dL]). Pre-ECMO median TNF〈 levels were not different between the groups (31 pg/dL [IQR, 16–60 pg/dL] v 25 pg/dL [IQR, 16–48 pg/dL]). These differences persisted over Day 1. IL8 levels remained higher on Day 5 and at explantation. WCCs were significantly higher in non-survivors than survivors (Table 3). The levels of CRP were not different between survivors and non-survivors. The multilevel modelling showed higher IL6, IL8 and TNF〈 levels in non-survivors during the study duration. There was a marked reduction in cytokine levels after ECMO initiation in both groups for IL6 and IL8, which lasted until ECMO Day 5. In contrast, for TNF〈, a reduction occurred after Day 1.

Discussion

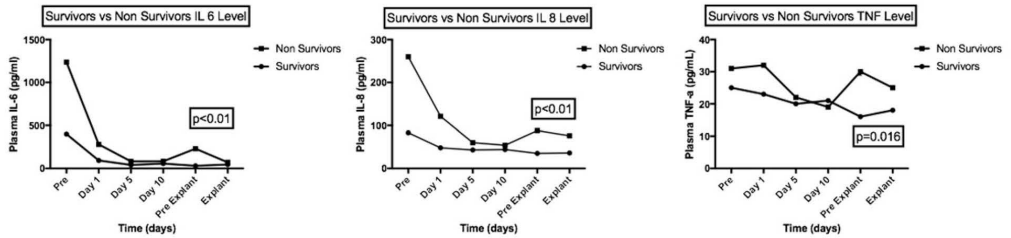
In this large, prospective, cohort study of patients with severe ARDS, we found that cytokine levels decreased rapidly after VV ECMO initiation. We showed that extra-pulmonary ARDS was associated with distinctly higher interleukin levels, and higher PEEP and driving pressures before VV ECMO were associated with higher cytokine levels. High cytokine levels were associated with an increased risk of in-hospital mortality.

Table 3. Estimated associations between pre-ECMO ventilation parameters and cytokine levels during the study period, from multilevel models

	Pre-ECMO PEEP ≥ 15 cmH_2O v < 15 cmH_2O*			Pre-ECMO driving pressure ≥ 19 cmH_2O v < 19 cmH_2O*			Pre-ECMO tidal volume > 7 mL /kg v ≤ 7 mL/kg*		
Variable	% Change†	95% CI	*P*	% Change‡	95% CI	*P*	% Change§	95% CI	*P*
IL6	150.4	29.64 to 383.51	< 0.01	18.4	–38.18 to 126.73	0.61	–7.43	–51.97 to 78.41	0.82
IL8	82.5	3.93 to 220.36	0.04	104.0	17.5 to 254.19	0.01	6.1	–39.35 to 85.52	0.84
TNFα	45.5	17.71 to 79.83	< 0.01	14.9	–6.9 to 41.89	0.2	22.13	–1.14 to 50.87	0.06

ECMO = extracorporeal membrane oxygenation. PEEP = positive end-expiratory pressure. CI = confidence interval. IL = interleukin. TNF = tumour necrosis factor. TV = tidal volume. * Reference category in the comparison groups. † Per cent change of geometric mean of the comparison group cytokine level (PEEP ≥ 15 cmH_2O) compared with the reference group (PEEP < 15 cmH_2O). ‡ Driving pressure was calculated as peak pressure minus the PEEP (in cmH_2O) and grouped according to > 19 cmH_2O and ≤ 19 cmH_2O.[13] § TV per kg of predicted bodyweight (TV/kg PBW) was calculated based on the equation by the ARDSnet trial,[14] and TV/kg PBW of > 7 mL/kg or ≤ 7 mL/kg were compared.

Figure 3. Cytokine level changes for hospital survivors and non-survivors



IL = interleukin. TNF = tumour necrosis factor.

Effect of ECMO on cytokine levels

VV ECMO patients constitute a heterogeneous population with a wide range of underlying diseases and comorbidities. Patients with ARDS already have high levels of circulating inflammatory mediators before initiation of ECMO. Previous studies have shown that extracorporeal circuits may be pro-inflammatory in addition to the underlying illness.[5,6,15] However, many of these studies have investigated cardiopulmonary bypass (CPB). CPB differs from ECMO in its shorter duration, a concomitant surgical insult and the ischaemia–reperfusion injury.[15]

In a randomised controlled trial of extracorporeal CO_2 removal ($ECCO_2R$) combined with ultralow tidal volumes (3 mL/kg) v conventional protective ventilation (6 mL/kg), a reduction in IL6 over the first 3 days with $ECCO_2R$ was observed, and levels were unchanged in the control arm. It is not clear whether this was an effect of the lower tidal volumes, or of the $ECCO_2R$ device.[16] In our study, levels of all cytokines fell rapidly (Figure 1). Several potential mechanisms could account for this. VV ECMO allows for a highly protective lung ventilation and partial lung rest. The improved oxygen delivery may have resulted in a reduction in metabolic and inflammatory activation. The ECMO circuit itself may also absorb cytokines. It seems that the induction of inflammation by ECMO shown in experimental models may be too small to be of clinical relevance, as the levels of cytokines are very high in patients with ARDS. However, these hypotheses need testing in future studies.

Routinely used markers such as CRP and WCC are slow to react and reflect the extent of acute inflammation poorly. In contrast, IL6 has a central role in leucocyte growth and activation and is a key acute-phase reactant with a rapid onset and a short half-life. It has been shown to be a predictor of severity of ARDS.[1] IL8 is a key neutrophil chemotactic stimulus that recruits neutrophils from the blood to the pulmonary site,[17] and activates neutrophil degranulation.[18] TNF(is pro-inflammatory factor too, and is thought to play an important role in the development of shock, rising after 30–90 minutes and activating other inflammatory mediators.[18]

The differences between levels of cytokines, WCC and CRP show the complexity of the inflammatory response. ARDS is a syndrome that may have several phases, from an initial acute inflammatory exudative phase (Days 1–6), to a subacute proliferative phase (Days 7–14), or fibrotic phase (≥ Day 14).[19] In our population, the median time for initiation of ECMO was 1 day from intubation (IQR, 1–5 days). Concomitant treatments such as antibiotics, haemofiltration[20] or hydrocortisone for septic shock may have influenced the level of cytokines. However, the rapidity and size of the drop suggests these factors cannot fully explain the magnitude of cytokine level decrease.[21]

Effect of cause of ARDS on cytokine levels

The aetiology of ARDS results in distinct patterns of disease. Pulmonary ARDS is more likely to have a local alveolar inflammatory response, but extra-pulmonary ARDS primarily results from vascular endothelial damage mediated through the bloodstream.[22] In our study, the patients with extra-pulmonary ARDS had higher scores for illness severity and higher mortality. They also had significantly higher IL6, IL8 and TNF(levels. In contrast, the CRP level and WCC, markers commonly used in clinical practice to judge severity of disease, were not significantly different from those of patients with pulmonary ARDS. Routine measurement of interleukins, which have a faster and more extensive response to inflammation, may therefore be a useful tool for early recognition of a grave prognosis.

Effect of mechanical ventilation on cytokines: biotrauma

Lung-protective ventilation in ARDS has been shown to reduce the inflammatory response, and to improve overall outcomes.[23-25] VV ECMO can potentially facilitate an even further reduction of VILI by using ultra-protective settings. We found that PEEP levels ≥ 15 cmH_2O and driving pressures ≥ 19 cmH_2O at baseline were associated with elevated cytokine levels up to Day 5. Driving pressure is directly related to the stiffness of the lung and, therefore, indicates severity of ARDS, as shown in the recent study by Amato and colleagues.[13] However, the association between cytokine levels and mechanical ventilation is complex. It is likely that patients with higher driving pressures also had higher illness severities, so we cannot separate the effects of mechanical ventilation from the underlying illness. Prospective randomised studies are necessary to further explore the direct impact of ventilator settings on cytokines.

Cytokines and mortality

Previous studies have shown that IL6, IL8 and CRP levels are associated with mortality in ARDS, although these results have not been consistent. IL6 level was a predictor of mortality in a heterogeneous population of ECMO patients,[7] but not predictive in another trial.[26] In the current study of VV ECMO patients, non-survivors showed persistently increased levels of IL6, IL8 and TNF(before and during ECMO support (Table 2 and Figure 3). Excessive activation of the inflammatory response has been associated with a risk of progression to multiple organ dysfunction and death.[27] This has formed the basis for potential therapeutic interventions aimed at curbing the inflammatory process. However, these interventions have to be assessed in the light of our results, which showed a massive decrease in cytokines levels within 24 hours by the implementation of ECMO and the associated reduction of aggressiveness of ventilator use alone.

Strengths and limitations

The strengths of our study include the prospective design, the large number of patients with ARDS on VV ECMO and the extensive dataset. The study limitations include its non-randomised study design, which means that causality cannot be proved. A control group of patients without VV ECMO would be desirable. However, it is questionable whether patient datasets with comparable disease severity could be collected, as VV ECMO was initiated in many patients as a rescue procedure.

Conclusions

Our study showed that cytokine levels, on average, fall rapidly after initiation of VV ECMO. The magnitude of this decline makes it likely that this is related to the decrease of aggressiveness of mechanical ventilation, which was the major change in treatment after implementation of VV ECMO. Higher cytokine levels before and during VV ECMO are associated with extra-pulmonary causes of ARDS, a more invasive mechanical ventilation (shown by a higher PEEP and driving pressures), and are associated with an increased risk of death. Finally, this article must be seen in the context of a dedicated issue that explores multiple aspects of extracorporeal life support in the critically ill.[28-31]

Competing interests

None declared.

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Chapter 4: Cannulation techniques for initiating venovenous extracorporeal membrane oxygenation

This chapter presents a published review of the various cannulation techniques that are available for initiating V-V ECMO. The primary aim in this chapter was to describe an ultrasound guided percutaneous technique used by intensive care specialists, and to compare the advantages and disadvantages of this technique against those of alternatives. It also contains reviews of the process of cannula selection, site selection, explanation, and the training aspects of ECMO cannulation. This work related to thesis aim 3.

Review Article

Cannulation technique: femoro-femoral

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Abstract: The cannulation technique used during veno-venous extracorporeal membrane oxygenation (VV ECMO) insertion can have a major impact on a patients' overall outcome. We have developed a technique that aims to combine speed and effectiveness, with minimal risk. The steps include: (I) percutaneous cannulation using the Seldinger technique; (II) ultrasound guided access and positioning of cannulas; (III) femoro-femoral circuit configuration with a later option of high flow; (IV) a no skin cut serial dilation technique; (V) non-suturing securing of cannulas and (VI) a non-surgical manual pressure technique of explantation. The following is a discussion around these techniques and their various advantages and disadvantages.

Keywords: Veno-venous extracorporeal membrane oxygenation (VV ECMO); acute respiratory distress syndrome (ARDS); cannula; ultrasound-guided

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Introduction

Optimal cannulation technique is essential for the initiation and management of patients with severe respiratory failure requiring veno-venous extracorporeal membrane oxygenation (VV ECMO). Cannulation must be rapid and with a technique that minimizes tissue trauma, which can lead to bleeding and transfusion requirements, reoperation, infection risk and longer-term morbidity. Inappropriately positioned cannulas can result in poor circuit flows, recirculation and inadequate support. Moving malpositioned cannulas can expose the patient to non-sterile parts of the cannula and increase the risk of infection. Poorly secured cannulas can lead to catastrophic decannulation. In the following discussion, we will describe in detail the VV ECMO cannulation techniques that have been developed in our hospital in over 25 years of practice and discuss the various advantages and disadvantages of each technique.

Surgical versus percutaneous cannulation

The surgical or "open" cut down procedure was the preferred method of venous cannulation until the 1990s (1). This technique could either be a direct cut down to expose the vessel, which required a large incision, or a smaller proximal incision to expose the vessels, with a second more distal incision to enable percutaneous tunneling of the cannulas to the vessel opening. This facilitated a lower angle of incidence with the vessel, and reduced infection risk and bleeding (2). The advantages of the surgical technique include direct visualization of the anatomy, confirmation of cannula entry into the vessels, and purse string sutures for haemostasis (3).

Since the 1990s, the development of thin-walled wire-reinforced cannulas and improved quality and availability of ultrasound (US) machines has enabled the percutaneous technique to become more widespread. Rather than moving an unstable patient to the operating room, clinicians can

Table 1 Percutaneous versus open surgical cannulation insertion. See text for discussion and references

Variables	Percutaneous insertion	Open/surgical cut down
Infection rates	Low	Mod/high
Availability of cannulators with skill set	Widespread	Limited
Bleeding risk	Low	Mod/high
Speed of insertion	Fast	Slow (if requires move to OR)
Lymphocele risk	Low	Moderate
Decannulation	Simple compression	Operative/reconstruction

OR, operating room.

Table 2 A comparison of cannulation configurations (5). See text for discussion and references

Variables	Femoro-femoral	Femoro-jugular	Dual lumen cannula
Speed of insertion	Fastest	Moderate	Moderate
Preparation areas	One	Two	One
Recirculation risk	Potentially high	Potentially moderate	Potentially low, but high when poor position
Blood flow, L/min	2–6	2–7	3–5
Insertion complexity	Simple	Moderate	Potentially complex
Imaging requirements	Vascular/TTE	Vascular/TTE +/– TOE	Vascular/TOE/II
Patient mobilization potential	Complex	Complex	Less complex
Infection risk potential	High	High	Low
Risk of air embolism during removal	Low	Moderate*	High*

*, especially if spontaneously breathing. TTE, transthoracic echocardiogram; TOE, transoesophageal echocardiogram; II, image intensifier.

perform the cannulation at the patient's bedside, which may be in the intensive care unit (ICU) or emergency department (4). More importantly, there is an awareness that the amount of bleeding, infection risk, lymphocele and timeliness can be improved (see *Table 1*)

Femoro-femoral VV ECMO cannulation

The femoro-femoral ("fem-fem" or bifemoral) VV ECMO cannulation configuration has both the access (drainage) and return cannula inserted via the common femoral veins. Blood is accessed from one cannula positioned in the inferior venous cava (IVC), pumped through the oxygenator of the ECMO circuit and returned to the patient at the level of the right atrium (RA) via the contralateral femoral vein.

Advantages of fem-fem configuration

There are a number of factors that make the fem-fem configuration advantageous for VV ECMO (*Table 2*).

Speed and simplicity of circuit

The left and right femoral veins are usually large and easily accessible and enable rapid central access for the initiation of VV ECMO. Both veins are accessible at the groin so only one area of the body requires preparation. Furthermore, the femoral area allows rapid access to the femoral artery if veno-arterial (VA) ECMO support is required. Fem-fem cannulation can also be inserted without the requirement of transoesophageal echocardiogram (TOE) or radiology, which add to the complexity of cannulation and may be difficult to arrange during ECMO retrievals.

Safety and complications

All ECMO cannulation is associated with significant risks

to the patient. The advantage of the femoral veins is that they are almost always accessible and require less skill for insertion. Adverse effects such as bleeding can usually be controlled with local pressure. The main alternative to femoral cannulation includes the internal jugular vein (IJV), which is used in both femoro-jugular (fem-jug) and dual lumen configurations. The major risk is pneumothorax, which although uncommon, can be fatal in patients with severe respiratory failure. The large diameter dual lumen catheter can be particularly challenging to place. Accidental distal hepatic vein or right ventricle cannulation can occur from misplaced wires and dilators, and can result in catastrophic bleeding or pericardial tamponade, as occurred in two patients out of 72 cannulations in one study (2). Other specific complications to IJV cannulation include cannula movement, cerebral venous congestion and air embolism upon removal (6). Patients with long-term central venous lines may also develop superior vena cava (SVC) stenosis which poses significant risk during IJV cannulation but is often not easy to exclude prior to cannulation.

ECMO blood flow

The maximum blood flow of an ECMO circuit is particularly important in patients with high cardiac outputs and severe respiratory failure: if the circuit cannot capture a sufficient proportion of cardiac output, then ongoing hypoxia is likely (7). The fem-fem configuration can support between 2–6 L/min of blood flow which is usually adequate. The fem-jug configuration may theoretically enable higher blood flows, as the return cannula directs flow directly across the tricuspid valve, and was found to have higher flows than atrio-femoral configurations (8). However, in a recent retrospective study, blood flows were similar (4.1 *vs.* 4.0 L/min, P=0.5) between fem-fem and fem-jug configurations (9). Blood flow rates are usually limited by flow into the access cannula which likely explains this non-significant difference between the two configurations. The dual lumen catheter also has more limited maximum flows [typically, the 23 Fr cannula allows a maximum flow of 3 L/min, the 27 Fr cannula is limited to 4.5 L/min, and the 31 Fr double lumen bicaval (DLB) cannula allows not more than 5 L/min (5)]. In practice, a poorly positioned dual lumen cannula can result in low ECMO flows and/or high recirculation, resulting in hypoxia. In our practice, if inadequate flow results in hypoxia following a fem-fem cannulation, we insert an additional IJV access cannula. This "high flow" configuration enables improved blood flow and oxygenation (10).

Interhospital and intrahospital transport

The transport of ECMO patients is logistically complex and associated with multiple risks for the patient (11). This may occur in interhospital transports, or in intrahospital transports to the operating room (OR) or to radiology. The fem-fem configuration allows for positioning of the ECMO console at the foot of the bed, either attached to the bed itself or on a stretcher bridge. All tubing can be safely positioned on the lower half of the bed away from the patient's head and airway. In both dual lumen and fem-jug configurations there is a requirement for tubing to run near to the patient's head along with ventilation circuits. In the fem-jug configuration tubing needs to run along the length of the patient whether the console is positioned at the head or the foot of the bed. This can lead to difficulties turning the patient, accidental cannula dislodgment, or kinking of tubing with circuit compromise.

Disadvantages of fem-fem configuration (*Figure 1*)

Recirculation

Recirculation occurs when returned blood is withdrawn though the access cannula rather than flowing forward through the pulmonary circulation (12). In fem-fem cannulation, the return blood is directed toward the SVC rather than the tricuspid valve, potentially creating abnormal flows away from the valve and more recirculation. Fem-jug and dual lumen configurations have potentially less recirculation as they direct the blood towards the tricuspid valve. In practice, we have found that recirculation is rarely a problem if ≥8 cm of separation of cannulas tips in the inferior vena cava (IVC) can be maintained.

Infection

Although there is no definitive comparative data on risk of infection, extrapolating rates from central venous catheters (CVCs) may suggest that infection rates may be higher with dual femoral access (13) compared with single access in the IJV. The dual lumen cannula may therefore have the lowest rate of infection when compared to configurations that require femoral cannulation.

Challenging access and cannula position

Morbidly obese patients can make exposure of the femoral vessels challenging, and IVC filters are a contraindication to femoral cannulation, and require alternative access. Taller

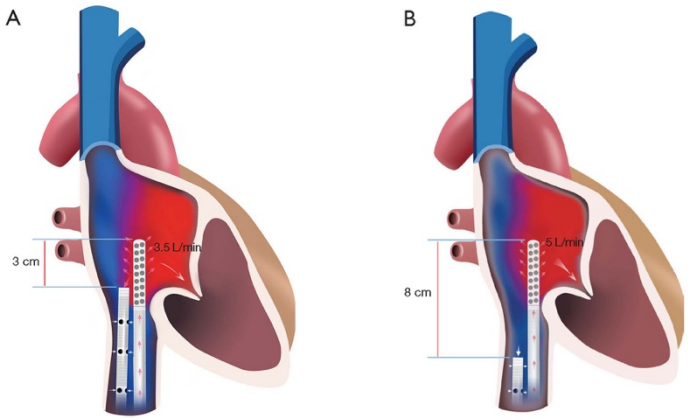

Figure 1 Recirculation during fem-fem VV ECMO. (A) Inadequate separation of access and return cannulas can lead to high recirculation; (B) adequate separation of access and return cannulas will reduce recirculation. VV ECMO, veno-venous extracorporeal membrane oxygenation.

patients may have a distance from groin to the RA/IVC junction that exceeds the length of a cannula.

Mobilization

Femoral cannulation was traditionally thought to be a contraindication for mobilization. However, we have found that this can be done safely if appropriately trained staff are present. A key advantage of the dual lumen cannula is that mobilization can be more easily managed.

Cannula selection

Cannula selection is a critical component of any ECMO configuration. Fem-fem ECMO requires the selection of two long (50–55 cm) cannula capable of reaching the central circulation. Consideration needs to be given to the desired ECMO blood flow, size of the vessels, as well as the percentage of recirculation.

Options for the access limb include both multi-stage (multiple access points) and single-stage (access only from tip of catheter) cannula. Only a single stage cannula should be used for the return limb of the circuit, as multistage return cannulas cause significant recirculation. The multistage cannula has a flow profile that allows blood to enter via a number of holes along the distal length of the cannula (usually 20–30 cm). In the femoral position, this means that blood can be accessed not only from the distal tip of the cannula in the IVC, but all the way down to the iliac vessels. The theoretical advantage of this catheter is that it is less likely to be compromised by access insufficiency, therefore maintaining high access flows (14). It also has the ability to access blood a distance from the central circulation, resulting in less recirculation.

Sizing

Increasing cannula diameter will improve the maximum blood flow through the circuit but is also more likely to result in vessel and tissue damage. The size of the cannula on the access side of the circuit is especially important, as cannula that are too small result in impaired blood flow, higher revolutions per minute (RPM) with potential for blood trauma, and access insufficiency. Several methods of estimating cannula size can be used. One method is to calculate the patients cardiac output, and then estimate the peak flow through a cannula using the information provided by the manufactures. Our technique is to place the largest cannulas possible that are safe, based on the size of the femoral vessels. We do this by measuring the diameter of the femoral vessels on US. The diameter of the femoral vessel at the insertion point is measured and the circumference of the vessel calculated using the formula πD. The result in millimeters will give the largest French size

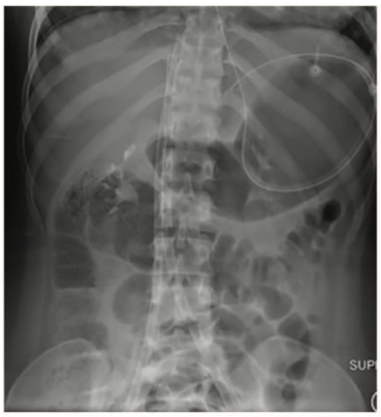

Figure 2 Abdominal X-ray showing the longer course of the left-sided femoral cannula.

cannula capable of being passed. For example:

- Measured vessel diameter =10 mm;
- Calculated circumference: πD =3.1×10 mm =31 mm;
- Max size of cannula =31 F.

It is important that the cannula is smaller than the maximum size of the vessel in order to allow some venous drainage around the cannula (3). If ≥2/3 of the vessel is occluded by the cannula, then oedema, stasis, and severe venous hypertension can lead to deep vein thrombosis, lower limb venous congestion and catastrophic ischemic injury. For the majority of patients, we use 19–25 Fr access and 17–21 Fr return.

Site selection

There is no clear evidence that one side is better than the other when choosing access or return orientation. Factors to consider are that the left femoral/iliac vein is more tortuous than the right, the angle with the IVC is sharper, and it is marginally longer as it crosses in front of the aorta (see *Figure 2*). The length of the vein in particular can lead to problems during advancing and positioning of the cannulas. In general, we place the access cannulas on the left in small stature patients as the shorter right side may lead to exposure of the proximal multistage holes and air embolism. And return cannulas are in general placed on the right in tall stature patients as a left sided return cannula may not reach the RA/IVC junction, leading to reduced separation (<8 cm) and recirculation.

The insertion technique

We prefer an US-guided percutaneous insertion technique, with serial dilation using a Seldinger technique (15). There is no skin incision. This technique results in a snug passage of the cannula through both the skin and femoral sheath. This technique results in minimal bleeding and has the theoretical advantage of decreased risk of infection, particularly for a long VV ECMO run. Using this technique, we have found near 100% successful cannulation rates. This has been replicated in other groups (16).

US

US-guided vascular access has been shown to improve success rates for insertion of central venous lines, and decrease complications such as infections, mechanical complications, and thrombosis, compared to the landmark techniques (17). Avoiding these complications is even more important for ECMO cannulation, where large dilators and cannulas can cause significant damage and morbidity. While inadvertent arterial puncture is not usually a problem during CVC insertion, in unwell anticoagulated ECMO patients this can result in prolonged bleeding or hematoma formation requiring operative management (18).

US and insertion technique

Two trained cannulators perform the procedure. Both groins are prepared, cleaned and draped.

We employ both vascular US with a linear probe for the guided insertion of wires and transthoracic echocardiography with a phased array probe to confirm the wires are in the correct vessel and to position the cannulas (19). We begin with a pre-scan (an US of the vessels prior to sterile scrubbing) to assess for any barriers to cannulation, such as small size of the vessels, thrombosis or stenosis. US is then used to guide the shallow angle passage of the needle into the common femoral vein in real-time, by continuously visualizing the tip of the needle in the US field (20). This technique ensures a single pass of the needle into the vessel. Non-visualised techniques of insertion into the vessel may result in steep or off-center penetration that can make subsequent dilation more difficult and increases the risk of vessel perforation or kinking of the guide wire.

We use soft 140–180 cm J-tipped wires to minimize the risk of damage to venous structures or the heart and confirm their position in the IVC using a subcostal view

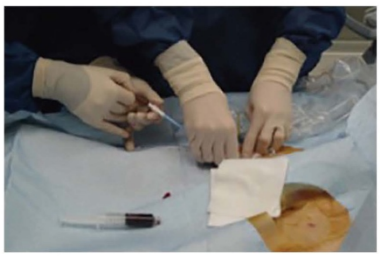

Figure 3 Two-person technique of serial dilation during fem-fem VV ECMO cannulation. VV ECMO, veno-venous extracorporeal membrane oxygenation.

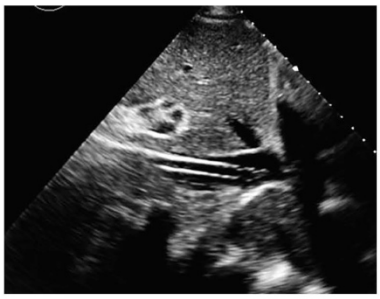

Figure 4 Ultrasound-guided positioning of the return cannula in the IVC. IVC, inferior venous cava.

of the heart. We also intermittently check the position of the wires throughout the procedure to confirm there has been no wire migration. In difficult cases, such as tortuous vessel or repeated kinking of the wire, we may employ stiffer wires (such as an Amplatz Super Stiff™ Guidewire, Boston Scientific, USA). However, this requires careful monitoring to ensure the wires do not migrate inwards as the risks of internal damage are higher with a stiffer, straight tipped wire.

Serial dilation (*Figure 3*)

Without the use of a skin incision, we serially dilate the cannula passage, stepping up by one dilator (2 French sizes) sequentially leading to a gradual stretching of the skin, subcutaneous tissue and insertion point into the vessel. The primary cannulator advances the dilator, while the second cannulator continuously moves the wire in and out of the dilator, ensuring the wire is not being kinked. If kinking begins to occur, there is increased resistance of the wire being moved in and out. The second cannulator can inform the primary cannulator to retract the dilator and adjust the technique. If a kink forms on the wire, the wire should be withdrawn a few centimeters past the kink prior to continuation of cannulation (14).

At the end of cannula insertion, we use US to assess for any complications which may have occurred during the procedure, such as hematoma formation, pseudoaneurysm, or arterial transection, and therefore steps can be taken to mitigate these effects.

Cannula positioning (*Figure 4*)

Correct cannula positioning is essential for effective VV ECMO blood flow. It is important to get this correct the first time, as advancing the cannulas later can result in loss of sterile field and infection risk. In all forms of VV ECMO the return cannula needs to be positioned in the RA. This allows for oxygenated returning blood from the extra-corporeal oxygenator to be directed into the right heart and subsequently pumped into the pulmonary circulation.

Positioning of the access cannula in fem-fem cannulation can require some skill. The cannula tip needs to be positioned high enough into the central venous circulation to maximise blood flow, but far enough away from the return cannula to minimise recirculation. We aim to position the tip of the access cannula in the IVC just distal to the junction of the hepatic vein. At this site, the IVC is often non-collapsible even when hypovolemic as it is held open by the liver architecture. In this position there should be 7–10 cm of separation between the tips of the two cannulas (with the tip of the return cannula 4–5 cm into the RA).

Imaging for positioning

There are a number of modalities that can be used to confirm the position of cannula in the fem-fem configuration (see *Table 3*). These include both transthoracic echocardiogram (TTE) and TOE echocardiography, plain radiography and image intensifiers (II).

Underwater seal connections and administration of heparin

Once inserted, each cannula is flushed and locked with approximately 1,500 units of heparin (in 150 mL of normal

Table 3 Imaging methods for confirming position of cannulas. See text for discussion and references

Variables	Ultrasound	X-ray/II
Location and availability	Bedside	Radiology
Repositioning cannulas	Immediate	May be delayed
Reliability	High	High
Skill requirement	Moderate	Low

II, image intensifier.

saline) to prevent clot formation (total approx. 3,000 units). The heparin bolus is omitted in patients with active bleeding, and heparin is started once bleeding has settled. Next the cannulas are connected to the ECMO circuit using an "underwater seal" technique. This involves continuously dripping water from a syringe onto the connections as they are joined and ensures no air bubbles are present.

Cannula securing

Once the cannulas have been correctly positioned they are secured. Needle and suture techniques are commonly described, but can cause ischemia of the skin, are a nidus for infection and also can lead to inadvertent puncturing of the cannulas and/or circuit. We prefer to use a large Tegaderm at the skin insertion sites and self-adhesive dressings or "Grip-Locks", in a minimum of two places securing the length of the cannula. It is important that the first Grip-Lock is not too far away from the insertion site as this can allow movement and the potential for inadvertent decannulation (21).

Sedation

All patients who undergo cannulation for VV ECMO should be intubated prior to the procedure. Patients requiring VV ECMO usually have a high work of breathing and the risk of air embolism during cannulation is high. Once cannulation is complete sedation may not be required. The patient may be able to be desedated and even extubated in some circumstances. As an example, in patients with cystic fibrosis, early extubation should be attempted to facilitate coughing and respiratory physiotherapy.

Explantation

Following a successful VV ECMO weaning study, the cannulas are removed using a manual compression technique. Heparin is stopped for 2 hours prior to removal (22). The patient should be positioned supine and prepared for the procedure. Care is taken to remove any clot that has formed on the tip of the cannula. Firm manual pressure for 20 minutes is used and sufficient in the majority of cases. If there is ongoing bleeding after this, then this is continued for a further 20 minutes. Rarely a suture can be placed, or operative management is required for recalcitrant bleeding (23).

Training and accreditation

VV ECMO cannulation is a technically challenging and highly invasive procedure with high inherent risks for bleeding, tissue injury and air embolism. All staff undergo regular training, accreditation, supervision, and practice including in the animal lab to ensure the procedure is done in a standardised manner to minimize the potential risk to patients.

Conclusions

US-guided percutaneous fem-fem cannulation has advantages of being quick and simple to insert, with minimal complications and adequate blood flows in the majority of patients. Disadvantages include insufficient blood flow in a subset of patients, and the potential for recirculation. VV ECMO cannulation requires a balanced analysis of these factors in order to tailor the correct techniques for the right patient.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Chapter 5: Complications of mechanical circulatory and respiratory support

This chapter is a published review of the current literature of the complications that occur during ECMO and VAD support. The primary aim of the work was to describe the incidence and mechanisms of early and late complications of patients undergoing ECMO and VADs. This work related to thesis aim 4.

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CHAPTER

c0080 # Complications of mechanical circulatory and respiratory support

16

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s0010 ## INTRODUCTION

p0085 The last 20 years have seen great advances in mechanical circulatory and respiratory support (MCS) technology. Improved biocompatibility and a reduction in the size and complexity of the devices have led to a clear reduction in MCS-caused complications [1]. Despite these improvements, patients continue to experience high morbidity and mortality [2,3]. The devices are complex, with multiple mechanical parts that can fail. They are invasive and technically difficult to insert, have large nonendothelialized surfaces, and continue to require systemic anticoagulation. Furthermore, the patients themselves are becoming more complex and critically unwell at the time of implantation, contributing to high periprocedural complication rates and long-term morbidities.

p0090 Complications in MCS typically occur in a bimodal pattern. Early complications are usually related to insertion and severe critical illness, while the late, second peak occurs with sepsis and inadequate support leading to multiorgan failure [4]. Between these two periods, many other complications also can occur as detailed in Fig. 16.1.

p0095 This chapter will emphasize the clinical aspects of MCS complications. Part 1 will focus on the complications of extracorporeal membrane oxygenation (ECMO), including venoarterial (VA) and venovenous (VV) ECMO and ECMO cardiopulmonary resuscitation (ECPR). Part 2 will focus on the short-term and long-term complications of ventricular assist devices (VAD). The aim is for clinicians to gain a greater understanding of the incidence and mechanisms of these problems, and to assist them with decisions about the appropriateness of MCS in a particular patient.

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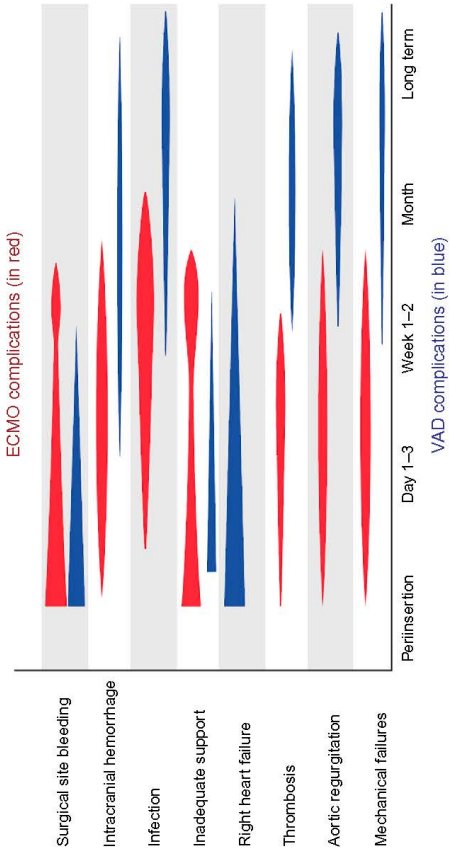

f0010 **FIG. 16.1** Schematic showing timing of common complications during mechanical cardiac and respiratory support. Width of bars represents incidence rate over different time periods. DIC*= disseminated intravascular coagulopathy.
Modified with permission from the International Summary ECMO, Registry of the Extracorporeal Life Support Organization (ELSO). Ann Arbor, Michigan, July, 2016;2016:1–26.

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s0015 # PART 1: ECMO-RELATED COMPLICATIONS

s0020 ## INTRODUCTION

p0100 Commencing ECMO support for the critically unwell patient is associated with a substantial number of potential complications in addition to its benefits (see Table 16.1). Cannulation requires the opening of major blood vessels with the potential for significant tissue disruption. The ECMO circuit itself is a hyperoxic, large nonendothelialized blood/circuit interface, which stimulates significant systemic inflammatory

t0010 **Table 16.1** Complication Rates for Venovenous and Venoarterial ECMO

Complications	VV ECMO Rate (%)	VA ECMO Rate (%)
Mechanical complications		
Oxygenator clot	13.6	8.8
Oxygenator failure	9.1	6.6
Pump malfunction	1.5	0.8
Mechanical clots (other)	5.5	5.8
Rupture	0.6	0.2
Bleeding complications		
Gastro intestinal bleeding	6.1	4.4
Cannulation site bleeding	13.2	18.5
Surgical site bleeding	10.5	20.2
Tamponade	1.5	5.1
Pulmonary hemorrhage	6.1	3.1
Medical complications		
Hemolysis	5.8	5.6
DIC*	3.3	3.3
CNS infarction by CT/US	2.0	3.8
CNS hemorrhage by US/US	3.9	2.2
Renal failure requiring dialysis	9.9	10.5
Hemofiltration	17.6	13.1
Inotropes	41.0	54.2
Infections "culture proven"	17.5	13.0
Cannulation complications		
Limb ischemia	0.9	3.1
Limb compartment syndrome	0.3	0.8
Limb amputation	0.2	0.5

DIC = disseminated intravascular coagulopathy.*
Modified and presented with permission from the International Summary ECMO, Registry of the Extracorporeal Life Support Organization (ELSO). Ann Arbor, Michigan, July, 2016;2016:1–26.

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response and coagulation disturbance [5]. High negative pressures in the pump can lead to blood trauma, coagulopathy, and oxidative stress [6].

s0025

BLEEDING AND COAGULOPATHY

p0105 Significant bleeding is the most common complication during ECMO, occurring between 20% to 40% of patients. It has been shown to be an independent predictor of mortality [7]. It is most commonly defined in the literature as "bleeding requiring surgery." However, significant variation exists between studies on bleeding, where complications may range from minor cannula site bleeding to the devastating complication of intracranial hemorrhage (ICH) (see the section "Neurological Complications" of ECMO).

p0110 According to the Extracorporeal Life Support Organization (ELSO) registry, which includes data from over 20,000 adult patients, the most common bleeding sites include open wounds at cannula sites (15.1%), surgical sites (13.6%), pulmonary hemorrhage (7.4%), and cardiac tamponade (1.5%–5.1%) [8]. Periprocedural bleeding can be a particular problem. Even relatively minor interventions, such as intercostal catheter insertion, bronchoscopy, or cannula wounds, can lead to disproportionately large or even fatal bleeding, despite a relatively normal coagulation profile on testing [8]. Mucosal bleeding from the nasopharynx or gut can also be troublesome. ECMO-related risk factors include arterial cannulation, open rather than percutaneous cannulation, and central cannulation [7].

p0115 Multiple factors lead to the coagulopathy of ECMO. Thrombocytopenia and platelet dysfunction result from platelet activation on the circuit surface, shear stress, and dilution [9], Acquired vWF, heparin-induced thrombocytopenia (HITS), and hyperfibrinolysis may also contribute (see the section "Other Hematological Complications"). Systemic anticoagulation aims to prevent thrombus formation but can contribute to bleeding in some patients. Finally, the underlying illness of the patient may also cause bleeding, including multiorgan dysfunction syndrome (MODS), liver disease, or disseminated intravascular coagulopathy (DIC).

s0030

THROMBOSIS

p0120 Thrombosis can occur anywhere along the ECMO circuit, most commonly at sites of stasis or increased turbulence, as well as intravascularly. Oxygenator thrombosis is the most common site and is seen more frequently in VV (13.6%) than VA ECMO (8.8%) [10], possibly related to the inflammatory and prothrombotic state in sepsis; hyperoxia may also be a factor [11]. Clots in the oxygenator can cause significant hemolysis, increased resistance to flow, and reduced oxygenation and carbon dioxide (CO_2) transfer efficiency (see Fig. 16.2). This presents clinically as an increase in transmembrane pressure drop and falling postoxygenator PaO_2 levels. If severe, it requires immediate circuit change.

p0125 Thrombosis is less common in other parts of the circuit but does occur in the pump head, cannulae, and circuit tubing (5.5%) [10]. This may manifest clinically

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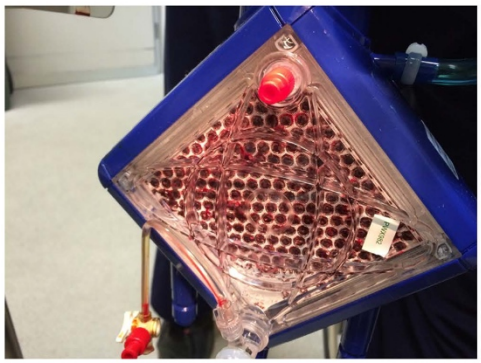

FIG. 16.2

f0015 Oxygenator thrombosis.

as reduced circuit flow if near occlusive, but more commonly as a slow reduction in flow of unclear origin. Of particular concern is thrombus in cannulas or in vessel walls that can dislodge during decannulation to cause pulmonary embolism in the venous circulation and/or distal ischemia, commonly in the lower limbs, in the arterial circulation.

p0130 Thrombus formation is a result of blood-surface interaction. Platelets adhere to the nonendothelialized circuit surface and are activated, setting up a cascade of events leading to fibrin and thrombus formation [12]. Further fibrin deposition results in mature thrombus formation that can become occlusive or embolize (see "Cannulation Complications" section). The main risk factors for thrombosis during ECMO support are increased duration of support, no anticoagulation, lower ECMO flows (especially <1 L/min), and an underlying prothrombotic state in the patient. For more information, please refer to Chapter 19.

p0135 Newer low-resistance oxygenators with a lower propensity to develop thrombin at the membrane have been shown to have longer life than older generations [13]. Modern centrifugal pumps and heparin bonding to the circuit have also reduced anticoagulation requirements, leading some to trial low dose or even no anticoagulation protocols [14].

s0035 OTHER HEMATOLOGICAL COMPLICATIONS

s0040 *Hemolysis*

p0140 Hemolysis occurs in 5%–18% of ECMO patients. It usually results from circuit-related red blood cell (RBC) damage but may also be also due to the patient's underlying illness. Excessive (≤ -700 mmHg) negative pressure on RBCs results in either cavitation or release of gaseous microbubbles, leading to increased shear stress and

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irreversible damage. Risk factors include the development of clot within the circuit or near the cannula orifices or excessive centrifugal pump speed ($\geq$3500 min^{-1}) [15]. RBCs may also be damaged as they pass fibrinous clot in partially thrombosed oxygenators or centrifugal pumps. Severe hemolysis (free hemoglobin >50 mg/dL) has been shown to be associated with a greater than three-fold increase in risk of death [16], probably due to a combination of overwhelming of scavenging systems, depletion of nitric oxide stores, and the release of nephrotoxic myoglobin [14].

s0045 ### *Heparin-induced thrombocytopenia syndrome (HITS)*

p0145 HITS is a rare (1%) but potentially serious acquired autoimmune condition that occurs in patients exposed to heparin. It is due to generation of antibody to platelet factor 4 and subsequent immune complex formation on repeat exposure to heparin [8]. This results in a prothrombotic state, and patients present with unusual clotting, frequently both venous and arterial.

s0050 ### *Disseminated intravascular coagulation (DIC)*

p0150 This rare (3%–5%) and potentially catastrophic complication can present with simultaneous bleeding and thrombosis. It can be triggered by thrombosis in the circuit, leading to a consumptive coagulopathy, and requires a circuit change [8]. It may also be related to the underlying condition (e.g., sepsis or pregnancy).

s0055 ### *Hyperfibrinolysis*

p0155 Excessive fibrinolysis leading to bleeding is known as hyperfibrinolyisis. Typically, generalized coagulopathic bleeding occurs, e.g., mucus membrane oozing. Laboratory values show falling fibrinogen levels of <200 mg/dL, very high levels of D-dimer, and relatively normal levels of platelets [17]. This results from subacute oxygenator thrombosis and improves post exchange of the oxygenator.

s0060 ## CANNULATION COMPLICATIONS

p0160 ECMO cannulation differs from other types of indwelling cannulation devices as they are large diameter (15–27 Fr), in situ for prolonged periods, and the capacity to change cannulas is often limited. Insertion may damage vessels leading to bleeding or thrombosis and also injure surrounding structures such as nerves, leading to chronic pain.

p0165 Cannulation may be via an open/surgical cutdown approach, or via a percutaneous Seldinger procedure [18]. Open cutdown enables direct vision and control of the vessels and correct sizing of cannulas. However, the larger open wound can be more prone to bleeding and infection (see Fig. 16.3). Percutaneous techniques have become more widespread, although this method may have a higher risk of damage to the vessel wall, such as puncturing the back wall of the vessel. Inadvertent cannulation of the wrong vessel can lead to devastating complications (such as CVA post carotid artery cannulation) and critical time delays. A variety of methods can be used by proceduralists to confirm that the correct vessel has been identified (see Table 16.2).

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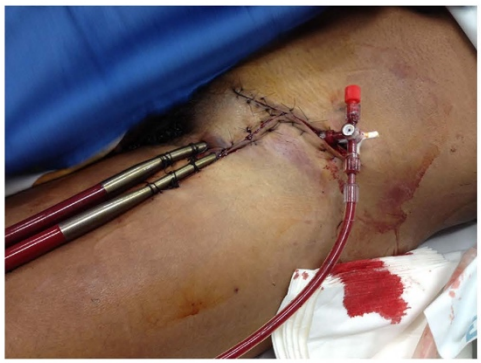

FIG. 16.3

f0020 Surgical site bleeding following open venoarterial cannulation. Anterograde backflow cannula in situ.

t0015 **Table 16.2** Methods to Confirm Vessel Anatomy During Cannulation

More Reliable	Less Reliable
Realtime ultrasound (US) guidance	Palpation/landmark/anatomical methods
US confirmation of wire in the IVC or aorta	Color of aspirated blood
X-ray/fluosocopy of guidewire	Oxygen saturations
	Pressure transduction

p0170 External bleeding at the time of cannula placement can be significant. Also problematic is covert bleeding, such as hematoma formation in the thigh or retroperitoneal bleeding, which can result from either perivascular bleeding tracking backward or from perforations during cannulation in stiff tortuous femoral vessels as they traverse the pelvic brim. Covert bleeding is harder to control and may be associated with a worse outcome, e.g., when retroperitoneal, where it can cause renal failure.

s0065 ## *Arterial cannulation*

p0175 Arterial cannulation is associated with higher complication rates than venous, especially in the presence of peripheral vascular disease [19]. The incidence of arterial damage through cannulation ranges from 5.6%–8% [10,20]. Intimal damage can result from the guidewire, the dilator, or the cannula. The large diameter of the cannulas can completely occlude the vessel, preventing any distal flow unless a backflow cannula is inserted. The artery usually requires surgical reconstruction upon decannulation.

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p0180 The most frequently used site for peripheral arterial return VA ECMO is the common femoral artery. The femoral artery allows rapid access to a large vessel, and many clinicians are familiar with this site. Subclavian artery return is an alternative that may reduce risk of differential hypoxia and is tolerated for longer periods (see Venoarterial ECMO).

s0070 Peripheral cannulation

p0185 However, upper limb hyperperfusion may result from increase arterial flow and venous obstruction, leading to arm swelling and brachial plexus nerve injury [21].

p0190 Lower limb ischemia occurs in 3.1% of VA ECMO patients and 0.9% of VV ECMO patients [10] and, if severe, can require fasciotomy and amputation [22]. The mechanisms include cannula-related obstruction of flow, thrombosis, or embolization. Diagnosis is often delayed as patients are often sedated and unable to communicate pain, and nonpulsatile flow may be difficult to detect using the Doppler probe. Early insertion of percutaneous backflow cannulae can prevent these complications (see Fig. 16.3). They direct blood from the circuit in an anterograde fashion via the superficial femoral artery or, rarely, in a retrograde fashion via the posterior tibial/dorsalis pedia artery to improve perfusion in the ipsilateral limb. Although the cannulae can be challenging to insert, they are becoming more widely used [23].

s0075 Venous cannulation

p0195 Venous cannulation is associated with less damage compared with arterial cannulation, although it still may result in significant complications, such as bleeding, infection, and deep vein thrombosis (DVT). In the case of internal jugular vein cannulation, care must be taken to prevent the wire traveling across the tricuspid valve as it can lead to right ventricle puncture and cardiac tamponade [24].

s0080 ECMO cardiopulmonary resuscitation (ECPR)

p0200 ECPR presents a uniquely challenging situation for cannulation due to a lack of arterial pulsatility, movement during ongoing CPR, and reduced arterial volume during CPR. Often it is necessary to interrupt CPR in order to place wires in the correct vessel (see Table 16.2). Percutaneous cannulation failure is significantly higher in ECPR, necessitating higher rates of femoral cut downs [25], as are complications such as inadvertent cannulation of the incorrect vessel.

s0085 Central cannulation

p0205 Central cannulation during ECMO allows direct access to the aorta, enables higher ECMO flows, and avoids the problems of differential hypoxia (see "Venoarterial ECMO" section). It is associated with much higher rates of bleeding and infection [26]. Furthermore, physiotherapy, general ICU care, and extubation are impeded with central cannulation.

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s0090

INFECTION AND SEPSIS

p0210 Infection and sepsis during ECMO lead to increased length of stay and are independently associated with higher mortality [4,27]. The incidence of infections on ECMO ranges from 13%–64% depending on how infection is defined [28]. While many studies do not define it, ELSO defines it as "culture proven infections."

p0215 Important ECMO-related risk factors include the presence and site of ECMO cannulae and the duration of support [29]. Other patient factors include prolonged ICU stay, immunosuppression, high sequential organ failure assessment (SOFA) scores, exposure to antibiotics, and multiple indwelling medical devices. In addition, a recent outbreak of mycobacterium chimera from infected heater coolers has also lead to infections in small numbers of cases [30].

p0220 Ventilator-associated pneumonia (VAP) is the most common infection, with a rate of 55 per 1000 ECMO days [31]. It typically occurs after 1 week (median day 8), and Pseudomonas, Enterobacteriaceae, and multiresistant Staphylococcus aureus (MRSA) are the most commonly isolated bacteria. Although the extracorporeal circuit usually supports any deterioration in respiratory function, significant hemodynamic deterioration may result.

p0225 Bloodstream infection occurs at a rate of 14–16 per 1000 ECMO days and typically occurs around day 8 [31]. Diagnosis can be difficult, as typical signs of sepsis, such as fever, may be masked by cooling in the extracorporeal circuit. Possible sources include bacterial translocation from the gastrointestinal tract [32], cannulae, VAP, and mediastinitis [27]. Gram-negative bacteria are the most common (*Pseudomonas*, *Enterococcus species*, *Escherichia coli*, and *Stenotrophomonas maltophilia*) as well as *Staphylococcus aureus* and *Candida species* [31].

p0230 Cannula infections occur at a rate of 7.1 per 1000 ECMO days, typically between days 12 and 23 [31]. Percutaneous cannulae break down the usual protective skin barrier and provide an entry portal for bacteria. Micro-pistoning of the cannula through the insertion point may also increase infection risk. Bacteria-induced biofilm surrounding the cannulae may lead to antibiotic resistance: see Chapter 21 for more details. Bleeding with hematoma formation also increases the risk of subsequent infection, making good cannulation technique mandatory. Escherichia Coli (24%), Enterococcus species (19%), and gram positives such as Coagulase-Negative Staphylococci (19%) were the pathogens most frequently associated with cannula infection.

p0235 Patients on ECMO are also at risk for other types of infections, including mediastinitis, gastrointestinal infection, and sinusitis, reflecting the overall severity of illness in this population.

s0095

NEUROLOGICAL COMPLICATIONS

p0240 Neurological damage, in particular intracranial hemorrhage (ICH) and cerebrovascular accidents (CVAs), represents devastating complications during ECMO and is often fatal [33]. When defined narrowly, i.e., ICH and CVA alone, the incidence

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varies from 6%–8% [10,34]. Using a more broad definition, including subarachnoid hemorrhage (SAH), coma, and anoxic brain injury, the estimate increases to 13%–50% [35].

p0245 Multiple mechanisms make the brain vulnerable to injury during ECMO. Anticoagulation, hypoxia, hypotension, sepsis, ischemia reperfusion injury, and critical illness are all important. In a prospective study of neurological outcomes after ECMO, 9 out of 10 patients who died without evidence of stroke had histopathological evidence of hypoxic/ischemic lesions of vascular origin [35]. Rapid reductions in CO_2 after ECMO initiation have also been associated with cerebral vasospasm and ischemic/hemorrhagic injury; thus, such reductions should be avoided. Finally, VA ECMO can cause direct embolization to the cerebral arteries via retrograde aortic flow.

p0250 ECPR patients represent a subgroup with a particular vulnerability to neurological damage. Prolonged native low flow states can lead to catastrophic ischemic injuries. ECPR appears to improve survival with good neurological outcome compared to conventional CPR, probably as a result of improved intraarrest cerebral blood flow [36]. Although there was initial concern that ECPR could create survivors with severe neurological disability, this doesn't appear to be the case [37]

s0100 INADEQUATE SUPPORT

p0255 Inadequate support on ECMO means exposing the patient to the risk of MCS without the benefits. In VV ECMO, this leads to greater dependence on the ventilator (through increased tidal volumes and higher pressures), which can lead to further ventilator-induced lung injury (VILI) [38]. In VA ECMO, failure to support the circulation results in ongoing shock [39] and higher doses of inotropes. Common reasons for inadequate support include access insufficiency and hypovolemia as well as pump and oxygenator failure.

p0260 Access insufficiency occurs when the negative pressure around the inflow cannula causes the vein to collapse around it. This leads to occlusion of flow into the cannula, resulting in high negative pressures, cavitation of RBCs, and hemolysis. Low circulating volume, high pump speed, small cannula size, poor cannula position, inadequate sedation, coughing, and raised intraabdominal pressure can all cause this problem [15].

p0265 Renal failure is one of the most common complications associated with ECMO, with 15%–46% patients requiring renal replacement therapy (RRT) ([10,28]. Hemofiltration is often indicated for loss of glomerular filtration, profound acidosis, or to manage fluid balance. Patients requiring hemofiltration prior to ECMO have higher mortality rates; in one study, however, initiation of hemofiltration during ECMO was not associated with worse outcomes [40]. There is still conjecture whether the ECMO is causative, or whether the pathology necessitating ECMO is more important [41].

p0270 Multiorgan dysfunction syndrome (MODS) is a complex and potentially end-stage condition that is a common cause of death on ECMO [42]. Inadequate or delayed resolution of initiating injury, inadequate support, recurrent sepsis, and prolonged illness all contribute. Patients post ECPR are at an especially high risk [43].

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s0105 ## MECHANICAL FAILURE

p0275 Mechanical complications include failure of any part of the circuit, pump, or oxygenator. The incidence is between 0.5%–13.6% during ECMO support, and complications can present as catastrophic bleeding or sudden loss of ECMO flow. Mechanical failures have been associated with higher rates of infection [31].

p0280 Gas embolism (1.4%) is a life-threatening condition where gas is entrained into the venous/access side. Potential sources of air include taps that are accidently opened, fractures or tears at joints between components (0.4%), or tubing damage from clamping or erosion from the use of alcohol cleaning products. Small leaks can be difficult to see or hear but over time can be sufficient to fill the pump with air, resulting in sudden airlock and cessation of ECMO flow. Entrainment of gas on the return side is uncommon but can result in massive gas embolism with catastrophic ischemic injury and death.

p0285 Cannula dislodgement, although rare, may occur during transportation or turning of patients, with catastrophic results. Damage to the porous oxygenator capillaries resulting in plasma leak is now rare with current generation oxygenators. Other complications, such as pump malfunction and heat exchanger malfunction, can also occur.

s0110 ## SPECIFIC PROBLEMS RELATED TO TYPE OF SUPPORT

p0290 Table 16.3 lists some of the more specific complications of ECMO by mode of operation. Following is an in-depth summary of each of these complications.

t0020 **Table 16.3** Specific Complications of ECMO by Mode

Specific Complications of ECMO by Mode
Venoarterial ECMO
Differential hypoxia
Left ventricular distension
Venovenous ECMO
Recirculation
Right heart failure
ECMO cardiopulmonary resuscitation
Severe neurological injury

s0115 ## VENOVENOUS ECMO

p0295 Recirculation during ECMO support occurs when oxygenated blood from the return cannula is recirculated via the access cannula without delivery to the patient. If significant, it leads to inadequate ECMO support, causing potentially severe systemic hypoxia and end-organ damage. The risk of recirculation increases with the

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configuration type (femoral-femoral and femoral-jugular the highest, dual lumen cannulation the lowest if positioned correctly), the distance between the cannulae (highest risk <10cms apart), and during higher ECMO flow rates [44].

p0300 Cor pulmonale, or right ventricular failure that occurs secondary to severe pulmonary disease, can occur in patients undergoing VV ECMO [45]. The incidence is not known, but factors likely to contribute include increased pulmonary vascular resistance secondary to hypoxic pulmonary vasoconstriction, high levels of PEEP, and volume overload. Patients may present with increasing hemodynamic instability while on VV ECMO, necessitating inotropic support and ECMO reconfigurations such as venoarterial-venous (VAV) ECMO.

s0120 ## VENOARTERIAL ECMO

s0125 ### *Peripheral cannulation*

p0305 LV distension can occur during peripheral VA ECMO when the LV is inadequately decompressed [46]. Normally, VA ECMO is effective at reducing LV volume overload by removing volume from the venous system, causing a reduction in LV preload. However, blood returning via ECMO to the aorta causes increased LV afterload, which the failing LV may not be able to accommodate. This results in a reduction or even cessation in native blood flow, and, ultimately, in LV stasis and distension. Aortic regurgitation (AR) exacerbates this problem. It may also diminish intramyocardial microvascular flow. Worsening valvular regurgitation (aortic or mitral) and poor forward flow can lead to intractable pulmonary edema. This is usually fatal unless the process is reversed. Treatment options include: increasing forward flow through the aortic valve via inotropes, increasing peak positive end pressure (PEEP), atrial septostomy, LV venting, and concomitant Impella usage [47].

p0310 Differential hypoxia occurs in peripheral VA ECMO. The combination of improving native cardiac function with poor respiratory gas exchange leads to the circulation of deoxygenated blood through the native pulmonary circulation into the aorta. This blood preferentially supplies the proximal aortic branches, such as the major cerebral and coronary vessels, while the remainder of the systemic circulation is well supported by the ECMO circuit. Differential hypoxia can lead to catastrophic cerebral anoxic injury if not recognized and reversed.

s0130 ## PATIENT-RELATED COMPLICATIONS

s0135 ### PRE-ECMO SEVERITY OF ILLNESS

p0315 The patient's condition at the time of MCS initiation has a major impact on the overall incidence and severity of complications. Factors such as SOFA score [48,49], duration of prior mechanical ventilation, lactate, $ETCO_2$, and the number of organ failures [50] are important predictors of complications and outcomes and feature strongly in predictive scores such as the SAVE [51] score and RESP [50] score.

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s0140 ## TIMING AND NATURAL HISTORY OF THE DISEASE

p0320 Delays in initiating MCS, with resulting prolonged periods of shock or hypoxia, lead to the establishment of ventilator- induced lung injury (VILI), irreversible organ failures, and death [46]. There is some evidence that earlier initiation of MCS is associated with improved outcomes in cardiac arrest patients [43,52] and cardiac transplantation [53,54]. However, "preemptive" initiation may unnecessarily expose patients to the risks of MCS while providing minimal benefit. Many experts believe earlier initiation of ECMO will lead to improved outcomes; however, the data supporting this practice is currently inconclusive.

s0145 ## ETIOLOGY

p0325 Despite similar degrees of illness severity, certain conditions are associated with reduced complications and better outcomes. VV ECMO for the H1N1 respiratory outbreak in 2009 was associated with consistently better outcomes than for other forms of pneumonia, especially extrapulmonary ARDS [55]. VA ECMO for myocarditis and postcardiac and lung transplantation graft dysfunction is also associated with fewer complications and improved outcomes. In general, acute etiologies of severe cardiorespiratory failure are more likely to reverse, whereas acute or chronic causes are more likely to require ongoing supports such as durable VAD support and cardiac or lung transplantation [56].

s0150 ## LONG-TERM COMPLICATIONS OF ECMO

p0330 As survival post ECMO has improved, longer-term morbidity has become a more important consideration for patients and their clinicians. Cognitive impairment and psychological problems, including anxiety (34%), depression (25%), and post-traumatic stress disorder (PTSD) symptoms (16%), are common; they are also higher than for age-matched controls [57,58]. Much is related to prolonged critical illness rather than to ECMO per se. In the CESAR trial, patients in both VV ECMO and conventional treatment groups had comparable rates of depression, anxiety, and cognitive impairment, but both were higher than matched controls at 6 months [59].

p0335 Other long-term physical problems may follow cannulation, such as femoral nerve damage and chronic pain, brachial plexus injuries, arterial stenosis leading to claudication, pressure areas from prolonged immobilization, and poor wound healing following initiation of immunosuppression post transplantation.

p0340 ECMO is a temporary intervention that usually lasts for a maximum of 2–3 weeks. While ventricular assist devices share many of the same early complications with ECMO, they often remain in situ for months and often years. In Part 2, we detail the early and late complications of VAD support and address the important overlap areas with ECMO.

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s0155

PART 2: COMPLICATIONS IN DURABLE VAD SUPPORT

p0345 Since the advent of continuous flow (CF) VADS in the early 21st century, VAD support is increasingly well tolerated and is becoming a realistic alternative to heart transplant. In the United States, the implant strategy is increasingly destination therapy (DT) (46%) followed by bridge-to-transplant (BTT) (30%), and bridge-to-decision (remaining 24%) [60]. As use of DT strategy increases, avoiding the complications that occur with increasing frequency with longer support, e.g., infection and mechanical failure, is particularly important.

p0350 Heart transplantation continues to be a limited resource available only to a minority of patients with advanced heart failure. Therefore, destination VAD support, which is well tolerated and offers good quality of life and symptomatic control with a low risk of complications, is of increasing importance. This remains somewhat elusive, unfortunately, as complications of long-term support remain considerable. According to the seventh annual report (2015) of the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS), 70% of patients had a major adverse event related to VAD support within 1 year of implantation (infection, bleeding, device malfunction, stroke, and death), as shown in Fig. 16.3 [60]. Some complications of durable VAD support can occur at any stage of support, for example, thrombosis and right heart failure. Others are more specific to the temporal course (see Fig. 16.1 and Table 16.4).

s0160

COMPLICATION RATES IN PULSATILE VADS

p0355 Design improvements and advances in the technology and management of continuous flow VADS have reduced the rates of the most significant complications compared to the rates with pulsatile VADS. New complications, however, have emerged with continuous flow pumps (e.g., gastrointestinal bleeding related to angiodysplasia and aortic insufficiency) and may potentially be related to lack of pulsatile flow and LV afterload differences [61]. Fully implantable continuous flow VADs now account for greater than 90% of the devices implanted, and they will be the focus of the remainder of this chapter [60] (see Table 16.4 and Fig. 16.4).

s0165

BLEEDING

p0360 As with ECMO, bleeding is the most common adverse event following VAD implantation [62–65]. Bleeding complications impact greatly on morbidity and contribute to mortality events. In the setting of major bleeding, anticoagulation is necessarily reduced, predisposing the patient to thromboembolic complications. Increase in blood transfusion requirements can lead to allosensitization, which has a negative impact on survival after heart transplantation in non-MCS-supported patients [66]. Allosensitization can also lead to difficulty in crossmatching for transplantation and to longer duration of support. In a study of 468 HeartMate II (Abbott, Abbott Q1 Park, IL, USA) BTT patients, bleeding, as defined by the requirement for 2 or more

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t0025 **Table 16.4** Adverse Event Rates (Events/100 Patient Months) in the First 12 Months Postimplant by Era for CF LVADs/BiVADs ($n = 12,030$)

	Era 1 ($n = 4744$) Continuous 2008–11		Era 2 ($n = 7286$) Continuous 2012–14		Era 1 vs. Era 2 (2008–11/2012–14)	
Adverse Event	**Events**	**Rate**	**Events**	**Rate**	**Ratio**	***P*-value**
Bleeding	3932	9.41	4420	7.79	1.21	<0.0001
Cardiac/vascular						
Right heart failure	238	0.57	276	0.49	1.17	0.07
Myocardial infarction	29	0.07	34	0.06	1.16	0.55
Cardiac arrhythmia	2007	4.80	2303	4.06	1.18	<0.0001
Pericardial drainage	271	0.65	305	0.54	1.21	0.02
Hypertension	182	0.44	115	0.20	2.15	<0.0001
Arterial non-CNS thrombosis	70	0.17	94	0.17	1.01	0.93
Venous thrombotic event	304	0.73	286	0.50	1.44	<0.0001
Hemolysis	200	0.48	314	0.55	0.87	0.11
Infection	3435	8.22	4132	7.28	1.13	<0.0001
Stroke	487	1.17	916	1.61	0.72	<0.0001
Renal dysfunction	601	1.44	876	1.54	0.93	0.19
Hepatic dysfunction	246	0.59	326	0.57	1.02	0.76
Respiratory failure	1104	2.64	1551	2.73	0.97	0.39
Wound dehiscence	81	0.19	96	0.17	1.15	0.36
Psychiatric episode	486	1.16	525	0.93	1.26	0.0003
Total burden	13,673	32.72	16,569	29.20	1.12	<0.0001

BiVAD, *biventricular assist device*; CF, *continuous flow*; CNS, *central nervous system*; LVAD, *left ventricular assist device*.

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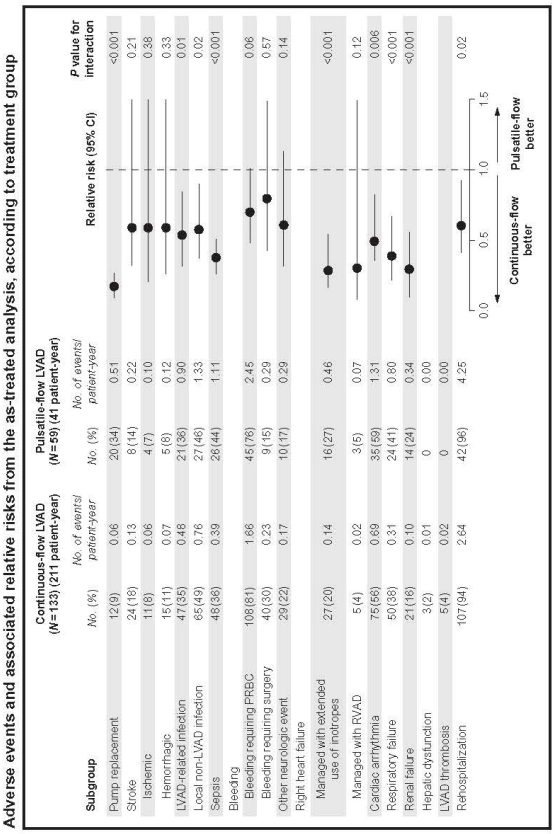

FIG. 16.4

f0025 Comparison of complications with continuous flow versus pulsatile flow VADs. The "other neurologic event" subcategory included transient ischemic attack and neurologic events other than stroke. For the "rehospitalization" subcategory, the rates were calculated on the basis of patient-years after initial hospital discharge. *LVAD*, left ventricular assist device; *PRBC*, packed red cells; *RVAD*, right ventricular assist device.
Reprinted with permission from Slaughter MS, Rogers JG, Milano CA, Russell SD, Conte JV, Feldman D, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. N Engl J Med 2009;361:2241–51. doi:10.1056/NEJMoa0909938.

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units of blood in a 24 h period, was associated with a significant decrease in survival at 1 year following transplantation (82% vs. 94%, $p < 0.03$) [67].

p0365 Early postoperative bleeding related to surgery is a significant complication. However, bleeding can be nonsurgical (e.g., epistaxis, gastrointestinal bleeding, genitourinary tract bleeding) and out of proportion to the degree of anticoagulation or antiplatelet treatment. The mechanisms are complex and can include alterations in hemostasis due to the underlying heart failure state (e.g., coagulopathy from liver dysfunction related to chronic right heart failure and congestion), surgery (blood loss, hemodilution), and mechanical support (altered rheology and platelet dysfunction due to high shear stresses).

p0370 Comparing studies quoting bleeding rates can be difficult due to nonstandardized definitions. The INTERMACS description, (see Box 16.1) while providing standardization, is lacking in detail.

p0375 Acquired von Willebrand Syndrome (AvWBS) is common in VAD support [68,69]. Loss of high molecular weight (HMW) multimers is due to a conformational change in the von Willebrand protein, exposing the A2 domain to proteolysis by ADAM TS 13 (A Disintegrin and Metalloprotease with Thrombospondin Type I Motifs). This occurs with the high shear stresses seen in vitro with VAD support. High molecular weight von Willebrand multimers induce platelet activation and aggregation; their loss, therefore, explains the bleeding seen in the AvWBS, which may occur in the absence of a bleeding stimulus.

p0380 AvWBS is practically ubiquitous in CF VADS, and additional mechanisms are required to explain the bleeding diathesis commonly seen. Reduction of pulsatility may contribute, and in one study of HeartMate II patients, lowered pulsatility as demonstrated by a pulsatility index <4.6 and lack of aortic valve opening was associated with an increase in major nonsurgical bleeding [70].

b0010 **Box 16.1 INTERMACS DEFINITION OF BLEEDING**

p0030 An episode of SUSPECTED INTERNAL OR EXTERNAL BLEEDING that results in one or more of the following:

- Death
- Reoperation
- Hospitalization
- Transfusion of red blood cells as follows:

p0055 If transfusion is selected, apply the following rules:

- During the first 7 days post implant

p0065 *Adults* (≥*50 kg*): ≥ 4U packed red blood cells (PRBC) within any 24 h period during first 7 days post implant.

- After 7 days post implant

p0075 Any transfusion of packed red blood cells (PRBC) after 7 days following implant, with the investigator recording the number of units given. (record number of units given per 24 h period).

p0080 Note: Hemorrhagic stroke is considered a neurological event and not a separate bleeding event.

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s0170 ### Tamponade

p0385 Perioperative bleeding can lead to cardiac tamponade, which is more common in VAD patients than in other cardiac surgery patients. In the modern era, reporting reoperation for tamponade occurs in 30%–40% of patients [71,72], while in the pulsatile VAD era, reoperation for tamponade was even higher at 40%–60% [73].Tamponade in LVAD patients may present as low pulsatility and rising CVP (and left atrial pressure if monitored), combined with low-flow alarms from the VAD. There may be an increase in suction events and/or ventricular tachyarrhythmias. With LVAD support, intracardiac pressures are lowest in the left ventricle throughout the cardiac cycle, and this often collapses first.

p0390 Any unstable patient requires urgent echocardiography (often transesophageal) to evaluate this problem. Tamponade may occur late (ten days or more after surgery) and may follow clinical events such as pacing wire removal.

s0175 ### Gastrointestinal hemorrhage

p0395 Gastrointestinal (GI) hemorrhage accounts for significant morbidity with continuous flow pumps and is the most frequent cause of bleeding in Heartmate II-supported patients [68]. It occurs with increasing frequency later in the patient course and is the most common cause for readmission to hospital [74]. It is ten times more frequent in patients with continuous flow VADS as compared with pulsatile flow (0.63 events per patient year [EPPY] in CF VADS vs. 0.068 EPPY in pulsatile flow VADS) [75]. It is seen more frequently with axial flow VADs (HeartMate II) than with the centrifugal HeartWare HVAD (Medtronic Inc, FL, USA) (19%–30% vs. 10%–13%) [65,68,76,77]. GI bleeding is more common with increasing age, so some centers alter their anticoagulation approach on this basis [78]. Gastrointestinal bleeding is associated with a significant increase (7.4-fold) in subsequent thromboembolic events, most probably due to a reduction in the intensity of anticoagulation management [78].

s0180 ### Heyde's syndrome

p0400 The association of CF LVAD support and GI bleeding related to arteriovenous malformations is of major importance. This is a well-recognized syndrome in severe aortic stenosis [79]. More recently, it has been described also in prosthetic valve dysfunction [80].

p0405 Contributors to angiodysplasia may include nonpulsatile flow, high shear stress, and AvWBS. Angiodysplasia-related bleeding frequently is recurrent and resolves with heart transplantation. It is seen particularly in older patients and with reduced pulsatility. Pump designs such as HeartMate 3 (Abbott, Abbott Park, IL, USA), which Q2 aim to reduce circulatory shear stresses and preserve pulsatility, may help to reduce the incidence of GI hemorrhage related to angiodysplasia and AvWBS [81]. However, this has not resulted in a change in the rate of GI hemorrhage, as seen in the Momentum 3 trial (15% in both the HeartMate II and HeartMate 3 cohorts) [82].

p0410 Upper and lower GI bleeding can be seen from a range of sources other than angiodysplasia, including peptic ulceration, oesophagitis, colonic polyps, and diverticular disease [76].

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s0185 ## THROMBOSIS

p0415 Bleeding and thrombotic complications are intrinsically linked, and the optimum balance between prevention of bleeding and prevention of thrombosis can be difficult to achieve.

p0420 Thrombosis and thromboembolism are significant complications. Anticoagulation and antiplatelet medication aim to prevent such complications. There is no standard antithrombotic protocol recommended for all patients with VAD support, and there is considerable variability in published approaches [83]. Older patients are at risk from both bleeding and thrombotic side effects [76]. Relaxation of anticoagulation targets may in turn lead to more thrombotic side effects, which, although less frequent, are more likely to be fatal. The interplay between inflammation and sepsis is well known, and increasing the intensity of antithrombotic therapies may be a reasonable approach during intercurrent septic episodes. Factors potentially associated with thrombotic events in mechanical support are summarized in Table 16.5.

s0190 ### *Pump-associated thrombosis*

p0425 Thrombus can develop on any part of a continuous flow pump at any point during mechanical circulatory support.

p0430 Pump thrombosis affected 8.1% of 382 patients in the HeartWare ADVANCE study (BTT and continued access protocol trial), at a rate of 0.08 per patient years [84]. One-year survival in that study was 69% versus 85% for patients without pump thrombosis. A sudden sharp increase in pump thrombosis events with HeartMate II was described in three large-volume centers, with a dramatic increase in rate for pumps implanted after March 2011, approximately, compared with implants prior to that date. Confirmed pump thrombosis at 3 months occurred in 8.4% of patients in January 2013 versus 2.2% in March 2011 [85]. An INTERMACS study confirmed the small but significant increase in pump thrombosis and pump exchange in 2011–2012 compared with the 2008–2009 era. Freedom from pump thrombosis was 99% in 2008–2009 but had dropped to 94% by 2010–2011 [86]. The cause for this increase is not clear, with no manufacturing changes to explain it. Hypotheses for the increase in rate include using lower pump speeds to maintain aortic valve opening, a shift to destination therapy, and a change in anticoagulation intensity due to hemorrhagic concerns [87].

t0030 **Table 16.5** Factors Associated With Thrombosis in VAD Support

Patient-related factors	Procoagulant state of advanced heart failure Infection Atrial fibrillation Reduced anticoagulant intensity Thrombophilia Heparin-induced thrombocytopenia
Pump factors	Design, e.g., sintering with HeartWare pump earlier version
Anatomic and surgical factors	Angulation of cannula, trabeculation Reduced blood flow in aortic root

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s0195 ## *Right heart failure*

p0435 Right heart failure after LVAD implantation is one of the most common complications, reportedly occurring in 20%–50% of patients post-VAD implant, and is a significant cause of mortality [60,88,89]. Patients with RV failure after LVAD have lower survival to transplant, to recovery, or with continuing support at 180 days [90]. Definitions vary, making it difficult to compare different case series. The INTERMACS definition of right heart failure after VAD implantation requires 7 days of support (suggesting that transient right heart failure is virtually inevitable). The incidence in the INTERMACS 7 report was 0.57 EPPY in the 2008–2011 era and 0.49 EPPY in the 2012–2014 era. There was an increased incidence of right heart failure as a cause of death in more debilitated patients (INTERMACS 1–2 vs. 4–7) [60].

p0440 Right heart failure can occur at different time points: acute (less than 48 h), early (48 h–14 days), and late (after 14 days) [91]. The etiology of acute, early, and late right heart failure differs (see Table 16.6).

p0445 Late right heart failure is increasingly recognized as one reason patients may fail to thrive after LVAD implant [92]. In a study of 537 HeartMate II destination patients, Rich and colleagues described late right heart failure associated with treatment with inotropes and hospitalization for more than 30 days after VAD implantation [93]. Late right heart failure occurred in 8% of patients with a median time to diagnosis of 1.3 years after VAD implantation. Late heart failure had a significant effect on mortality, quality of life, and functional capacity.

p0450 Numerous preoperative scoring systems to predict right heart failure have been proposed [92,94–98]. Many of these are derived from small individual center populations and from the era of pulsatile support, and may not be generalizable to other centers' experience. Their number indicates that not one scoring system is perfect or widely accepted [99].

p0455 Management of RV failure after LVAD will be described comprehensively in Chapter 17.

t0035 **Table 16.6** Mechanisms of Right Heart Failure During VAD Support

Depressed right ventricular (RV) function post bypass
Preexisting RV failure
Blood product use
Negative effects of ventilation and increased RV afterload
Hemodynamic interaction of the LVAD and the right heart
• Septal shift (parallel ventricular interdependence) o Loss of the interventricular septal contribution to RV systolic function • In-series ventricular interdependence o Hemodynamic loading of the marginal right heart with increase in cardiac output, i.e., the right heart must pump what the LVAD delivers

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s0200 ## Infection

p0460 Like ECMO, infection in the setting of LVAD support causes increased morbidity and mortality, and is a significant risk factor in transplant surgery for BTT patients [60,100].

p0465 Infection can be device related (driveline or pump pocket) or non-device related. In the era of pulsatile VADs, infection was a major cause of morbidity and the leading cause of mortality in the REMATCH study [89]. The rate of device- related infection in the Heartmate II and the HeartWare BTT trials were 0.37 EPPY and 0.29 EPPY, respectively [63,65]. In the HeartMate II postapproval destination trial, the rate had fallen but was still significant at 0.22 EPPY.

p0470 The occurrence of sepsis post-LVAD implant increases mortality [101,102]. Nosocomial infection can have very significant consequences as bloodstream infection in the setting of an implanted device is generally impossible to eradicate and often requires antibiotic treatment for the lifetime of the device. This causes antibiotic selection pressure, and antibiotic resistance can emerge, potentially leading to an increase in complications during and after transplantation. Destination VAD patients are at increased risk of septic complications, which may be due to the prolonged nature of support. Obesity and diabetes are also independent risk factors for infectious complications [102,103].

p0475 Prevention of infection is a key goal at every point of the patient's journey as per Table 16.7.

s0205 ## Driveline infection

p0480 The driveline is a critical source of ascending infection if driveline colonization occurs. Biofilm formation by typical organisms involved in driveline infections (e.g., staphylococcus species, pseudomonas) means that eradication is very difficult [104]. Essentially, any serious driveline infections that are refractory to treatment may necessitate an entire new VAD and driveline insertion—at substantial physiological and financial cost

t0040 **Table 16.7** Measures to Prevent Infection in VAD Support

Pre-VAD implant	Removal of preexisting lines that may be colonized
During VAD implant	Strict asepsis by all team members
Post operatively	Attention to hand hygiene by all team members (medical, nursing, allied health, ward support, and cleaning staff) in ICU, wards, outpatient setting
	Avoid excessive sedation in ICU
	Prevention of ventilator-associated pneumonia and other nosocomial infections (e.g., head up 30°)
	Pressure injury care
	Removal of lines and catheters once no longer required
	Antimicrobial stewardship

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s0210 ### Multisystem organ failure

p0485 One of the main complications in the ICU following LVAD support is the development of multiorgan failure. The etiology of this is complex, and it may follow a combination of other complications, such as infection, right heart failure, etc. Advanced heart failure is a proinflammatory state. Inflammation in continuous-flow VAD implantation can be associated with the development of multisystem organ failure [105]. The level of inflammatory markers vary with INTERMACS profiles, with highest level of preimplant IL-6 seen in INTERMACS profile 1 patients [106].

p0490 Timing of support is crucial, and the debility of the patient at the time of implantation correlates with the development of multisystem organ failure. This may become less common with the trend to implant at INTERMACS 3–4 and beyond. Preoperative optimization of hemodynamics and treatment of right heart function may also be very important. Also, implantation of VAD support as a bridge to a decision in more debilitated patients allows evaluation of those who will benefit as well as optimization of those who are at INTERMACS 1 or 2 [107].

p0495 Postoperatively, early and prompt treatment of complications such as tamponade, bleeding, sepsis, and right heart failure, including timely mechanical support where indicated, may also help prevent the development of multiorgan failure, which can be considered the sequelae of a variety of insults.

s0215 ### Vasoplegic shock

p0500 Vasoplegic shock can occur in up to one-third of patients post implant and in a minority of cases can be very severe [108,109]. The presence of hypotension should prompt early investigation and management of conditions such as sepsis, right heart failure, and tamponade as well as other complications. Mechanisms of vasoplegic shock may include relative deficiency of endogenous vasopressin, preoperative medications such as angiotensin-converting enzyme inhibitors, and inflammation post-cardiopulmonary bypass [109].

s0220 ### Arrhythmia

p0505 Arrhythmias are common after LVAD placement, occurring in 25%–60% of patients with continuous flow VADS [110]. The most important predictor of post-LVAD ventricular arrhythmia (VA) is pre-LVAD VA [110–112]. Ventricular arrhythmias have previously been considered relatively benign in an LVAD population. As is not the case in other heart failure populations, arrhythmias may not cause sudden cardiac death as the LVAD itself provides alternative support to the native heart [113–115]. Reports of patients with prolonged ventricular arrhythmia without loss of consciousness are common. The mechanism hypothesized is a Fontan-type univentricular circulation with passive flow though the right ventricle in the setting of low pulmonary vascular resistance [116]. The effect of VAs on morbidity, mortality, and quality of life are undoubted, however [117]. Arrhythmia affecting the right heart can reduce delivery to the left ventricle and cause acute left ventricular suction events. Arrhythmias may also be the result of suction events. Prolonged VAs may be associated with right heart failure and acute kidney injury. They increase readmission rates to hospital and cause a significant deterioration in

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quality of life. Arrhythmia is most common early post-VAD implantation in the first 2–4 weeks, but a significant proportion of patients can have arrhythmia later posthospital discharge. Causes are multifactorial and may include electrolyte disturbance preoperatively. In addition, myocardial scars in the setting of ischemia, scar formation from the VAD implant, prolongation of the QT interval, and right heart failure are possible causes [118]. However, primary prevention of VAD-related arrhythmias with an automated implantable cardioverter defibrillator (AICD) is controversial. A recent metaanalysis failed to detect any mortality benefit from AICDs implanted in a continuous flow VAD population [112]. There are potential downsides to this therapy, with infection-related complications, electromechanical interference, and inappropriate shocks. Thus, future randomized trials to guide therapy would be useful.

s0225 ## LONG-TERM COMPLICATIONS

s0230 ### *Neurological*

p0510 Neurological events are the primary cause of death post-VAD implant, accounting for 18% in the most recent INTERMACS report [60]. The annual risk of stroke in patients with an LVAD is approximately 15% per year [119,120]. Stroke-related morbidity is also very high and may significantly impair functional capacity in survivors. Systemic infection is consistently reported to increase the stroke risk in VAD support [119–121].

p0515 Stroke can be ischemic or hemorrhagic in nature. The etiology of stroke in mechanical support is multifactorial [122,123]. Risk factors for stroke include device thrombosis, preexisting medical comorbidities, e.g., atrial fibrillation and aortic valve closure. The most significant risk remains infection, which doubles the risk [123]. Elevated mean arterial pressure (MAP) and prior stroke are also significant risk factors. In a study of risk factors for neurological events in a HVAD BTT and continued access protocol trial, Teuteberg found that atrial fibrillation and aspirin dose <81 mg/day were independent risk factors for ischemic stroke (6.8% of patients). Mean arterial pressure >90 mmHg, aspirin <81 mg/day, and International Normalized Ratio (INR) > 3.0 were independent risk factors for hemorrhagic stroke (prevalence 8.4%) in multivariable analysis [122]. Hemorrhagic stroke has a much greater survival impact than ischemic stroke [122,124]. There was preponderance of right hemispheric infarction, a likely site for cardiogenic emboli via the innominate artery. The authors hypothesized that the seemingly paradoxical link between lower aspirin and hemorrhagic stroke may be explained by hemorrhagic transformation of thromboembolic stroke.

s0235 ### *Device failure/mechanical issues*

p0520 Device failure is exceedingly rare with the current generation of continuous flow VADS. In the landmark Heartmate II destination therapy trial, the failure rate for HMII was 0.06 per patient-year compared with 0.51 per patient-year with the Heartmate XVE [62,125]. In the majority of patients who required pump exchange in this trial, the cause of exchange was due to damage to the percutaneous lead. There was

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no episode of pump failure. Similarly, in the ADVANCE BTT HVAD study, device failure was rare, with the majority of pump exchanges occurring because of infection or pump thrombus [65].

s0240 ### Outflow graft obstruction

p0525 Outflow graft obstruction can present with late heart failure, and may be difficult to diagnose. Sources of obstruction may be graft stenosis, cannula thrombus, or extrinsic compression/kinking. Gated cardiac computed tomography angiography (CTA) of the pump may diagnose an outflow graft problem. Intravascular ultrasound may also be useful [126]. Novel approaches to treatment include endovascular stenting [127]. This less common complication should be considered in any patient who is showing signs of insufficient support in the absence of other causes, such as right heart failure and aortic insufficiency. The symptoms and signs may mimic pump thrombosis, and indeed pump thrombosis and outflow graft obstruction may coexist. A search for this complication is, therefore, important as it will change the nature of the pump-exchange surgery [126,128].

s0245 ### Aortic valve and aortopathy

p0530 Continuous flow VAD support alters local hemodynamics and can affect valvular function and cause ultrastructural changes in heart tissues. Aortic valve commissural fusion and leaflet thickening leading to aortic stenosis and regurgitation is common in VAD support with both pulsatile and CF VADS [129–131], although it is more frequent with CF VADs [132]. This complication occurs de novo in patients with normal valves preoperatively and progresses over time [132,133]. Preexisting aortic regurgitation may worsen in severity. Mechanisms may include high shear stress on the ventricular aspect of the valve and lack of aortic valve opening. Aortic regurgitation is frequently eccentric and continuous throughout the cardiac cycle [132]. It is difficult to evaluate severity using conventional echocardiographic parameters, and alternative approaches have been proposed [134]. Aortopathy may also contribute to a worsening of aortic regurgitation [132,135,136]. Hemodynamically significant aortic regurgitation or stenosis will limit efficiency of left ventricular unloading and can cause cardiac failure symptoms, leading to a requirement for surgery. The time-dependent nature of aortic insufficiency is of particular concern for destination support.

s0250 ## CONCLUSION

p0535 MCS support in critically unwell patients is associated with multiple complications despite improvements in technology over the last 20 years. These may be related to initiation of the support, the device itself, or to the patient population and underlying illness. Reducing and preventing MCS complications remains an important goal for the future uptake of this technology, particularly in the pursuit of improving patient-centered outcomes and longer-term support.

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Chapter 6: **Retrieval of adult patients on extracorporeal membrane oxygenation by an intensive care physician model**

This chapter describes a single-centre, retrospective observational study investigating the retrieval of patients on ECMO to a specialist ECMO centre. The primary aim was to assess the feasibility of an intensivist-led team for ECMO retrieval. In addition, the safety, complications and outcomes of retrieved patients were compared to those patients initiated on the supports at the ECMO centre. This work related to thesis aim 5.

Artificial Organs

Retrieval of Adult Patients on Extracorporeal Membrane Oxygenation by an Intensive Care Physician Model

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Abstract: The optimal staffing model during the inter-hospital transfer of patients on extracorporeal membrane oxygenation (ECMO) is not known. We report the complications and outcomes of patients who were commenced on ECMO at a referring hospital by intensive care physicians and compare these findings with patients who had ECMO established at an ECMO center in Australia. This was a single center, retrospective observational study based on a prospectively collected ECMO database from Melbourne, Australia. Patients with severe cardiac and/or respiratory failure failing conventional supportive treatment between 2007–2013 were placed on ECMO via a physician-led model of ECMO retrieval, including two intensivists in a four person team, using percutaneous ECMO cannulation. Patients (198) underwent ECMO over the study period, of which 31% were retrieved. Veno-venous (VV)-ECMO and veno-arterial (VA)-ECMO accounted for 27 and 73% respectively. The VA-ECMO patients had more intra-transport interventions compared with VV-ECMO transported patients, but none resulting in serious morbidity or death. There was no overall difference in survival at 6 months between retrieved and ECMO center patients: VV-ECMO (75 vs. 70%, $P = 0.690$) versus VA-ECMO (70 vs. 68%, $P = 1.000$). An intensive care physician-led team was able to safely place all critically ill patients on ECMO and retrieve them to an ECMO center. This may be an appropriate staffing model for ECMO retrieval. **Key Words:** Extracorporeal membrane oxygenation—respiratory failure—cardiac failure—retrieval—interhospital transportation—long term outcomes.

Patients with severe cardiac and/or respiratory failure may require extracorporeal membrane oxygenation (ECMO) as a supporting therapy (1). Many hospitals do not have the expertise or equipment for the provision of ECMO, and transfer to an ECMO-capable hospital may be required. However, the inter-hospital transfer of such critically ill patients is associated with significant risk (2). This risk may be decreased with the provision of ECMO at the sending hospital by a specialized team and subsequent inter-hospital transfer of the patient on ECMO.

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Previous studies of ECMO retrieval have reported that ECMO provision at the sending hospital has generally been undertaken by a surgeon for the cannulation and a perfusionist for circuit management (3–5). In Victoria, Australia, we have developed an intensive care physician-led ECMO retrieval service for the provision of ECMO for critically ill patients with severe cardiac and/or respiratory failure who require inter-hospital transfer. The aim of this study was to report the complications and outcomes of patients who were commenced on ECMO at a referring hospital and compare these findings with patients who had ECMO established at The Alfred Hospital. Our hypothesis was that an intensive care physician-led model of ECMO retrieval is feasible, safe and is associated with satisfactory patient outcomes.

PATIENTS AND METHODS

Setting

The Alfred Hospital is a 400-bed tertiary university teaching hospital in Victoria, Australia. This facility is a referral center for ECMO, major trauma, heart and lung transplantation, hyperbaric oxygen, burns, and cystic fibrosis patients for the states of Victoria, South Australia and Tasmania, servicing a total population of over 6 million people.

The Alfred Hospital intensive care unit (ICU) has 20 critical care physicians, 45 beds and approximately 2400 admissions per year. There are 17 critical care physicians who are trained to initiate peripheral veno-arterial ECMO (VA-ECMO) and veno-venous ECMO (VV-ECMO), including percutaneous cannulation and management of the ECMO circuit.

Indications for ECMO

The indication for VA-ECMO included refractory left ventricular failure with evidence of persistent shock despite high dose inotropes (i.e., adrenaline or noradrenaline >0.3 μg/kg/min), pulmonary edema formation despite positive pressure ventilation or persistent right ventricular failure despite pulmonary artery vasodilator therapy. The indication for VV-ECMO included refractory respiratory failure as a result of an acute deterioration with a potentially reversible cause. Specific entry criteria included an inability to maintain oxygen saturation >88% or pH >7.20 with 100% inspired oxygen fraction and optimal positive end expiratory pressure (PEEP) titration, while maintaining a safe lung ventilation mode, including a plateau pressure <35 mm Hg and tidal volume ≤6 mL/kg.

Contra-indications to ECMO included presence of additional severe chronic organ failure (liver, lung or renal), presence of severe acute brain injury, known malignancy and/or age >75 years. Specific contra-indications for VA-ECMO included cardiac arrest with an initial cardiac rhythm of asystole or >60 min from arrest to return of spontaneous circulation, severe chronic pulmonary artery hypertension with right ventricular failure, severe aortic or mitral valve regurgitation with poor left ventricular function, late presentation of cardiogenic shock as indicated by lactate >15 mmol/L or the development of purpura. Contra-indications to VV-ECMO included end stage irreversible or chronic pulmonary processes (i.e., interstitial lung disease/pulmonary fibrosis, bronchiolitis obliterans), lung transplant >30 days, requirement for immunosuppression (other than during the first 30 days post lung transplant) and/or microcirculatory failure with established purpura.

Population

All patients from January 2007 to April 2013 treated with ECMO at The Alfred Hospital ICU were included in this study. Patients were either commenced on ECMO at a referral hospital and then transported ("retrieved") or had ECMO initiated at The Alfred ("ECMO center"). Patients with cardiac failure were commenced on VA-ECMO, whilst those with respiratory failure were commenced on VV-ECMO.

ECMO retrieval program

The ECMO retrieval service for the southern states of Australia (Victoria, Tasmania, and South Australia) commenced in 2007. Transportation of patient on ECMO is by either road ambulance or fixed wing medical aircraft. The retrieval team comprised three medical staff, and one paramedic or ECMO trained critical care nurse. From 2007–2009, the two intensive care physicians were accompanied by a perfusionist. Cannulation and subsequent transport management was managed by the intensivists, while all ECMO related management (priming and maintenance) was undertaken by the perfusionist. From 2010–2013, the role of the perfusionist was incorporated into the intensive care physician role, and a retrieval physician from Ambulance Victoria (Adult Retrieval Service) was added to the team to assist with non-ECMO patient management during transport.

All referrals for ECMO were evaluated by The Alfred Hospital on-call intensive care physician. For those cases considered appropriate for retrieval on ECMO, the team departed from the ICU with all the necessary equipment including cannulae, ECMO console, rotary pump, oxygenator, primed circuit, and all disposables.

Upon arrival, the patient was then assessed by the retrieval team for ECMO suitability. If the patient had shown no signs of improvement and they met our inclusion criteria, the patient was placed on ECMO and retrieved. ECMO referrals that were deemed not suitable for ECMO (either too well or too unwell) were excluded from this study.

Patients were established on ECMO at the referring hospital with ultrasound guided percutaneous cannulation using a Seldinger technique. A 3000 U heparin bolus was used for all patients unless active bleeding was present at the time of cannulation. For VV-ECMO, the femoral vein was accessed

with a 21 Fr multi-stage venous cannula (Maquet, or Biomedicus, 55 cm length). A 19 Fr single stage return cannula was positioned in the right atrium predominantly via the contralateral femoral vein due to the relative ease and speed of insertion of the femoral route. If complicated, a shorter single stage return cannula was placed into the internal jugular vein (Maquet or Biomedicus, 25 cm length). For VA-ECMO, return to the femoral artery used a 17 or 19 Fr cannula. For patients on VA-ECMO, a 9 Fr retrograde perfusion cannula was inserted under ultrasound guidance into the superficial femoral artery to prevent leg ischemia at the time of cannulation at the distal hospital. On occasion during difficult cases, the perfusion cannula was inserted once returned to the ECMO center. Transthoracic and/or upper abdominal ultrasound was used to confirm guide-wire and venous cannula positions during cannulation. If patients had already been commenced on ECMO by the referring hospital, then console and rotary pump were changed to Alfred Hospital equipment, and the patient was transported by the Alfred ECMO retrieval team.

ECMO circuit and maintenance during transport and at The Alfred Hospital

The ECMO circuit comprised a centrifugal pump (Rotaflow, Maquet, Rastatt, Germany) and oxygenator (Quadrox Bioline, Maquet, Rastatt, Germany). The circuit was heparin bonded. No heater unit was used during retrievals. Mechanical ventilation was continued during transportation using an Oxylog 3000 (Draeger Medical, Inc., Lübeck, Germany).

In The Alfred Hospital ICU, daily management of each patient was carried out by ICU medical and nursing staff. VV-ECMO was maintained until lung recovery, with regular trials of weaning of ECMO support. VA-ECMO was maintained until cardiac recovery, or as a bridge to left ventricular assist device or cardiac transplantation. Venous cannulas were removed in the ICU with 30 min external pressure applied, whilst arterial cannulas were removed surgically in the operating theatre.

Data collection

Demographic, severity of illness, and in-hospital outcome data were extracted from the ECMO database. Post discharge outcome data were collected from medical records. Data on complications/interventions and physiological changes during the retrieval were collected from ambulance and medical records.

Demographic variables included height, gender, cardiac and respiratory disease, and predefined comorbidities. We assessed severity of illness at the time of ECMO initiation by oxygenation status, lactate level, renal function, inotrope doses and, for patients on VA-ECMO, troponin levels and echocardiography data. APACHE II and III scores were calculated during the first 24 h of admission to The Alfred Hospital ICU.

The following complications during retrieval were recorded: bleeding requiring blood transfusion, leg ischemia (VA-ECMO), air embolism, urgent interventions (ECMO pump failure requiring hand cranking, loss fresh gas flow, monitor failure, transport delays during retrieval (minor <2 h, significant >2 h), and difficulty of cannulation (nil, difficult, failed) as reported by the cannulator.

The primary outcome measure was mortality at six months. Secondary outcomes included complications related to ECMO cannula insertion, liver dysfunction (defined as 2× increase in ALP/AST/GGT/bilirubin), ventilation days, need for renal replacement therapy, bleeding requiring surgery, number of units of packed red blood cells, cerebrovascular accident (defined as either ischemic stroke with clinical manifestations or any intracranial hemorrhage on brain CT scan), days on ECMO, ICU, and hospital length of stay and survival to hospital discharge.

The study was approved by The Alfred Human Research Ethics Committee (HREC number 296/11).

Statistical analysis

All analyses were performed using SPSS Version 21 for Mac. Categorical variables were compared between groups with a Fisher's exact test, and continuous variables were compared using a student *t*-test or Mann-Whitney as appropriate. Missing data were excluded from the analysis.

RESULTS

Over a 7 year period, 198 patients underwent ECMO at The Alfred Hospital by intensive care physicians (Figure 1). Of these 62 (31%) were retrieved and 136 (68%) were placed on ECMO in The Alfred. VA-ECMO was undertaken in 144/198 (72%), and accounted for 25/62 (40%) of those retrieved whilst VV-ECMO was used in 54/198 (27%) overall and accounted for 37/62 (59%) of those retrieved.

The baseline demographics and indications for retrieved patients and at ECMO center patients for

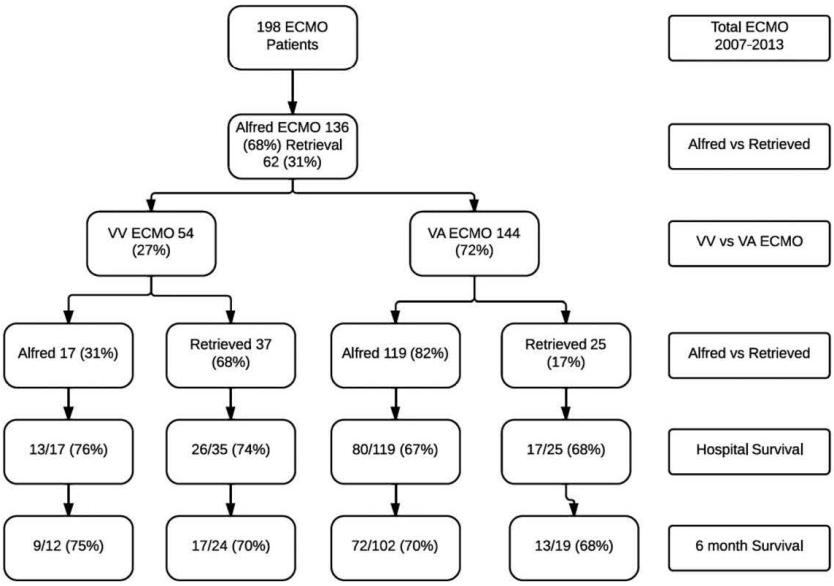

FIG. 1. Summary of Retrieval and ECMO Center patients and 6 month survival.

VA-ECMO is shown in Table 1 and VV-ECMO in Table 2.

The most common mode of transport for retrieved patients was road (67%), with the remainder by fixed wing aircraft (33%). The median distance travelled for VV-ECMO patients was 57 km (range 5–724 km) and for VA-ECMO patients was 25 km (range 5–650 km).

For VA-ECMO patients, a higher number of those retrieved were female (72 vs. 36% $P = 0.01$). The ECMO center group were more likely to be post cardiac surgery, including post heart transplant, and/or to have undergone central VA-ECMO.

For VV-ECMO patients, retrieved patients were more likely to be smokers, and have a high body-mass index, but less likely to have chronic respiratory disease, cystic fibrosis, or be immunosuppressed. Retrieved patients were more likely to have the diagnosis of H1N1 influenza pneumonia, while ECMO center patients were more likely to be postoperative or post lung transplant. The early period of our study coincided with an increase in incidence of H1N1 requiring VV-ECMO during 2007–2008. Of the VV-ECMO patients, 11 (27%) required VV-ECMO because of H1N1 infection.

Surgical intervention at the referral hospital for cannulation placement was not required for any of the retrievals. All patients assessed by the retrieval team as being suitable for ECMO were successfully percutaneously cannulated and retrieved back to The Alfred Hospital.

The outcomes for VA-ECMO patients are shown in Table 3 and VV-ECMO in Table 4. There was no difference in survival at ICU discharge, hospital discharge and 6 months between retrieved and ECMO center VA-ECMO or VV-ECMO patients. Both VV and VA-ECMO retrieved patients had shorter length of stay compared with ECMO Center patients.

In the VA-ECMO patients, 6/25 (24%) of retrieved patients ultimately bridged to either ventricular assist device (VAD) or underwent cardiac transplantation, while only 14/119 (11%) of the ECMO center did ($P = 0.11$). Retrieved VA-ECMO patients had higher rate of stroke (21 vs. 4% $P = 0.015$).

No patients died during the transport, and complications events that occurred during the transport are detailed in Table 5. Four (16%) of VA-ECMO patients required urgent interventions, which included hand cranking in three patients (two for battery failure, and one for low-flow due to hypovolemia). In one patient, there was transient hypoxia due to loss of oxygen flow to the oxygenator.

TABLE 1. *Veno-arterial ECMO baseline demographics*

	Retrieved $N = 25$	ECMO Center $N = 119$	Total $N = 144$	P value
General Characteristics				
Age, (years)	50 (30–56%)	48 (37–59)	48 (36–58)	0.33
Male	9 (36%)	86 (72%)	95 (66%)	0.001
Body Mass Index, (kg/m^2)	25 (24–28)	24 (22–27)	25 (22–27)	0.33
Comorbidities				
Current or Ex smoker	4 (17%)	31 (28%)	35 (26%)	0.27
Ischemic Heart disease	7 (30%)	28 (25%)	35 (26%)	0.61
Diabetes Mellitus	2 (8%)	14 (12%)	16 (12%)	0.58
Baseline Creatine, (mmol/L)	3 (13%)	22 (20%)	25 (18%)	0.57
Previous Heart Failure	6 (27%)	63 (58%)	69 (53%)	0.010
Previous Cardiac Transplant	1 (4%)	17 (15%)	18 (13%)	0.17
Factors present at ECMO initiation				
pH	7.2 (7.0–7.3)	7.2 (7.0–7.4)	7.2 (7.0–7.3)	0.97
PaO_2/FiO_2	139 (75–292)	123 (72–289)	130 (72–289)	0.57
Lactate, (mmol/L)	3 (1–9)	6 (3–11)	6 (3–10)	0.033
International Normalized Ratio	1.5 (1.1–1.5)	1.7 (1.3–2.4)	1.7 (1.3–2.3)	0.28
Troponin I, (μg/L)	27 (0–89)	3 (0–20)	3 (0–32)	0.08
Creatinine, (mmol/L)	132 (84–195)	117 (90–167)	118 (90–168)	0.80
Not intubated	0 (0%)	18 (16%)	18 (13%)	0.036
Cardiac Arrest	12 (52%)	50 (45%)	62 (47%)	0.65
APACHE II	22 (15–27)	22 (15–26)	22 (15–26)	0.89
APACHE III	64 (41–98)	64 (51–88)	64 (50–89)	0.71
Indication				
Cardiomyopathy	8 (34%)	20 (18%)	28 (21%)	0.10
Arrest/Acute Coronary Syndrome	8 (34%)	19 (17%)	27 (20%)	0.09
Post Cardiac Transplant	0 (0%)	35 (32%)	35 (26%)	0.001
Post Lung Transplant	0 (0%)	15 (12%)	15 (10%)	0.015
Postoperative VA-ECMO	4 (16%)	63 (52%)	67 (46%)	0.001
Central VA-ECMO	0 (0%)	30 (25%)	30 (20%)	0.002

Data presented as number (percentage) or median (interquartile range).

TABLE 2. *Veno-venous ECMO baseline characteristics*

	Retrieved $N = 37$	ECMO Center $N = 17$	Total $N = 54$	P value
General Characteristics				
Age, (years)	36 (25–50)	36 (25–50)	36 (25–52)	0.96
Male	19 (51%)	11 (64%)	30 (55%)	0.36
Body Mass Index, (kg/m^2)	29 (25–39)	23 (21–25)	28 (22–35)	0.02
Pregnant	2 (5%)	0 (0%)	2 (3%)	0.20
Comorbidities				
Current or Ex smoker	16 (43%)	2 (11%)	18 (33%)	0.049
Chronic Respiratory Disease	7 (18%)	9 (52%)	16 (29%)	0.011
Chronic Immunosuppression	7 (18%)	7 (41%)	14 (25%)	0.08
Cystic Fibrosis	2 (5%)	5 (29%)	7 (13%)	0.015
Previous Lung Transplant	0 (0%)	6 (35%)	6 (11%)	0.000
Prior Cardiac Arrest	4 (10%)	2 (11%)	6 (11%)	0.79
APACHE II	17 (13–19)	18 (9–27)	17 (13–22)	0.045
APACHE III	75 (59–91)	62 (41–81)	59 (45–72)	0.25
Factors present at ECMO initiation				
PaO_2/FiO_2	79 (62–120)	70 (56–143)	76 (61–99)	0.36
Lactate, (mmol/L)	1 (1–3)	3 (1–3)	1 (1–3)	0.09
Prior ICU duration, (days)	2 (1–3)	0 (0–3)	2 (0–2)	0.08
Prior Ventilation duration, (days)	2 (1–5)	1 (0–1)	1 (0–2)	0.006
Indication				
Bacterial Pneumonia	12 (34%)	7 (41%)	19 (35%)	0.53
Viral Pneumonia	15 (40%)	0 (0%)	15 (27%)	0.002
ARDS, Non Pneumonia	10 (27%)	5 (29%)	15 (27%)	0.86
Post Lung Transplant	0 (0%)	5 (29%)	5 (9%)	0.001
H1N1	10 (27%)	1 (5%)	11 (20%)	0.18
Postoperative	1 (2%)	4 (23%)	5 (9%)	0.042

Data presented as number (percentage) or median (interquartile range).

TABLE 3. *Veno-arterial ECMO outcomes*

	Retrieved $N = 25$	ECMO Center $N = 119$	Total $N = 144$	P value
Bleeding Requiring Surgery	8 (57%)	44 (54%)	52 (54%)	1.00
Vascular Surgery	14 (17%)	25 (22%)	29 (22%)	0.78
Cerebral Vascular Accident	5 (21%)	5 (4%)	10 (7%)	0.015
Ventilation, (days)	6 (2–12)	7 (2–12)	12 (7–26)	0.69
Renal Replacement Therapy	14 (87%)	75 (67%)	89 (69%)	0.15
Died on ECMO	7 (30%)	16 (14%)	23 (17%)	0.13
Red Blood Cells, (units)	8 (7–11)	13 (5–23)	11 (5–22)	0.11
ECMO duration, (days)	8 (4–10)	6 (4–11)	7 (4–11)	0.77
Bridge to VAD or Transplant	6 (24%)	14 (11%)	20 (14%)	0.11
Intensive Care duration, (days)	12 (7–23)	17 (9–44)	16 (8–26)	0.26
Hospital duration, (days)	25 (12–41)	41 (22–63)	38 (20–60)	0.010
Died in Hospital	7 (28%)	32 (26%)	39 (27%)	0.90
Died at 6 months	6 (31%)	30 (29%)	36 (29%)	1.00

Data presented as number (percentage) or median (interquartile range).

One patient had bleeding from a cannula site requiring blood transfusion during transport and one had an ischemic leg post cannula insertion which resolved after a retrograde perfusion cannula was inserted at The Alfred Hospital. Three patients on VV-ECMO required urgent interventions: two required hand cranking (hypotension second to hypovolemia, and battery failure) and one patient had noradrenalin commenced due to persistent hypotension. One patient on VV-ECMO developed suspected pneumothorax which improved once the intercostal catheters were recommenced on suction in the ambulance (8%) and had ECMO cannula insertion classed as "difficult" with prolonged time required to dilate the vessel and insert the cannula. In one patient, the return femoral vein cannula could not be passed, so return via the internal jugular vein was successfully used.

DISCUSSION

In this study, we found all patients with severe cardiac or respiratory failure had ECMO successfully established in a referral hospital by an intensive care physician-led team before transporting to the tertiary ECMO center. There were no life-threatening complications during transport and the patients had similar survival rates to patients who had ECMO commenced in the tertiary center.

Our transport model differs from most previous reports in that a surgeon or anesthetist and/or perfusionist were not part of our retrieval team (2–7). In a large Swedish study of predominantly VV-ECMO in adult and pediatric patients, all cases of cannulation were undertaken by a surgeon often with an additional scrub nurse in the team or from the retrieved hospital (8). The remainder of the transport was managed by an ECMO physician and ECMO specialist nurse. Adult VV-ECMO survival was 65/93 (70%), while survival in VA-ECMO was 4/8 (80%). In a previous Australian report (4), Forrest et al. described the retrieval of predominantly VV-ECMO patients utilizing two separate teams. One team consisted of a surgeon, anesthetist, and perfusionist for cannulation and commencement of the circuit, and a second medical team undertook

TABLE 4. *Veno-venous ECMO complications*

	Retrieved $N = 37$	ECMO Center $N = 17$	Total $N = 54$	P value
New Liver Dysfunction	3 (8%)	3 (17%)	6 (11%)	0.07
Ventilation duration, (days)	14 (9–26)	20 (8–25)	14 (9–26)	0.86
Renal Replacement Therapy	23 (62%)	9 (52%)	32 (59%)	0.07
Bleeding Requiring Surgery	3 (8%)	1 (5%)	4 (7%)	0.91
Red Blood Cells, (units)	6 (4–11)	11 (5–20)	7 (4–13)	0.16
ECMO duration, (days)	9 (5–11)	10 (5–20)	9 (5–14)	0.27
Died on ECMO	5 (13%)	3 (17%)	8 (14%)	0.69
Intensive Care duration, (days)	18 (12–28)	23 (15–36)	20 (13–30)	0.13
Hospital duration, (days)	23 (15–35)	43 (22–60)	28 (19–44)	0.007
Died in Hospital	9 (24%)	4 (23%)	13 (24%)	0.61
Died at 6 months	7 (29%)	3 (23%)	10 (27%)	0.69

Data presented as number (percentage) or median (interquartile range).

TABLE 5. *Veno-venous and veno-arterial transportation details and complications*

	VV-ECMO $N = 37$	VA-ECMO $N = 25$	P value
Patient Complications	1 (2%)	2 (8%)	0.56
- Cannula site bleeding	–	1 (4%)	
- Leg ischemia	–	1 (4%)	
- Pneumothorax	1 (2%)	–	
Urgent Interventions	3 (8%)	4 (16%)	0.43
- Hand cranking	2 (5%)	3 (12%)	
- Loss of oxygen flow	–	1 (4%)	
- Noradrenalin for low BP	1 (3%)	–	
Difficult Cannulation	3 (8%)	5 (20%)	0.17
Significant Delay	6 (16%)	1 (4%)	0.23
Distance Travelled (km)	57 (13–265)	25 (10–76)	0.007
Range (km)	5–729	5–650	–

Data presented as number (percentage) or median (interquartile range).

the retrieval. That staffing model successfully retrieved 38 patients on VV-ECMO and 2 on VA-ECMO. The median retrieval distance was 250 km (range 12–1 960 km) with 65% transported by road ambulance, 25% by fixed wing aircraft and 10% by helicopter. Survival to hospital discharge in that study was 87% in the VV-ECMO patients and 50% (1/2) in the VA-ECMO patients.

These models of ECMO transport involved large numbers of staff, creating logistical challenges and multiple transport vehicles to accommodate all team members (9). Our model based on a team of four people, with two intensive care physicians with support from a retrieval physician and nurse or paramedic, has advantages including being a smaller team without commitments to the operating theater, enabling rapid mobilization, and the use of a single transport vehicle. Furthermore, both intensivists had skills across all ECMO related domains (priming, cannulation, and maintenance) which is advantageous for trouble-shooting during transportation. With intensive care physician cannulation using an ultrasound guided Seldinger approach, cannulation was successful in 100% of cases. This approach reduces the complexity and time required to commence ECMO compared with a surgical approach.

Survival in both our VV-ECMO (70%) and VA-ECMO groups (68%) was relatively high compared with other reports, and compares favorably with the outcomes from the Extracorporeal Life Support Organization (ELSO) database for in hospital mortality rates of VV-ECMO and VA-ECMO (39 vs. 55% survival respectively) (10). Studies of longer term outcomes have reported even lower long term survival rates post ECMO ranging from 35–42% (11,12). Possible factors include our relatively young population, and the higher numbers of transplant patients in our population (9–26%).

In the VV-ECMO group, a large proportion of our patients had VV-ECMO commenced for H1N1 pneumonia. Previous work suggests this group may have a better survival rate (78–87%) with ECMO support compared to other indications (4,9,13). In our VA-ECMO patients, a total of 20/144 (14%) went onto bridge to VAD or cardiac transplant. These procedures generally have higher survival rates compared with other indications for VA-ECMO support (14–16), possibly related to the selection of less unwell patients who are eligible for VAD or transplant. In our study the rates of retrieved versus ECMO center patients undergoing these procedures were 24 versus 11% ($P = 0.11$). Larger studies are needed to see if differing rates of VAD or transplantation between retrieved versus ECMO center groups has an impact on overall outcomes.

Our findings differ from a pediatric ECMO retrieval study which showed decreased survival for retrieved ECMO patients compared with children placed on ECMO at the ECMO center hospital (75 versus 97% in-hospital survival) (17). Other studies have shown no difference between these groups. For example, Clement et al. (5) showed no difference between retrieved and ECMO center patients in 112 pediatric transfers. Wagner et al. (18) showed a 30 days survival of 66% of retrieved ECMO patients compared with 56% at the ECMO Center, however the majority (17/23) of these were VV-ECMO. Huang et al. (19) showed similar survival for 31 retrieved VA-ECMO patients as ECMO center VA-ECMO patients at 32%.

In our study, successful cannulation and provision of ECMO was achieved in all cases. In more VA-ECMO cases, the cannulation was described as "difficult", and this was predominantly related to difficulty passing the wire or dilating the femoral artery.

Few major complications occurred during transport. This finding differs from previous reports which found adverse event rates ranging up to 42% (3,4,9,20). For example, Foley et al. (9) reported an adverse event rate of 16% in 100 ECMO retrievals (10 electrical failure, 3 circuit breakages, 1 circuit rupture, oxygenator thrombosis, oxygenator leakage). Forrest et al. (4) reported a 42% rate of minor complications during 38 VV-ECMO and 2 VA-ECMO retrievals.

One unexpected finding in our study was a higher rate of stroke in the retrieved VA-ECMO group compared with the ECMO Center group. The reason for this is unclear. Heparinization was protocolized for all patients, and none of the retrieved group had central ECMO which has been previously reported as being a risk factor for stroke (21). Further studies will need to investigate this association.

Strengths and limitations

This study is one of the first to report that an intensivist led retrieval team can safely commence transport patients severe heart and respiratory failure on ECMO with few clinically significant complications or delays. It includes detailed information on intratransport complications of both VV and VA-ECMO. It is however limited by its retrospective nonrandomized study design. More detailed ventilator data was not available to calculate Murray scores, nor were detailed transportation times. Differences in baseline characteristics, illness severity, and indications between retrieved and ECMO center patients may have influenced outcomes between the two groups. Finally the model proposed requires adequate staffing of the ICU, which may limit generalizability to ICUs without available staff.

CONCLUSION

This study demonstrates that an intensive care physician-led team was able to safely place patients with severe cardiac or respiratory failure on ECMO and transport to an ECMO center. Patients undergoing this management strategy showed the same overall survival as patients placed on ECMO at the ECMO center. We conclude that an intensive care physician-led team may be an appropriate strategy for ECMO retrieval.

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Chapter 7: **Long-term survival of adults with cardiogenic shock after venoarterial extracorporeal membrane oxygenation**

This chapter describes a single-centre, retrospective cohort study of the long-term outcomes of patients after V-A ECMO for cardiogenic shock. The primary aim was to describe the long-term survival of the subgroup of patients who were weaned from V-A ECMO. The secondary aims were to investgiate baseline factors which would predict the long-term outcomes, and whether these could be used to develp a relaible predictive model. This work related to thesis aim 6.

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Long-term survival of adults with cardiogenic shock after venoarterial extracorporeal membrane oxygenation ☆

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ABSTRACT

Purpose: This study was designed to examine the long-term survival of patients who survived to be weaned from venoarterial extracorporeal membrane oxygenation (VA ECMO) and to determine which factors present at initiation and during ECMO predict long-term survival. We further sought to develop the preliminary long-term outcome after VA ECMO score that would predict patient outcome and to assess its accuracy at various time points.
Methods: We conducted a retrospective, observational cohort study of all patients with cardiogenic shock treated with VA ECMO at the Alfred Hospital, Australia, from January 2007 until February 2013. Overall, 125 patients underwent ECMO, and 104 patients were successfully weaned and formed the study population, with a median follow-up of 21 months (range, 0-84).
Results: Survival rates of those weaned from ECMO at 3 months, 12 months, and 2 years were 87%, 79%, and 71%, respectively, corresponding to overall survival rates at 3 months of 90 (72%) of 124; at 12 months, 80 (65%) of 122; and 24 months, 57 (57%) of 100. Ischemic heart disease, higher lactate and higher bilirubin at initiation of VA ECMO, and a longer duration of renal replacement therapy during ECMO were all independently associated with decreased length of survival. Long-term survival was found to be highly related to the number of these risk factors present up to 2 years afterward.
Conclusion: Good long-term survival can be achieved in patients who have been successfully weaned from VA-ECMO. The factors present at initiation and during ECMO can relate to altered risk of long-term survival.

1. Introduction

Refractory cardiogenic shock and circulatory failure are conditions, which carry mortality rates in excess of 70% despite aggressive treatments [1-9]. Venoarterial (VA) extracorporeal membrane oxygenation (ECMO) has emerged as a useful rescue therapy for the temporary stabilization of such patients allowing more definitive treatment or recovery from the acute disease process. Although it has been shown that ECMO is associated with improved short-term survival [4,7,9-18], the longer term survival of this population once weaned off ECMO is less well described.

Studies of longer term outcomes after VA ECMO (ranging from 1 year to 10 years) have shown overall survival rates ranging from 17% to 40% [2,4,6-9,19]. To date, few of these studies have investigated the outcomes of the subgroup of patients who has been successfully weaned from ECMO and if factors present at ECMO initiation influence long-term survival.

In view of high in-hospital mortality, costs, and resource requirement, it is important to determine predictors of longer term outcomes. The aim of our study was to describe the long-term survival of the subgroup of patients at a university affiliated hospital who was weaned from VA ECMO and to identify if there were factors present at initiation or during ECMO therapy that might predict long-term survival. We further sought to develop a preliminary score that would predict patient outcome and to assess its accuracy at various time points.

2. Materials and methods

2.1. Study population

All consecutive patients from January 1, 2007 to February 28, 2013, managed with VA ECMO at The Alfred Hospital in Melbourne,

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Australia, were assessed. Patients who survived to be weaned from ECMO formed the study cohort. Based on the indication for ECMO, patients were classified into 2 major groups and a number of subgroups as follows: all patients who had ECMO instituted during or after any operative procedure (eg, heart or lung transplantation and cardiac surgery) were classified as "postoperative ECMO." All other patients were classified as "medical ECMO" patients even if they later underwent an operation after initiation of ECMO. This group included (bridge to ventricular assist device [VAD] or cardiac transplant or bridge to recovery [BTR]) patients. Postoperative ECMO was further classified as either central or peripheral.

2.2. Setting

The Alfred Hospital is a quaternary referral teaching hospital in Melbourne, Australia, which offers heart and lung transplantation for South Eastern Australia covering a population of more than 7 million people. The intensive care unit (ICU) has more than 2800 admissions each year. The Alfred Hospital operates a regional ECMO referral service for cannulation and retrieval of patients requiring ECMO at other hospitals and is a member of the Extracorporeal Life Support Organization.

2.3. Extracorporeal membrane oxygenation circuit, indications, and program

The ECMO circuit used was a continuous flow device with a centrifugal pump (Rotaflow; Maquet, Rastatt, Germany) and oxygenator (Quadrox Bioline; Maquet). All lines were heparin bonded. Cannulation was performed peripherally via the femoral artery and vein or centrally via ascending aorta and right atrium. Where a percutaneous femoral arterial return line was used, a smaller (9F catheter) antegrade perfusion cannula was inserted into the superficial femoral artery to prevent distal limb ischemia.

The decision to institute ECMO was made by the treating intensivist or cardiac surgeon (for intraoperative cardiac support) after consultation between different treating units and based on locally available guidelines [20]. Cases in the operating theater were cannulated either centrally or peripherally by cardiothoracic surgeons. All other patients had peripheral cannulation performed by intensive care specialists. If considered possible, cannulation while a patient was conscious and without endotracheal intubation was preferred. Indications were not defined by a specific protocol but typically included severe and refractory circulatory failure with evidence of persistent shock despite maximal treatments where a potential for recovery or transplantation was believed to exist. Refractory shock was defined as any one of poor tissue oxygenation; cardiac index less than 2.0 (L/min/m^2); persistent hypotension or pulmonary edema, despite inotropic and vasopressor support; invasive ventilation where indicated; and optimal ICU care. The following criteria were typically considered contraindications to provision of ECMO: death expected within 12 to 24 hours, irreversible organ damage, malignancy, age older than 65 years, drug or alcohol dependence, or irreversible cardiac pathology in patients who were not suitable for transplantation or VADs. Daily management of each patient was carried out by a single trained bedside nurse under the supervision of the intensive care team, with daily coagulation and hemolysis monitoring and regular echocardiography to assist hemodynamic management. If a patient was unable to be weaned and had not

Table 1
Differences between medical and postoperative ECMO survivors

	Medical, n = 50	Postoperative, n = 54	Total, n = 104	*P*
General characteristics				
Age, y	50 (36-56)	48 (34-58)	49 (36-58)	.32
BMI, kg/m^2,	26 (24-29)	24 (20-26)	25 (22-28)	.01
Male	35 (48%)	37 (51%)	72 (69%)	.87
Comorbidities				
IHD	14 (13%)	9 (8%)	23 (22%)	.16
Diabetes mellitus	8 (7%)	7 (6%)	15 (14%)	.66
Chronic renal failure	8 (7%)	11 (10%)	19 (18%)	.56
Previous heart failure	16 (15%)	39 (37%)	55 (52%)	.01
Previous cardiac transplant	4 (3%)	12 (11%)	16 (15%)	.05
Diagnosis				
Cardiomyopathy	19 (18%)	1 (1%)	20 (19%)	.01
Acute coronary syndrome	16 (15%)	1 (1%)	17 (16%)	.01
CA	30 (28%)	16 (15%)	46 (44%)	.01
Posttransplant (heart or lung)	1 (1%)	44 (42%)	45 (43%)	.01
Postcardiac surgery[a]	0 (0%)	9 (8%)	9 (8%)	.01
Factors present at ECMO initiation				
Retrieved	13 (12%)	1 (1%)	14 (13%)	.01
Central cannulation	4 (3%)	24 (23%)	28 (26%)	.01
Bilirubin, μmol/L	20 (10-40)	29 (16-48)	24 (12-43)	.09
pH, U	7.28 (7.05-7.44)	7.22 (7.14-7.35)	7.24 (7.12-7.40)	.09
ALT, U/L	244 (57-700)	31 (18-135)	90 (25-315)	.01
Lactate, mmol/L	5.6 (2.9-6.9)	6.7 (4.1-8.6)	6.4 (3.6-10.9)	.19
INR	1.5 (1.2-1.9)	2.1 (1.5-2.5)	1.7 (1.3-2.2)	.01
Troponin I, μg/L	1.4 (0.1-33.3)	11.1 (3.4-30.9)	4.4 (0.2-32.9)	.13
Creatinine, mg/dL	133 (93-201)	103 (78-141)	114 (84-163)	.01
APACHE III score	82 (50-101)	60 (51-75)	64 (51-88)	.03
In-hospital complications				
Bleeding needing surgery	17 (23%)	23 (31%)	40 (54%)	.25
Vascular surgery	12 (11%)	13 (12%)	25 (24%)	.99
Cerebral vascular accident	6 (12%)	2 (4%)	7 (7%)	.11
New liver dysfunction	15 (14%)	18 (17%)	33 (31%)	.72
RRT, h	24 (73-491)	161 (33-497)	218 (67-494)	.60
Red blood cells, U	12 (8-24)	22 (10-32)	11 (7-23)	.39
Days on ECMO	8 (5-11)	7 (5-9)	7 (5-10)	.52
ICU days	19 (12-36)	19 (9-28)	19 (10-29)	.24
Hospital days	39 (22-55)	53 (31-73)	43 (28-65)	.02

Results are presented as median (and interquartile range) or n (%).
[a] Post-left ventricular assist device insertion, 5; double valve replacement, 1; postmyomectomy, 1; and other, 2.

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developed multiorgan failure, then a VAD insertion and/or listing for cardiac transplantation was considered. Red cell transfusion was administered for acute bleeding with hemodynamic instability or symptomatic anemia.

2.4. Post-ECMO care

Patients were weaned using a standardized protocol involving daily echocardiographic assessment and titration of inotropes. Once weaned off, patients were managed in the ICU until stabilized, then discharged to the ward for ongoing care. This involved extensive medical input, rehabilitation, physiotherapy, occupational therapy, and nursing support. Patients were offered rehabilitation services before them being discharged home. Patients with VADs and heart and lung transplantation had additional educational and support programs, with the majority eventually discharged home with a carer.

All patients were followed up at the Alfred Hospital in outpatient departments, where ongoing care was facilitated by surgical, medical, transplantation, and allied health services. If deemed stable, they could be discharged to the care of their own local physician, with 3 to 6 monthly follow-up at the Alfred Hospital.

2.5. Study design

Data were collected retrospectively from a prospectively updated local registry of ECMO patients and from the ICU clinical database. Further clinical details were obtained from review of patient medical records, outpatient notes, and pathology services. The following demographic data were collected: age, sex, body mass index (BMI), smoking history, past heart transplant, past heart failure, past ischemic heart disease (IHD), past liver dysfunction, past diabetes mellitus, past hypertension, and past chronic renal disease (estimated glomerular filtration rate less than 60 mL/min for >3 months). The following parameters were collected at ECMO initiation: cardiac arrest (CA) in the previous 48 hours, arterial blood gas, lactate, arterial partial pressure of oxygen to inspired oxygen fraction ratio, liver function tests, international normalized ratio (INR), troponin I, urea, creatinine, echocardiography data, and APACHE III scores. Additional variables recorded included bleeding requiring surgery, presence and duration of renal replacement therapy (RRT), cerebrovascular accident (CVA), new liver dysfunction, number of days on ECMO, total units of packed red blood cells, days in ICU, and total days in hospital. When ECMO was initiated at other hospitals, severity of illness scores and number of units of blood were calculated only after arriving at the Alfred Hospital. Long-term survival status was determined by a patient's date of last contact with Alfred Hospital heart failure or transplant services, including outpatient, emergency records, and mortuary records. Data collection for follow-up of patients was closed in February 2014. No assessments of functional status were made.

2.6. Ethics statement

This study was approved by the Alfred Health Human Research Ethics Committee (project no. 585-13). Patient consent was not obtained; therefore, patient records/information were anonymized and deidentified before analysis.

2.7. Outcomes

Primary outcomes were time to death after weaning from the ECMO and survival status at 12 months.

2.8. Statistical analysis

All analyses were performed using SPSS version 21 for Mac (Chicago, IL). Group comparisons were performed using Pearson χ^2 test for categorical variables and Mann-Whitney or Student t tests for continuous variables as appropriate depending on distribution of data. A logistic regression model was used to assess the univariable factors that were associated with 12 months' survival. Multivariable Cox proportional hazards regression modeling was used to identify factors independently associated with survival using backward stepwise selection of variables with univariate P values <.1. The 4 identified predictors of survival were then used to derive the long-term outcome after VA ECMO (LOVE) score in the following way: continuous predictors were dichotomized into binary variables by assessing the discriminatory ability of clinically relevant univariate "cut off" values to predict survival at 12 months. β coefficients for each dichotomous predictor were then derived from

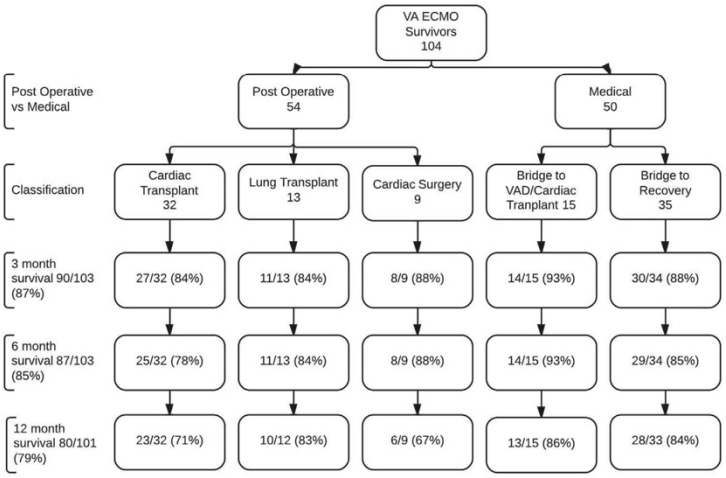

Fig. 1. Twelve-month survival outcomes post-VA ECMO based on ECMO classification and indication.

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Table 2
Survival at 12 months

	Survivors	Nonsurvivors	Univariate	
	n = 80[a]	n = 21	OR[b]	P
Demographics				
Age/10, y	4.9 (±1.3)	5.1 (±1.7)	1.05 (0.75-1.48)	.77
BMI, kg/m^2	25.0 (±6)	24.5 (±6)	1.01 (0.89-1.14)	.87
Male	47 (66%)	16 (76%)	1.73 (0.63-4.70)	.29
Ex or current smoker	17 (68%)	8 (32%)	1.73 (0.63-4.80)	.29
Previous heart failure	38 (53%)	14 (66%)	1.90 (0.69-5.21)	.21
IHD	14 (19%)	7 (33%)	2.17 (0.75-6.23)	.16
APACHE III score	59.0 (±34)	74.0 (±36)	1.02 (0.99-1.03)	.07
Diagnosis				
Cardiomyopathy	16 (22%)	1 (5%)	0.17 (0.02-1.37)	.09
Acute coronary syndrome	14 (87%)	2 (13%)	0.49 (0.10-2.38)	.38
PLTx[c]	10 (13%)	2 (10%)	0.74 (0.15-3.65)	.70
Postcardiac transplant	24 (30%)	8 (38%)	1.35 (0.49-3.70)	.55
Postcardiac surgery	6 (7.5%)	3 (14.3%)	2.05 (0.47-9.01)	.34
Medical ECMO	37 (52%)	7 (33)	0.48 (0.17-1.30)	.15
Pre-ECMO insertion				
Retrieved from another hospital	14 (19%)	0 (0%)	0.99 (0.99-0.00)	.99
Central cannulation	17 (23%)	10 (47%)	3.13 (1.15-8.55)	.026
pH, U	7.2 (±0.3)	7.2 (±0.2)	0.08 (0.01-1.17)	.06
Lactate, mmol/L	6.2 (±5.5)	7.6 (±6.6)	1.15 (1.03-1.28)	.015
Bilirubin/10, μmol/L	2.0 (±2.6)	3.6 (±3.0)	1.19 (0.99-1.43)	.06
INR	1.6 (±0.8)	2.2 (±1.1)	2.02 (1.15-3.55)	.014
Creatinine, mg/dL	116 (±77)	118 (±90)	0.99 (0.99-1.01)	.84
Noradrenaline dose/10, μg/min	1.1 (±1.7)	0.8 (±1.5)	0.87 (0.62-1.22)	.42
Adrenaline dose, μg/min	7 (±7)	8.7 (±10)	0.98 (0.95-1.03)	.57
In-hospital Complications				
ECMO bridge to VAD/OHTx	12 (17%)	2 (10%)	0.54 (0.11-2.61)	.44
ECMO BTR	27 (84%)	5 (16%)	0.58 (0.19-1.80)	.33
Bleeding requiring surgery	26 (51%)	11 (73%)	2.65 (0.76-9.33)	.13
RRT	40 (64%)	17 (85%)	3.56 (0.95-13.30)	.059
Renal replacement/10, h	14.8 (±32)	49.7 (±47)	1.03 (1.00-1.05)	.012
New liver dysfunction	16 (23%)	12 (57%)	3.75 (1.38-10.15)	.009
In-hospital CVA	5 (7%)	2 (10%)	2.50 (0.55-11.44)	.24
Ventilation duration, h/10	32.6 (±33.7)	65 (±35)	1.02 (1.00-1.03)	.004
Red blood cells/10, U	1.1 (±1.5)	2.6 (±1.7)	1.55 (1.16-2.07)	.003
Days on ECMO	7 (±5)	11 (±9)	1.11 (1.02-1.22)	.016
Days in ICU	23 (±17)	25 (±24)	1.03 (1.00-1.06)	.022
Days in hospital	55 (±47)	36 (±80)	1.00 (0.99-1.01)	.13

[a] Results are presented as median (and interquartile range) or n (%).
[b] OR, odds ratio and 95% CI.
[c] Only patients requiring VA ECMO.

Table 3
Cox regression analysis: HRs for overall mortality

	Univariate		Multivariate	
	HR[a] (95% CI)	P	HR[a] (95% CI)	P
Demographics				
Age/10, y	1.18 (0.87-1.58)	.28	–	–
BMI, kg/m^2	1.05 (0.95-1.16)	.34	–	–
Male sex	1.68 (0.63-4.49)	.29	–	–
Ex or current smoker	1.63 (0.71-3.71)	.25	–	–
Previous heart failure	1.47 (0.65-3.35)	.35	–	–
IHD	2.85 (1.28-6.37)	.010	4.74 (1.57-14.31)	.006
APACHE III score	1.02 (1.00-1.03)	.024	–	–
Diagnosis				
Cardiomyopathy	0.18 (0.02-1.30)	.09	–	–
Acute coronary syndrome	0.44 (0.11-1.89)	.27	–	–
PLTx	1.44 (0.49-4.21)	.50	–	–
Postcardiac transplant	1.06 (0.46-2.45)	.89	–	–
Postcardiac surgery	1.58 (0.47-5.31)	.46	–	–
Medical	0.53 (0.23-1.23)	.14	–	–
Pre-ECMO insertion				
Retrieved from another hospital	0.27 (0.04-1.98)	.20	–	–
Central cannulation	2.38 (1.08-5.24)	.032	–	–
CA prior	0.62 (0.27-1.44)	.27	–	–
pH, U	0.13 (0.02-1.00)	.051	–	–
Lactate, mmol/L	1.09 (0.99-1.18)	.062	1.17 (1.04-1.32)	.008
Bilirubin/10, μmol/L	1.10 (1.03-1.18)	.006	1.14 (1.04-1.24)	.006
INR	1.40 (1.14-1.71)	.002	–	–
Troponin I, μg/L	0.99 (0.98-1.01)	.85	–	–
Creatinine, mg/dL	0.99 (0.99-1.00)	.79	–	–
In-hospital complications				
ECMO bridge VAD/OHTx	0.49 (0.11-2.09)	.33	–	–
ECMO BTR	0.67 (0.27-1.68)	.39	–	–
Days ventilated/10, h	1.01 (1.00-1.02)	.001	–	–
Bleeding requiring surgery	2.53 (0.81-7.85)	.11	–	–
Renal replacement	3.72 (1.10-12.52)	.034	–	–
Renal replacement hours/100	1.15 (1.02-1.29)	.022	1.20 (1.05-1.37)	.009
New liver dysfunction	1.95 (0.87-4.32)	.10	–	–
CVA	2.01 (0.62-6.98)	.24	–	–
Red blood cells/10, U	1.25 (1.01-1.45)	.003	–	–
Days on ECMO	1.07 (1.02-1.14)	.007	–	–
Days in ICU	1.02 (1.00-1.04)	.014	–	–
Days in hospital	1.00 (0.99-1.00)	.19	–	–

[a] Hazard ratio and 95% CI.

a multivariable logistic regression model. Score values were derived from the β coefficient with the total score representing the sum of these values. Area under the receiver operator characteristic (AUROC) for discrimination and calibration of all models were assessed using the AUROC and Hosmer-Lemeshow C statistic and associated *P* value, respectively. Performance of the LOVE score at different time points (3, 6, 12, 24, and 36 months) was assessed by examining cumulative survival at 3 separate levels of risk using the Kaplan-Meier method. Kaplan-Meier survival curves stratified by each dichotomous predictor value were obtained. A 2-sided *P* value < .05 was considered to be statistically significant.

3. Results

3.1. Patients

Over a 6-year period from January 2007 until February 2013, 125 patients received VA ECMO for circulatory failure, and 104 patients (the study sample) were successfully weaned from ECMO. The median age was 49 years (inter quartile range [IQR], 36-58), the median APACHE III score was 64 (IQR, 51-88), and the median duration of ECMO was 7 days (IQR, 5-10). Other baseline characteristics are shown in Table 1.

The different ECMO groups and indications are shown in Fig. 1. Fifty-four patients (51%) had ECMO after surgery ("postoperative" ECMO), whereas 50 (48%) either had no surgery or had surgery after ECMO initiation ("Medical" ECMO). Of 104, 28 (27%) were centrally cannulated (all postoperative patients), whereas all other 76 (73%) of 104 patients were peripherally cannulated. Of 54, 13 (24%) of postsurgical patients were postlung transplant (PLTx), 32 (59%) of 54 were postheart transplant (OHTx), and 9 (16%) of 54 were posthigh-risk cardiac surgery. In the medical group, 35 (70%) of 50 were weaned from ECMO ("BTR"). The remaining 15 patients in the medical group were either bridged to VAD (14/15) or to cardiac transplant (1/15).

The median follow-up was 21 months (IQR, 8-35; absolute range, 0-84). Survival data were available for 99% (103/104), 97% (101/104), 66% (69/104), and 61% (64/104) of eligible patients at 6, 12, 24, and 36 months, respectively. One (1%) patient was lost to follow-up at 6 months, and 3 (3%) patients at 12 and 24 months, and 5 (5%) patients at 36 months. The long-term survival of the study cohort was 90 (87%) of 103 at 3 months, 87 (84%) of 103 at hospital discharge, 80 (79%) of 101 at 12 months, and 57 (72%) of 79 at 24 months (Fig. 1). The survival rates of all VA ECMO patients at 3 months was 90 (72%) of 124; at 12 months, 80 (65%) of 122; and 24 months, 57 (57%) of 100.

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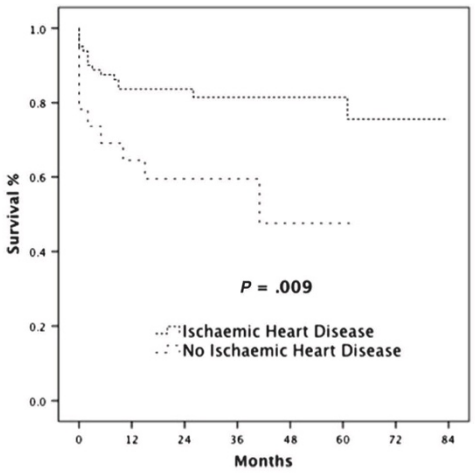

Fig. 2. Kaplan-Meier curve showing survival for those with and without IHD.

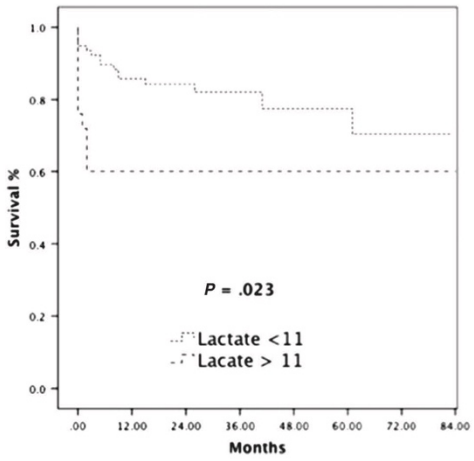

Fig. 3. Kaplan-Meiercurve showing survival for those with lactate greater than or equal to or less than 11 mmol/L.

3.2. Factors related to survival at 12 months

Survivors had higher pH, lower lactate levels, lower INRs at ECMO initiation, and were less likely to have had central ECMO (Table 2). They also had shorter duration of RRT, lower incidence new liver dysfunction, fewer number of units of blood transfused, shorter duration of ventilation while on ECMO, and shorter number of days on ECMO and in ICU.

3.3. Factors associated with decreased survival

Factors associated with reduced probability of survival are shown in Table 3. The presence of IHD (hazard ratio [HR], 4.74; confidence interval [CI], 1.57-14.31; $P = .006$), higher lactate (HR, 1.17; CI, 1.04-1.32; $P = .008$), higher bilirubin (HR, 1.14; CI, 1.04-1.24; $P = .006$), and longer duration of RRT (HR, 1.20; CI, 1.05-1.37; $P = .009$) was associated with reduced survival on multivariate analysis.

3.4. Development of the LOVE score

Optimal discriminatory binary levels for the 3 continuous variables identified as independent predictors of time-related survival were lactate greater than or equal to 11 (AUROC, 0.605), bilirubin greater than or equal to 30 (AUROC, 0.623), and RRT duration greater than or equal to 400 hours (AUROC, 0.634). Figs. 2 to 5 show Kaplan-Meier curves confirming differences in survival for patients stratified by the binary levels. Long-term outcome after VA ECMO score components derived from the β coefficients of these 3 variables and the presence of IHD are shown in Table 4. Of a possible total LOVE score of 10, 3 "risk categories" were created. Group 1 (low risk, scores 0-3) had a 12-month survival of 90.6% (58/64). Survival for group 2 (intermediate risk, scores 3.5-6.4) was 69.2% (18/26). For group 3 (high risk, scores 6.5-10), 12-month survival was 36.4% (4/11). See Table 5 and Fig. 6.

3.5. Internal validation of LOVE score and survival at specific time points

Observed survival and performance of the LOVE Score at 3, 6, 12, 24, and 36 months are shown in Table 6. Performance was best for earlier time points, but reasonable discrimination with AUROC greater than or equal to 0.75 was retained up to 3 years.

4. Discussion

This article describes the long-term survival of patients successfully weaned from VA ECMO after presenting with cardiogenic shock. The survival rate was (1) higher than previously reported; (2) lower in those with IHD, higher bilirubin, and higher lactate at the time of initiation and lower in those requiring longer duration of RRT during their ECMO; and (3) progressively lower depending on how many of the above risk factors were present.

4.1. Survival outcomes

Survival at all time points in our population was higher than currently reported by the Extracorporeal Life Support Organization registry, which quotes survival of all ECMO patients to hospital discharge as

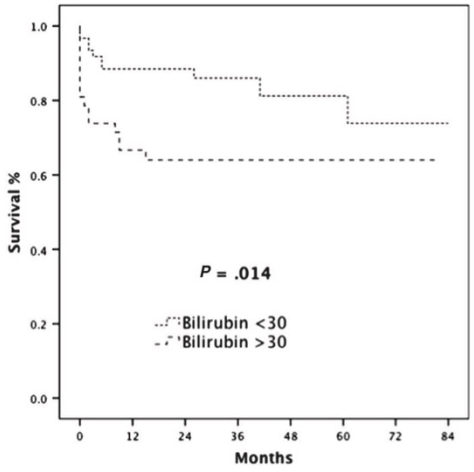

Fig. 4. Kaplan-Meier curve showing survival for those with bilirubin greater than or equal to or less than 30 μmol/L.

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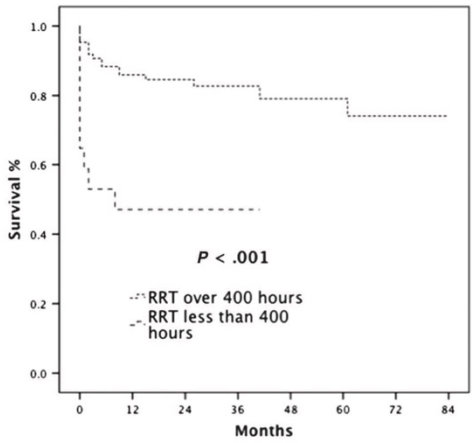

Fig. 5. Kaplan-Meier curve showing survival for those with RRT greater than or equal to or less than 400 hours.

only 41% [21]. Similarly previous studies looking at longer term survival have ranged between 18% and 48% [4,7,8,11,13,16,22,23]. Several potential reasons may explain this. Patients put on ECMO at our institution may have different characteristics from those reported in other institutions. However, multiple variables, including mean APACHE III score, inotrope dosage, age, and lactate, are in keeping with other studies. Many longer term studies have focused on postcardiotomy patients, who may have lower overall survival [4,7]. In our population, 45 (43%) of 104 were either postheart or postlung transplantation. However, despite outcomes in transplant patient being traditionally considered better than other groups, in our study, 12-month survival was no better: transplanted survival, 35 (77%) of 45 vs nontransplanted patients, 45 (80%) of 56; $P = .75$. Furthermore, many studies have included patients who were not able to be weaned from ECMO, whereas we specifically excluded these. However, if the 21 patients who failed to wean are added to the 25 patients who died during follow-up period in our study, then the overall survival of the whole population would be 79 (63%) of 125, which still remains higher than most published studies.

Most deaths in our population occurred in the first year, with survival of 90 (87%) of 103 at 3 months and 80 (79%) of 101 at 12 months. Compared with overall survival after other critical illnesses, this is favorable, with 1-year survival in acute respiratory distress syndrome, 55% [1,4,7,11,13,16,22]; cardiogenic shock, 40% to 60% [4,10,23]; and severe sepsis, 7% and 46% [6,19,22].

4.2. Predictors of long-term survival

To date, the factors identified as associated with worse longer term outcomes after VA ECMO have included age and diabetes [4,6,23,24], elevated INR, chronic renal function [6,8,11,22,25], chronic obstructive pulmonary disease [8,11,23,26], duration of ECMO [6,24,25], and Sequential Organ Failure Assessment Score [8,11,24,25,27-30]. This suggests that both the degree of acute physiologic derangement and the burden of chronic disease are important in determining the longer term outcome after VA ECMO. Many of these factors were also significantly different between survivors and nonsurvivors at 12 months, including factors present at the time of ECMO initiation (pH, lactate, INR, and central configuration of ECMO), during ECMO (duration of RRT, new liver dysfunction, no. of units of blood transfused or the no. of hours ventilated, and days on ECMO), and number of days in ICU (post-ECMO). In patients with a history of CA, there was no obvious survival disadvantage.

Table 4
Dichotomized risk factors for time-dependent survival, β coefficients from logistic regression for 12-month survival and derived LOVE score component

Risk factor	β coefficient	LOVE score
IHD	0.82	1.5
Bilirubin ≥30 μmol/L	1.01	2.0
RRT ≥400 h	1.55	3
Lactate ≥11 mmol/L	1.85	3.5
AUROC[a] = 0.77 (0.64-0.90); Hosmer-Lemeshow C statistic = 4.012, P value = .778		

[a] Combined value for the model.

Table 5
Survival within each LOVE score risk group

Risk group	LOVE score	Median (IQR)	Survival at 12 mo
1 (Low)	0-3	0 (±2)	58/64 (90.6%)
2 (Intermediate)	3.5-6.0	4.0 (±1.5)	18/26 (69.2%)
3 (High)	6.5-10	7.0 (±2.5)	4/11 (36.4%)

We identified 4 factors independently associated with long-term survival. The presence of IHD before ECMO was a strong predictor for reduced long-term survival. Ischemic heart disease is not only the leading cause of death worldwide [4,26,27], it is also as a generalized marker of vascular disease, including CVAs and renovascular disease. The association with IHD was independent of the reason for going on to ECMO and whether the patient was undergoing ECMO for postsurgical or medical indications.

A higher bilirubin level at initiation of ECMO was also independently associated with worse long-term survival. Bilirubin has been shown to be an independent predictor of longer term mortality in heart failure [25]. The relationship between liver disease and cardiac failure is complex, but mechanisms include elevated central venous pressures causing hepatic congestion and hypoperfusion. Hemolysis, another known cause of elevated bilirubin on ECMO, occurs only after ECMO initiation and is infrequent.

Lactate also is an established marker of acute physiologic derangement and severe cellular hypoxia and dysfunction as well as marker of adverse outcomes in many critically unwell patients, including ECMO [24,27-30].

Finally, the duration of RRT independently predicted 12-month mortality. Renal failure has been described as the most common complication of VA ECMO, ranging from 58% to 87% [4,27] and is a well-

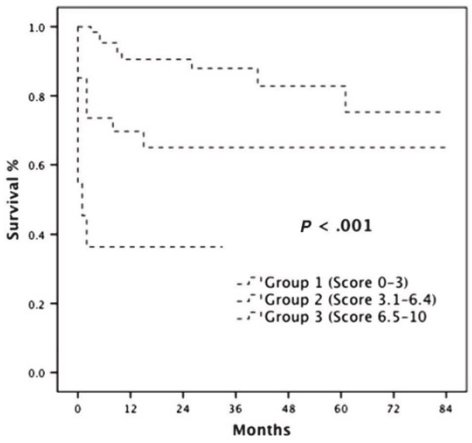

Fig. 6. Kaplan-Meier curve showing survival according to grouped risk score.

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Table 6
Survival and performance of LOVE score at different time points

	3 mo	6 mo	12 mo	24 mo	36 mo
Observed survival	90/103 (87%)	87/103 (85%)	80/101 (79%)	49/69 (71%)	41/64 (64%)
AUROC	0.86	0.84	0.75	0.75	0.74
95% CI for AUROC	0.76-0.97	0.73-0.95	0.62-0.88	0.62-0.88	0.60-0.87
P	<.001	<.001	<.001	.001	.002
Hosmer-Lemeshow C Stat and *P* value	$\chi^2 = 1.17$ $P = .279$	$\chi^2 = 0.492$ $P = .482$	$\chi^2 = 0.006$ $P = .939$	$\chi^2 = 0.702$ $P = .402$	$\chi^2 = 0.409$ $P = .522$

Stat indicates statistic.

established independent risk factor for mortality in critically ill patients [31]. Interestingly, the creatinine at baseline and immediately before ECMO was not significantly different between survivors and nonsurvivors. It is possible that a longer requirement for RRT represented less effective ECMO support and organ perfusion leading to the higher mortality. Other possible hypotheses include that RRT was itself harmful, or another unmeasured factor was responsible. These could not be confirmed with our data and are important question for future studies.

There was no detectable relationship between the indication for ECMO, transplantation, prior CA, or other comorbidities on the long-term outcomes, in contrast with other studies [3,5,23]. It is not possible to know whether this represents selection by clinicians of patients in whom comorbidities, although present, were not considered likely to affect long-term outcome or whether our study was underpowered to detect an effect due to other comorbidities. Although central ECMO was associated with worse outcomes at a univariate level, this no longer appeared significant after controlling for other factors.

4.3. The LOVE score—predictive modeling

The LOVE score was predictive of survival at multiple time points, and Hosmer and Lemeshow's goodness-of-fit test indicated that our model fits the data well. Although most patients had a score of 0 to 3, those patients with higher scores (≥3.5) had much lower survival. The median score of survivors vs nonsurvivors was 2 (±3) vs 5 (±5), $P = .001$.

4.4. Clinical implications

This study shows that good long-term survival can be obtained in patients who are weaned from VA ECMO and that preexisting comorbidity (the presence of IHD), the degree of physiologic insult at the time of ECMO initiation (as evidence by lactate and bilirubin), and factors present during ECMO (duration of RRT) all combine to influence long-term survival.

Several previous studies have suggested that earlier initiation of ECMO may be associated with improved outcomes [9,12,14,15,17,18,32]. It is unclear whether earlier initiation of ECMO before the development of severe acidosis, acute renal failure, or high bilirubin will result in improved long-term survival.

The LOVE score identified a subpopulation of patients who is more likely to have poor long-term outcomes. Although this model is preliminary and has only been tested on a single cohort of patients, it is possible that it might allow interventions such as aggressive management of IHD risk factors and more intensive post-ECMO care to be targeted to patients who are most likely to benefit. This study provides the rationale for further prospective interventional research in this area and, in particular, validation of the LOVE score in larger multicenter cohorts.

4.5. Study strengths and limitations

Limitations of this study include that it is a single-center study, and its retrospective nature meant it did not control for any changes in practice over the 6-year study period. In the absence of specific and consistent protocols, it is recognized that indications and thresholds for institution of ECMO may have changed during the study period and have influenced the observed outcomes. Limited information on the therapies given during the hospital stay and after discharge into the community was included, and no information on the cause of death or functional status of survivors was available. Patients' survival may have been underestimated, as status was assessed at the time of last contact with the Alfred Hospital, which occurred for some patients at 3 to 6 monthly time intervals. The sample size means that the study was not powered to detect differences in survival between specific diagnostic groups. Furthermore, the sample size did not allow the development of separate derivation and validation cohorts for the LOVE score, although internal validation showed it performed well at multiple time points. The strengths of this article are it is a large cohort of VA ECMO survivors, the length of follow-up, the relatively low attrition rate, and the spread of indications.

In conclusion, good long-term survival can be obtained in patients who are weaned from VA ECMO. Factors present prior, at initiation, and during ECMO affect long-term survival. The LOVE score may identify patients at risk for poor long-term survival based on 4 specific risk factors.

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Chapter 8: Clinical utility of invasive exercise hemodynamic evaluation in LVAD patients

This chapter describes a multicentre observational study of the long-term haemodynamic and structural changes that occur in patients following the insertion of a LVAD. The primary aim was to characterise the hemodynamic response to exercise that occurs with patients on a continuous-flow LVAD's. Secondary aims were to determine whether formal exercise hemodynamic evaluation could provide a more sensitive indicator of long-term complications that had not yet become manifest clinically. This work related to thesis aim 7.

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RESEARCH CORRESPONDENCE

Clinical utility of invasive exercise hemodynamic evaluation in LVAD patients

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Implantation of a left ventricular assist device (LVAD) improves survival, functional capacity, and quality of life in patients with advanced heart failure.[1] These benefits are mirrored by a combination of improved resting hemodynamics, reverse remodeling,[2] and improved end organ function. However, the magnitude of the benefit varies considerably over the short-term and long-term. This variability reflects the contributory influence of factors associated with advanced heart disease at the time of LVAD implantation, including right ventricular dysfunction, renal impairment, and skeletal muscle deconditioning. The benefit of mechanical circulatory support is also often limited by the development over time of significant, well-recognized complications, including right heart failure, neurologic complications, aortic regurgitation (AR),[3] and infection. Given that approximately 50% of patients with LVADs currently receive the LVAD as destination therapy and patients with LVADs as bridge to transplant are experiencing longer waitlist times, it is likely that the incidence of intermediate and late complications will continue to increase. In contrast to other complications, the secondary cardiac sequelae of LVAD implantation are progressive and may be sub-clinical in their early stages and may be difficult to detect using evaluation imaging and hemodynamic techniques under resting conditions.

The hemodynamic response to exercise in heart failure per se and its impact on clinical outcomes have been well described; however, this relationship is not well characterized in patients with LVADs. In the present study, we aimed to evaluate in detail exercise hemodynamic responses in patients supported with continuous-flow LVADs and to determine whether these data provided predictive capacity for the development of late cardiac complications.

Detailed methods are described in the Supplementary data (available in the online version of this article at www.jhltonline.org). The study was performed at Alfred Hospital, Melbourne, and St. Vincent's Hospital, Sydney, Australia, with the approval of institutional ethics committees under the guidance of the Declaration of Helsinki (2008). Briefly, symptom-limited exercise right-side heart catheterization (see Supplementary data available in the online version of this article at www.jhltonline.org) was performed in 48 patients with LVADs (26 HeartWare HVAD [HeartWare Inc.], 15 VentrAssist [Ventracor], and 7 HeartMate II [Thoratec Corporation]) approximately 5 months after LVAD insertion. Serial echocardiography was performed as a part of ongoing follow-up in a subset of patients. Statistical methods are described in detail in the Supplementary data (available in the online version of this article at www.jhltonline.org).

Resting and exercise hemodynamics are provided in Table 1. The type of LVAD implanted was not associated with differences in either the thermodilution cardiac output or the LVAD output (data not shown). Mean pulmonary artery pressure and pulmonary capillary wedge pressure increased during exercise in association with the increasing cardiac output, whereas pulmonary vascular resistance did not change (Table 2). Pulmonary artery pressure responses

Table 1 Hemodynamic Indices at Baseline and at Peak Exercise in Patients with LVADs

	Rest ($n = 55$)	Peak ($n = 55$)	p-value
Cardiac index, liter/min/m^2	2.7 ± 0.6	3.9 ± 1.1	< 0.05
VAD cardiac output, liter/min	5.2 ± 1.2	6.2 ± 1.1	< 0.001
Heart rate, beats/min	76 ± 18	106 ± 18	< 0.001
MAP, mm Hg	83 ± 12	94 ± 16	< 0.001
Systolic PAP, mm Hg	32 ± 12	57 ± 15	< 0.001
Mean PAP, mm Hg	21 ± 8	36 ± 9	< 0.001
Mean PCWP, mm Hg	12 ± 6	25 ± 8	< 0.001
PVR, wood units	1.6 ± 0.6	1.6 ± 1.1	NS
SvO_2, %	65 ± 8	38 ± 16	< 0.001
Peak work, watts	—	80 ± 43	
Exercise duration, minutes	—	7 ± 3	

LVAD, left ventricular assist device; MAP, mean arterial pressure; NS, not significant; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; SvO_2, mixed venous oxygen saturation; VAD, ventricular assist device.

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Table 2 Serial Echocardiographic Changes

Outcomes	Baseline (pre-VAD)	3 months	Final	*p*-value baseline vs final
LVDD, mm	68 ± 10	60 ± 11	61 ± 11	< 0.001
LVSD, mm	63 ± 10	56 ± 11	52 ± 15	< 0.01
RV function (grade)	2.0 ± 0.8	2.0 ± 0.7	1.8 ± 0.7	NS
TAPSE, cm	1.4 ± 0.2	1.2 ± 0.3	1.3 ± 0.3	NS
AR grade	0.4 ± 0.6[a]	0.2 ± 0.3	0.5 ± 0.6	NS
MR grade	1.7 ± 0.6	1.0 ± 0.6	1.0 ± 0.5	< 0.001
TR grade	1.0 ± 0.6	0.9 ± 0.5	0.9 ± 0.6	NS
LA volume, cm^3	122 ± 64	85 ± 43	95 ± 46	NS
RA area, cm^2	27 ± 7	25 ± 7	23 ± 6	NS
Explanted/transplanted			3/10	
Death	0	0	3	

AR, aortic regurgitation; LA, left atrial; LVAD, left ventricular assist device; LVDD, left ventricular diastolic dimension; LVSD, left ventricular systolic dimension; MR, mitral regurgitation; NS, not significant; RA, right atrial; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; VAD, ventricular assist device.

[a]Includes 7 patients with moderate to severe AR requiring aortic valve replacement at LVAD implantation.

to exertion were heterogeneous, with pulmonary artery systolic pressures >60 mm Hg in 18 patients and >70 mm Hg in 8 patients.

Intermediate-term to long-term echocardiographic follow-up data were available in 29 patients (Table 2). Left ventricular size was significantly reduced across the cohort. Right ventricular function improved in 10 patients, but deteriorated by 1 grade or more in 6 patients. Mitral regurgitation improved by 1 grade or more in 12 patients; mitral regurgitation did not deteriorate 1 grade or more in any patients.

AR was at least moderate in 7 patients before LVAD insertion, and these patients underwent concomitant bioprosthetic aortic valve replacement. In 7 patients (3 VentrAssist, 3 HeartWare HVAD, 1 HeartMate II; p = not significant), progression of AR of 1 grade or more developed. These patients had impaired workload capacity (48 ± 28 W vs 83 ± 23 W, $p < 0.05$) and reduced exercise time (5 ± 2 minutes vs 9 ± 3 minutes, $p < 0.05$). Peak exercise cardiac index was also lower in patients with AR (3.6 ± 0.9 liter/min/m^2 vs 4.6 ± 1.2 liter/min/m^2, $p < 0.05$). Baseline and exercise pulmonary artery diastolic pressures were higher in patients with AR (rest, 18 ± 10 mm Hg vs 11 ± 3 mm Hg, $p < 0.05$; exercise, 31 ± 12 mm Hg vs 21 ± 5 mm Hg, $p < 0.05$). Significant univariate markers of AR progression were also identified, including peak pulmonary artery systolic pressure >60 mm Hg (area under the receiver operating characteristic curve 0.750, $p = 0.021$), baseline mean pulmonary artery pressure >20 mm Hg (area under the receiver operating characteristic curve 0.739, $p = 0.019$), and peak duration of exercise <7 minutes (area under the receiver operating characteristic curve 0.827, $p = 0.007$).

The aim of the present study was 2-fold. First, we aimed to characterize the central hemodynamic response to exercise in a large cohort of patients with continuous-flow LVADs. Second, we aimed to determine whether formal exercise hemodynamic evaluation could provide a potentially more sensitive indicator of complications that had not yet become manifest clinically. To the best of our knowledge, this is the largest multicenter study to date to characterize the hemodynamic response to exercise in patients with continuous-flow LVADs and to investigate the role of this approach in detecting clinically relevant AR at an early stage. Exercise induced a modest increase in estimated ventricular assist device output and a more substantial increase in the thermodilution-based assessment of total cardiac output. In many patients, we observed a rapid increase pulmonary pressures and pulmonary capillary wedge pressure, despite normal baseline measures.

In the present study, we showed that patients who had echocardiographic evidence of progressive AR had limited exercise capacity and impaired cardiovascular responses during a graded invasive exercise hemodynamic study. Several mechanisms may account for this observation. By increasing mean arterial pressure and cardiac output, it is likely that exercise unmasked the presence of AR, which may have been difficult to detect at rest. Although the peak pulmonary capillary wedge pressure did not differ in the AR group, it is likely that this observation was influenced by differences in maximal workload based on previous studies by our group and others.[4,5] We did not identify the specific mechanism for AR in the present study.

In conclusion, we demonstrate that invasive exercise hemodynamic testing provides novel insights into the integrated native and ventricular assist device circulation performance after LVAD implantation and provides a means of early detection of progressive AR.

Disclosure statement

None of the authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

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Author contributions to this work are as follows: A.B., data collection, data analysis, manuscript preparation and editing; C.H., data collection, data analysis, manuscript preparation and editing; J.M., data collection; A.L., data collection; D.M.K., data collection, data analysis, manuscript preparation and editing.

Supplementary data

Supplementary data associated with this article can be found in the online version at www.jhltonline.org.

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Chapter 9: Discussion and conclusion

The aim of this research was to improve the evidence base for the application of ECMO and VADs for patients with advanced heart and lung disease. It was motivated by the desire to improve patient outcomes after heart or lung failure through the effective and evidence-based use of these mechanical devices.

9.1 Summary of main findings and contribution to the field

Chapter 2 highlighted that most published V-A ECMO studies are retrospective observational studies, representing an overall low quality of evidence to guide current practice. The specific outcome measures reported and definitions of complications varied considerably across the studies. These issues underline the difficulty of comparing or aggregating results across studies in systematic reviews.

Chapter 3 demonstrated that the initiation of V-V ECMO for severe respiratory failure is followed by a striking fall of the patients cytokine levels. This finding contrasts with previous reports that suggested the initiation of ECMO, through blood contact with the ECMO circuit and oxygenator, is associated with increased inflammation and cytokine levels. It is possible that this is the mechanism for V-V ECMO resulting in lower mortality than conventional mechanical ventilation strategies, as suggested in the EOLIA trial. The non-randomised study methodology prevented definition of the exact cause of this reduction in cytokines, but it was concluded that less aggressive ventilation was likely to be a key factor. Initiation of V-V ECMO decreased the invasiveness of ventilation rapidly, and was the major acute intervention. However, to show convincingly that this was the reason for the observed interleukin decrease, a control group without ECMO would be needed to exclude other modulations in treatment, such as hydrocortisone or antibiotics. It was also found that increased cytokine levels were associated with mortality.

The research showed that more aggressive ventilation prior to ECMO (positive end expiratory pressure >15 cm H_2O and driving pressure >19 cm H_2O) was associated with higher cytokine levels, which are most likely a consequence of severity of disease. The study was not designed to prove that less aggressive ventilation will result in less inflammation or improved patient outcomes, but does provide the rational for further studies in this area focusing on reducing inflammation. Moreover, higher IL-6, IL-8 and TNF-alpha levels before and during ECMO were associated with an increased risk of death. Importantly, this study was not designed to develop new markers for prediction of survival on V-V ECMO. As much interpatient variation in cytokine levels was observed, it is unlikely the concentration of cytokines alone would be a valuable predictive tool for these patients.

Chapter 4 reported on an appraisal of the femoral–femoral approach when performing V-V ECMO cannulation. This review also evaluated cannulation selection, site selection, explanation, and training aspects of ECMO management. The initiation of extracorporeal membrane oxygenation is a complex and technical process, and if done poorly, can result in significant harm to the patient, including bleeding, vessel damage and infection. The recently published EOLIA trial showed that 10% of cannulations were femoro-femoral, while the rest were femoral–jugular, suggesting ongoing worldwide practice variation [55,106]. Further research is needed to find the optimal approach for cannulation in different services. In addition, as the number of providers of ECMO continues to increase, an emphasis on training and credentialing will be crucial to maintain safety of the procedure.

Chapter 5 presented a review of the common complications that occur in ECMO and VAD patients. It highlighted that despite improvements in technology, patients still suffer from a wide range of serious complications that contribute to significant mortality and morbidity. It is important that caution is used when initiating such therapies. The complications follow a biphasic distribution, with early complications related to both the patient's underlying illness and to the insertion of the devices. Later complications, such as device failure and sepsis, also remain problematic. The complications described in this chapter continue to be a major drawback for the uptake of these devices, and clinicians need to be aware of them in order to make sensible and economically sound decisions for their patients.

The research described in chapter 6 demonstrated the feasibility of a mobile ECMO retrieval service staffed by intensive care specialists. Traditionally ECMO transports comprised of a large numbers of people, which make transportation complex, labour intensive and slow [107]. In this study, it was shown to be possible to cannulate patients with an ultrasound-guided percutaneous technique with a 100% success rate and that no life-threatening complications occurred during patient transport to the ECMO centre. This is a very reassuring result for services that are unable to provide surgical backup support in the case of a difficult cannulation. The research also showed that retrieved patients had similar survival rates to patients who had ECMO commenced in the ECMO centre. This implies that a patient can present to a non-ECMO hospital, be transported safely to the ECMO centre, and have a similar outcome to patients already in the ECMO centre. Potential limitations of this paper are that the intensivist model was not compared directly with either retrieval without ECMO or with a surgically staffed ECMO retrieval team. The populations of non-EMCO centres and ECMO centres differed at baseline, and this may have influenced the overall outcomes. Further work in this area will enable more direct comparisons.

Chapters 7 and 8 focused on the long-term outcomes of patients after ECMO and VAD therapy. Critical care research has traditionally focused on short-term outcomes, such

as hospital mortality. However, it is becoming clear that survivors have high ongoing risk of death even after hospital discharge, as well as significant morbidity [108].

The study described in chapter 7 demonstrated that patients continue to die even after their acute stay in hospital following V-A ECMO. It showed that patients with ischaemic heart disease, a higher lactate and bilirubin on admission, and a longer duration of renal replacement therapy had a reduced probability of long-term survival. Although ischaemic heart disease is not modifiable, initial lactate and bilirubin could be reduced if ECMO was initiated earlier, raising the question of whether earlier initiation could result in better long-term outcomes. The long term outcomes of V-A ECMO (LOVE) score may also help clinicians select the patients who are most likely to benefit from ECMO in the long term. It can help clinicians inform patients, family caregivers, and other clinical staff about the long-term outcomes after critical illness, and potentially let us target the population at highest risk for death with preventive interventions. Limitations of this study include the small sample size and the fact that only patients already initiated on V-A ECMO were included in the LOVE score. Other long-term outcome studies of ECMO will be important in defining the exact role of ECMO in the treatment of advanced heart failure.

Chapter 8 highlighted that patients with long-term VADs still suffer symptoms of cardiac insufficiency during exercise through a limited capacity to augment their VAD output. This study showed that increases in cardiac output during exercise were primarily related to recruitment of native circulation. This suggests that the native circulation continues to have an important role in the clinical management of these patients despite the VAD, and should remain a focus for drug therapies. It was also shown that the exercise response was different for those patients who went on to develop late aortic valve disease, suggesting earlier subclinical disease can be unmasked by the exercise haemodynamic testing. The implication is that more dynamic tests should be incorporated into the testing of VAD patients, allowing earlier identification of patients at high risk for developing aortic regurgitation.

9.2 Future work

The major pressing challenge for ongoing ECMO and VAD use is to continue to improve the evidence base to inform clinical practice. In a recent position paper authored by ECMONet, multiple areas for development – including further RCTs, cohort studies which refine patient selection, improved scoring systems, and an emphasis on long term outcomes – were identified as key areas to pursue [109]. In addition, standardisation of data definitions and outcome measures will be important when planning future studies and systematic reviews.

Conducting research into ECMO and VADs has been difficult for multiple reasons:

- small patient numbers: ECMO and VADs are used only in the sickest patients, and therefore numbers in each individual centre are low. Accumulating enough patients to answer research questions usually requires extensive national and international collaboration. This takes time, effort and money;
- lack of clinician equipoise to enrol patients in RCTs: individuals and hospitals are often “for” or “against” ECMO and VADs, and therefore changing practice can be very slow and difficult;
- lack of blinding: it is not possible to blind clinicians or patients from these interventions, unlike in a drug trial;
- prospective consent: the urgency to initiate ECMO and VADs can often limit the capacity of clinicians and researchers to gain consent; and
- withholding treatment may be unethical: these treatments are often used as rescue therapies, and it is often ethically difficult to withhold the treatment in the control arms of trials (e.g., EOLIA).

Despite these challenges, there are reasons to believe there will be great progress in research into mechanical heart and respiratory supports:

- improving international collaboration, e.g. ECMONet, Australian and New Zealand ECMO collaborators;
- development of a core outcome set to standardise the reporting of ECMO studies;
- the increasing role of RCTs in guiding practice; and
- more funding of research into ECMO and VAD studies.

The author is working on the following projects to extend the work described in this thesis.

- SCOPE Study
  This study aims to develop a new internationally recognised core outcome set, which will standardise outcomes measures and definitions of complications. The methodology will include performing multiple international surveys as part of a Delphi process.
- EXCEL Registry
  The EXCEL registry will be a large, prospective, binational ECMO registry which will collect detailed prospective data on all ECMO patients from five centres in Australia and New Zealand. This National Health and Medical Research Council (NHMRC)-funded project will investigate knowledge gaps, practice variation, and provide detailed information on ECMO practice and outcomes.

- BLENDER trial
  Concerns about oxygen toxicity during V-A ECMO has led to a group of Australian and New Zealand investigators collaborating on the largest V-A ECMO trial ever performed. The BLENDER trial is an NHMRC-funded trial which will randomise patients into either a conservative or liberal oxygen target strategy. The primary outcome will be ICU-free days at day 60. Recruitment will begin January 2019.
- National ECMO guidelines
  The author is part of a working group for a new Australian ECMO and VAD guideline which is being developed to help standardise practice in Australia and New Zealand, to improve collaboration, and to encourage translation of research into practice.

Although the evidence base for VADs has improved substantially in recent years, and large RCTs have already led to improvements in design and patient selection, many knowledge gaps remain. Some authors have argued that for severe heart failure and cardiogenic shock, LVAD insertion has become the standard of care [87], yet many centres do not practise it. Ongoing work with INTERMACS will be crucial in the design of future RCT and studies – particularly around the optimal timing of VAD insertion, optimal patient selection, cost-effectiveness and long-term outcomes.

9.3 Strengths and limitations

This thesis identifies key gaps in the knowledge of the provision of ECMO and VADs for critically ill patients with advanced cardiac and respiratory disease. The studies within it covered the field of ECMO and VAD utilisation from initiation to long-term outcomes. A range of study designs was employed, including a systematic review, retrospective and prospective observational studies, single and multicentre studies.

One limitation of the research was the lack of interventional studies. As pointed out in the systematic review in chapter 2, a retrospective study design is limited by many potential biases and confounders. However, these studies will underpin the abovementioned trials.

9.4 Conclusion

Mechanical circulatory supports evolved out of cardiac bypass circuits in the operating theatre, with cardiac surgeons and perfusionists initiating and maintaining patients. Over the last 40 years there has been a steady move away from the operating room, and into the ICU, emergency department, and finally from hospital to home-based patient care. Many factors have contributed to this change, including improvements in the technology of the devices, the ease of initiating ECMO by non-surgeons using percutaneous insertion techniques, the avoidance of complications, and in some cases, robust trials to inform practice.

This thesis and the published papers it contains contribute substantially to knowledge in this field through improvements in the evidence base for the use of ECMO and VADs. They highlight the lack of high-quality evidence that can be used to inform practice, and will form the basis of important ongoing work and collaborations designed to improve the outcomes of ECMO and VAD patients.

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