Early Rehabilitation and Functional Outcomes in Patients Requiring Extracorporeal Membrane Oxygenation

Submitted by

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Abstract

Extracorporeal membrane oxygenation (ECMO) is a temporary form of mechanical support of the heart and lungs and is used in the sickest of patients in the intensive care unit (ICU). Patients requiring ECMO often require prolonged periods of bed rest which has been associated with severe muscle weakness and poor functional recovery. Early rehabilitation may have an important role in mitigating these adverse outcomes. The body of work in this thesis sought to explore early physical function and rehabilitation for patients on ECMO. This was addressed in the following studies:

1. A scoping review of rehabilitation on ECMO, including 152 original studies, demonstrating that rehabilitation was feasible and appeared to be safe, however, more detailed intervention reporting is required in future studies.

2. Two retrospective studies describing the physical function outcomes and leg complications in 25 patients requiring ECMO for severe cardiac failure, and 17 patients with severe respiratory failure. Strength and mobility at ICU discharge were poor, and leg complications were common.

3. A prospective cohort study using ultrasound imaging to quantify early changes in quadriceps muscle size and quality in 25 patients on ECMO, showing that muscle wasting was profound and occurred early and rapidly in the ICU stay (20% over 10 days). In addition, these ultrasound measures were related to muscle strength and highest mobility level.

4. A randomised controlled trial of early rehabilitation versus standard care in 15 patients on ECMO, showing minimal impact of rehabilitation on respiratory and haemodynamic parameters. In addition, the rehabilitation group spent more time exercising and achieved standing 15 days earlier than the standard care group.

The findings of these studies will help to inform future development of rehabilitation guidelines and assist in planning for a definitive randomised controlled trial on rehabilitation in patients on ECMO.

Statement of Authorship

This thesis includes work by the author that has been published or submitted for publication as described in the text. Except where reference is made in the text of the thesis, this thesis contains no other material published elsewhere or extracted in whole or in part from a thesis accepted for the award of any other degree or diploma.

No other person's work has been used without due acknowledgment in the main text of the thesis.

This thesis has not been submitted for the award of any degree or diploma in any other tertiary institution.

All substantive contributions by others to the work presented including jointly authored publications, is clearly acknowledged.

All research procedures reported in the thesis were approved by the relevant Ethics Committee (Appendix 1).

Student Signature: Kathryn Hayes

Date: 10 December 2020

Candidates Declaration

For Chapters 2 to 6, the extent of the candidate's contribution was as follows:

Chapter	Publication Title	Publication Status	Contribution
2	Rehabilitation of patients on extracorporeal membrane oxygenation (ECMO): a scoping review	Submitted and under review in *Intensive Care Medicine*	70%
3	Physical function after extracorporeal membrane oxygenation in patients pre or post heart transplantation - an observational study	Published	80%
4	Physical function in subjects requiring extracorporeal membrane oxygenation before or after lung transplantation	Published	80%
5	Acute skeletal muscle wasting and relation to physical function in patients requiring extracorporeal membrane oxygenation (ECMO)	Published	75%
6	Early rehabilitation during extracorporeal membrane oxygenation has minimal impact on physiological parameters: a pilot randomised controlled trial	Published	70%

Signed: Date: 10 December 2020

Supervisors Declaration

I hereby certify that the declaration above is a correct reflection of the extent of the contributions made by the student candidate towards each chapter in the thesis.

Name of Supervisor	Signature
Anne Holland	

The extent and nature of contributions of the student candidate, and all co-authors, towards each study have been clearly acknowledged at the beginning of Chapters 2 to 6.

List of Figures

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List of Abbreviations

ARDS	Acute Respiratory Distress Syndrome
CERT	Consensus on Exercise Reporting Template
DLC	Dual Lumen Cannula
ECMO	Extracorporeal Membrane Oxygenation
ECPR	Extracorporeal Cardiopulmonary Resuscitation
ELSO	Extracorporeal Life Support Organization
FSS-ICU	Functional Status Score-Intensive Care Unit
HRQOL	Health-Related Quality of Life
ICU	Intensive Care Unit
ICUAW	Intensive Care Unit Acquired Weakness
IMS	Intensive Care Unit Mobility Scale
IQR	Interquartile Range
MOF	Multi-organ Failure
MRC	Medical Research Council
PGD	Primary Graft Dysfunction
PRISMA ScR	Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
VA	Veno-arterial
VV	Veno-venous

Publications and Presentations

All manuscripts (published and submitted) presented in this thesis were conducted and written during the period of candidature for the specific purpose of obtaining the degree of Doctor of Philosophy. Each manuscript was formatted in accordance with the requirements specific to the relevant journal. Sections of this thesis that were not submitted for publication (Chapters 1 and 7) use the *JAMA* referencing style, modified to include all authors in the references section, and are written in Australian English.

Publications arising from this thesis

1) **Hayes K**, Holland AE, Pellegrino VA, Leet AS, Fuller LM, Hodgson CL. Physical function after extracorporeal membrane oxygenation in patients pre or post heart transplantation - An observational study. *Heart Lung.* 2016;45(6):525-531. doi:10.1016/j.hrtlng.2016.07.007
2) **Hayes K**, Hodgson CL, Pellegrino VA, Snell G, Tarrant B, Fuller LM, Holland AE. Physical function in subjects requiring extracorporeal membrane oxygenation before or after lung transplantation. *Respir Care.* 2018;63(2):194-202. doi:10.4187/respcare.05334
3) **Hayes K**, Holland AE, Pellegrino VA, Mathur S, Hodgson CL. Acute skeletal muscle wasting and relation to physical function in patients requiring extracorporeal membrane oxygenation (ECMO). *J Crit Care.* 2018;48:1-8. doi:10.1016/j.jcrc.2018.08.002
4) **Hayes K**, Holland AE, Pellegrino VA, Young M, Paul E, Hodgson CL. Early rehabilitation during extracorporeal membrane oxygenation has minimal impact on physiological parameters: A pilot randomised controlled trial. *Aust Crit Care.* 2020. doi:10.1016/j.aucc.2020.07.008

Submitted Manuscripts

1) **Hayes K**, Hodgson CL, Webb MJ, Romero L, Holland AE. Rehabilitation of patients on extracorporeal membrane oxygenation (ECMO): a scoping review. *Intensive Care Medicine*. Submitted 23/9/2020

Published Abstracts arising from this thesis

1) **Hayes K**, Holland AE, Pellegrino V, Leet AS, Fuller LM, Hodgson CL. Functional outcomes and quality of life in heart transplant patients requiring extracorporeal membrane oxygenation. *J Heart Lung Transplant.* 2015;34(4):S73-S74. doi:10.1016/j.healun.2015.01.191
2) **Hayes K**, Hodgson CL, Pellegrino VA, Snell G, Tarrant B, Fuller LM, Holland AE. Functional outcomes and quality of life in patients undergoing extracorporeal membrane oxygenation pre or post lung transplantation-an observational study. *J Heart Lung Transplant.* 2016;35(4 SUPPL. 1):S147. doi:10.1016/j.healun.2016.01.406
3) **Hayes K**, Holland AE, Pellegrino VA, Mathur S, Hodsgson CL. Acute skeletal muscle wasting and relation to physical function in patients requiring extracorporeal membrane oxygenation (ECMO). *The Journal of Heart and Lung Transplantation.* 2018;37(4):S120. doi:10.1016/j.healun.2018.01.286

Other publications during candidature

1) Skinner EH, Haines KJ, **Hayes K**, Seller D, Toohey JC, Reeve JC, Holdsworth C, Haines TP. Future of specialised roles in allied health practice: who is responsible? *Australian Health Review* 2015;39(3):255-259. doi:10.1071/AH14213

2) Lay S, Bernhardt J, West T, Churilov L, Dart A, **Hayes K**, Cumming TB. Is early rehabilitation a myth? Physical inactivity in the first week after myocardial infarction and stroke. *Disability and Rehabilitation* 2016;38(15):1463-1499. doi:10.3109/09638288.2015.1106598
3) Cosic F, Kimmel L, Valsalan R, **Hayes K**, Liew S. Outcomes of total arthroplasty surgery in heart and lung transplant recipients. ANZ J Surg. 2019,89(6). doi:10.1111/ans.15262
4) Hodgson CL, **Hayes K**, Linnane M, Tronstad O, Reddy N, Young M, Buhr H, Linke NJ, Engeler DM, Fulcher BJ, Higgins AM, Sheldrake J, Cooper J, Bailey MJ, Pellegrino VA, International ECMO Network. Early mobilisation during extracorporeal membrane oxygenation was safe and feasible: a pilot randomised controlled trial. *Intensive Care Med*. 2020;46(5):1057-1059. doi:10.1007/s00134-020-05994-8

Conference Presentations

1) Functional outcomes and quality of life in heart transplant patients requiring extracorporeal membrane oxygenation, International Society of Heart and Lung Transplantation (ISHLT) Annual Scientific Meeting. Nice, France, April 2015 (Oral)
2) Functional outcomes and quality of life in patients undergoing extracorporeal membrane oxygenation pre or post heart transplant - an observational study, Australian Physiotherapy Association National Conference. Gold Coast, Australia, October 2015 (Oral).
3) Functional Outcomes and Quality of Life in Patients Undergoing Extracorporeal Membrane Oxygenation Pre or Post Lung Transplantation - An Observational Study, International Society of Heart and Lung

Transplantation (ISHLT) Annual Scientific Meeting. Washington, USA, April 2016 (Oral)

4) Acute skeletal muscle wasting and relation to physical function in patients requiring extracorporeal membrane oxygenation (ECMO), International Society of Heart and Lung Transplantation (ISHLT) Annual Scientific Meeting. Nice, France, April 2018 (Oral)
5) Acute skeletal muscle wasting and relation to physical function in patients requiring extracorporeal membrane oxygenation, Alfred Research Week. Melbourne, Australia, June 2018 (Poster)
6) Early intensive rehabilitation does not affect respiratory or haemodynamic parameters in patients requiring ECMO, Alfred Research Week. Melbourne, Australia, June 2019 (Poster)
7) Early intensive rehabilitation does not affect respiratory or haemodynamic parameters in patients requiring extracorporeal membrane oxygenation, World Congress of Intensive Care. Melbourne, Australia, October 2019 (Oral)

Invited Presentations

1) Physiotherapy considerations in the ambulation of ECMO patients, International Society of Heart and Lung Transplantation (ISHLT) Annual Scientific Meeting. Washington, USA, April 2016 (Oral)
2) Early mobilisation of patients requiring ECMO, Toronto Rehabilitation Institute, Muscle Function and Performance Lab and Toronto General Hospital Intensive Care Unit. Toronto, Canada, May 2016 (Oral)

Grants and Awards

Grants

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Dedication

In memory of

Graeme

he was and is my inspiration. His memory has driven me for most of my career

&

My Nan

unwavering in her love and support and my loudest champion. I believe this achievement would have made her so proud

Chapter 1: INTRODUCTION

1.1. Overview of Chapter 1

Extracorporeal membrane oxygenation (ECMO) is based on a modified cardiopulmonary bypass circuit and provides cardiac as well as gas exchange support for a period of days to even months. It is used in some of the sickest patients in the intensive care unit (ICU) who have failed conventional medical management. Whilst it is a potentially life-saving intervention for critically ill patients it can be associated with significant complications and morbidity.

This chapter provides a description of the components and different types of ECMO, the indications and prevalence of use, along with a review of current knowledge regarding complications and survival outcomes. Prolonged periods of immobility and bed rest are identified as serious consequences of the current management of patients on ECMO and their association with the development of severe muscle weakness and poor functional recovery are described. The role of early rehabilitation as a strategy to mitigate these adverse outcomes is discussed, along with identification of the gaps in the evidence base for early rehabilitation in patients on ECMO. The lack of data on early physical function outcomes for patients on ECMO are highlighted, including the limitations in the use of standard functional outcomes in this cohort. Profound skeletal muscle wasting and deterioration in muscle quality are described as contributors to poor physical function in critically ill patients; however, the applicability of these findings to patients on ECMO is unknown. Concerns regarding cardiorespiratory strain are identified as a barrier to early rehabilitation in patients on ECMO, and the paucity of studies investigating the effect of rehabilitation on the cardiorespiratory system in patients on ECMO is highlighted. This chapter concludes with an outline of the aims of the thesis and the included chapters.

1.2. Extracorporeal membrane oxygenation (ECMO)

1.2.1. Description of ECMO and indications for use

Extracorporeal membrane oxygenation (ECMO) is a form of extracorporeal life support where a modified cardiopulmonary bypass machine carries venous blood from the patient to an artificial lung where blood becomes enriched with oxygen and has carbon dioxide removed. This blood then re-enters the patient's circulation.[1] It includes a control console, a centrifugal blood pump, an artificial lung or oxygenator, a heat exchanger and large drainage and return cannula that are frequently positioned in the large vessels of the leg or upper body (Figure 1.1).

There are two basic types of ECMO: veno-venous (VV) ECMO and veno-arterial (VA) ECMO, with the nomenclature describing the sites of drainage and reinfusion of blood to the body. Veno-venous (VV) ECMO is used for isolated respiratory failure and requires adequate native cardiac function,[2] whilst VA ECMO is used in cardiogenic shock or combined cardiac and respiratory failure.[3]

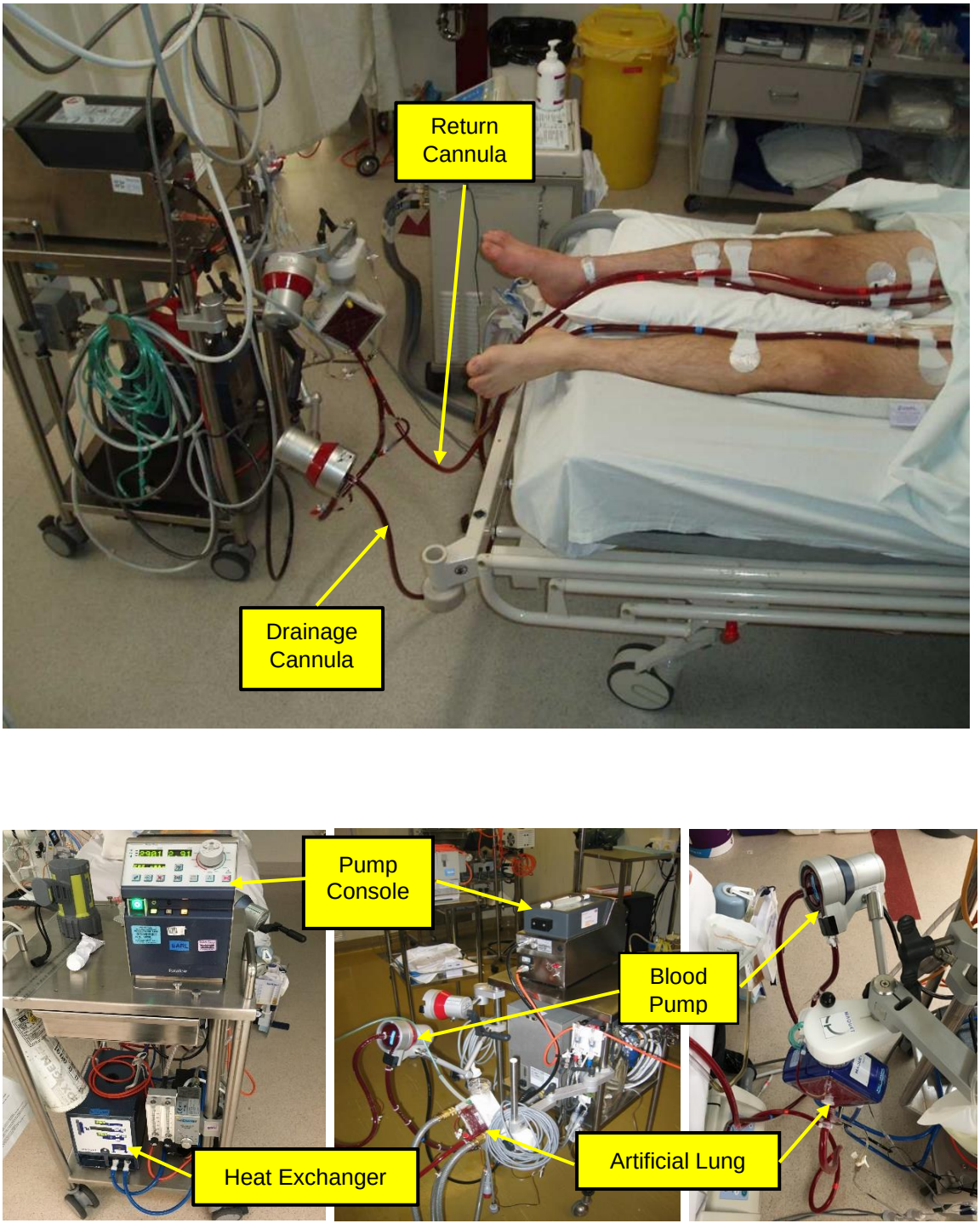


Figure 1:1 Basic components of ECMO

ECMO, extracorporeal membrane oxygenation. Basic components of ECMO including the main pump console, centrifugal blood pump, artificial lung or gas-exchange membrane, heat exchanger, drainage and return cannula

ECMO frequently involves cannulation of two separate vessels (Figure 1.2). An antegrade distal perfusion cannula is typically required in femoral VA ECMO to prevent ischaemia to the lower limb distal to the arterial cannulation site (Figure 1.3). Cannulation of a single vessel, typically the internal jugular vein, with a dual lumen cannula (DLC) may also be used in VV ECMO (Figure 1.4).

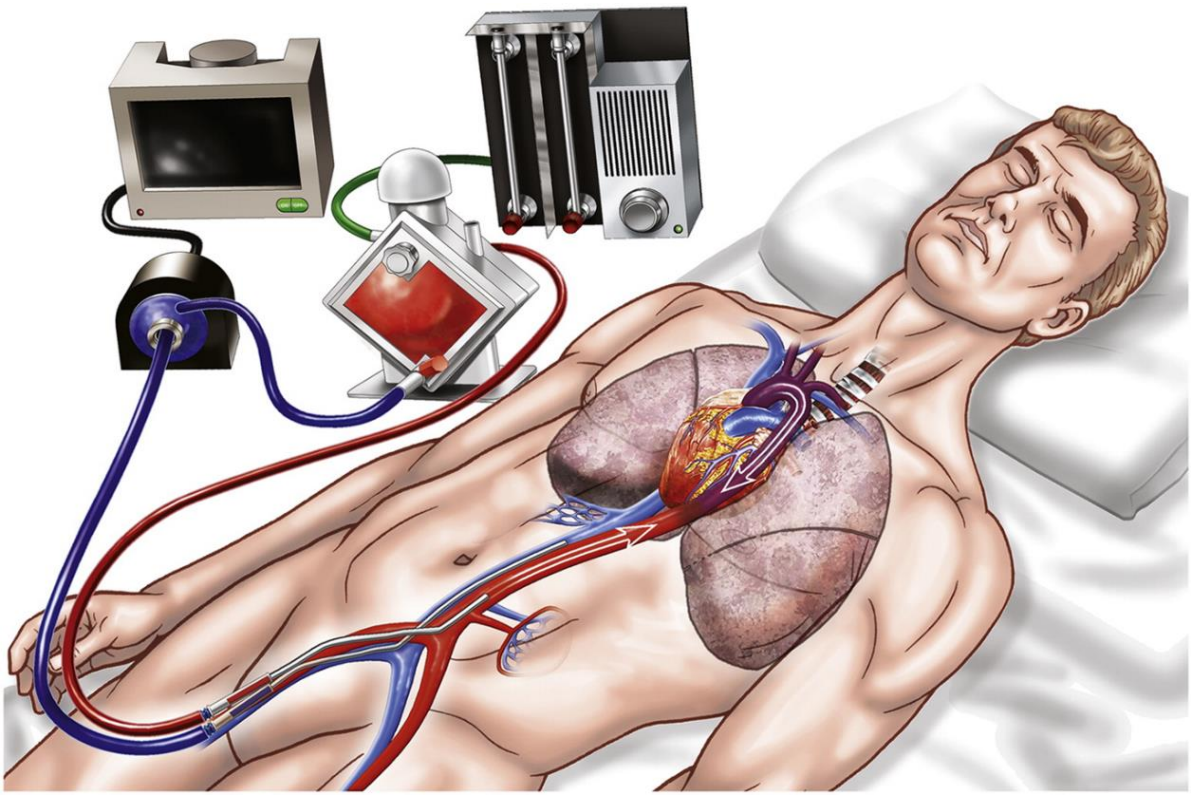


Figure 1:2 Femoral VA ECMO

Femoral VA ECMO (veno-arterial extracorporeal membrane oxygenation) showing a drainage cannula in the femoral vein and return cannula in the femoral artery.[4] Figure reprinted with permission (See Appendix 2)

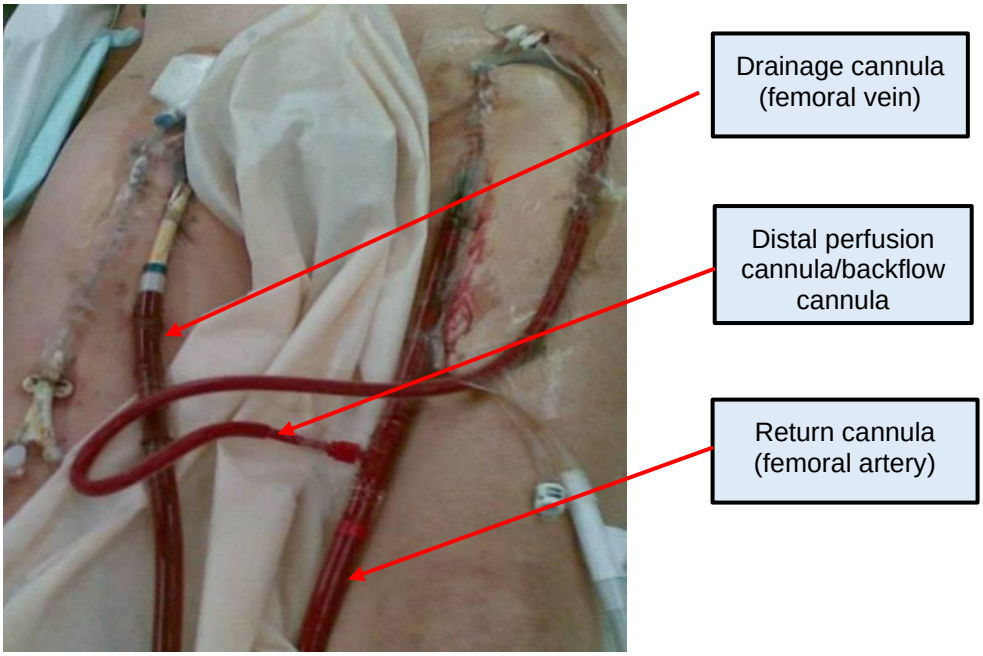


Figure 1:3 Femoral VA ECMO with distal perfusion cannula

Femoral VA ECMO (veno-arterial extracorporeal membrane oxygenation) showing antegrade distal perfusion cannula inserted to prevent ischaemia to the lower limb

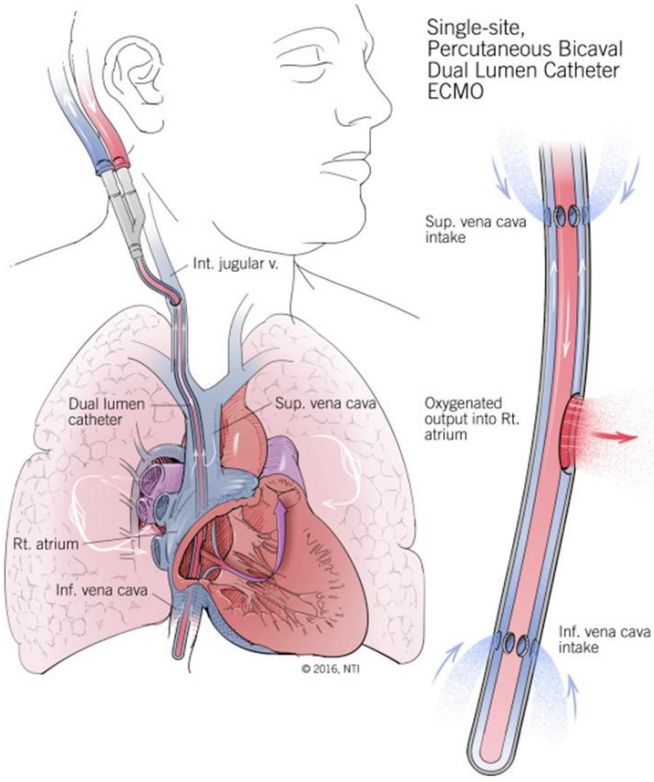


Figure 1:4 Single-vessel dual lumen cannula for VV ECMO

VV ECMO, veno-venous extracorporeal membrane oxygenation. Figure reprinted with permission[5] (See Appendix 2)

ECMO is indicated for patients with potentially reversible, life-threatening forms of respiratory and/or cardiac failure, which are unresponsive to conventional therapy and may be instituted for a period of days to months.[6] ECMO has also been utilised as a rescue therapy for patients both prior to and following heart and lung transplantation.[7-10] Table 1.1 outlines the indications and contraindications for ECMO.[6,11,12]

Table 1:1 Indications and contraindications for VV and VA ECMO

	VV ECMO	VA ECMO
Indications	Severe pneumonia	Myocardial infarction-associated cardiogenic shock
	Severe ARDS	Fulminant myocarditis
	Aspiration	Refractory ventricular arrythmias
	Influenza	Cardiac arrest
	Chronic lung disease (with an exit strategy)	Chronic cardiomyopathy (with an exit strategy)
	PGD after lung transplantation	PGD after heart or heart-lung transplantation
	Status asthmaticus	Post cardiotomy cardiogenic shock
	Pulmonary contusion	Massive pulmonary embolism
	Pulmonary haemorrhage or massive haemoptysis	Sepsis with profound cardiac depression
	Alveolar proteinosis	Drug overdose with profound cardiac depression
		Isolated cardiac trauma
		Periprocedural support for high-risk percutaneous cardiac interventions
Contraindications	Progressive and non-recoverable disease and not suitable for transplantation	Progressive and non-recoverable disease and not suitable for transplantation
	Severe neurologic injury or intracerebral bleeding	Severe neurologic injury or intracerebral bleeding
	Severe coagulopathy	Severe coagulopathy
	Severe cardiac failure	Unrepaired aortic dissection
	Mechanical ventilation> 7 days	Severe aortic valve regurgitation
	Severe chronic pulmonary hypertension	Severe peripheral vascular disease
	MOF	MOF

ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; MOF, multi-organ failure; PGD, primary graft dysfunction; VA, veno-arterial; VV, veno-venous. Data extracted from Fraser et al.[6] Abrams et al.[11] and Extracorporeal Life Support Association[12]

1.2.2. ECMO prevalence, mortality, and morbidity

The use of ECMO has exploded globally over the past 20 years (Figure 1.5). The Extracorporeal Life Support Organization's (ELSO) *International Summary* reported that there were 114 adult cases/year globally of ECMO for respiratory support in the year 2000.[12] This increased to 4575 cases in 2019, representing a 3,913% increase. The use of ECMO for cardiac support has increased even more dramatically from 46 cases/year in 2000 to 5479 cases in 2019 (11,810% increase).[12]

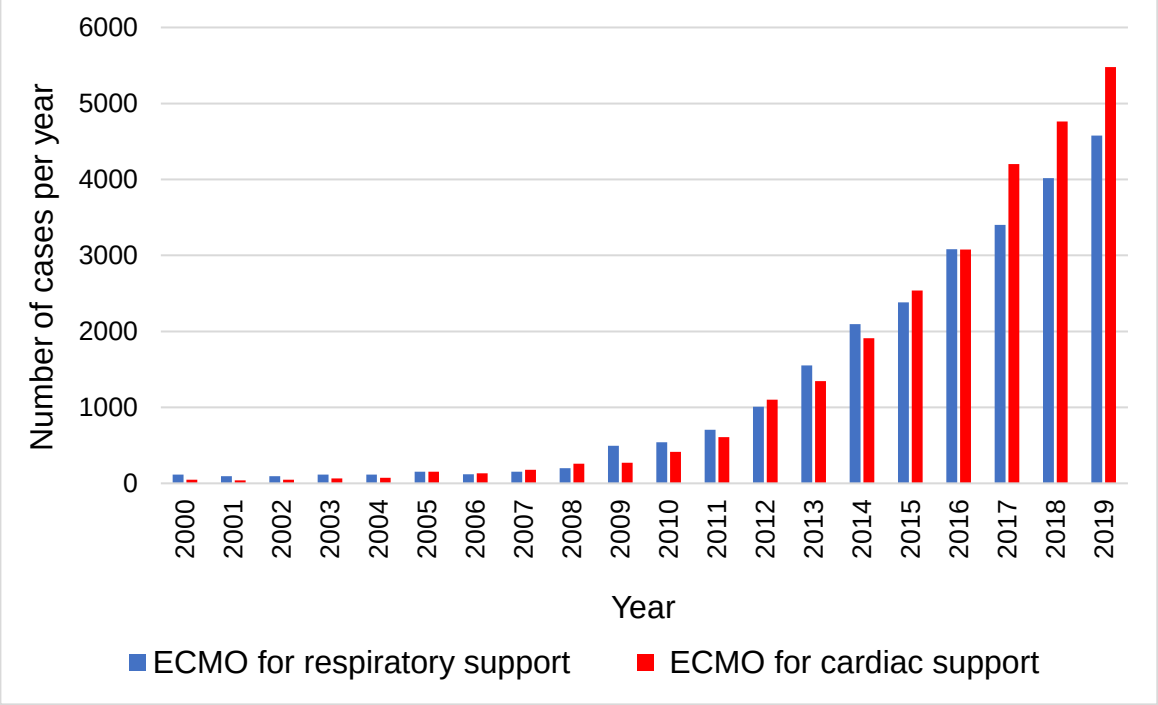


Figure 1:5 Number of cases of ECMO per year

ECMO, extracorporeal membrane oxygenation. Data extracted from the Extracorporeal Life Support Organization ECLS Registry Report International Summary, July 2020[12]

Although there has been improvement in survival rates with ECMO over time (Figure 1.6), it is important to note that ECMO is used often as a rescue therapy for patients that have a high mortality risk. A systematic review and meta-analysis to determine outcomes and complications of ECMO in adult patients showed that ECMO has an overall in-hospital mortality of 54% (in-hospital survival 46%), an impressive result in patients at high risk of death.[13] For all ages, survival to discharge was higher in patients supported with ECMO for respiratory failure compared with cardiac failure or for refractory cardiac arrest [extracorporeal cardiopulmonary resuscitation (ECPR)]. Of note, approximately 10-20% of patients who successfully weaned off ECMO died before hospital discharge[14] (see Table 1.2).

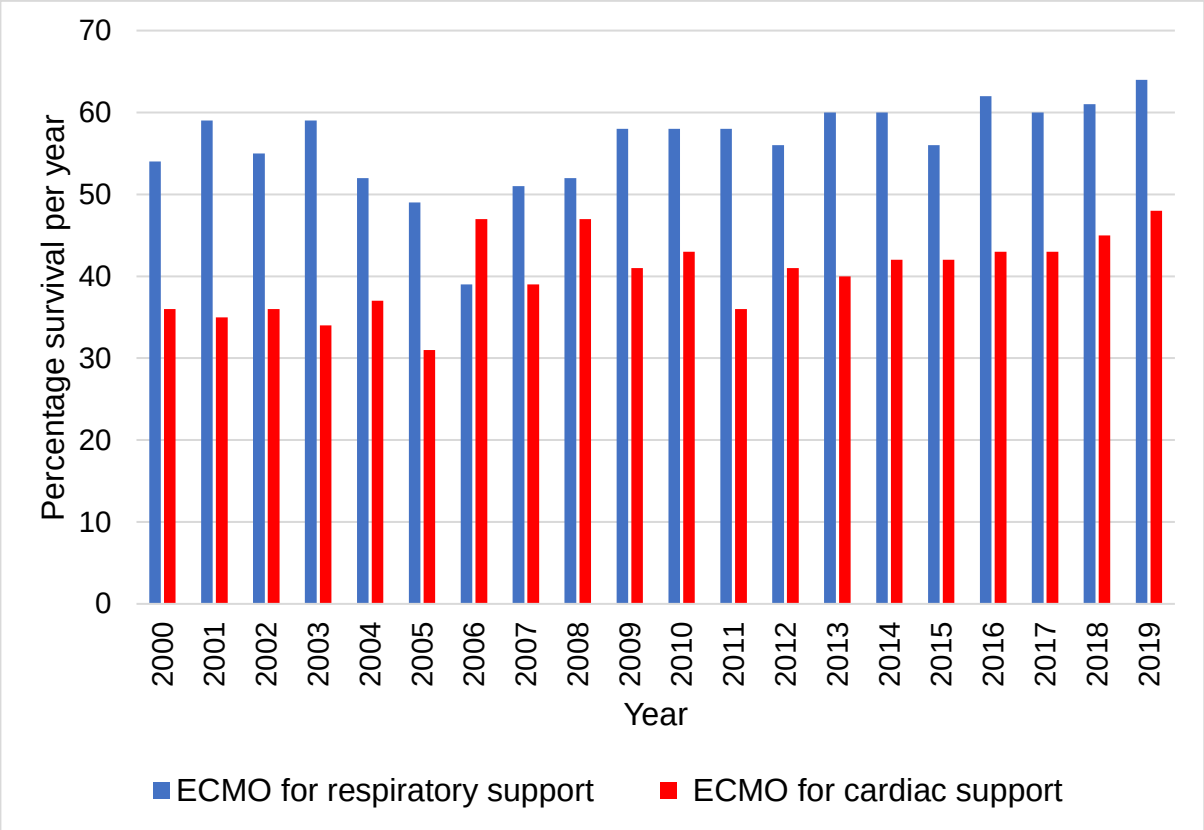


Figure 1:6 Percentage survival on ECMO over time

ECMO, extracorporeal membrane oxygenation. Data extracted from Extracorporeal Life Support Organization ECLS Registry Report International Summary July 2020[12]

Table 1:2 Overall survival outcomes for ECMO

Type of ECMO	Total ECMO runs	Survived ECMO	Survival (%)	Survived to discharge	Survival (%)
Respiratory	25,631	17,832	69%	15,471	60%
Cardiac	27,004	16,117	59%	11,891	44%
ECPR	8,558	3,582	41%	2,549	29%

ECMO, extracorporeal membrane oxygenation; ECPR, extracorporeal cardiopulmonary resuscitation (involves implantation of veno-arterial ECMO during a cardiac arrest). Data extracted from Extracorporeal Life Support Organization ECLS Registry Report, International Summary July 2020[12]

Although ECMO may be lifesaving,[15] complications are common and it can be unclear whether they are related to the underlying patient condition and comorbidities or the ECMO therapy itself.[6] These complications include: bleeding (including cannula sites, lung, brain, gastrointestinal system), infection and sepsis, acute kidney injury requiring haemodialysis, thrombo-embolic events including stroke and venous thrombosis, mechanical failure or oxygenator dysfunction requiring replacement, liver dysfunction, and haemolysis.[6,13,14] In addition, a number of cannula related complications are described including: vessel perforation with haemorrhage, arterial dissection, vessel stenosis, distal ischaemia of the limb, amputation, lymphocele, and peripheral nerve deficits.[16-18]

In the Australian context, a retrospective single centre study of 105 adult ECMO episodes reported on the incidence of bleeding, neurological, vascular, and infectious complications.[19] Bleeding was the most common complication reported, with more patients on VA ECMO requiring surgery for bleeding (34/105, 32%) than patients on VV ECMO (9/53, 17%). In ECMO runs of > 48 hours,

14.4% had a blood stream infection, with an even distribution between VA and VV ECMO. Neurological complications, defined as haemorrhagic or ischaemic stroke, were rare (<2%) whilst vascular complications were reported in eight patients, all of whom were on VA ECMO and all but one undergoing femoral cannulation for ECMO. Two of these patients required amputation of the lower limb. To date, the impact of lower limb complications on patient-centred outcomes such as physical function and health-related quality of life (HRQOL) have not been reported.

Complications from ECMO have been shown to alter with age of the patient, the indication for ECMO, and the type of ECMO utilised (higher in VA-ECMO).[13,14] Due to the complex medical issues of patients on ECMO and the high risk of complications, it is recommended that ECMO programs include both a highly skilled team with specialised training in ECMO, and a health care infrastructure that can help prevent or manage these complications.[11] This is supported by recent reports describing an association between ECMO centre volume and survival.[11,20] In a retrospective study including 290 ECMO centres, there was an inverse linear relationship reported between the number of ECMO cases and mortality.[20] Centres performing more than 30 cases of adult ECMO per year had a significantly lower mortality than those that performed less than six cases per year (adjusted odds ratio 0.61, 95% confidence interval 0.46–0.80)[20]; however, these results were based on retrospective registry data and the level of expertise was not reported.

1.2.3. Standard care for patients receiving ECMO

Standard care during ECMO involves interventions to mitigate the known complications of ECMO and optimise the function of other organ systems.[21] Patients requiring ECMO for severe respiratory failure are frequently

mechanically ventilated using an ultraprotective lung ventilation strategy.[22,23] Careful fluid resuscitation and the use of inotropic agents may be used to optimise intravascular volume and systemic perfusion with regular monitoring of cardiac function with echocardiography. Acute kidney injury is common partly due to the acute inflammatory reaction to the ECMO circuit resulting in capillary leak and intravascular volume depletion.[21] In a single-centre retrospective study of patients on VV and VA ECMO, 60% of patients required continual renal replacement therapy for acute kidney injury.[24] To reduce the risk of infection strict aseptic techniques are required, along with regular cultures and appropriate use of antibiotics when infection is detected. Haematological considerations include targets for haemoglobin and platelets and maintaining a strict limit for activated clotting time to minimize bleeding.[21]

Deep sedation and the use of neuromuscular blockers may be required, particularly early after ECMO commencement.[25,26] In a retrospective review of 45 patients with acute respiratory distress syndrome (ARDS) requiring VV ECMO, 96% were deeply sedated for a median duration of 6 days [interquartile range (IQR): 3-10 days].[25] Paralysis often accompanied deep sedation (80% of patients).[25] This finding was supported by an international survey of 209 ECMO clinicians from centres within the ELSO registry, in which 97% of respondents reported administering sedation when commencing VV ECMO for severe acute respiratory failure.[26] The sedation target was reported to be “sedated to very sedated” by 59% of respondents.[26] One of the potential consequences of these standard care practices, particularly the use of deep sedation and paralysis, is long periods of immobility and bed rest. Prolonged immobility in patients on ECMO may also result from clinical instability, concerns over cardio-respiratory strain with exercise, bleeding issues, cannula position and fear of cannula kinking

or dislodgement, which may increase the risk of muscle wasting and weakness and poor functional outcomes.

1.3. Effects of bed rest and critical illness on functional recovery

The combination of critical illness and prolonged immobility have been identified as key factors in poor functional recovery in ICU survivors. In a multi-centre, prospective, longitudinal study involving 222 survivors of acute lung injury, serial measurements of muscle strength and physical function were performed over 2 years after onset of the acute lung injury.[27] The only consistent factor associated with the development of severe prolonged neuromuscular weakness was the duration of bed rest during the critical illness.[27] Described clinically as intensive care unit acquired weakness (ICUAW), the impairments are frequently severe and persistent and have been associated with increased hospital length of stay and mortality,[28,29] along with long-lasting physical and cognitive deficits that may persist for up to 5 years after the ICU stay.[30]

ICUAW has been defined as generalised muscle weakness that is usually symmetrical, predominantly affects the proximal limb and respiratory muscles and develops whilst a patient is critically ill and has no other explanation aside from the critical illness itself.[31,32] There is no diagnostic gold standard for ICUAW.[32,33] In clinical practice, an examination of muscle strength is performed in awake and cooperative patients using the Medical Research Council (MRC) manual muscle test.[34] Muscle strength is graded on an ordinal 0-5-point scale, where 0 represents no visible muscle contraction and 5 represents normal power against full resistance.[34] Three muscle groups in each of the upper and lower limbs are assessed to obtain a maximum score of 60.[34] An MRC sum score of < 48/60 is diagnostic for ICUAW.[35] The MRC sum score was utilised to diagnose ICUAW in

the majority of studies (84% of studies) included in a systematic review on ICUAW.[36] Inter-rater reliability of the MRC sum score is excellent in critically ill patients (Pearson's r = 0.96).[37] The minimum clinically important difference has been reported as 2-3.6 points.[38] Of note, this was in patients with chronic inflammatory demyelinating polyradiculoneuropathy and not specifically in the critically ill population.

A number of risk factors have been identified for development of ICUAW and can be divided into pre-admission risk factors and factors related to the ICU stay.[39] Pre-ICU risk factors included: age, the type and number of comorbidities, frailty, and level of independence prior to admission.[39] Risk factors related to the ICU admission included: hyperglycaemia, sepsis and inflammation, severity of illness, prolonged duration of mechanical ventilation, use of corticosteroids, prolonged use of neuromuscular blockers, and prolonged immobility or duration of bed rest.[31,36] The majority of these risk factors are commonly seen in critically ill patients on ECMO.

Severe muscle weakness is frequently reported in critically ill patients, with approximately 25% of patients who require prolonged mechanical ventilation developing ICUAW.[33,35] In a more recent prospective, multi-centre cohort study including 192 patients from 12 ICU's in Australia and New Zealand, approximately half of the patients that were mechanically ventilated for > 48 hours and survived to ICU discharge developed ICUAW.[29] Patients who develop ICUAW take longer to wean from mechanical ventilation,[40,41] have higher in-hospital and post discharge mortality,[29,33,36,42] reduced mobility and HRQOL at ICU discharge and over 2 years[27] and are less likely to be discharged directly to home.[29] Furthermore, the presence and severity of ICUAW at ICU discharge has been associated with increased 1-year mortality.[28] The impact of ICUAW on

acute outcomes, mortality, and costs in patients requiring ECMO remains unclear.

1.4. Early rehabilitation in the intensive care unit

1.4.1. Timing

Early rehabilitation commenced in ICU is a potential treatment strategy to prevent the development of ICUAW and improve muscle strength and physical function.[43] The timing of initiation of rehabilitation in ICU varies considerably in the literature, ranging from 1 day to more than a week after ICU admission.[44] In the ECMO population, rehabilitation may not be commenced until late in the ICU stay,[45] sometimes not starting until after ECMO therapy has ceased.[46,47] The rationale for starting rehabilitation early is based on the rapid physiological deterioration in muscle structure and function observed in general ICU patients over the first few days of an ICU admission.[48,49] Patients requiring ECMO may have more profound early muscle wasting and weakness than other ICU populations, given the likelihood of relevant risk factors for ICUAW, and this will be addressed in more detail in section 1.8.

1.4.2. Safety and efficacy

Early rehabilitation in the ICU has been shown to be safe and feasible in general ICU populations.[50,51] In a recent systematic review and meta-analysis of safety of rehabilitation in the ICU, that included over 7,500 patients and 22,000 rehabilitation sessions, the incidence of potential safety events was low (2.6%) and very rare (0.6%) for events that required additional care requirements.[51] A number of guidelines have been published recommending the implementation of early rehabilitation in ICU with an emphasis on safety,[52,53] along with definition of criteria for commencing and ceasing the intervention.[52-55] In addition, practical guides explaining how to implement early rehabilitation, with tools to assist

clinical decision-making regarding appropriate type and progression of intervention have been developed.[56,57] Strong leadership, a culture that prioritises early rehabilitation, adequate resources and training including a mobility champion have been identified as facilitators for safe and effective early rehabilitation in ICU.[58,59] These factors have also been identified as important facilitators of rehabilitation in patients requiring ECMO.[60]

Patients who receive early rehabilitation in ICU have shown improved rates of returning to independent functioning,[43,61] improved muscle strength,[44,61] earlier liberation from mechanical ventilation, reduced rates of delirium, shorter length of stay in ICU and hospital[43] and more days alive and out of hospital at 6 months.[44] The applicability of these results to patients requiring ECMO is not clear, where there are additional challenges related to the severity of illness of these patients, increased use of sedation and neuromuscular blockers impacting the ability to participate in active rehabilitation and the ECMO cannulation configuration effecting the feasibility of certain types of interventions. The existing knowledge on rehabilitation in patients on ECMO is described in the following section.

1.5. Rehabilitation during ECMO

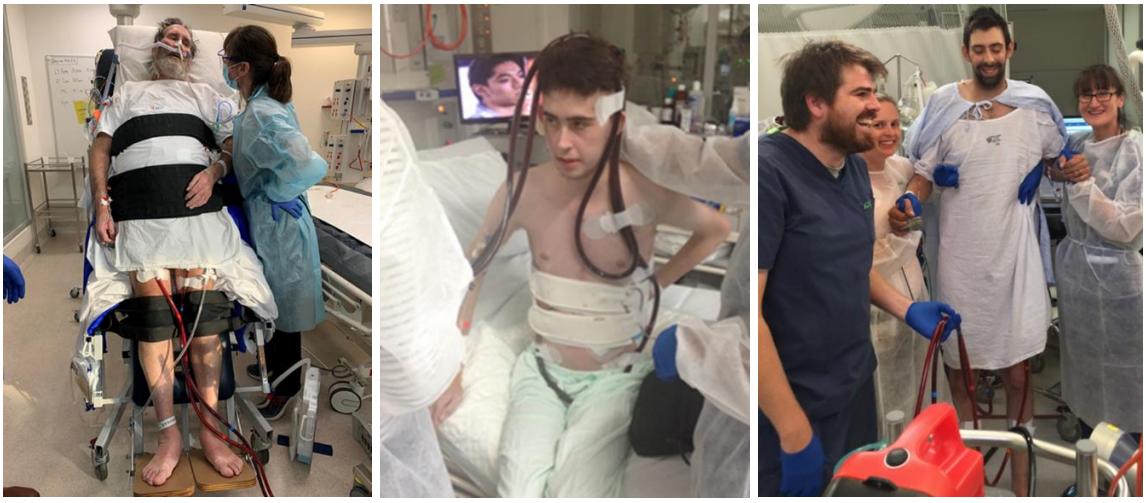
1.5.1. Level of evidence for rehabilitation during ECMO

Over the last decade, there has been an explosion of studies reporting on active rehabilitation whilst on ECMO.[25,46,47,62-73] Despite the large volume of publications, the quality of the evidence is low on account of the retrospective nature of the majority of studies and small sample sizes. Methodological heterogeneity and incomplete reporting of the intervention and outcomes has limited the synthesis of data, which was highlighted in two systematic reviews[74,75] with meta-analysis unable to be performed. This was addressed in a scoping review presented in Chapter 2. The scoping review addressed the key gaps in

knowledge relating to intervention characteristics, feasibility, safety, resources, and patient outcomes, which are explored in the following sections.

1.5.2. Intervention characteristics and feasibility of rehabilitation

Early literature shows that standard management of patients on ECMO includes minimal active rehabilitation whilst on ECMO. In an international survey of 209 ECMO clinicians regarding rehabilitation during VV ECMO for acute respiratory failure, passive exercises performed in bed were identified as the most common type of intervention performed (84% of respondents), whilst 16% of respondents did not engage patients in any rehabilitation during ECMO.[26] Less than half of all respondents commenced any intervention within the first 3 days of ECMO cannulation.[26] Approximately one third of respondents reported mobilising patients out of bed, with only 22% ambulating patients on ECMO.[26] Figure 1.7 provides examples of some of the different types of active rehabilitation performed on ECMO.



A *B* *C*

Figure 1:7 Examples of active rehabilitation on ECMO

ECMO, extracorporeal membrane oxygenation. A: standing on a tilt table; B: dynamic balance exercises in sitting on the edge of the bed; C: ambulation on femoral veno-arterial ECMO. Images used with consent

Several retrospective studies have also reported low levels of participation in active rehabilitation, particularly out-of-bed interventions, and have highlighted issues with feasibility of screening and delivery of rehabilitation.[46,47,67] In a retrospective cohort study describing active rehabilitation in patients on VV and VA ECMO, 100 patients were screened for eligibility for rehabilitation, but only 35% were able to participate,[46] with the main barriers being sedation, paralysis and severity of illness. Of the 35 patients that performed active rehabilitation, the highest level of activity achieved was active exercises performed in bed in 11 patients (32%) and ambulation in 18 patients (51%). The majority of patients who ambulated were on VV ECMO via a DLC (74%) and were being bridged to lung transplant (n=12/18, 67%). In terms of feasibility of delivering the intervention, the median number of sessions delivered per patient per week was 2.8 (IQR: 0.5 – 7.8); however, there was no description of the duration or intensity of the sessions. Similarly, Ko et al.[67] reported active rehabilitation in eight patients on VV and VA ECMO; however, the majority of sessions involved passive range of motion exercises (31/62 sessions, 50%), and only one session (2% of sessions) involved ambulation. Screening for eligibility was not reported in this study, so it is unclear how many patients were unable to participate in any form of rehabilitation. A median of six sessions per patient (IQR: 3 – 11) were delivered; however, the time frame over which these sessions were delivered was not reported. In a further retrospective cohort study including patients on VV and VA ECMO, Wells et al.[47] screened 254 patients, with 167 (66%) eligible for participation in rehabilitation. Only eight patients (4.8%) ambulated on ECMO. A total of 607 sessions of rehabilitation were delivered; however, the feasibility of delivery was not reported in terms of number of sessions delivered per patient per week nor the duration or intensity of sessions. These studies highlight the

incomplete reporting of important intervention characteristics and feasibility of both selection for and delivery of rehabilitation, which was addressed in the scoping review in Chapter 2.

1.5.3. Safety

Two systematic reviews have reported on the safety of rehabilitation during ECMO[74,75] and both have reported a low adverse event rate. Nil specific safety events were identified in the earlier systematic review[75]; however, this review only included patients on VV ECMO, and was limited to nine studies, the majority being case reports or case-series with inherent issues of bias and confounding. Ferreira et al[74] included adults on VV and VA ECMO and included 20 observational studies. No adverse events associated with rehabilitation during ECMO were reported in the majority of studies (12/20, 60%), with only five studies (25%) reporting minor events that were transient. No serious adverse events associated with rehabilitation were reported in this review. However, there have been further publications on safety of rehabilitation during ECMO since these systematic reviews, and much of the literature on this topic is in the form of small retrospective studies, including conference abstracts, that were not included in the systematic reviews as they did not meet inclusion criteria. A comprehensive summary of all the available evidence is required to describe the current state of knowledge regarding safety of rehabilitation during ECMO, and this was included in the scoping review in Chapter 2.

1.5.4. Resources for rehabilitation

Studies have reported that the delivery of rehabilitation to patients on ECMO is both labour and time intensive[26,46,47,69,73,76]; however, the ideal number and skill-mix of staff have not yet been determined. A number of studies have recommended a multi-disciplinary team of between three to five staff for

rehabilitation out of bed[26,46,62,67,70,72,77,78] but the number may be even higher and is dependent on the functional level of the patient and the mobility task being undertaken.[70] Given the complexity of patient management and risk of potentially life-threatening complications, a number of studies have recommended a multidisciplinary rehabilitation team of skilled staff with specialised training in ECMO[76,79]; however, the type of credentialing required for staff delivering rehabilitation remains unknown. There is also a paucity of data on the type of equipment utilised in the delivery of rehabilitation. The optimal way to organise a rehabilitation service to patients on ECMO has not yet been determined and this knowledge is essential for the safe delivery of rehabilitation, workforce planning and future research trial planning. This gap is addressed in the scoping review in Chapter 2.

1.6. Physical function in patients requiring ECMO

To date, much of the research on rehabilitation during ECMO has focused on short-term hospital outcomes such as in-hospital mortality[62,73,80] and complications,[67,80,81] ICU and hospital length of stay[62,73] and costs.[82] As survival improves with ECMO, understanding the quality of survivorship, and the effect of ECMO on patient-centred outcomes such as physical function is becoming more important.

Physical function refers to the ability to perform both basic and instrumental activities of daily living; tasks that are essential for basic functioning and those that are more complex and allow an individual to live independently in a community.[83] A complex integration of physiological systems, such as the cardiorespiratory, musculoskeletal, and neurological systems are required to enable these physical activities to be performed. The function of one or more of

these systems may be adversely affected in patients on ECMO secondary to critical illness, disease, or injury, and this may be clinically manifested by a deterioration in physical function.

An international, modified Delphi study identified a set of core outcomes to be included in all research evaluating the use of ECMO.[84] Physical function was mapped to the domain of life impact, with core outcomes that included disability or impairment (e.g. muscle strength), activity limitation (e.g. activities of daily living, highest level of mobility or walking distance), participation restriction (e.g. return to work) and measures of HRQOL. The World Health Organization International Classification of Functioning, Disability and Health[85] describes similar domains that includes recommended outcomes related to physical function. Despite these recommendations physical function was rarely reported in studies involving patients on ECMO, and this gap is addressed in Chapters 3 and 4.

Physical function outcomes for patients on ECMO are not well understood. Few studies have reported functional outcomes during the ICU and hospital period in patients requiring ECMO.[72,86-88] When physical function has been reported it has mostly been measured during the ICU stay[46,47,86,89] and often is only measured once[72,90] so the trajectory of recovery is unclear. There is a paucity of data related to physical function outcomes at hospital discharge and beyond hence it is unknown whether patients requiring ECMO recover to their baseline level of function or have a persistent functional legacy following ECMO. It is also unclear whether patients requiring ECMO have worse recovery of physical function than a matched cohort not requiring ECMO. The studies presented in Chapters 3 and 4 address the gaps in knowledge around early physical function by describing physical function outcomes at ICU and hospital discharge and 3 months post

discharge in two different ECMO cohorts; those with cardiac failure and those with respiratory failure. Chapter 4 will also compare functional outcomes of patients requiring ECMO before or after lung transplant to a matched cohort of lung transplant patients who did not receive ECMO over the same time period.

1.7. Measurement of physical function in patients requiring ECMO

A variety of outcome measures have been used to assess physical function in patients on ECMO,[86-88,91] which has made comparison of studies and synthesis of data challenging. They range from measures that are quick to perform and require minimal training to more complex and time-consuming measures that require specialised training to complete. Measurement tools used to assess impairment have included measures of muscle strength, such as the MRC sum score[88,91] and hand-held dynamometry to assess quadriceps strength[91] and grip strength.[88] Level of mobility has been assessed using the Intensive Care Unit Mobility Scale (IMS) or a modified version,[46,47,86,89] or mobility distance.[46,91] More complex measures of physical function that require multiple tests and then sum the results of the individual components have also been used, such as the Functional status score-ICU (FSS-ICU).[87] Currently there is a lack of consensus regarding the optimum measurement tool and timing of measurement for physical function in patients on ECMO.

There is often a significant delay in measurement of physical function in patients on ECMO resulting in valuable information related to the trajectory of recovery being missed. This delay in measurement may be due to the difficulties in applying many of the conventional measurement tools to patients whilst on ECMO. Conventional measurement tools used to assess muscle strength in the ICU setting, including the MRC sum score and hand-held dynamometry, require

the patient to be awake, alert, and able to follow commands. This may limit the early usefulness of these volitional assessments in patients on ECMO due to high levels of sedation and delirium, clinical instability, and constraints related to ECMO cannulation configuration. The ICU mobility scale (IMS), used to measure the highest level of mobility, has face validity and strong inter-rater reliability (interclass correlation 0.80, 95% confidence interval 0.75-0.84),[92] is feasible to complete at all stages of recovery in ICU, even in patients that are sedated and critically unwell and this outcome measure is now embedded into the ELSO registry. In the studies presented in Chapters 3 and 4, the IMS was used to assess the highest level of mobility achieved prior to, during and following ECMO at ICU and hospital discharge.

1.8. Contributors to poor physical function

Deficits in physical function are common in patients following a critical illness[30,93] and a number of contributing factors have been identified.[94] These include pre-existing factors such as age, frailty, and comorbidities along with factors specific to the ICU admission such as severity of illness, dosage of sedation and neuromuscular blockers, sepsis, and inflammation along with prolonged immobility.[94] Early and rapid loss of skeletal muscle mass and deterioration in muscle composition have been associated with poor physical function in ICU survivors.[48,49,95] The trajectory and severity of muscle wasting, along with changes in muscle quality have not been previously reported in patients requiring ECMO.

Ultrasound imaging has been shown to be a useful technique for capturing the early deterioration in both muscle mass and muscle quality in general ICU patients[48,49] and is an inexpensive and readily available technique in the ICU

setting that is non-invasive and radiation free. It provides objective data on skeletal muscle size and quality (echogenicity) and does not require the patient to be awake and cognitively intact, and is valid and reliable.[96-99] This makes it an ideal technique for assessing longitudinal changes in muscle size and quality in the ECMO population.

Significant reductions in the size of the quadriceps muscle over the first 10 days of an ICU admission have been reported using ultrasound imaging in a general ICU population.[48,49] Similarly, muscle quality has also been shown to decrease, demonstrated by an increase in echogenicity (increased whiteness of the image).[48,95] This higher echogenicity may result from muscle necrosis and loss of the normally well-organised muscle architecture, along with increases in fibrotic and fatty tissue within the muscle.[48,100,101] An increase in echogenicity has been reported to occur early and rapidly in general ICU patients and was correlated with a reduction in strength and function.[48] The applicability of these results to patients on ECMO is unclear, where there are additional challenges related to the severity of illness of these patients, increased use of sedation and neuromuscular blockers and potentially more prolonged periods of bed rest. The use of ultrasound imaging to objectively quantify the severity and trajectory of muscle wasting, along with changes in muscle quality, over the course of the ICU admission have not been previously reported in patients requiring ECMO and was addressed by the study presented in Chapter 5. Understanding the extent and impact of peripheral muscle wasting on physical function in patients requiring ECMO is an important step to progressing the rehabilitation management for patients on ECMO.

1.9. Physiological response to rehabilitation in patients on ECMO

Critically ill patients have demonstrated significant haemodynamic and respiratory responses to mobilisation in ICU, although most of these events were transient and not considered clinically significant.[102] Patients requiring ECMO already have borderline cardiac and/or respiratory reserve, and concern over cardiorespiratory strain with rehabilitation during ECMO has been reported as a barrier to implementation of rehabilitation.[26] There is a paucity of studies describing the haemodynamic and respiratory responses to early rehabilitation during ECMO. In a case report involving a 46-year-old female with post viral acute interstitial pneumonitis requiring VV ECMO, respiratory and cardiovascular measures were reported before, during and after an episode of sitting on the edge of the bed.[45] Heart rate and systolic blood pressure increased with the intervention, whilst oxygen saturation level reduced and had not recovered to baseline 30 minutes after the session. Of note, rehabilitation was not commenced in this case study until day 45 on ECMO.[45] There is a lack of data on the physiological effects of a more intensive rehabilitation program started early after ECMO commencement, and there is an urgent need for more robust methodological designs to investigate the cardiorespiratory impact of rehabilitation during ECMO. This gap was addressed in the randomised controlled trial presented in Chapter 6.

1.10. Summary of Introduction

ECMO provides temporary circulatory and respiratory support for patients with advanced cardiac and respiratory failure and is indicated when conventional treatments fail. The use of ECMO has increased greatly over the last 20 years with improvements in technology and survival, particularly in centres with a high volume of cases. The standard management of patients on ECMO often involves

use of sedation and neuromuscular blockers, resulting in prolonged periods of immobility. This may predispose patients on ECMO to ICUAW and poor functional outcomes. Early rehabilitation in general ICU patients has been shown to be safe, feasible and effective in mitigating these adverse outcomes. However, despite an increase in reporting of rehabilitation of patients on ECMO, the majority of studies are small, retrospective studies and the intervention characteristics, safety and feasibility, resource requirements and patient outcomes are unclear (addressed in Chapter 2). Although survival following ECMO has improved, little is known about the quality of survivorship, specifically the physical function of survivors (addressed in Chapter 3 and 4) and it is unclear whether patients requiring ECMO have worse physical function than a matched cohort not receiving ECMO (addressed in Chapter 4). Muscle wasting and weakness have been shown to be severe in critically ill patients, but to date this has not been investigated in patients on ECMO (addressed in Chapter 5). Furthermore, the association between measures of muscle size and quality and measures of physical function in patients requiring ECMO are unknown (addressed in Chapter 5). Finally, the cardiorespiratory impact of early rehabilitation in patients on ECMO has not previously been described and is important information in building a foundation for future rehabilitation trials (addressed in Chapter 6). All the aforementioned studies are the essential building blocks for a definitive rehabilitation study in ECMO.

1.11. Aims and scope of the thesis

The overarching aim of this thesis was to optimise early rehabilitation delivered to patients on ECMO with the goal of improving functional outcomes.

To achieve the aims of the thesis and to address important gaps in knowledge, five studies were conducted:

Chapter 2 was a scoping review which aimed to comprehensively describe the literature on rehabilitation of adult patients on ECMO. In particular this study sought to describe the intervention characteristics, safety, feasibility, and patient and hospital outcomes related to rehabilitation during ECMO and identify gaps in the existing literature along with potential areas of future research.

Chapter 3 was a retrospective study describing early physical function outcomes and lower limb complications in patients with cardiac failure who required ECMO prior to or following heart transplant.

Chapter 4 was a retrospective study describing early physical function outcomes and lower limb complications in patients with respiratory failure who required ECMO prior to or following lung transplant. This study also compared functional outcomes of the patients requiring ECMO with a matched cohort who did not require ECMO.

Chapter 5 was a prospective cohort study involving ultrasound measurement of the quadriceps muscle to quantify the change in muscle size and quality (echogenicity) in patients requiring ECMO. This study also investigated the relationship between ultrasound measures, muscle strength and highest mobility level.

Chapter 6 was a randomised controlled pilot study to investigate the effect of early rehabilitation versus usual care during ECMO on respiratory and haemodynamic parameters. Furthermore, this study aimed to evaluate the highest level of mobility achieved during early rehabilitation and the relationship to respiratory and haemodynamic parameters.

Chapter 7 summarises the thesis including key findings of Chapters 2 to 6 and discusses the strengths and limitations of the thesis, and recommendations for future research in this field. This chapter concludes with implications of the key findings for clinical practice.

Chapter 2: REHABILITATION OF PATIENTS ON EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO): A SCOPING REVIEW

2.1. Declaration of authorship: Chapter 2

Student's declaration:

The nature and extent of contributions to Chapter 2 of this thesis are as follows:

Name	Nature of contribution	Contribution
Kate Hayes	Study concept and design, search strategy, study selection and data extraction, writing of manuscript and review	70%
Carol Hodgson	Study concept and design, drafting and revision of manuscript	10%
Melissa Webb	Study design, study selection and data extraction, revision of manuscript	5%
Lorena Romero	Designing and executing search strategy, revision of manuscript	3%
Anne Holland	Study concept and design, revision of manuscript	12%

Supervisor's declaration:

I hereby certify that the declaration above is a correct reflection of the extent and nature of contributions made toward Chapter 2 of this thesis by the student and all listed co-authors.

Name of supervisor	Signature
Anne Holland	

2.2. Preface to Chapter 2

The scoping review in Chapter 2 has been submitted to *Intensive Care Medicine* and is formatted in accordance with the requirements specific to the journal. The citation is as follows:

Hayes K, Hodgson CL, Webb MJ, Romero L, Holland AE. Rehabilitation of patients on extracorporeal membrane oxygenation (ECMO): a scoping review. Intensive Care Medicine. Submitted 25/9/2020.

See Appendix 2 for the email of submission confirmation from *Intensive Care Medicine* (Paper under review) and the citation requirements upon acceptance.

Title: Rehabilitation of patients on extracorporeal membrane oxygenation (ECMO): a scoping review

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Author contributions:

All authors contributed to the study design. LR and KH contributed to the search strategy. KH and MW contributed to the study selection and data extraction. The first draft of the manuscript was written by KH and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Abstract

Patients requiring extracorporeal membrane oxygenation (ECMO) have demonstrated severe muscle weakness and poor functional recovery. Rehabilitation has been proposed as a strategy to address these deficits, but there is a lack of evidence to guide clinical practice, for both intervention characteristics and patient outcomes. We conducted a scoping review to comprehensively map the breadth of literature related to the rehabilitation of adult patients on ECMO and identify gaps and areas for future research. The review was conducted in accordance with the PRISMA extension for scoping reviews. We searched seven databases from inception to June 2020 and included all study designs and grey literature evaluating adult patients receiving rehabilitation whilst on ECMO. Two independent reviewers screened titles, abstracts and full texts for inclusion and extracted data related to intervention characteristics, patient outcomes, feasibility, safety, hospital outcomes and mortality. Of 6236 reports, 152 original studies met inclusion criteria with the majority being small retrospective studies. Rehabilitation was more commonly reported in patients on veno-venous rather than veno-arterial ECMO. Ambulation was the most commonly reported intervention (49% of studies). Less than two-thirds of patients met eligibility criteria to participate, but screening for eligibility was infrequently reported (9% of studies). Rehabilitation during ECMO appears to be a safe intervention with few adverse events reported, and delivery may be facilitated by an expert multi-disciplinary team, along with a strategy that targets low sedation levels and an upper body cannulation approach. Future research should include detailed reporting of intervention characteristics and a defined core outcome set.

Take home message

Rehabilitation on ECMO was feasible and appeared to be safe, but less than two thirds of patients were eligible to participate. To progress this field, future research requires more robust methodological designs that include comprehensive screening of potential candidates with reporting of eligibility; more detailed descriptions of the rehabilitation interventions; inclusion of a core outcome set with defined measurement tools; and consistent timing of outcome measurement.

Introduction

Extracorporeal membrane oxygenation (ECMO) is an advanced temporary form of mechanical life support used in patients with severe respiratory and/or cardiac failure [1,2]. Veno-venous (VV) ECMO is used for patients with isolated respiratory failure, whereas veno-arterial (VA) ECMO is used for patients with either isolated cardiac failure or combined cardiac and respiratory failure. Patients on ECMO support often require periods of prolonged immobility due to medical instability and concerns over dislodgement of the cannula with movement. As a result, they often develop severe muscle weakness [3,4] and delayed functional recovery [5] that can persist for years after an ICU admission [6].

Rehabilitation in the intensive care unit (ICU) has been shown to improve muscle strength, mobility status and days alive and out of hospital in a non-ECMO population [7]. Over the past decade there has been an increase in the number of publications reporting on rehabilitation of patients whilst on ECMO, however they have predominantly been retrospective studies [8-10]. Two systematic reviews have recently been completed on rehabilitation during ECMO [11,12], highlighting the inconsistencies in reporting and a lack of data preventing meta-analysis.

Whilst systematic reviews analyse a narrow range of studies in the attempt to answer specific questions related to efficacy, a scoping review has a broader goal to provide a comprehensive picture of the knowledge and gaps in a field and can incorporate a range of study designs in both published and grey literature [13]. The primary objectives of this study were to systematically map the research related to the rehabilitation of adult patients on ECMO and identify gaps in the existing literature along with potential areas of future research. Our research question was, "What is the current state of knowledge of rehabilitation of adult patients on ECMO?"

Methods

We conducted our review using the scoping review framework proposed by Arskey and O'Malley [14], and revised recommendations of Levac et al [13]. The scoping review protocol was drafted and revised using the PRISMA-ScR guideline (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) [15]. The final protocol was registered prospectively with the Open Science Framework on 25th April 2019 (https://osf.io/2d56t).

Eligibility criteria

The PICOT [16] format was used to define our inclusion criteria and is reported in detail in the Online Resource 1 (Methods). Our inclusion criteria consisted of adult patients (aged ≥ 18 years) on VV or VA ECMO support for > 24 hours, that participated in rehabilitation whilst on ECMO. We excluded paediatric patients (<18 years old), or combined adult and paediatric populations where it was not possible to separate out the adult data, studies published in languages other than English, animal

studies, studies that only described rehabilitation after ECMO removal, extracorporeal carbon dioxide removal or temporary mechanical cardiac support such as temporary left and right ventricular assist devices, isolated respiratory physiotherapy interventions, basic nursing care (i.e. rolling/positioning), music therapy, original research reports that made no mention of rehabilitation on ECMO in the methodology or results section, and letters, editorials or review articles with no original patient data.

Search Strategy

In consultation with a health research librarian, we developed search strategies to identify all types of publications involving rehabilitation on ECMO. The following bibliographic databases were initially searched from database inception to 28th April 2019: MEDLINE (Ovid), EMBASE (Ovid), EMCARE (Ovid), CINAHL (EBSCO), CENTRAL (Wiley), Physiotherapy Evidence Database (PEDro), and SCOPUS. A repeat search was run on 12th June 2020 to identify any further reports published since the original search. The search strategy used a range of subject headings and free text items applicable to each database, in order to increase the sensitivity and inclusiveness of the searches. The final search strategy for MEDLINE is provided in the Online Resource 1 Table E1. The reference lists of all included articles, and of the systematic reviews and review articles, were hand searched to ensure that all relevant articles were identified. We searched the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP; www.who.int/ictrp/en/) for studies that may have been missed or unpublished and reviewed relevant proceedings and abstracts of relevant conferences. A search of Web Search Engine "Google Scholar", with no date restrictions, was also conducted. Only the first 100 hits (as sorted by relevance by Google) were screened as it is reported that further screening is unlikely to yield many more relevant articles [17].

Selection of studies

The search results were imported from the databases into Covidence (https://www.covidence.org). Titles and abstracts were screened for eligibility by two independent reviewers (KH and MW). Studies that met the inclusion criteria, or if it was unclear whether the study met the inclusion criteria, were reviewed in full text. Any disagreement in study selection was resolved by consensus or with consultation with a third reviewer (AH).

Data Charting Process:

Data from the included sources of evidence were charted using a custom-designed, piloted form (KH and MW). Two review authors (KH and MW) separately and independently charted the data from the eligible studies. Disagreements regarding the data charting between authors was resolved by discussion. If consensus could not be reached, a third author (AH) reviewed the study and arbitrated.

We extracted the following data from each included report: author, year of publication, country where the study was performed, study design or source of information (e.g. clinical guideline or letter), clinical setting (e.g. type of ICU), sample size, demographic data (age, gender), severity of illness score (e.g. APACHE, SOFA), presenting diagnosis, type of ECMO (VV versus VA), ECMO configuration, duration of ECMO, and days on ECMO and days in ICU prior to inclusion in the study. Information related to the key outcomes (patient outcomes, feasibility, rehabilitation intervention and delivery, safety, hospital outcomes, mortality, and reported barriers and facilitators, outlined in detail in the Online Resource 1 - Methods), were extracted. Time frames related to outcome measurement were separated into two time periods; hospital stay including ICU and ward stay, and post hospital discharge.

Risk of bias (Quality assessment)

Scoping reviews are generally conducted to provide an overview of the existing evidence regardless of methodological quality or risk of bias [18]. Therefore, the included sources of evidence are usually not critically appraised for scoping reviews [15]. As such, we did not undertake a quality assessment of the included sources of evidence.

Synthesis of results:

Descriptive statistics were used to describe all data. Categorical data were reported as counts and percentages, and continuous data as the mean and standard deviation or median and interquartile range (IQR) depending on the data distribution. No inferential statistics were performed.

Results

The database and grey literature searches resulted in 6236 reports, of which 152 original studies (n=186 reports) and 4 guidelines related to rehabilitation on ECMO were included (Figure 1). Twenty-four of the included studies resulted in multiple publications, with 51 related reports, including duplication of subjects or over-lapping time periods. The report that had the most comprehensive reporting of relevant outcomes was included in the final count of unique studies.

The majority of studies were conducted in North America (94/152, 62%) and Europe (35/152, 23%) and mostly comprised of single case studies (58/152, 38%) and retrospective case series or cohort studies (79/152, 52%) (Online Resource 1 Table E2). There was one randomised controlled trial [19] and most prospective studies included less than 25 patients. Sixty-four of the studies (42%) were published as conference abstracts only. A small number of studies (7/152, 5%) provided no patient data, instead being descriptive reports [20-24] and two surveys of ECMO clinicians [25,26]. Of the remaining 145 studies, a total of 2,768 patients on ECMO were included, with demographic and clinical characteristics reported in Table 1. Four clinical practice guidelines [27-30] were identified

that included patient screening information to inform suitability for rehabilitation, along with suggestions on progression of rehabilitation.

The types of rehabilitation provided to patients on ECMO were reported in 109 studies (Table 2). Ambulation was more commonly reported in patients on VV ECMO (767 patients) than on VA ECMO (562 patients). Eight studies reporting ambulation on ECMO did not report the type of ECMO support. Specific equipment used for rehabilitation on ECMO was reported in 39 studies (Table 2) and most commonly included cycle ergometer, tilt table, treadmill, or rehabilitation chairs involving passive transfer of the patient. Forty-three studies did not describe the type of rehabilitation delivered. Instead, general descriptions such as "physical therapy", "exercise" or "mobilisation" were used, and the specific exercise intervention was unclear.

The dosage and intensity of exercise performed on ECMO was infrequently reported (Table 2). Exercise dosage was more commonly reported than intensity, with 30 studies providing detail on dosage (Online Resource 1 Table E3), most commonly ambulation distance or duration of the rehabilitation session. Seven studies provided detail on intensity of exercise (Online Resource 1 Table E4). Most commonly intensity of exercise was individually adjusted to meet specific respiratory or haemodynamic limits. For example, Camboni et al [31] monitored blood gases intermittently during exercise to aim for a partial pressure of oxygen of greater than 60mmHg, a mixed venous oxygen saturation of close to 50% and a normal lactate. Modification to the ECMO settings during rehabilitation was reported in five studies [31,32,19,33,34]. This included altering ECMO flow, fresh gas flow, or FiO_2. Modifications to ECMO settings during rehabilitation occurred predominantly in patients on VV ECMO [32,19,33,34] and was only reported in one case study of a patient on VA ECMO [31].

The type and/or number of staff required for rehabilitation on ECMO was reported in 50 studies (Table 2) and depended on several factors: the functional level of the patient, the type of activity being undertaken, and whether the patient was being supported on mechanical ventilation. When bed-based activities were performed, typically one staff member (physical therapist or nurse) was required, whilst activities including sitting on the edge of the bed or standing at the bedside usually required 3 staff, and ambulation away from the bedside typically required 3-5 staff. The most common staff involved in rehabilitation were physical therapists, nursing staff and physicians. Specialist or advanced training in ECMO in at least one team member was reported in 12 studies [8,35-37,19,38-42,24,10], however no detail was provided on what this training involved.

Feasibility of selection for and delivery of rehabilitation during ECMO were infrequently reported (60 studies, Online Resource 1 Table E5). Single case studies did not provide information relating to feasibility of selection of patients for rehabilitation. Thirteen studies reported the number of patients screened for inclusion in rehabilitation [8,36,37,5,43,44,19,45,46,38,40,47,10], with a median of 61%

of patients (IQR:34-66%) meeting inclusion criteria (Table 3). The percentage of the total sample size that received rehabilitation during ECMO was reported in 59 studies with a median of 60% however this ranged widely (5-100%) (Table 3), and the screening process was unclear in these studies. The reasons for exclusion from rehabilitation whilst on ECMO were not commonly reported (20 studies), but were mostly related to high sedation levels, failure to meet screening criteria, femoral cannulation and mechanical ventilation (Table 3, Online Resource 1 Table E5). Four studies reported the number of sessions delivered per patient [8,9,48,49] [median of 5-15 sessions (range 0-30)], with Abrams et al [8] also reporting the number of sessions per patient per week [median 2.8 (IQR:0.5-7.8].

Forty-six studies (46/152, 30%) reported on safety, with 21 studies (46%) reporting no potential safety events or adverse events during rehabilitation (Table 3). The remaining 25 studies reported complications during ECMO, with 12 of those directly attributing the adverse event to the rehabilitation activity (Online Resource 1 Table E6). Salam et al [50] described a fracture in one cannula of a dual lumen cannula, necessitating insertion of a new cannula, which they attributed to potential movement of the cannula during ambulation. Seven studies [37,51,19,9,52,34,10] described potential safety events or altered physiological parameters that resolved with cessation of the exercise session or alteration of the ECMO settings (Supplementary Table E6). One study reported four adverse events out of 110 rehabilitation sessions (3.6%) but did not report the type of adverse event [53]. Pasrija et al [40] reported minor bleeding around the cannula insertion sites in three patients that resolved with additional sutures. Similarly, Decker et al [48] reported bleeding from the cannula site in one patient at the end of a rehabilitation session that required surgical exploration. In a retrospective study investigating risk factors for the development of an iliopsoas haematoma in patients on VV ECMO [54], univariate analysis identified mobilisation beyond sitting on the edge of the bed as an independent risk factor.

Facilitators to rehabilitation on ECMO were reported in 76 studies, whereas barriers to rehabilitation were less commonly reported (31 studies) (Table 4). The most common facilitators reported were upper body cannulation, weaning of sedation and having a multidisciplinary team with expertise in ECMO, whereas femoral cannulation, heavy sedation and medical instability were the most common barriers (Table 4).

Mortality on ECMO was reported in 113 studies (range 0-66%), with 75 studies (66%) reporting zero mortality and 92 studies (81%) reporting less than 30% mortality. Mortality post ECMO removal was reported in 102 studies (range 0-100%) and was recorded to various endpoints ranging from ICU discharge to more than one year following hospital discharge. Fifty-six studies (55%) reported zero mortality and 69 studies (68%) reported less than 30% mortality. The only randomised controlled trial by Hodgson et al [19] reported four deaths in the intervention group and one in the usual care

group, however this was not statistically significant, and the study was not powered for mortality. The majority (3/5, 60%) had not participated in any active rehabilitation. Bailey et al [55] reported two deaths in the rehabilitation group versus none in the non-rehabilitation group in a retrospective case series involving 21 patients. In contrast, Munshi et al [39] reported that physiotherapy during ECMO was significantly associated with a lower mortality (OR, 0.19, 95% CI 0.04-0.98, p=0.048) and Wells et al [10] also reported lower mortality in the rehabilitation group (20% versus 43%). Both were retrospective studies and could be affected by selection bias.

Discharge destination was reported in 50 studies (368 patients) with most patients discharged to an inpatient rehabilitation facility (228 patients, 62%) or directly to home (123 patients, 33%). Length of stay in ICU was described in 30 studies and ranged from 7–272 days, whilst total hospital LOS was described in 40 studies (range 8-284 days). Seven controlled studies presented the ICU LOS data separated by groups [55,35,44,56,19,57,41] and all reported a shorter LOS in the rehabilitation group (Table 5). Similarly, total hospital LOS tended to be shorter in the rehabilitation group compared to the no rehabilitation group (Table 5). Differences in LOS were generally non-significant, however sample sizes were small (Table 5) and studies were not powered to detect this.

Patient outcomes were described in 55 studies, most commonly distance ambulated, physical function, muscle strength and quality of life (Table 6). No measurement tool was described in 63% (5/8) and 26% (5/19) of studies that reported on quality of life and physical function respectively. Instead descriptive terms such as “excellent” were reported. A wide range of measurement tools were used to evaluate physical function and quality of life (Table 6). Cost was reported in two studies [35,45], with both reporting cost savings in the group that received rehabilitation over those that received no rehabilitation. A retrospective study [35] reported a 22% ($60,204) reduction in total hospital costs and 73% ($104,939) reduction in post-transplant ICU cost in the ambulatory ECMO group compared to the non-ambulatory group. The use of different patient outcome measures and measurement tools and the variation in the timing of measures makes comparison of studies difficult. Furthermore, the majority of patient outcomes were only measured on one occasion (Table 6), with a pre ECMO baseline measure often precluded due to the speed and severity of deterioration in health, and so the relationship between rehabilitation and change in patient outcomes could not be determined.

Discussion

This scoping review has comprehensively described the literature on rehabilitation of adult patients on ECMO. Our review identified 152 unique eligible studies from around the world, with nearly two thirds of the studies conducted in North America. The majority were retrospective and over one third were conference abstracts, with only one randomised controlled trial identified [19]. Patients from a wide age range (18-72 years) participated in rehabilitation during ECMO, with males and females

equally represented. Rehabilitation whilst on VV ECMO was more frequently described than VA ECMO. Our scoping review identified a number of important deficiencies in the literature.

Reporting of rehabilitation interventions was limited, with key details often missing altogether or only partly described. Whilst the type of rehabilitation intervention was frequently reported, details relating to timing, dosage and intensity were sparse. This provides challenges for evaluating feasibility, replicating the intervention and comparing outcomes. The Template for Intervention Description and Replication (TIDieR) checklist [58] and the Consensus on Exercise Reporting Template (CERT) [59] are two examples of tools developed to improve the completeness of reporting in interventional trials. The use of such guidelines and checklists in future ECMO rehabilitation studies would facilitate full reporting of rehabilitation interventions allowing replication and comparison of studies.

Our scoping review identified that both screening for suitability and delivery of rehabilitation were infrequently reported. Only 13 studies reported on the number of patients screened for eligibility. These studies reported a median of 61% of screened patients met eligibility criteria, meaning that a significant proportion of patients on ECMO were not deemed suitable to participate. Given the small number of studies, this information must be considered hypothesis generating, and there is an urgent need for future studies, including observational studies, to report information relating to eligibility screening. Once selected to participate, the feasibility of delivery of the intervention was reported more frequently (in 59 studies) but ranged widely (5-100%), but this is difficult to interpret in the absence of screening data. Data relating to the duration or number of sessions delivered per patient was scarce, and reporting was variable. For example, one study [8] reported the number of sessions per patient per week (median 2.8, IQR: 0.5-7.8), whilst another study [19] reported the total number of minutes of rehabilitation over 7 days for the intervention versus usual care group (133 [82 – 220] versus 27.5 [20.4 – 31]). There is currently no consensus on how data should be reported. As rehabilitation on ECMO has been described as resource intensive [39], feasibility data are vital to assist with planning for resource allocation and to facilitate safe delivery.

One of the major challenges in interpreting the existing data was the heterogeneity in the type and timing of outcome measures used. Studies that described the same type of rehabilitation intervention, often used multiple different outcome measures. Even when the outcome measure used was the same, the measurement tool was often different as was the timing of measurement, limiting data synthesis. Frequently no validated measurement tool was described, instead general descriptions were used to describe the outcome of interest. Previous studies have identified the need for a minimum core outcome set for trials investigating rehabilitation in the critical care setting [60,61]. A recent international, modified Delphi study identified core outcomes to include in all research evaluating the use of ECMO [62]. Under the domain of life impact, recommended core outcomes included health-

related quality of life, disability, activities of daily living, neurologic recovery and return to work. Evaluation of these core outcomes will require the identification of the most appropriate measurement tools, which will then allow the synthesis of data from individual trials to inform evidence-based clinical decision-making.

Two systematic reviews have been completed on rehabilitation during ECMO. Polastri et al [12] included adult and paediatric patients on VV ECMO, whereas the most recent review by Ferriera et al [11] limited the population to adults but included both VV and VA EMCO. One of the main limitations identified in both systematic reviews was the lack of randomised controlled trials, with the majority of data from observational studies. As a result, the efficacy of rehabilitation during ECMO could not be assessed in these reviews. One randomised controlled trial [19] has since been published and included 20 patients randomised to early intensive rehabilitation versus usual care. This small pilot study reported that early rehabilitation on ECMO was safe and feasible, but only when completed in a major ECMO centre with a dedicated and experienced multidisciplinary team. Given the difficulty in recruitment to this trial, it was recommended planning for future large randomised controlled trials would require international collaboration between the major ECMO centres.

The clinical implications of this scoping review are that rehabilitation during ECMO was associated with a low number of adverse events with few sessions needing to be ceased, however more information is required on feasibility in terms of selection for rehabilitation and the number of sessions able to be delivered. Out of bed rehabilitation was labour intensive, requiring 3-5 staff, and an experienced, multi-disciplinary team was typically utilised, with specialised training in ECMO. This is important information for future trial and workforce planning. There may be a signal for a reduced length of stay in ICU and reduced costs in patients that received rehabilitation versus no rehabilitation, however these data were from uncontrolled trials.

There were limitations in our review. The majority of data come from small observational studies with an inherent risk of bias. The inclusion of a wide range of admission diagnoses and patients on both VV and VA ECMO could limit the validity of the results as specific patient groups and modes of ECMO may have different responses to rehabilitation and trajectories of recovery. The length of stay was not always reported separately for survivors and non-survivors, making it difficult to interpret. We excluded studies published in languages other than English, and so results may not reflect rehabilitation interventions reported in other languages. We also excluded the paediatric population, and so results from this review may not be generalisable to this cohort.

Our review has several important strengths. To our knowledge this is the first scoping review completed on rehabilitation during ECMO. Scoping review methodology allows a more comprehensive mapping of the current state of knowledge than a systematic review allows, and we were able to identify several important deficiencies in the existing literature. Our review included a

comprehensive search strategy of seven electronic databases from inception to June 2020 and also incorporated grey literature. We used clearly defined inclusion and exclusion criteria and a rigorous methodology including use of the PRISMA ScR checklist [15] to ensure consistency in reviewer agreement, data extraction and synthesis. This review included wide representation from around the world with 19 countries represented and detailed patient demographic and clinical data presented. The majority of studies included in this review (n=132) have not been included in previous systematic reviews on rehabilitation during ECMO, including the one randomised controlled trial [19].

Conclusion

Rehabilitation during ECMO is an emerging area of research with the majority of the literature consisting of small observational studies. This scoping review demonstrated that it was feasible to deliver rehabilitation to a wide age range of patients on ECMO, however less than two thirds of patients met eligibility criteria to participate. More data related to eligibility screening are required. Rehabilitation was more commonly reported in patients on VV ECMO than VA ECMO, and ambulation was the most commonly reported intervention. There were few adverse events reported, suggesting rehabilitation is a safe intervention, and delivery may be facilitated by an expert, multi-disciplinary team, along with an upper body cannulation strategy and low sedation levels. A number of critical gaps were identified including the lack of detailed reporting of the rehabilitation intervention, along with heterogeneity in the type and timing of outcome measures. To advance the knowledge in the area of rehabilitation during ECMO, future research needs to focus on robust methodological designs including complete intervention reporting and inclusion of a defined core outcome set.

Figure captions

Fig. 1 PRISMA flow diagram of included studies

Compliance with ethical standards

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Conflicts of interest/competing interests

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Consent to participate/Consent to publish

Not applicable

Ethical approval

An approval by an ethics committee was not applicable.

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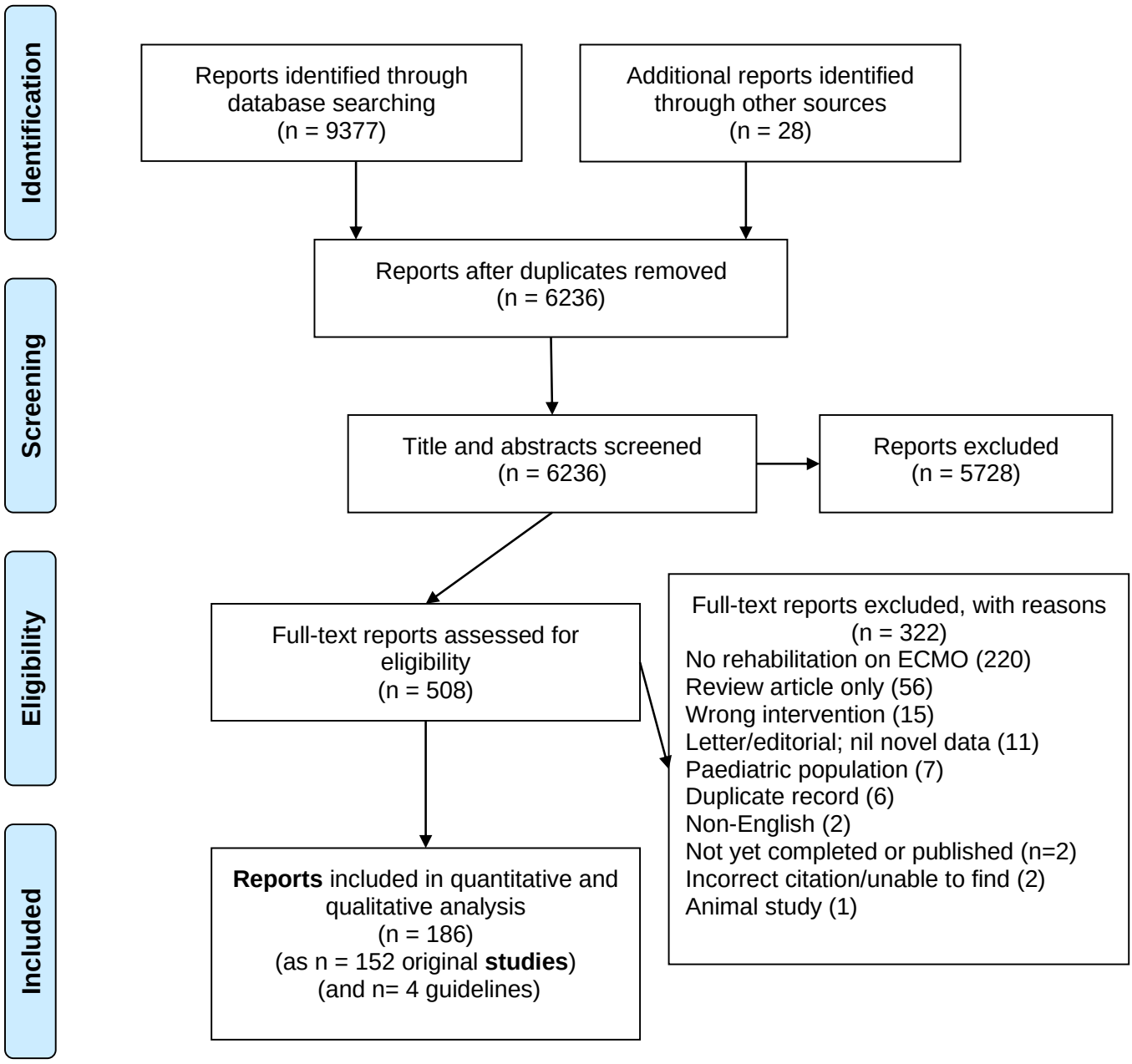
Identification
Screening
Eligibility
Included
Reports identified through database searching (n = 9377)
Additional reports identified through other sources (n = 28)
Reports after duplicates removed (n = 6236)
Title and abstracts screened (n = 6236)
Reports excluded (n = 5728)
Full-text reports assessed for eligibility (n = 508)
Full-text reports excluded, with reasons (n = 322)
No rehabilitation on ECMO (220)
Review article only (56)
Wrong intervention (15)
Letter/editorial; nil novel data (11)
Paediatric population (7)
Duplicate record (6)
Non-English (2)
Not yet completed or published (n=2)
Incorrect citation/unable to find (2)
Animal study (1)
Reports included in quantitative and qualitative analysis (n = 186)
(as n = 152 original studies)
(and n= 4 guidelines)

Table 1 Demographic and clinical characteristics from 145 studies

Variable	Summary data
Patient demographics	
Age, range	18-72 years
Gender male, n patients (%)	1104/1929 (57)
ECMO type	
VV ECMO only	75 (913)
VA ECMO only	33 (206)
VV and VA ECMO	27 (VV=627, VA=533)
Not described	10
ECMO duration (days); Range	1.5 - 403
Admission Diagnosis Type	
Respiratory	73 (781)
Cardiovascular	18 (90)
Mixed cohort of respiratory and cardiac diagnoses	39 (906)
Severe hypothermia	1 (19)
Not reported	14
Specific Admission Diagnosis	
Acute respiratory distress syndrome (ARDS)	38 (288)
Cystic fibrosis	32 (222)
Idiopathic pulmonary fibrosis or interstitial lung disease	27 (336)
Pneumonia, pneumonitis or influenza	28 (213)
Pulmonary hypertension	29 (188)
Heart failure, cardiogenic shock, post cardiac surgery	25 (135)
Cardiac arrest	6 (40)
ECMO as a bridge to transplant	
Bridge to lung transplant	62 (809)
Bridge to heart transplant	8 (12)
Bridge to heart-lung transplant	5 (5)
Bridge to re-transplant	5 (6)
Reported Severity of illness Scale; Range	
APACHE II (8 studies)	18.4 - 28
SOFA (6 studies)	5.2 - 18.2
SAPS II (4 studies)	25 - 30
Not reported (127 studies)	NA

Data are n studies (n patients), except where stated. ECMO, extracorporeal membrane oxygenation; VV, veno-venous; VA, veno-arterial; APACHE, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; SAPS, simplified acute physiology score.

Table 2 Description of rehabilitation intervention

Variable	N studies (%)
Rehabilitation Type: (109 studies)	
Bed-based exercise	45 (41)
Sitting on the edge of the bed	32 (29)
Cycle ergometer	23 (21)
Standing activities	39 (36)
Ambulation	75 (69)
Rehabilitation dosage (30 studies)	
Ambulation distance	19 (63)
Duration of rehabilitation in minutes	14 (47)
Number of repetitions of exercise	2 (7)
Rehabilitation intensity (7 studies)	
Workload in Watts	2 (29)
Modified Borg Rating of Perceived Exertion	1 (14)
Intensity adjusted based on physiological parameters	5 (71)
Equipment for rehabilitation (39 studies)	
Cycle ergometer: in-bed/recumbent bike	12 (31)
Upright cycle	11 (28)
Tilt table	11 (28)
Treadmill	7 (18)
Rehabilitation chairs involving passive transfer	7 (18)
Gait aides	6 (15)
Hand weights or resistance bands	4 (10)
EMS including FES	3 (8)
In-bed leg press device	1 (3)
Staffing Type for rehabilitation (50 studies)	
Physical therapist	43 (86)
Nursing staff	33 (66)
Physicians	20 (40)
Perfusionist	18 (36)
Respiratory therapist	15 (30)
Occupational therapist	7 (14)

Bed-based exercise included passive range of motion exercise, active range of motion exercise, electrical muscle stimulation, resistance exercises, sitting up in bed, and being passively transferred out of bed to a rehabilitation chair; Standing activities included sit to stand transfers, standing balance exercise, tilt table, marching on the spot at the bedside. EMS, electrical muscle stimulation; FES, functional electrical stimulation

Table 3 Feasibility and safety of rehabilitation in patients on ECMO

Variable	Studies reporting the variable N (%)	Summary data
Feasibility: 60 studies		
Number of patients screened for eligibility	13 (22)	62 (17 – 254)
Percentage of patients screened for eligibility	13 (22)	100 (63 – 100)
Percentage of screened patients meeting eligibility criteria	13 (22)	61 (14 – 100)
Percentage of sample size receiving the intervention	59 (98)	60 (5-100)
Reason provided for exclusion from rehabilitation:	20 (33)	
High sedation levels	6 (10)	
Failure to meet protocolised screening criteria	6 (10)	
Femoral cannulation	4 (7)	
Intubated and mechanically ventilated	4 (7)	
Historical cohort – no rehab provided	2 (3)	
Transplant within 48hrs of ECMO – no chance to mob	1 (2)	
Number of sessions per patient	4 (7)	5-15 (0-30)
Percentage of sessions ceased or deferred	8 (15)	1.9 (0 - 42)
Safety: 46 studies		
Studies reporting zero adverse events	21 (46)	
Studies reporting adverse events not linked to rehab	13 (28)	
Studies directly attributing adverse events to rehab	12 (26)	
Type of adverse event linked to rehabilitation		
Respiratory or haemodynamic instability	7 (15)	
Minor bleeding	2 (4)	
Fractured cannula	1 (2)	
Iliopsoas haematoma	1 (2)	
Increased pain	1 (2)	
Increased agitation	1 (2)	
Percentage incidence of adverse events	8 (17)	0.8 (0 – 4.8)

Data are reported as number of studies (%), median and range unless stated. ECMO, extracorporeal membrane oxygenation.

Table 4 Facilitators and Barriers to rehabilitation of patients on ECMO

Facilitator or Barrier to rehabilitation	**N studies (%)**
Facilitator (76 studies)	
Upper body cannulation	31 (41)
Weaning of sedation	25 (33)
MDT, expertise and leadership, education to staff	25 (33)
Weaning from mechanical ventilation/extubation	17 (22)
Tracheostomy insertion	11 (14)
Screening tool for rehabilitation	9 (12)
Method to secure cannula (e.g. helmut, sutures, Velcro strap)	5 (7)
Appropriate equipment for rehabilitation	4 (5)
Psychological support, antidepressants	3 (4)
No delirium/cognitively appropriate	2 (3)
Ability to manipulate ECMO settings during rehabilitation	1 (1)
Small size patient	1 (1)
Barrier (31 studies)	**N studies (%)**
Femoral cannulation	15 (48)
Sedation level	9 (29)
Medical instability/bleeding	8 (26)
Resources (staffing, time, equipment)	4 (13)
Patient anxiety/psychological issues	3 (10)

ECMO, extracorporeal membrane oxygenation; MDT, multidisciplinary team

Table 5 Relationship between rehabilitation during ECMO and length of stay in ICU and hospital

Study	Number of patients		ECMO Type	ICU LOS (days)		Hospital LOS (days)	
	Intervention	Usual Care		Intervention	Usual Care	Intervention	Usual Care
Bailey et al 2018	14	7	VA 7, VV 14	8	13	NA	NA
Bain et al 2016*	5	4	NA	Pre-transplant: 20 (17-30) Post-transplant: 8 (6-22)	Pre-transplant: 12 (4-41) Post-transplant: 45 (34-56)	50 (31-63)	94 (51-151)
Hakim et al 2018	5	25	VA 6, VV 24	20	37	31	57
Hartwig et al 2012	4	4	VV 8	10.5	27.5	49.2	80
Keibun et al 2016	10	13	VV 23	13.6	21.7	41.9	60
Rehder et al 2013	4	3	VV 7	27	49	49	98
Hodgson et al 2020	10	10	VA 12, VV 8	Survivors: 22 (12-36) Non-survivors: 7 (5-17)	Survivors: 29 (17-40) Non-survivors: 19 (19-19)	Survivors: 48 (36-58) Non-survivors: 11 (6-20)	Survivors: 35 (28-83) Non-survivors: 19 (19-19)

Data presented as median (interquartile range) when provided

*2 paediatric patients included in LOS data.

ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LOS, length of stay; VA, veno-arterial; VV, veno-venous; NA, data not available

Table 6 Types of patient outcomes reported

Patient Outcomes 55 studies	N studies (%)	Change over time
Symptoms:	7/55 (13)	NA
Pain – no measurement tool reported	1/55 (2)	NA
Fatigue – no tool reported	2/55 (4)	NA
Shortness of breath – no tool reported	2/55 (4)	NA
Symptom free – no tool reported	3/55 (5)	NA
Quality of life:	8/55 (15)	
EQ-5D	2 (4)	NA
SF-36	1 (2)	NA
SF-12	1 (2)	NA
No measurement tool reported	5 (9)	NA
Mental Health Disorder – no tool reported	1 (2)	NA
Delerium – CAM-ICU	1 (2)	NA
Cognition – MoCA-BLIND	2 (4)	NA
Muscle strength:	10 (18)	
MRC SS	6 (11)	4 (7)
HHD	3 (5)	2 (4)
Oxford scoring	1 (2)	1 (2)
EMG studies	1 (2)	NA
Presence of myopathy – no tool reported	2 (4)	NA
Muscle size - ultrasound imaging	2 (4)	2 (4)
Physical function:	19 (35)	
IMS	4 (7)	2 (4)
Modified IMS	3 (5)	2 (4)
FSS-ICU	2 (4)	NA
JH-HLM scale	1 (2)	1 (2)
AM-PAC 6-Clicks	4 (7)	2 (4)
Karnofsky Score	1 (2)	1 (2)
No measurement tool reported	5 (9)	NA
Activities of daily living:	8 (15)	
Katz Index of Independence in ADL	1 (2)	NA
Lawton IADL	1 (2)	NA
Barthel Index	1 (2)	NA
No measurement tool reported	7 (13)	NA
Peripheral neuropathy	4 (7)	NA
Mobility:	25 (45)	
Distance ambulated	19 (35)	1 (2)
Mobility milestones	2 (4)	NA
Six-minute walk test	4 (7)	2 (4)
Return to work	3 (5)	NA
Other:	12 (22)	
Long-term Oxygen therapy	4 (7)	NA
Lung function tests	3 (5)	NA
Joint range of motion	2 (4)	NA
Costs	2 (4)	NA
Advanced care directive for no further ICU or resuscitation	1 (2)	NA

NA, not available; SF-36, 36-Item Short Form Health Survey; SF-12, 12-Item Short Form Health Survey; CAM-ICU, confusion assessment method score for use in ICU patients; MoCA-BLIND, Montreal cognitive assessment BLIND, adapted version of the original MoCA; MRC SS, medical research council sum score; HHD, hand-held dynamometer; EMG studies, electromyography studies; IMS, ICU mobility scale; FSS-ICU, functional status score for the intensive care unit; JH-HLM scale, John Hopkins highest level of mobility scale; AM-PAC 6-Clicks, activity measure for post-acute care 6-clicks; ADL, activities of daily living, Lawton IADL scale, Lawton instrumental activities of daily living scale.

Electronic Supplement:

Rehabilitation of patients on extracorporeal membrane oxygenation (ECMO): a scoping review.

Journal: Intensive Care Medicine

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Methods

Eligibility criteria

The PICOT [1] format was used to define our inclusion criteria: Population- adult patients (aged ≥ 18 years) on VV or VA ECMO support for > 24 hours; Intervention-"Rehabilitation" defined as any intervention that was provided to patients whilst on ECMO with the purpose of maintaining or improving physical function, and including, but not limited to: passive and active range of motion exercises, electrical muscle stimulation, tilt table therapy, resistance exercises, functional mobilisation tasks including bed mobility exercises, sitting on the edge of the bed, static and dynamic balance exercises, transfer practice, marching on the spot at the bedside, in-bed and out-of-bed cycling, and ambulation; Comparator- any or none; Outcomes- patient related outcomes, hospital outcomes, safety outcomes, mortality, intervention description and feasibility of delivery, reported barriers and facilitators to rehabilitation; Type of study-all study types included along with grey literature. We excluded paediatric patients (< 18 years old), or combined adult and paediatric populations where it was not possible to separate out the adult data, studies published in languages other than English, animal studies, studies that only described rehabilitation after ECMO removal, extracorporeal carbon dioxide removal or temporary mechanical cardiac support such as temporary left and right ventricular assist devices, isolated respiratory physiotherapy interventions, basic nursing care (i.e. rolling/positioning), music therapy, original research reports that made no mention of rehabilitation on ECMO in the methodology or results section, and letters, editorials or review articles with no original patient data.

Health outcomes of interest

1) Patient related outcomes: Evaluated at two different time points; those measured whilst in hospital (including the ICU stay and ward stay) and those measured post hospital discharge.

i) Physical function: as measured with a validated scale or physical performance task (e.g. Time to reach mobility milestones [stand, sit out of bed, ambulate], Physical Function ICU Test [PFIT], ICU Mobility Scale [IMS], Functional Independence Measure [FIM], Acute Care Index of Functional Status [ACIF], walking tests/distance walked)

ii) Health related quality of life or well-being as measured with a validated scale for use in ICU (e.g. The Medical Outcomes Study (MOS) 36-item Short-Form Health Survey (SF-36) questionnaire, The Hospital Anxiety and Depression Score (HADS), the presence of delirium (CAM-ICU) or Post-Traumatic Stress Disorder (PTSD)

iii) Muscle strength (e.g. Medical Research Council (MRC) sum-score, or hand-held dynamometry measures)

iv) Return to work rate

v) Symptoms (fatigue, pain, neurological symptoms including but not limited to altered peripheral sensation, limb weakness)

2) Feasibility outcomes: We will collect data relating to both the selection of patients for rehabilitation and the ability to deliver the intervention. This will include: the number of patients screened for inclusion in rehabilitation, the number of patients that were eligible and received the intervention, reasons why patients were excluded from rehabilitation, number of interventions delivered, number of interventions ceased, reasons why rehabilitation not delivered or ceased, and time to start rehabilitation (days post ECMO cannulation).

3) Rehabilitation intervention and delivery: To facilitate understanding of the components of the interventions across studies, we will use the Template for Intervention Description and Replication (TIDieR) checklist to report interventions [2]. This will allow collection of data related to who provided the intervention, level of training of staff, type of exercise performed, dosage and intensity of exercise, equipment used, where it was performed (type of ICU and country where study performed), tailoring of intervention to individual patients, and modification of intervention.

4) Safety outcomes:

i) Potential safety events during rehabilitation will be defined as "clinical deterioration in patient status or an event exceeding each study's a priori safety limits requiring stopping of the rehabilitation or where interventions or additional therapy were required to address the event (i.e. hypotension during rehabilitation requiring increase in vasopressor dose) [3].

ii) Adverse events occurring during rehabilitation may include but are not limited to falling to the floor, cardiac arrest, accidental dislodgement of attachments, major bleeding from ECMO cannula or other sites or any other adverse event defined by study authors.

5) Hospital outcome measures: including ICU and hospital length of stay, discharge destination.

6) Mortality: including death whilst on ECMO, death post ECMO removal

7) Barriers and facilitators to rehabilitation: We will record when a study explicitly identifies barriers and facilitators to rehabilitation (e.g. sedation practice, cannulation strategy, haemodynamic and respiratory system stability, teamwork and equipment). These may be qualitative or quantitative data.

Supplementary Table E1. MEDLINE (Ovid) search strategy

Medline (Ovid) ECMO Search strategy V7: run on 28/4/19 at 11:13 Database: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946 to April 26, 2019> Search Strategy:
1 exp Extracorporeal Membrane Oxygenation/ (9042)
2 exp Extracorporeal Circulation/ (66470)
3 exp Oxygenators, Membrane/ (1693)
4 (ECMO or ECLS).mp. (7474)
5 ((extracor* or extra-cor*) and membra* and oxygen*).mp. (13321)
6 (lung assist* or respiratory assist* or pulmon* assist*).mp. (822)
7 ((extracor* or extra-cor*) and circulat*).mp. (20197)
8 ((extracor* or extra-cor*) and life support).mp. (2152)
9 ((extracor* or extra-cor*) and lung support).mp. (134)
10 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 (75865)
11 exp REHABILITATION/ (285857)
12 exp Exercise Therapy/ (45915)
13 exp EXERCISE/ (177581)
14 exp Physical Fitness/ (27242)
15 exp Early Ambulation/ (2687)
16 exp Physical Therapy Modalities/ (142857)
17 exp WALKING/ (49590)
18 exp Physical Therapy Specialty/ (2693)
19 exp Physical Therapists/ (1451)
20 exp Physical Therapy Department, Hospital/ (322)
21 exp Muscle Strength/ (29874)
22 exp Physical Endurance/ (31709)
23 exp "Range of Motion, Articular"/ (47577)
24 exp Exercise Movement Techniques/ (7454)
25 (rehabili* or mobili*).mp. (530010)
26 physical function.mp. (11824)
27 (physiotherap* or physical therap*).mp. (65727)
28 ambulat*.mp. (164427)
29 exercis*.mp. (353488)

30 electric* muscle stimulat*.mp. (305)

31 ((cycle or bicycle) adj1 ergomet*).mp. (11326)

32 (walk or walking).mp. (98132)

33 (physical* adj3 (exertion or endurance or therap* or train* or conditioning or activ* or fit*)).mp. (269023)

34 ((isometric or isotonic or isokinetic or eccentric or concentric) adj (action* or contraction*)).mp. (20388)

35 (muscle strengthen* or progressive resist*).mp. (2011)

36 (bed adj3 activ*).mp. (717)

37 (pregait or gait).mp. (54261)

38 or/11-37 (1401652)

39 10 and 38 (1976)

40 exp animals/ not humans.sh. (4574312)

41 39 not 40 (1848)

42 limit 41 to english language (1547)

****

Supplementary Table E2: Characteristics of 152 included studies

Study Characteristics	
Location of study, n (%)	
USA	89 (59)
Canada	5 (3)
England	7 (5)
Germany	7 (5)
Netherlands	5 (3)
France	4 (3)
Italy	3 (2)
Poland	2 (1)
Croatia	2 (1)
Turkey	1 (1)
Switzerland	1 (1)
Sweden	1 (1)
Austria	1 (1)
Belgium	1 (1)
Japan	5 (3)
Australia	4 (3)
South Korea	4 (3)
Columbia	2 (1)
Argentina	1 (1)
No Country specified	7 (5)
Study Design, n (%)	
Randomised Controlled Trial	1 (1)
Case studies	58 (38)

Retrospective case series or cohort studies	79 (52)
Prospective cohort studies	6 (4)
Surveys (two of clinicians practice, one providing patient data)	3 (2)
Other (opinion pieces, commentaries)	5 (3)
Sample size, median (IQR; Range)	4 (1-18; 1-280)
Number of centres, n studies (%)	
Single-centre	148 (97)
Multi-centre	4 (3)
ICU type, n (%)	
Medical	7 (5)
Cardiovascular	5 (3)
Mixed medical/surgical	2 (1)
Trauma/burns ICU	1 (1)
Paediatric ICU (managed 2 patients > 18yrs old)	1 (1)
Not specified	136 (89)

Supplementary Table E3. Dosage of exercise provided to patients on ECMO

Study	Sample size	Age (years)	ECMO type (n)	Cannulation (n)	Exercise type	Dosage
Abrams et al 2013	3	26.3 ± 6.7	VA (2), VV (1)	IJV to SCA (2), DLC (1)	Ambulation	Distance 30-850 feet
Biscotti et al 2014	3	37.3 ± 19.2	VA (3)	IJV to SCA (3)	Ambulation	Distance 300-400 feet
Blum et al 2013	4	Mean 46 (range 25-63)	VV (4)	DLC (4)	Recumbent bike	Time: minimum of 10 minutes to be listed for transplant
Boling et al 2016	18	49 ± 15	VV (18)	DLC (18)	Ambulation	median distance: 200 feet per session, "distances up to 300 feet or more" (only 9/18 had precise distance recorded, the rest walked outside of their ICU cubicle
Buchtele et al 2016	1	64	VV (1)	DLC (1)	SOEOB	Time: up to 1 hour
Chavez et al 2015	1	41	VV (1)	NA	SOEOB and Standing	SOEOB: 10mins 2 x day, stand 45 secs, 3 x day
Decker et al 2019	6	NA	VV (6)	DLC (6)	Progressive program from bed exercises to ambulation	Mean ambulation distance recorded in 2 patients: 196 feet and 5 feet

Downey et al 2019	17	Mean 50 (range 24-67)	VA (17)	Central	Ambulation	16/17 pts mob > 50 feet
Godula et al 2012	1	19	VV (1)	IJV to femoral vein	PROM, passive SUIB, AA and AROM, isometric ex's	30-40mins, 2-3 x day, slow speed and small number of reps per set, By D30, most of day spent SUIB.
Goodwin et al 2018	3	Range:21-58	VV (3)	Femoral	Ambulation	all 3 pts mob > 50 feet by time of ECMO decannulation
Guru et al 2015	8	Median 24 (IQR: 8-51)	VA (5), VV (3)	Central 5, DLC (3)	Ambulation	5 to > 100 yards, 5/8 amb > 100 yards
Hermens et al 2017	14	Median 37 (IQR: 27-44)	VV (14)	DLC (3), femoral-IJV (5), femoral-femoral (6)	Ambulation	One patient ambulated 80m on day 5, increasing to 333m by day 26
Hodgson et al 2020	20	Intervention: 49.3 ± 13.4, Standard Care: 50.6 ± 17.1	VA (12), VV (8)	DLC 1, R IJV and fem 3, Any fem cannulation 20	Int: PROM, AA or AROM, SOOB passively to chair, SOEOB, stand, MOS. Standard Care: usual physical therapy	Int: min 20mins if PROM, 30mins if active and up to 1 hr for 7 days; Standard Care: no set dosage per day for 7 days
Hoopes et al 2013	31	45 ± 15	VA (17), VV (13), Other (1)	VA fem 12, VV fem 2, DLC 11, central 5, mixed 1	Ambulation	aim to amb > 200 feet prior to LTx
Kulkarni et al 2015	1	36	VV (1)	DLC (1)	Ambulation	Distance: > 800 feet/day

Liu et al 2019	19	NA for ECMO pts	NA	NA	Maebashi early mobilisation protocol progressing from bed exercises to ambulation	One rehabilitation session per day for 20 minutes
Pastva et al 2015	1	30	VV (1)	DLC (1)	FES cycling	7 sessions of which 3 were on ECMO: Cycle duration: 20-43mins, cycle distance: 3.62-6.89 miles
Pruijsten et al 2014	6	53 ± 8	VV (6)	DLC (6)	SOEOB (2), MOS (2), ambulation (2), bed ex's (6)	MOS in 2 pts: few steps; ambulation in 2 pts: range 20m to 100m
Rahimi et al 2013	3	28 ± 8	VV (3)	IJV - fem V (1), DLC (2)	Recumbent bike	up to 30mins of in-bed cycle in one patient
Rehder et al 2013	7 adults	41 ± 18	VV (7)	DLC (4) in rehab adult group, fem-fem or fem-IJV (3) in no rehab group	ambulation	Amb in 3/4 rehab group: distance up to 396m in one session.
Salam et al 2017	1	55	VV (1)	DLC (1), Initially IJV to femoral vein but changed for rehab	Progressive program from bed based ex to ambulation	ambulation < 10 feet; mini leg press in supine, progress from 5 reps to 50 reps over 6 weeks

Shudo et al 2018	1	41	VA (1)	Fem-fem (1)	Tilt table, MOS, ambulation	initial tilt: 45 degrees for 30mins on D2, full tilt for 30mins D9, progression MOS with straps loosened, sidesteps on tilt table, amb several feet at bedside to 30mins amb on D15 and strength ex
Skrzat et al 2011	1	25	VV (1)	NA	Recumbent bike	30minutes completed in one session
Tipograf et al 2019	121	Median 44 (30-58)	VA (52); VV (63); Other (6)	DLC (63); VA not clear	Ambulation	55-525 feet per session; 82/121 ambulated
Tipograf et al 2019	9	Median 58 (IQR:56-64)	VV (9)	DLC (9)	Physical therapy including ambulation	Median daily distance ambulated 130 feet (IQR:100-290)
Tobin et al 2016	1	54	VA (1)	Fem-fem (1)	Standing, MOS, ambulation	progression of time in stand: 2 x 30sec D13 to MOS 15mins on D26, Ambulation 300 feet D27, 1200 feet D38
Tobin et al 2017	1	62	VA (1)	NA	SOEOB, stand, ambulation	stand for 2 mins on D29, ambulation 98feet D43
Turner et al 2011	2	21.5 ± 3.5	VV (2)	DLC (2)	Progressive program: including ambulation	Ambulation distance in one patient: 5 feet on D7 to 700 feet D12

Ward CM 2020	4	29-66	"Different modes of ECMO"	NA	Progressive exercise program from bed exercises to ambulation	Duration of exercise sessions: 30-90 minutes
Zhu et al 2019	1	38	VV (1)	IJV to fem V, converted to high flow D24	Progressa Bed tilt, VitalGo bed/tilt table	Started Progressa Bed tilt Day17: 30 mins 3 x day until max tilt 18 degrees; then VitalGo bed 30 mins 3 x day progressing tilt to max of 82 degrees by Day32

Supplementary Table E4. Intensity of exercise provided to patients on ECMO

Study	Sample size	Age (years)	ECMO type (n)	Cannulation (n)	Exercise type	Intensity
Camboni et al 2009	1	57	VA (1)	Fem v to ascending aorta (1)	Ergometer adapted for in-bed training	Workload up to 30 watts. Adjustment of ECMO settings to allow aerobic training with PaO2>60, SvO2 near 50%, lactate normal
Godula et al 2012	1	19	VV (1)	IJV to femoral vein	PROM, passive SUIB, AA and AROM, isometric ex's	Intensity adjusted to suit pt, monitoring physiological parameters. ECMO parameters adjusted to allow rehab
Hodgson et al 2020	20	Intervention: 49.3 ± 13.4, Standard Care: 50.6 ± 17.1	VA (12), VV (8)	DLC 1, IJV and fem 3, Any fem cannulation 20	Int: PROM, AA or AROM, SOOB passively to chair, SOEOB, stand, MOS. Standard care: usual Physiotherapy intervention	Int: Modified Borg Score 3-5; Physiological guideline of when to start or stop, ECMO flow increased in one patient. Standard Care: no aim for intensity but same physiological guideline
Kurihara et al 2018	3	44.3 ± 13.6	VV (3)	IJV to femoral vein (3)	Ambulation	ECMO flow and FiO2 increased during exercise to meet physiological parameters. Aim for SpO2 ≥ 88%.

Morris et al 2014	1	46	VV (1)	IJV to femoral vein (1)	SOEOB	ECMO blood flow increased (4.12 L/min pre physio to 5.23 L/min during treatment) to manage desaturation
Pastva et al 2015	1	30	VV (1)	DLC (1)	FES cycling	Over the 7 sessions of which 3 were on ECMO: cycle power: range: 1.59-8.96 Watts
Pechulis et al 2014	1	24	VV (1)	NA	Bed ex's, SOEOB	Intensity of rehab was performed outside of normal physiological parameters: RR 40-50, HR 150-160, SpO2 nadir 75%

Supplementary Table E5: Feasibility of delivering rehabilitation to patients on ECMO

Author	Total sample size	Excluded from intervention	Exclusion reason	Received intervention	interventions provided (n)	interventions ceased (n)	Reason ceased/cancelled
Abrams et al 2014	100; all screened for inclusion in rehabilitation	65 (65%)	bleeding, arrythmia, thrombocytopenia, CVS instability, high dose vasopressors, severe hypoxemia, sedation, NMBs were all in the screening tool	35 (35%) did rehabilitation, of which 18 ambulated	median sessions/patient: 5 (IQR:1-13); median sessions/week: 2.8 (IQR: 0.5-7.8)	NA but no safety events recorded with rehab	NA
Absi et al 2017	35	NA	NA	7 (20%)	NA	NA	NA
Bailey et al 2018	21	NA	NA	14 (66%)	NA	NA	NA
Bain et al 2016	7 adult pts	3	Non ambulatory ECMO/historical cohort	4 (57%)	NA	NA	NA
Biscotti et al 2014	3, only included patients that participated in rehabilitation	NA	NA	3 (100%)	NA	NA	NA

Biscotti et al 2017	72; all screened for inclusion in rehabilitation	NA	NA	58 (64%) did rehabilitation of which 50 ambulated and 8 did bedside exercise	NA	NA	NA
Boling et al 2016	26	8	Femoral cannulation or CVS instability	18 (69%)	NA	1	1 patient became weak whilst ambulating and had to be assisted to a chair and transported back to bed
Bonizzoli et al 2019	160, all screened daily for eligibility for rehabilitation	59	screening criteria related to medical stability, sedation, NMB	101 (63%)	NA	NA	NA
Bridwell et al 2014	4	1	NA; rehabilitation commenced after ECMO removed	3 (75%)	NA	No adverse events during PT	0
Camboni et al 2012	36	NA	NA	13 (36%); 9 mobilised, 4 extubated and “partially mobilised”	NA	NA	NA

Chicotka et al 2018	50	NA	NA	37 (74%)	NA	NA	NA
Chimot et al 2013	52	NA	femoral cannulation was one reason in n=5 pts. Other reasons not given	9 (17%) mobilised; 3 SOOB in lounge chairs, 5 SOOB in upright chairs, 1 proned	NA	NA	NA
Colclough et al 2018	63, only included patients that participated in rehabilitation	NA	NA	63 (100%)	299 sessions: unclear number per patient	NA	NA
Decker et al 2019	6, only included patients that participated in rehabilitation	NA	NA	6 (100%)	94 sessions (range: 3-30 per patient) Median: 15 sessions per patient (IQR: 5-26)	NA	NA
DeBacker et al 2018	45	NA	NA	32 (71%)	NA	NA	NA
Downey et al 2019	17, all screened for inclusion in rehabilitation	1	Tx within 48hrs on ECMO, so no chance to mob	16 (94%)	NA	NA	NA

Farber et al 2013	4	1	not extubated	3 (75%)	NA	NA	NA
Garcia et al 2011	10	NA	NA	4 (40%)	NA	NA	NA
Goodwin et al 2018	3, only included patients that did rehab	NA	NA	3 (100%)	NA	NA	NA
Guru et al 2015	8, only included patients that did rehab	NA	NA	8 (100%)	NA	NA	NA
Hakim et al 2018	30, only 19 (63%) patients all with DLC screened for rehabilitation	25	non DLC pts were not assessed for rehab, those with DLC that did not ambulate no reason given	5/30 (17%) ambulated, 5/19 (26%) screened patients	NA	NA	NA
Hartwig et al 2012	8, only 4 (50%) screened for rehabilitation	4	Historically, not ambulated with dual cannula strategy.	4 (50%)	NA	NA	NA
Hayes L et al 2018	55, only included patients that participated in rehab	NA	NA	55 (100%)	154; unclear number of sessions per patient	111/265 documented attempts cancelled	NA

Hellyer et al 2017	280	NA	NA	15 (5%)	NA	NA	NA
Hermens et al 2017	14	NA	NA	9 (64%)	105 sessions (range: 0-26 per patient. Median: 6 sessions/patient (IQR: 3-10)	0	NA
Hodgson et al 2020	60 patients screened; 20 (33%) included; intervention = 10 Standard Care=10	0/10 excluded in the intervention group	NA	10/10 (100%) pts in the intervention group received intervention as per protocol	Intervention: 56 sessions on ECMO; Standard Care: 64 sessions on ECMO; IMS>3: intervention=7/56, standard care=0/64	4 sessions were ceased	Intervention: 2 sessions due to increased ECMO blood flow by 0.5L and increased pain. Standard Care: 2 sessions due to increased vasopressors and increased agitation
Hoetzenecker et al 2018	71	NA	NA	26 (37%)	NA	NA	NA

Hoopes et al 2013	31, all patients screened for participation in rehab	NA	NA	19 (61%)	NA	NA	NA
Javidfar et al 2011	27	NA	NA	7 (26%)	NA	NA	NA
Javidfar et al 2012a	20	NA	NA	7 (35%)	NA	NA	NA
Javidfar et al 2012b	18	NA	NA	7 (39%); 5 pts ambulated, 2 pts rode ex bike	NA	NA	NA
Keenan et al 2016	3	NA	NA	1 (33%)	NA	NA	NA
Keibun 2016	23	13	sedated	10 (43%), awake rehab	NA	NA	NA
Ko et al 2015	8, only included patients that participated in rehabilitation	NA	NA	8 (100%)	62 sessions (range: 1-20 per patient) Median: 6 sessions per patient (IQR: 3-11)	3	tachycardia (132 bpm); tachypnoea x 2 (46 and 47 breaths/min)

Kobayashi et al 2014	30	NA	NA	12 (40%), improving from 2007-2012 from 0% to 89%	NA	NA	NA
Kukreja et al 2020	62, all patients screened for inclusion in rehabilitation	NA	NA	21(34%) did out of bed rehabilitation	NA	NA	NA
Kurihara et al 2018	3, case-series including patients that were extubated and participated in rehabilitation	NA	NA	3 (100%)	NA	NA	NA

Lee et al 2016	NA for ECMO cohort	NA	NA	NA	12	2 in one pt	reduced SpO2, tachypnoea and hypotension requiring increase ECMO flow and FiO2; desaturation, tachycardia, tachypnoea but no intervention required
Liu et al 2018	6, only included patients that participated in rehabilitation	NA	NA	6 (100%)	110 sessions; unclear number per patient	4 (1 in AROM in bed, 1 in SOEOB, 2 in MOS or amb)	NA
Marhong et al 2017	209 clinicians	33 (16%) report no rehab (survey of ECMO clinicians)		176 (84%) did rehab	NA	NA	NA
Memon et al 2018	5	NA	NA	2 (40%)	NA	NA	NA

Morris and Osman 2017	56, all patients screened for inclusion in rehabilitation	30	deterioration or not meeting criteria for active rehab: RASS <-2 or >+2, neuro inapprop, unable to follow commands	26 (46%)	808 sessions	NA	NA
Munshi et al 2017	61	NA	NA	50 (82%) but data available only on 46 pts	NA	NA	NA
Nicolas et al 2013	10	4	Sedated and requiring mechanical ventilation	6 (60%)	NA	NA	NA
Olsson et al 2010	5	NA	NA	3 (60%)	NA	NA	NA
Pasrija et al 2019	104, all patients screened for rehabilitation	89	not meeting evaluation criteria	15 (14%)	NA	NA	NA
Rahimi et al 2013	3, case series	1	sedation and femoral cannula	2 (66%)	NA	1	Rehab deferred due to hypoxemia secondary to RHF, needing urgernt atrial septostomy
Rehder et al 2013	7, case series	3	sedated on MV	4 (57%)	NA	NA	NA

Rodriguez et al 2020	109	NA	NA	35 (32%)	NA	NA	NA
Robinson et al 2013	13	NA	NA	1 (8%)	NA	NA	NA
Rosenzweig et al 2019	98	NA	NA	50 (51%)	NA	NA	NA
Rubino et al 2014	72	NA	sedated	7 (10%)	NA	NA	NA
Schmid et al 2012	176	NA	NA	12 (7%)	NA	NA	NA
Sivam et al 2017	6	3	sedation and paralysis	3 (50%)	NA	NA	NA
Tipograf et al 2019a	121, all screened for inclusion in rehabilitation	0	NA	121 (100%) did rehab, 82 (68%) ambulated	NA	NA	NA
Tipograf et al 2019b	9	NA	NA	7 (78%) did rehab, of which 6 ambulated	NA	NA	NA
Todd et al 2017	12	11	9 out of 12 were deeply sedated	1 (8%)	NA	NA	NA

Wells et al 2018	254; all screened for inclusion in rehabilitation	87	failed medical screening tool: medical unstable, sedated, bleeding.	167 (66%) did rehab, 8/167 (4.8%) ambulated or 3.1% (8/254) of total sample	607 sessions	3	NSVT in 2 cases, hypotension in 1 case both in VV pts
Yanagida et al 2019	15	NA	NA	11 (73%)	NA	NA	NA
Yun et al 2010	7	NA	NA	2 (29%)	NA	NA	NA

Supplementary Table E6. Safety profile of rehabilitation of patients on ECMO

Author	Year	N	ECMO type (n)	Rehabilitation Type	AE (n)	AE type	AE related to rehab (Yes/No/not reported)
Abrams et al	2013	3	VA 2 VV 1	"Ambulation + Physical therapy"	1/3 (33%) patients	Bleeding from subclavian artery, causing brachial plexopathy	Not reported
Bemudez et al	2010	11	VV 11	"Mobilisation"	1 /11 (9%) patients	DLC displacement, producing recirculation and rapid desaturation	Not reported
Boling et al	2016	18	VV 18	Bed exercises and ambulation	1/18 (6%) patients	1 patient became weak whilst ambulating and had to be assisted to a chair and transported back to bed, no serious AEs	Yes
Carswell et al	2017	8	VV 8	Rehabilitation included sitting on edge of bed, cycling, standing, marching on the spot and ambulation	NA for number of events or patients	Mild desaturation or vertigo during mobilisation which settled quickly with rest	Yes

Chimot et al	2013	52	VV 52	Sitting out in a lounge chair (3 patients), and in an upright chair (5 patients)	19/52 (37%) patients	Bleeding (9 patients), migration of DLC (3 patients), thrombus formation (2 patients), acute renal failure (2), septic shock (2), MOF (1)	Not reported
Decker et al	2019	6	VV 6	Rehabilitation included bed exercises, sitting on edge of bed, sitting out of bed, standing activities, marching on the spot and ambulation	1 event in total of 94 sessions (1.1%)	Bleeding from the Avalon DLC at the end of the session requiring surgical exploration	Yes
Farber et al	2013	4	VV 4	"Mobilisation and Physiotherapy with assistance"	1/4 (25%) patients	Minor bleeding at DLC insertion site	Not reported
Garcia et al	2011	10	VV 10	Rehabilitation included, sitting out of bed, ambulation, treadmill, exercise bike	7/10 (70%) patients	Major bleeding n=4, right atrial perforation during DLC insertion n=1, thrombolic stroke n=2) but unclear if in patients that did rehabilitation	Not reported
Guru et al	2015	8	VA 5 VV 3	Active rehabilitation including ambulation in all patients	6/8 (75%) patients	ECMO circuit AE in 1 patient, patient related AE in 5 patients; type not defined	Not reported

Hermens et al	2017	14	VV 14	Dynamic quadriceps training by leg press, bed bike, bed to chair transfers, stand, marching on spot, squats, treadmill ambulation	3 /14 (21%) patients	3 AE during ECMO not linked to rehabilitation: 1 patient developed obstruction in the return cannula due to thrombus so convert to DLC; 1 patient (femoral-femoral cannulation) developed a large rectus haematoma and required ECMO removal; 1 patient had a dislocation of DLC during an interhospital transfer and changed to femoral-jugular cannulation. All rehabilitation sessions were uneventful.	No
Hodgson et al	2020	20	VA 12 VV 8	Intervention group: Aim for highest level of activity ranging from bed exercise to ambulation. Standard Care: standard care physiotherapy	4/120 (3.3%) sessions; 4/20 (20%) patients	4 minor AE: Intervention group: increased ECMO flow x 1, pain x 1; Standard Care: increase vasopressors x 1, patient agitation x 1 1 x major AE in Intervention group: ECMO cannula displacement and hypovolemic arrest; survived to hospital DC	Minor AE – Yes Major AE – No; had not commenced intervention yet

Ko et al	2015	8	VA 1 VV 7	Bed exercises including EMS, Sitting up or on edge of bed, stand exercise, ambulation	3/62 (4.8%) sessions. ?number of patients	tachycardia (132 bpm); tachypnoea x 2 (46 and 47 breaths/min)	Yes
Kukreja et al	2020	62	VA 34 VV 28	Goal of ambulation or minimum of out of bed rehabilitation in all patients	26 in 62 patients (42%)	Cannula dislodgement 1/62 (2%), Tubing rupture 1 (2%), ECMO access site bleeding 4 (6%), HIT 3 (5%), Limb ischaemia 2 (2%), Renal failure 8 (13%), PEA arrest 4 (6%), Neurological injury (SC paralysis, ICH or CVA 3 (5%)	No
Lee et al	2016	NA for ECMO patients	NA	Progression from bed exercise to standing at bedside and marching on spot	2 in 1 patient, not clear on number of sessions	2 AE in 1 patient: reduced SpO2, tachypnoea and hypotension requiring increase to ECMO flow and FiO2; desaturation, tachycardia, tachypnoea but no intervention required	Yes
Liu et al	2018	6	NA	Maebashi exercise protocol: progressive exercise program ranging from bed exercise to ambulation	4/110 (3.6%) sessions	Type of event unclear - 1 event during active exercise in bed, 1 in sitting on edge of bed, 2 during marching at bedside or ambulation	Yes

Mangi et al	2010	1	VA 1	Sitting out of bed and ambulation	1/1 (100%) patient	Reduced ECMO flow requiring configuration change, not clear if related to rehabilitation	Not reported
Morris et al	2014	1	VV 1	Sitting on edge of bed	1/1 (100%) patient	Oxygen desaturation during sitting on the edge of the bed was managed by increasing ECMO blood flow	Yes
Pasrija et al	2019	15	VA 15	Progressive rehabilitation with goal of ambulation: progress from sitting on edge of bed, marching at bedside to ambulation	3/15 (20%) patients	Minor bleeding around femoral cannula in 3 patients, repaired with sutures, and one had distal perfusion cannula removed due to persistent minor bleed after ambulation. No major AE.	Yes
Peris et al	2011	2	VV 2	"Mild Physio" in one patient	1/2 (50%) patients	Iliopsoas haematoma possibly related to combination of anticoagulation on VV ECMO with femoral cannulation and lower limb movements	uncertain
Rodriguez et al	2020	109	VA 77 VV 32	Ambulation defined as standing, marching on spot or walking	32 (29%) of patients	Vascular complications: no difference between those that ambulated or not	No

Salam et al	2017	1	VV 1	Progressive rehabilitation from bed exercise to ambulation	1/1 (100%) patient	Fracture of one cannula in the DLC (lumen fracture), necessitating change to new DLC, presumed due to ambulation	Yes
Schmid et al	2012	176	VV 176	Progressive mobility program, including out of bed activity	25/176 (14%) patients	Cannula complications occurred in 25 patients, with minor bleeding most common, no bleeding event identified after mobilisation	No
Taniguchi et al	2019	54	VV 54	Mobilisation	8/54 (15%) patients	Iliopsoas haematoma – univariate analysis identified mobilisation beyond sitting on the edge of the bed as a risk factor, $p < 0.05$	Yes
Tipograf et al	2019b	9	VV 9	Physical Therapy including ambulation	2 AE in 2 patients	Migration of DLCa requiring cannula repositioning in 2 patients	Not clear
Wells et al	2018	254	VA 119 VV 135	Progressive rehabilitation from bed exercise to standing and ambulation	3 AE in 2 patients (0.5% of sessions); 2/167 (1.2%) patients had an AE	NSVT x 2 in one patient on VV ECMO whilst standing; hypotension x 1 in one patient on VV ECMO whilst sitting up in bed. Both patients had femoral cannulation Nil major events	Yes

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Chapter 3: PHYSICAL FUNCTION AFTER EXTRACORPOREAL MEMBRANE OXYGENATION IN PATIENTS PRE OR POST HEART TRANSPLANTATION - AN OBSERVATIONAL STUDY

3.1. Declaration of authorship: Chapter 3

Student's declaration:

The nature and extent of contributions to Chapter 3 of this thesis are as follows:

Name	Nature of contribution	Contribution
Kate Hayes	Study concept and design, ethics application, data collection and analysis, manuscript preparation and revision for publication	80%
Anne Holland	Study concept and design, data analysis, drafting and revision of manuscript	5%
Vincent Pellegrino	Study design, revision of manuscript	4%
Angeline Leet	Study design, revision of manuscript	3%
Louise Fuller	Data collection and revision of manuscript	2%
Carol Hodgson	Study concept and design, data analysis, drafting and revision of manuscript	6%

Supervisor's declaration:

I hereby certify that the declaration above is a correct reflection of the extent and nature of contributions made toward Chapter 3 of this thesis by the student and all listed co-authors.

Name of supervisor	Signature
Anne Holland	

3.2. Preface to Chapter 3

Human Research Ethics Committee approvals for this study were granted from the Alfred Hospital Ethics Committee (Project number 314/14) and the La Trobe University Faculty of Health Sciences Ethics Committee (FHEC14/253). This ethics submission covered the studies presented in Chapters 3 and 4, describing functional outcomes in heart transplant patients and then lung transplant patients that received ECMO. See Appendix 1 for the ethics approval forms.

The observational study presented in Chapter 3 was published in *Heart & Lung* and is presented in its published format.

Hayes K, Holland AE, Pellegrino VA, Leet AS, Fuller LM, Hodgson CL. Physical function after extracorporeal membrane oxygenation in patients pre or post heart transplantation - An observational study. *Heart Lung.* 2016;45(6):525-531. doi:10.1016/j.hrtlng.2016.07.007

See Appendix 2 for permission for inclusion in this thesis

Aspects of this study were presented at the following conferences:

Oral presentations:

1. National Physiotherapy conference (APA) in October 2015.

Title: Functional outcomes and quality of life in patients undergoing extracorporeal membrane oxygenation pre or post heart transplant – an observational study.

2. International Society of Heart and Lung Transplantation (ISHLT) Annual Scientific Meeting in Nice, France, 16/04/2015.

Title: Functional outcomes and quality of life in heart transplant patients requiring extracorporeal membrane oxygenation

Abstract: the abstract related to the oral presentation of this study was published as follows:

Hayes K, Holland AE, Pellegrino V, Leet AS, Fuller LM, Hodgson CL. Functional outcomes and quality of life in heart transplant patients requiring extracorporeal membrane oxygenation. *J Heart Lung Transplant.* 2015;34(4):S73-S74. doi:10.1016/j.healun.2015.01.191

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Physical function after extracorporeal membrane oxygenation in patients pre or post heart transplantation – An observational study

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ABSTRACT

Objective: To describe physical function, leg complications and health-related quality of life (HRQOL) in the three months following extracorporeal membrane oxygenation (ECMO) pre- or post-heart transplantation (HTx).
Background: Little is known about functional recovery following ECMO before or after HTx.
Methods: A 2-year retrospective study in patients who received ECMO pre or post HTx. Strength, mobility, leg complications and HRQOL were recorded to hospital discharge. Six-minute walk distance (6MWD) was assessed at hospital discharge and 3 months.
Results: 25 patients were included, with 80% (20/25) survival to hospital discharge. At ICU discharge, strength and mobility were poor but improved by hospital discharge ($p < 0.001$) despite leg complications in 44% (11/25) of patients. The 6MWD improved over time (mean 203 m, 95% confidence interval 140–265). HRQOL scores were lower than Australian norms ($p < 0.05$).
Conclusion: Patients requiring ECMO pre or post HTx had impaired physical function at ICU discharge and leg complications were common.

Introduction

Extracorporeal membrane oxygenation (ECMO) is mechanical support of the heart and/or lungs for a period of days to weeks by a modified heart-lung machine.[1] The use of ECMO has increased dramatically in the past decade[2] with improvements in technology and survival. Veno-arterial (VA) ECMO has been increasingly used as a rescue therapy for patients in cardiogenic shock both prior to and following heart transplantation (HTx).[3,4] It can be instituted by central or peripheral cannulation. Veno-pulmonary artery (V-PA) ECMO provides short-term right ventricular support for severe right ventricular failure.

Whilst ECMO is a potentially life-saving intervention in a group of patients at high risk of death, it may result in complications such as bleeding, infection, vascular and neurological deficits.[5,6] Lower limb sequelae following femoral vessel cannulation have been reported, and have mostly included vascular injuries[4] and sensory nerve deficits.[7] Motor neurological deficits have rarely been described, and case reports have been limited to the upper limb following axillary artery cannulation.[8] Leg complications related to femoral vessel cannulation may have an impact on physical function and health-related quality of life (HRQOL). To date this has not been investigated.

Abbreviations: APACHE II, acute physiology and chronic health evaluation II; ARDS, acute respiratory distress syndrome; ECMO, extracorporeal membrane oxygenation; HRQOL, health-related quality of life; HTx, heart transplantation; ICU, intensive care unit; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; IMS, ICU mobility scale; LOS, length of stay; LVAD, left ventricular assist device; MCS, mental component score; MRC, medical research council sum-score; PCS, physical component score; SF-36, short-form general health survey; VA, veno-arterial; V-PA, veno-pulmonary artery; VV, veno-venous; 6MWD, six minute walk distance; 6MWT, six minute walk test.

Conflicts of interest: None.

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Femoral vessel cannulation has also been identified as a barrier to early mobilization in patients on ECMO.[9] This may result in prolonged bed rest whilst on ECMO, resulting in muscle weakness.[10] In addition, preadmission comorbidities may have a further deleterious impact on physical function. The relationship between ECMO cannulation strategy, immobility whilst on ECMO, pre-existing comorbidities and physical function has not previously been described.

Although survival following ECMO has improved,[11,12] there are few studies describing physical function, HRQOL and leg complications during the acute period from intensive care unit (ICU) to hospital discharge in patients requiring ECMO. This information may assist in the development of targeted treatment strategies and modify potential risk factors for complications in the future.

The aims of our study were to:

1. Describe the demographic and clinical characteristics of patients requiring ECMO pre or post HTx.
2. Describe physical function in patients that received ECMO pre or post HTx in the acute period from ICU to hospital discharge, and 3 months following discharge from hospital.
3. Describe the type and prevalence of vascular and neurological leg complications in this cohort from the time of ECMO insertion to hospital discharge, and to determine if there was any difference in physical function and HRQOL between those with a leg complication and those without.
4. Describe the HRQOL in this cohort at the time of hospital discharge.

Methods

A retrospective, single-center study was conducted between September 2012 and September 2014 at a tertiary referral hospital for ECMO in Australia which also provides heart and lung transplantation services. Data were extracted from the prospectively updated physiotherapy ECMO database. The sample size was determined pragmatically by the number of subjects in the database over the 2-year study period, which included all of the available data in the database. This study was approved by the Human Research Ethics Committee and no patient consent was required as the study used routinely collected clinical data.

Consecutive patients, aged over 18 years who received ECMO prior to or following HTx were included. Patients who were unable to be weaned from ECMO and required subsequent left ventricular assist device (LVAD) insertion as further bridge to HTx were also included. Patients were excluded if they had any of the following: presence of additional severe chronic organ failure (liver, lung, renal), severe acute brain injury, malignancy, age $>$ 75 years, any other contraindication to HTx or reversible cardiac failure not requiring listing for HTx (bridge to recovery).

ECMO criteria and configuration

Criteria for the use of VA ECMO at our institution have been presented elsewhere.[5] Peripheral VA ECMO involved femoro-femoral cannulae (Medtronic, Minneapolis, MN, USA) percutaneously placed under ultrasound guidance (Fig. 1). A routine ante-grade 8.5 French distal perfusion cannula (Mayo, Rochester, MN, USA) was inserted in all patients at the time of femoral artery cannulation to prevent limb ischemia. Femoral artery cannulation sites were repaired surgically after decannulation. Central VA ECMO was initiated intra-operatively at the discretion of the cardiothoracic surgeon (Fig. 1). V-PA ECMO involved a drainage cannula in the femoral vein and returned ECMO circuit blood to the pulmonary artery via an externalized surgical conduit (Fig. 1). It provided short-term ventricular and respiratory support following LVAD insertion, and decannulation occurred without the need for resternotomy. The ECMO circuit consisted of a Jostra Rotaflow centrifugal pump (Maquet, Rastatt, Germany) and a Quadrox oxygenator (Maquet, Rastatt, Germany).

Variables and measures

Demographic and clinical characteristics were recorded from the database. These included age, gender, etiology of heart failure, ECMO type and duration, ability to wean off ECMO, requirement for subsequent LVAD support, ICU and hospital length of stay (LOS), and in-hospital mortality.

The acute physiology and chronic health evaluation II (APACHE II) score, a severity of illness score with higher scores corresponding to more severe illness, was calculated at ICU admission. Inter-rater reliability for the APACHE II score is high (intraclass correlation coefficient (95% confidence interval) 0.90 (0.84, 0.94)).[13] Comorbidity data was collected on all patients at ICU admission as part of the calculation of the APACHE II score, and included the following categories: cardiovascular disease, respiratory disease, renal failure, liver disease, immune disease, immunosuppressive therapy and insulin dependent diabetes.

The Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) profiles of advanced heart failure,[14] which outlines the level of limitation at the time of implant of mechanical cardiac support, was recorded at the time of ECMO commencement. Despite heterogeneity in the assignment of INTERMACS profiles within and between centers,[15] it remains a useful tool for communication of pre-operative clinical status.[16]

Level of mobility prior to ICU admission was recorded from a retrospective review of the medical histories. Muscle strength was assessed using the Medical Research Council sum-score (MRC) at ICU and hospital discharge. The MRC classifies muscle strength on a 0–5 point ordinal scale ranging from 0 = no contraction to 5 = normal power against full resistance.[17,18] The sum-score includes assessment of three upper limb and three lower limb muscle groups bilaterally to obtain a maximum score of 60.[19] A score of $<$48/60 indicates intensive care acquired weakness.[17,18] Inter-rater reliability of the MRC is very good in critically ill patients (Pearson's r = 0.96).[20] The minimal important difference is 2–3.6 points.[21]

The highest level of mobility was assessed using the ICU mobility scale (IMS) and was recorded at ICU and hospital discharge. The IMS ranges from 0 to 10, with 10 being the best score, and has good inter-rater reliability (Weighted Kappa of 0.83; 95% confidence interval 0.76 – 0.90).[22]

An encouraged six minute walk test (6MWT) was performed following a standardized procedure[23] on discharge from hospital and 3 months post discharge. The 6MWT is a reliable, valid and responsive test for patients with heart failure.[24] The minimal important difference for six minute walk distance (6MWD) is 30 m.[25] All physical function data was collected according to standardized protocols by physiotherapists who underwent training in the collection of these outcome measures.

Leg complications were recorded from a review of the medical histories from the time of ECMO insertion to hospital discharge and included: 1) vascular: surgical wound debridement and repair, thrombectomy, seroma requiring repeated drainage or surgical intervention and vessel stenosis requiring angioplasty/stenting; 2) neurologic: defined as motor and sensory deficit on neurological exam and/or abnormal nerve conduction study.

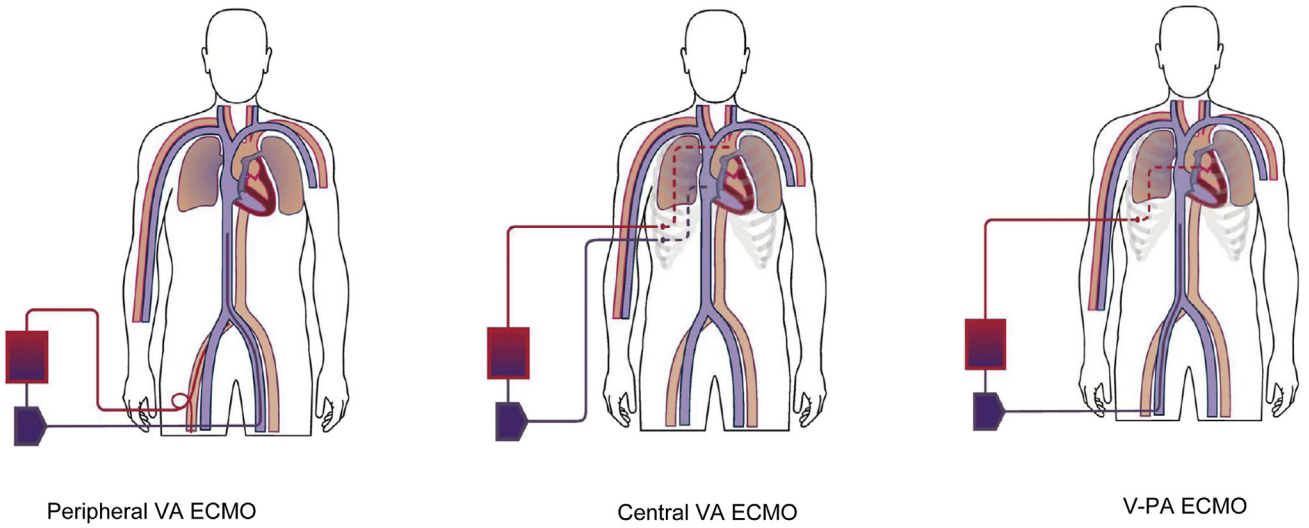

Fig. 1. ECMO configurations used in patients pre or post Heart Transplantation. ECMO, extracorporeal membrane oxygenation; HTx, heart transplantation, VA; veno-arterial; V-PA, veno-pulmonary artery.

The short-form general health survey (SF-36) Version 2 was used to assess HRQOL at hospital discharge. It yields eight domain scores: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. The eight domain scores are combined into two norm based summary measures, providing overall estimates of physical health (physical component score, PCS) and mental health (mental component score, MCS). Domain scores range from 0 (worst) to 100 (best), and are also standardized for population data, where mean ± standard deviation is 50 ± 10 for each domain.[26] The SF-36 is a reliable, valid, and responsive quality of life instrument.[27–29] Mean SF-36 scores were compared with Australian population normative values[30] and patients with acute respiratory distress syndrome (ARDS) requiring veno-venous (VV) ECMO.[31]

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics Version 22 for Windows (SPSS Inc., Chicago, Illinois, USA). Where patients received more than one run of ECMO or the configuration of ECMO was changed, only the first run or configuration was considered for analysis in order to describe ECMO type and duration. Continuous variables were expressed as mean ± standard deviation, and ordinal variables were presented as medians (interquartile ranges). Comparison between groups was performed using the independent *t*-test for continuous data or the Mann Whitney *U* test for nonparametric continuous variables. The chi-square or fisher's exact test was used for categorical variables. To investigate a change over time, a paired *t*-test was performed for continuous data or the Wilcoxon Signed Rank Test for nonparametric data. A two-sided *p*-value of ≤ 0.05 was considered to be statistically significant.

Results

During the 2-year study period, a total of 117 patients underwent ECMO support, of which 25 received ECMO either pre or post HTx. In the majority of patients ($n = 18/25$, 72%), ECMO support was prior to HTx (Fig. 2). Most ($n = 21/25$, 84%) received femoral VA ECMO (Table 1), whilst central VA ECMO and V-PA ECMO were uncommon ($n = 4/25$, 16%). Two patients changed ECMO configuration and four patients had two runs of ECMO.

Patients that underwent ECMO post HTx were significantly more likely to be weaned off ECMO than patients receiving ECMO pre HTx and had a shorter ICU LOS (Table 1). Bridge to HTx directly from ECMO was uncommon ($n = 2/18$, 11%). The majority of patients requiring ECMO pre HTx ($n = 14/18$, 78%) required subsequent LVAD insertion as a further bridge to HTx.

The mean APACHE II score was 22 ± 8. Despite this high severity of illness score, 80% ($n = 20/25$) survived to hospital discharge. The median number of comorbidities at ICU admission was 1.0 (1.0 – 2.0), with cardiovascular disease being the most prevalent comorbidity ($n = 18/25$, 72%). All patients were INTERMACS profile 1 at time of ECMO commencement, indicating critical cardiogenic shock. All of the patients were independently walking without assistance prior to their admission to ICU.

At ICU discharge most survivors ($n = 14/20$, 70%) had strength scores indicating intensive care acquired weakness (MRC < 48/60), however this improved by hospital discharge to near normal levels (Table 2). Functional mobility (IMS) was poor at ICU discharge (median = 7), indicating patients required assistance of two or more people to mobilize. This improved by hospital discharge to a level where patients were independently mobile without a gait aide (median = 10). There was significant improvement in 6MWD from hospital discharge to 3 months post discharge, and 90% of survivors ($n = 18/20$) were discharged directly home. There was no significant difference in physical function outcomes between patients who received ECMO pre versus post HTx.

Leg complications were observed in 44% ($n = 11/25$, Table 3). These included seromas that required multiple surgical interventions or long-term drain *insitu* ($n = 4$), vascular injury requiring thrombectomy ($n = 1$) or angioplasty and stenting ($n = 1$), cannula site infection requiring debridement ($n = 2$), lower motor neuron injury ($n = 3$) and spinal cord injury ($n = 3$). All complications occurred in patients with femoral vessel cannulation. Seromas were only observed in patients who received ECMO post HTx. The three patients who had a spinal cord injury suffered profound shock or cardiac arrest prior to commencement of ECMO. The spinal cord injuries were not detected until after ECMO was removed and sedation weaned. Two of the patients who had a leg complication died on the ward from complications unrelated to ECMO. Patients who had a leg complication had a significantly lower PCS than those

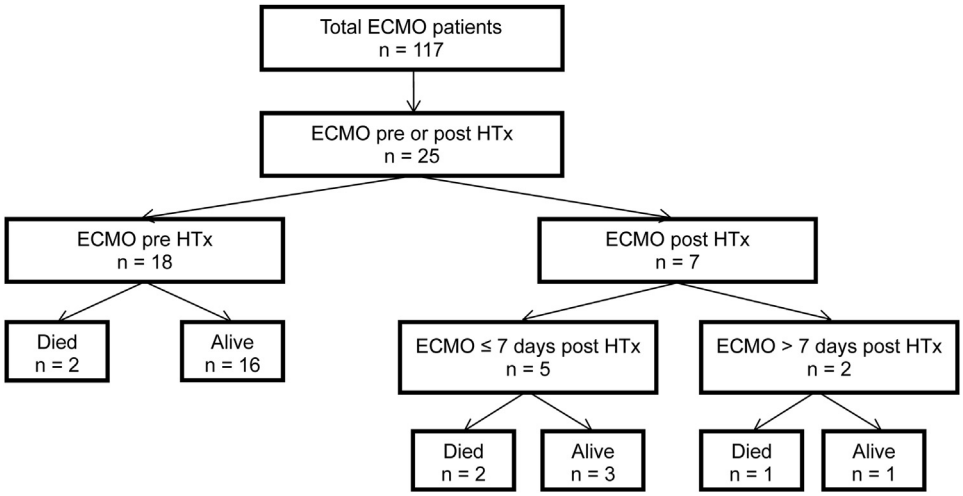

Fig. 2. Flow of patients receiving ECMO pre or post Heart Transplantation 2012–2014. ECMO, extracorporeal membrane oxygenation; HTx, heart transplantation.

who did not have a leg complication (Table 4, $p = 0.05$), and walked a mean of 64 m less in the 6MWT at hospital discharge, however this was not statistically significant (95% confidence interval, −30 to 158, $p = 0.17$). There was no significant difference in ECMO duration between those with or without a leg complication (mean difference 0.95 days, $p = 0.56$).

At hospital discharge, mean SF-36 scores in patients who received ECMO were significantly lower ($p < 0.05$) than in Australian norms in all domains (Fig. 3), but particularly in the domains related to physical health (role physical, physical functioning and bodily pain) and social functioning. Our cohort had similar scores in the domains of role emotional, mental health, and vitality compared to patients with ARDS who received ECMO but had significantly lower scores in the domains of physical functioning, role physical, social functioning and bodily pain (Fig. 3).

Discussion

To our knowledge this is the first study to describe physical function in patients receiving ECMO pre or post HTx. The majority of patients demonstrated severe muscle weakness at ICU discharge indicative of intensive care acquired weakness. Prolonged immobility during ECMO may contribute to this finding. Prolonged immobility is associated with decreased muscle protein synthesis and muscle atrophy,[10] whilst critical illness is associated with an increased catabolic state with up-regulation of pro inflammatory mediators and changes in muscle composition leading to muscle weakness.[32]

Early mobilization in the ICU setting is a potential therapeutic option to improve muscle strength, physical function and quality of survival.[33] Earlier active rehabilitation, including strengthening exercises for the upper and lower limbs and ambulation whilst on ECMO may be an effective intervention to reduce the incidence of intensive care acquired weakness observed in our cohort at ICU discharge. A number of barriers to ambulation whilst on ECMO have been identified in the literature,[9] including femoral cannulation, sedation and mechanical ventilation. The majority of our patients underwent femoral cannulation and was confined to bed whilst on ECMO. The use of alternative cannulation strategies involving vessels in the upper body may improve early ambulation in this group.

With physiotherapy rehabilitation after ICU discharge, our patients showed improvements in muscle strength and mobility status over time, with near normal muscle strength and independent walking by hospital discharge. These results compared favorably with those of 18 survivors of ARDS who underwent VV ECMO,[31] whose age, APACHE score, and ICU LOS resembled those of our ECMO patients and in whom 83% described muscle weakness at hospital discharge and only 67% were ambulant. Our study cohort had a longer hospital LOS compared to the ARDS cohort (41 days versus 28.4 days) possibly allowing for more rehabilitation and better physical function at hospital discharge. Furthermore, muscle strength and mobility were measured directly by the MRC and IMS scales in our study, whereas it was self-reported via telephone interview in the ARDS group. The longer LOS in our cohort may also be related to possible complications specific to HTx, such as rejection, or education related to LVAD or HTx that the ARDS group would not have required.

Premorbid mobility and preadmission comorbidities may not have played a major role in physical function in our cohort. The number of comorbidities at ICU admission in our cohort was low (median 1.0), and may be related to the study cohort being pre or post HTx. Patients are not listed for HTx at our center if they have additional severe chronic organ failure (lung, liver, renal). Although

Table 1
Demographic and clinical characteristics of patients that underwent ECMO pre or post Heart Transplant.

Characteristics of subjects	ECMO pre HTx ($n = 18$)	ECMO post HTx ($n = 7$)	p-value
Age	41.0 ± 15.6	48.4 ± 16.0	0.30
Male n (%)	14 (78)	5 (71)	1.00
Diagnosis			1.00
Ischemic CM	2 (11)	1 (14)	
Non ischemic CM	16 (89)	6 (86)	
ECMO type n (%)			0.15
VA central	0 (0)	1 (14)	
VA peripheral	15 (83)	6 (86)	
V-PA	3 (17)	0 (0)	
ECMO duration (days)	9.5 ± 3.7	7.1 ± 3.3	0.16
Weaning success n (%)	2 (11)	5 (71)	0.007
ICU LOS	21.5 (17.0–21.5)	13.0 (11.0–14.0)	0.002
Hospital LOS	44.0 (35.0–59.0)	33.0 (28.0–78.0)	0.20
Discharge destination n (%)			0.13
Home	15 (83)	3 (43)	
Inpatient rehabilitation	1 (6)	1 (14)	
Died	2 (11)	3 (43)	

Values are presented as mean ± SD, median (interquartile range), or as a number (%). p-value represents difference between pre and post HTx groups.
CM, cardiomyopathy; ECMO, extracorporeal membrane oxygenation; HTx, heart transplant; ICU, intensive care unit; LOS, length of stay; VA, veno-arterial; V-PA, veno-pulmonary artery.

Table 2
Physical function characteristics at ICU and hospital discharge and 3 months post discharge for ECMO patients.

Outcome measures	ICU discharge 19.0 (13–25.5) days	Hospital discharge 40.5 (33–56.5) days	3 months post hospital discharge	*p*-value
Strength				
MRC (/60)	46 ± 7 ($N = 20$)	54 ± 5 ($N = 20$)		<0.001
Mobility level				
IMS (/10)	7 (4–7) ($N = 22$)	10 (9.5–10) ($N = 20$)		<0.001
Functional exercise capacity				
6MWD (meters)		322 ± 81 ($N = 18$)	524 ± 102 ($N = 17$)	<0.001

Values are presented as mean ± SD or median (interquartile range) and *p* values are comparison between time points.
ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IMS, ICU mobility scale; MRC, Medical Research Council sum-score; 6MWD, six minute walk distance.

baseline strength was not assessed in our cohort, a retrospective review of the medical record revealed that all the patients were independently walking without assistance prior to their ICU admission. This would suggest that the poor strength observed at ICU discharge may not have been related to pre-existing deficits.

We have shown that vascular and neurological complications involving the leg were common in our cohort (44%). To our knowledge, our study is the first to report motor neurological complications in the leg following ECMO. Importantly, three patients had lower limb weakness consistent with spinal cord ischemia or infarct, which was confirmed with neurological exam, electrophysiological testing and magnetic resonance imaging in two cases. The mechanism of injury is unclear, however spinal cord ischemia has been reported in other case reports involving femoral artery cannulation.[34] In peripheral VA ECMO the arterial cannula is usually advanced to the level of the iliac arteries or abdominal aorta.[35] Blood supply to the distal spinal cord is variable but typically comes from the Adamkiewicz artery,[34] which arises from the left posterior intercostal artery or posterior lumbar artery off the abdominal aorta. This vessel is vulnerable to any reduction in flow and can lead to loss of function in the lower spinal cord. It is possible that retrograde flow from the ECMO arterial cannula may result in altered flow dynamics in the Adamkiewicz artery. It is unknown whether the motor neurological deficits seen in this study were related to the ECMO itself or the cardiovascular compromise leading to the requirement for ECMO, with all three patients suffering from profound hypo-perfusion or cardiac arrest prior to ECMO insertion. A further mechanism of injury may involve an embolic event at the time of ECMO removal.

Table 3
Leg complications following ECMO.

Patient	All lower limb complications
1	L groin seroma, multiple surgical repairs, drains, interventional radiology
2	R groin seroma requiring surgical drainage, and long-term drain *insitu* Spinal cord ischemia (incomplete injury) – R leg paraparesis
3	L femoral artery thrombectomy. L groin seroma with long-term drain *insitu*. Dense paresthesia umbilicus to bilateral knees.
4	Spinal cord infarct – paraplegia with flaccid paralysis bilateral lower limbs
5	R groin infection requiring vacuum dressing, surgical debridement and washout ×2 L groin seroma and drain *insitu*
6	L foot drop (LMN injury – common peroneal nerve) requiring splint
7	L groin wound breakdown + infection requiring debridement
8	L leg weakness and numbness (LMN injury – femoral nerve)
9	75% stenosis of femoral artery post ECMO requiring angioplasty and stent
10	Spinal cord infarct involving conus medullaris – bilateral paraplegia
11	R Foot drop (LMN injury – common peroneal nerve) requiring splint

ECMO, extracorporeal membrane oxygenation; LMN, lower motor neuron; R, right; L, left.

The vascular and sensory neurological complications were similar to those reported earlier in the literature.[4,7] Impaired wound healing post HTx secondary to immunosuppression and the need for femoral artery surgical repair following ECMO arterial decannulation may be related to the seromas seen in our post HTx cohort. Patients with identified leg complications had worse HRQOL PCS and a lower 6MWD that was clinically significant, which warrants further investigation in a larger study. Longer term monitoring of these leg complications is required to determine if these complications persisted over time. In addition, the impact of early rehabilitation and ambulation whilst on ECMO on muscle strength, function, HRQOL and leg complications warrants further investigation.

HRQOL in our ECMO survivors was impaired at hospital discharge compared to that of Australian norms, revealing problems with work or other daily activities because of physical health and pain, and frequent interference with normal social activities. This may be due to the number of patients in our cohort who required an LVAD as further bridge to HTx. Other studies have also reported on the bridge to bridge strategy, involving ECMO to LVAD to HTx, where waitlist times preclude a direct bridge from ECMO.[3] Previous studies have shown that HRQOL is impaired in patients with an LVAD[36] at hospital discharge and is lower than in patients following HTx,[37] but that it improves over time and as patients are discharged from hospital.[38] HRQOL was only measured at hospital discharge in our cohort and this may partly account for the lower scores.

Our mean SF-36 scores were also significantly lower than survivors of ARDS that underwent VV ECMO.[31] Our cohort had a longer hospital LOS than the ARDS cohort, with the majority of our

Table 4
SF-36 V2 standardized scores at hospital discharge for ECMO patients with and without leg complications.

SF-36 dimension	ECMO without leg complications ($n = 11$)		ECMO with leg complications ($n = 9$)		*p*-value
	Mean	SD	Mean	SD	
Physical functioning	31.59	7.84	27.99	9.24	0.35
Role-physical	20.34	5.42	19.63	3.61	0.73
Bodily pain	40.49	11.26	33.59	9.50	0.15
General health	43.96	8.12	39.34	8.54	0.22
Vitality	40.74	9.70	39.91	8.51	0.84
Social function	25.12	12.86	22.49	11.51	0.63
Role-emotional	40.33	17.30	44.21	10.36	0.55
Mental health	46.68	11.39	41.28	10.82	0.28
PCS	29.76	5.06	25.09	5.33	0.05
MCS	44.23	13.40	44.06	10.98	0.97

ECMO, extracorporeal membrane oxygenation; MCS, mental component score. PCS, physical component score; SF-36 V2, short-form general health survey version 2. *p* values are comparison between groups with and without leg complications.

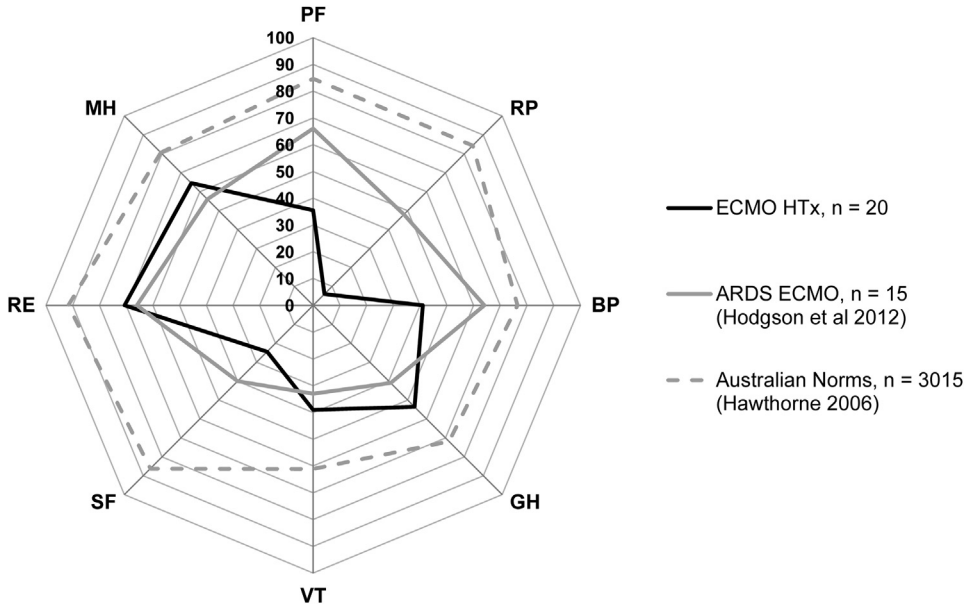

Fig. 3. Comparison of SF-36 scores in patients that receive ECMO versus Australian population norms. ECMO, extracorporeal membrane oxygenation; HTx, heart transplant; ARDS, acute respiratory distress syndrome; SF-36, short-form general health survey (version 2); PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health.

patients geographically isolated from their usual community and this may have impacted on social interaction with family and friends, resulting in the lower score for social functioning. The lower scores in our cohort may also be related to the difference in timing of measurement. HRQOL was measured at hospital discharge in our study, whereas it was measured at a median of 8.4 months post discharge in the Hodgson et al[31] study. This finding is supported by an earlier study of survivors of cardiogenic shock that underwent ECMO, which also had a later follow-up for HRQOL at a median of 11 months post hospital discharge in 28 patients.[7] They reported significantly higher SF-36 scores in patients with longer follow-up, suggesting a time dependent improvement in HRQOL. Our cohort had lower SF-36 scores in the domains related to physical function and social function than the patients in the Combes et al[7] study, however an earlier version of the SF-36 (Version 1) was used in their study, making direct comparisons difficult.

Our study has several limitations. Firstly, our study is a single-center retrospective study. Second, our population of patients was a mixed cohort receiving both central, peripheral and V-PA ECMO for a variety of medical and post heart transplant causes, however this was representative of the population of patients requiring HTx at our centre. Detailed evaluation of the different populations is warranted in future, larger studies. Thirdly, our results may not reflect the effects of ECMO alone, as a significant proportion of our cohort required an LVAD as further bridge to HTx. To our knowledge this is the first study to describe physical function, HRQOL and leg complications in patients who required ECMO pre or post HTx, however the small numbers precluded any detailed subgroup analyses. The small sample size has not allowed us to single out statistically significant differences between groups that could be clinically relevant, and as such our results should be seen as hypothesis generating and need to be repeated in larger trials. Finally, strength and HRQOL prior to the implementation of ECMO was not objectively assessed as patients often presented acutely, however a retrospective review of the medical history revealed all patients were independently mobile without a gait aide prior to the ICU admission. This may suggest that they did not have significant strength limitations at the time of ICU admission. Potential benefits from this study include new knowledge about the physical function and HRQOL of patients who have undergone ECMO pre and post HTx which may inform future research. To our knowledge, our study is the first to report on the prevalence and impact of leg complications on physical function and HRQOL during the acute post ECMO period, illustrating the importance of early detection and medical/surgical care of these complications.

Conclusions

Patients requiring ECMO pre or post HTx had poor physical function at ICU discharge and leg complications were common. Physical function improved by hospital discharge with the majority of patients discharged directly to home. HRQOL was poor at hospital discharge and warrants further investigation with longer term follow-up. Larger studies are required to determine the impact of leg complications on physical function and HRQOL in patients undergoing femoral VA ECMO.

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Chapter 4: PHYSICAL FUNCTION IN SUBJECTS REQUIRING EXTRACORPOREAL MEMBRANE OXYGENATION BEFORE OR AFTER LUNG TRANSPLANTATION

4.1. Declaration of authorship: Chapter 4

Student's declaration:

The nature and extent of contributions to Chapter 4 of this thesis are as follows:

Name	Nature of contribution	Contribution
Kate Hayes	Study concept and design, ethics application, data collection and analysis, manuscript preparation and revision for publication	80%
Carol Hodgson	Study concept and design, data analysis, drafting and revision of manuscript	5%
Vincent Pellegrino	Study design, revision of manuscript	3%
Greg Snell	Study design, revision of manuscript	2%
Benjamin Tarrant	Data collection and revision of manuscript	2%
Louise Fuller	Data collection and revision of manuscript	2%
Anne Holland	Study concept and design, data analysis, drafting and revision of manuscript	6%

Supervisor's declaration:

I hereby certify that the declaration above is a correct reflection of the extent and nature of contributions made toward Chapter 4 of this thesis by the student and all listed co-authors.

Name of supervisor	Signature
Anne Holland	

4.2. Preface to Chapter 4

Human Research Ethics Committee approvals for this study were granted from the Alfred Hospital Ethics Committee (Project number 314/14) and the La Trobe University Faculty of Health Sciences Ethics Committee (FHEC14/253). This ethics submission covered the studies presented in Chapters 3 and 4, describing functional outcomes in heart transplant patients and then lung transplant patients that received ECMO. See Appendix 1 for the ethics approval forms.

The observational study presented in Chapter 4 was published in *Respiratory Care* and is presented in its published format.

Hayes K, Hodgson CL, Pellegrino VA, Snell G, Tarrant B, Fuller LM, Holland AE. Physical function in subjects requiring extracorporeal membrane oxygenation before or after lung transplantation. *Respir Care.* 2018;63(2):194-202. doi:10.4187/respcare.05334

See Appendix 2 for permission for inclusion in this thesis

Aspects of this study were presented at the following conference:

Oral presentation:

1. International Society of Heart and Lung Transplantation (ISHLT) Annual Scientific Meeting in Washington, 29/04/2016.

Title: Functional Outcomes and Quality of Life in Patients Undergoing Extracorporeal Membrane Oxygenation Pre or Post Lung Transplantation - An Observational Study.

Abstract: the abstract related to the oral presentation of this study was published as follows:

Hayes K, Hodgson CL, Pellegrino VA, Snell G, Tarrant B, Fuller LM, Holland AE. Functional outcomes and quality of life in patients undergoing extracorporeal membrane oxygenation pre or post lung transplantation-an observational study. *J Heart Lung Transplant.* 2016;35(4 SUPPL. 1):S147. doi:10.1016/j.healun.2016.01.406

Physical Function in Subjects Requiring Extracorporeal Membrane Oxygenation Before or After Lung Transplantation

Kate Hayes PT MPhysio, Carol L Hodgson PT PhD, Vincent A Pellegrino MD, Greg Snell MD, Benjamin Tarrant PT, Louise M Fuller PT, and Anne E Holland PT PhD

BACKGROUND: Extracorporeal membrane oxygenation (ECMO) is used as a rescue therapy before and after lung transplantation, but little is known about functional recovery or complications after ECMO in this cohort. This study aimed to describe early physical function and leg complications in subjects who received ECMO before or after lung transplantation, and to compare functional outcomes to a matched cohort of subjects who did not require ECMO. METHODS: A retrospective study was conducted over 2 years. Highest mobility level was assessed, in both the ECMO and non-ECMO groups, prior to ICU admission, at ICU discharge, and at hospital discharge, while 6-min walk distance was measured at hospital discharge and at 3 months. Strength was assessed at ICU discharge and at hospital discharge in the ECMO subjects only, and leg complications were recorded up until hospital discharge. RESULTS: 17 subjects (mean age 43 ± 13 y; 65% (11 of 17 subjects) female) required ECMO before or after lung transplant. Survival to hospital discharge was 82% (14 of 17 subjects). At ICU discharge, strength and mobility levels were poor, but both improved by hospital discharge ($P < .001$). Leg complications were reported in 50% of survivors (7 of 14 subjects). ECMO survivors spent longer in the ICU ($P < .001$) and hospital ($P = .002$) and had worse physical function (ie, lower mobility level at ICU discharge, mean difference −1, $P = .02$; 6-min walk distance at hospital discharge: mean difference −99 m, $P = .004$) than lung transplant recipients not requiring ECMO ($n = 28$). CONCLUSIONS: In subjects requiring ECMO before or after lung transplantation, 82% survived to hospital discharge, but leg complications were common and physical function was poor at ICU discharge. Physical function improved over time, however subjects who required ECMO had a longer period of hospitalization and worse physical function at ICU and hospital discharge than those who did not require ECMO.
Key words: extracorporeal membrane oxygenation; lung transplantation; rehabilitation; quality of life.
[Respir Care 2018;63(2):194–202. © 2018 Daedalus Enterprises]

Introduction

Lung transplantation is an established therapy for select patients with end-stage lung disease. The number of lung transplants performed worldwide has steadily increased,[1] with the demand for lung transplantation outnumbering the donor organ supply, resulting in waiting list mortality.

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Ms Hayes presented a version of this paper at the 36th Annual Meeting of the International Society for Heart and Lung Transplantation, on April 29, 2016, in Washington, DC.

The authors have disclosed no conflicts of interest.

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In this setting, extracorporeal membrane oxygenation (ECMO) may be considered as a bridge to lung transplantation until compatible donor lungs become available.

ECMO provides temporary support of heart and/or lung function by a modified cardiopulmonary bypass machine.[2] It can be inserted in a venovenous configuration for pure respiratory support or in a venoarterial configuration for combined cardiac and respiratory support. Early reports of ECMO as a bridge to lung transplantation were not favorable,[3] and many centers considered ECMO and mechanical ventilation as a contraindication to lung transplantation. In recent years, with significant improvement in ECMO technology, several studies have shown promising outcomes related to the use of ECMO as a bridging strategy[4-6] as well as a rescue therapy after lung transplantation for primary graft dysfunction or other complications such as severe pulmonary hypertension.[7,8]

ECMO may involve cannulation of the femoral vessels, and lower limb sequelae have been reported in patients who required ECMO before or after heart transplantation.[9] These leg complications may have an impact on physical function, participation in rehabilitation, and health-related quality of life (HRQOL), but to date they have not been reported in patients before or after lung transplantation with differing ECMO configurations. Although survival after ECMO has improved, little is known about the early physical function of patients who require ECMO before or after lung transplantation, and whether it differs from transplant recipients not requiring ECMO. In addition, there may be a difference between the physical function outcomes of patients who require ECMO before versus after lung transplantation. This information may assist in the development of targeted treatment strategies and modification of potential risk factors for future complications.

The aims of this study were to describe early physical function and leg complications in subjects who received ECMO before or after lung transplantation, and to compare physical function with lung transplant recipients not requiring ECMO.

QUICK LOOK

Current knowledge

Extracorporeal membrane oxygenation (ECMO) is increasingly being used as a rescue therapy for patients both prior to and after lung transplantation. Survival after ECMO in this population has improved, but little is known about the early physical function, leg complications, or health-related quality of life of survivors and whether it differs between those requiring ECMO before versus after transplant. It is also unclear whether physical function outcomes are different for lung transplant patients not requiring ECMO.

What this paper contributes to our knowledge

Subjects requiring ECMO before or after lung transplantation had very poor muscle strength and mobility levels at ICU discharge. Physical function improved by hospital discharge and continued to improve after discharge from hospital. Lung transplant recipients requiring ECMO required longer periods of mechanical ventilation, spent longer in the ICU and hospital, and had worse physical function than non-ECMO subjects. ICU stay was the only significant predictor of physical function at hospital discharge. Vascular and sensory neurological leg complications were common in subjects who underwent ECMO via femoral vessel cannulation and accounted for 10% of hospital readmissions in the first year after lung transplantation.

Methods

A retrospective, single-center study was conducted between September 2012 and September 2014 at the Alfred Hospital in Melbourne, Australia, a tertiary referral hospital for ECMO in Australia, which also provides a lung transplantation program. This work was supported by an Australian Government Research Training Program Scholarship. This study received local ethics approval. Data were extracted from the prospectively updated physiotherapy ECMO database and hospital transplant database. Consecutive subjects, aged > 18 y who received ECMO before or after lung transplantation were included. Patients were excluded if they did not meet the criteria for ECMO and lung transplantation, including the presence of any additional severe chronic organ failure (liver, cardiac, renal), acute brain injury, recent malignancy, age > 70 y, any other contraindication to lung transplantation or reversible respiratory failure not necessitating listing for lung transplantation. All lung transplant patients who did not receive ECMO over the same time period were identified from the hospital transplant database and formed a comparison group for functional outcomes. They were matched (2:1) with the ECMO group for age (± 5 y) and gender.

ECMO Criteria and Configuration

The decision to use ECMO was made by a team composed of ECMO-trained intensive care specialists, lung transplant physicians, and cardiothoracic surgeons. Criteria for the use of ECMO were according to established hospital protocols.[10] Choice of ECMO configuration was determined by the clinical need and anatomical limitations of each subject. In hemodynamically stable subjects, venovenous ECMO was provided via a dual-lumen cannula

(Avalon, Maquet-Getinge, Rastatt, Germany) in the right internal jugular vein[11] or percutaneously placed femoro-femoral cannulae (Medtronic, Minneapolis, Minnesota) inserted under ultrasound guidance. Where concomitant cardiac support was required, peripheral venoarterial ECMO was delivered through percutaneously placed femoro-femoral cannulae under ultrasound guidance. This routinely included insertion of an ante-grade 8.5 French distal perfusion cannula (Mayo, Rochester, Minnesota) at the time of ECMO commencement to prevent limb ischemia. Femoral artery cannulation sites were repaired surgically after decannulation. The ECMO circuit consisted of a Jostra Rotaflow centrifugal pump (Maquet-Getinge) and a Quadrox oxygenator (Maquet-Getinge).

Routine Care and Medications

Our approach to steroid use before lung transplant is to prescribe steroids only for patients with pulmonary fibrosis or those requiring re-transplant; and these prescriptions are low in dose (<10 mg prednisolone per day). After lung transplant, all subjects received steroids (2 × 500 mg prednisolone intra-operatively, 150 mg on day 1 postoperatively and 1 mg/kg thereafter, reducing to 20 mg by 5 mg per day, and typically still at 15 mg by 3 months).

At our center, ECMO prior to lung transplantation requires that patients be awake and spontaneously breathing without ventilator support, therefore sedation and neuromuscular blockers were not used routinely. Subjects who required ECMO after transplantation were universally sedated and mechanically ventilated to facilitate safe lung ventilation. Daily sedation targets were generally aimed at a Richmond Agitation and Sedation Scale (RASS)[12] score of 0 to −2 with daily sedation breaks. Continuous neuromuscular blockers were not routine, although short-term paralysis was occasionally used to facilitate procedures where required. A retrospective review of the medical history was used to check for adherence to the above protocol.

Clinical and Demographic Characteristics

Demographic and clinical characteristics were recorded from the database and included age, gender, etiology of lung disease, ECMO type and duration, ICU and hospital length of stay (LOS), and in-hospital mortality. The Acute Physiology and Chronic Health Evaluation II (APACHE II) score was calculated at ICU admission. Development of organ system dysfunction was recorded during the ICU stay from a retrospective review of the medical histories. Multiorgan dysfunction syndrome was defined as the concurrent dysfunction of 2 or more organ systems not involved in the disorder that resulted in ICU admission.[13] Hospital readmissions, LOS, and cause for readmission were recorded for the first year after lung transplantation. Scheduled readmissions for routine follow-up (eg, endobronchial biopsy) were excluded.

Physical Function

All physical function data were collected according to standardized protocols by trained physiotherapists. The highest level of subject mobility was recorded in the week prior to ICU admission, and at ICU and hospital discharge using the ICU mobility scale (IMS). This was recorded in both the ECMO and non-ECMO lung transplant groups. The IMS measures the highest level of mobility on a scale of 0 to 10, with 10 being the best score.[14] While on ECMO, the highest level of mobility achieved was also recorded using the IMS. Where subjects continued on to transplant, 6-min walk distance (6MWD) was measured using a standardized procedure[15] at hospital discharge and at 3 months after discharge, and results were compared between the ECMO and non-ECMO lung transplant groups. Muscle strength was assessed in the ECMO subjects using the Medical Research Council sum-score (MRC) at ICU and hospital discharge. The MRC includes isometric strength assessment of 3 upper limb and 3 lower limb muscle groups bilaterally on a 0–5-point ordinal scale to obtain a maximum score of 60.[16] A score of < 48 indicates ICU-acquired weakness.[17,18] Muscle strength was not assessed in the non-ECMO cohort.

Standard care rehabilitation before lung transplant consisted of out-patient supervised exercise training classes 2–3 times a week while on the transplant waiting list. The content of these sessions was based on established pulmonary rehabilitation guidelines.[19]

Our standard rehabilitation program for patients after lung transplant, including those requiring ECMO, was initiated in the ICU as early as the first postoperative day with the goal of achieving the highest level of mobility each day and progressing to ambulation where possible. While on ECMO, rehabilitation began with resistance and range of motion exercises for the upper and lower limbs, progressing to sitting, standing, and, ultimately, ambulation, as medical stability allowed. When patients were discharged from ICU after lung transplantation and were able to independently mobilize on the ward, they commenced 12 weeks of supervised, gym-based, aerobic and strengthening exercises for 1 h, 3 times a week.

Leg Complications

Leg complications were recorded from the time of ECMO commencement until hospital discharge and included vascular complications (eg, multiple vascular repairs, fasciotomy, embolectomy, seroma requiring repeated drainage or surgical intervention and limb amputation during or after ECMO) and neurologic complications (eg, defined as

motor or sensory deficit on neurological exam, abnormal nerve conduction study, magnetic resonance imaging).

Health-Related Quality of Life

HRQOL was assessed in the ECMO group at hospital discharge using the Short-Form General Health Survey (SF-36) Version 2. The SF-36 yields 8 domain scores: physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. The 8 domain scores are combined into 2 norm-based summary measures, providing overall estimates of physical health (physical component score) and mental health (mental component score). Domain scores are presented as percentage scores ranging from 0 (worst) to 100 (best), and norm-based scores are standardized for population data, where mean ± SD is 50 ± 10.[20] To illustrate the degree of impairment and the domains particularly affected, median SF-36 scores were compared with Australian normative values.[21] HRQOL was not assessed in the non-ECMO group.

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics Version 22 for Windows (SPSS, Chicago, Illinois). Continuous variables were expressed as mean ± SD, and ordinal variables were presented as medians [interquartile ranges (IQR)]. Comparison between groups was performed using independent *t* tests for continuous data or Mann-Whitney U tests for nonparametric continuous variables. The chi-square or Fisher exact test was used for categorical variables. To investigate change over time, a paired *t* test was performed for continuous data or the Wilcoxon signed-rank test for nonparametric data. Results were considered statistically significant at $P < .05$. Univariate analyses were undertaken to determine the association between each potential predictor variable and 6MWD at hospital discharge. Variables demonstrating $P < .2$ on univariate analysis were entered into a multiple linear regression model. When variables were found to be collinear (eg, ICU LOS, ventilation days, hospital LOS), only one was included in the model (ICU LOS).

Results

Over the 2-year study period, a total of 117 patients underwent ECMO support, of which 17 (15%) received ECMO either before or after lung transplantation; 7 before lung transplant and 10 after lung transplant (Fig. 1). The majority of subjects (15 of 17, or 88%) underwent femoral vessel cannulation (Table 1). The median duration of mechanical ventilation was 7.5 d (IQR 4.0–15.0). Three subjects (1 with ECMO before lung transplant and 2 with ECMO after lung transplant) had multiorgan dysfunction

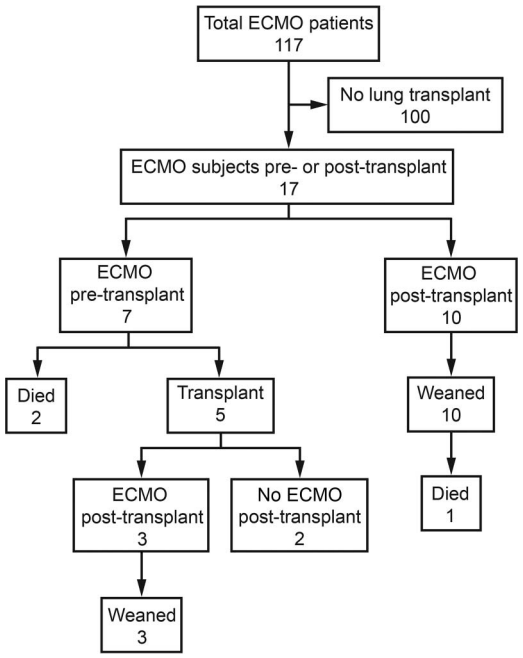

Fig. 1. Flow chart. ECMO = extracorporeal membrane oxygenation.

syndrome. Subjects who underwent ECMO before lung transplant had a higher APACHE II score than subjects receiving ECMO after lung transplant (Table 1). Of the 7 subjects who received ECMO before lung transplant, 2 required deep sedation (RASS = −4), intubation, and ventilation and became ineligible for transplant and were palliated. The remaining 5 subjects were managed per the routine sedation and paralysis protocol before lung transplant. Six of the subjects requiring ECMO after lung transplant required deep sedation (RASS = −4) while on ECMO, with the remaining 4 subjects having a RASS score between −1 and −2 as per protocol; none received continuous neuromuscular blockers after transplant.

Overall survival to hospital discharge was 82% ($n = 14$); 2 subjects died while on ECMO prior to lung transplant, and 1 subject died after lung transplant in the ICU from complications unrelated to ECMO. All subjects who survived to hospital discharge were alive 1 year after lung transplantation.

In the week prior to ICU admission, all subjects who required ECMO after lung transplant ($n = 10$) were ambulating independently with or without a gait aide, and 5 subjects were attending pre-transplant rehabilitation. In comparison, subjects who required ECMO before lung transplant were more debilitated; 1 subject was bed-bound in the 48 h prior to start of ECMO, 2 subjects were limited to transferring from the bed to an armchair, while the remaining 4 subjects were ambulating with or without a gait aide on the ward. All of the non-ECMO subjects

Table 1. Demographic and Clinical Details of Subjects Who Underwent ECMO Before or After Lung Transplantation

	ECMO Before Lung Transplant ($n = 7$)	ECMO After Lung Transplant ($n = 10$)	P
Age, y	42.1 ± 11.5	44.1 ± 14.2	.77
Female, *n* (%)	5 (71)	6 (60)	> .99
ECMO duration, d	10.0 (4.5–16.0)	5.0 (4.0–6.0)	.35
ICU LOS, d	17.0 (7.5–24.0)	12.0 (8.0–36.0)	.85
Hospital LOS, d	48.8 ± 25.5	35.2 ± 16.1	.24
APACHE II	24.0 (20.0–25.5)	14.5 (14.0–17.0)	.001
Diagnosis, *n* (%)			.07
Cystic fibrosis/bronchiectasis	4 (57)	1 (10)	
COPD, asthma, and obliterative bronchiolitis	1 (14)	4 (40)	
Pulmonary hypertension	0 (0)	4 (40)	
Pulmonary fibrosis	1 (14)	1 (10)	
Re-transplant	1 (14)	0 (0)	
ECMO type, *n* (%)			.02
Venoarterial femoral	1 (14)	8 (80)	
Venovenous femoral	4 (57)	2 (20)	
Venovenous dual lumen internal jugular vein	2 (29)	0 (0)	
In-hospital mortality, *n* (%)	2 (29)	1 (10)	.54
Discharge destination, *n* (%)			.51
Home	5 (71)	7 (70)	
In-patient rehabilitation	0 (0)	2 (20)	

Values are presented as mean ± SD, median (interquartile range), or as a number (%). P values represent the difference between before- and after-transplant groups.
ECMO = extracorporeal membrane oxygenation
LOS = length of stay
APACHE II = Acute Physiology and Chronic Health Evaluation II

($n = 28$) were ambulating independently with or without a gait aide in the week prior to ICU admission.

All subjects who required ECMO after lung transplant ($n = 10$) were sedated, ventilated, and resting in bed for the duration of ECMO, and they received only passive range of motion exercises of the upper and lower limbs. Two subjects who required ECMO before lung transplant mobilized out of bed while on ECMO, either to transfer from the bed to a chair or to march in place at the bedside. Both of these subjects had ECMO cannulation of the neck vessels via a dual-lumen cannula. Two more subjects who required ECMO before lung transplant were awake on ECMO and participated in active strength exercises of the upper and lower limbs in bed, while the remaining 3 subjects received passive range of motion exercises as they were sedated or medically unstable for the duration of ECMO. The main reasons for not mobilizing out of bed while on ECMO were venoarterial femoral cannulation, deep sedation, mechanical ventilation, and medical instability.

Lung transplant subjects who required ECMO had more days of mechanical ventilation and a longer ICU and hospital LOS than those who did not require ECMO (Table 2). The highest mobility level achieved at ICU discharge was also lower in the ECMO lung transplant group (IMS median 6) compared to the non-ECMO group (IMS median 7). This translates to the ECMO lung transplant subjects being limited to marching in place at the bedside versus the non-ECMO subjects ambulating away from the bedside with the assistance of 2 or more people at ICU discharge. This improved by hospital discharge in both groups (median = 10) to a level where subjects were independently walking without a gait aide (Table 2). There was more variability in the mobility levels of subjects in the ECMO group (IMS 7−10) compared to the non-ECMO group (IMS 9–10). The ECMO group took longer to reach mobility milestones than the non-ECMO group.

The ECMO lung transplant cohort had a lower 6MWD at hospital discharge (mean difference −99 m, 95% CI −33 to −165, $P = .004$). In a multiple regression analysis that included ICU LOS, group (ECMO vs no ECMO), and diagnosis (cystic fibrosis vs no cystic fibrosis), a longer ICU LOS was the only significant predictor of lower 6MWD at hospital discharge (standardized beta = −.50, $P = .004$). Use of ECMO was not an independent predictor in this model (standardized beta = 0.11, $P = .50$), reflecting the much longer ICU LOS in the ECMO group (Table 2). Both groups had significantly improved their 6MWD by 3 months after discharge ($P < .001$), with no differences between groups at this time point.

Muscle strength at ICU discharge was poor in the ECMO cohort (MRC score 44 ± 10), with 64% of survivors (9 of 14 subjects) having an MRC strength score of < 48/60, indicating ICU-acquired weakness. Muscle strength improved by hospital discharge but remained below normal

Table 2. Lung Transplant Survivors Who Underwent EMCO vs No ECMO, Matched for Age and Gender

	ECMO (n = 14)	No ECMO (n = 28)	P
Age, y	41.8 ± 12.8	41.2 ± 13.4	.90
Female, n (%)	8 (57.1)	16 (57.1)	> .99
Hospital data			
APACHE II	16.5 (14.0–20.0)	14.0 (12.0–20.0)	.16
Ventilation, d	5.0 (3.5–14.0)	1.0 (1.0–1.5)	< .001
ICU LOS, d	15.0 (8.0–26.0)	5.0 (3.0–7.5)	< .001
Hospital LOS, d	40.1 ± 20.1	19.2 ± 5.8	.002
Diagnosis, n (%)			.07
Cystic fibrosis/bronchiectasis	5 (35.7)	18 (64.3)	
COPD, asthma, and obliterative bronchiolitis	4 (28.6)	5 (17.9)	
Pulmonary hypertension	4 (28.6)	1 (3.6)	
Pulmonary fibrosis	1 (7.1)	4 (14.3)	
Physical function			
IMS ICU at discharge	6 (5–7)	7 (6–8)	.02
IMS at hospital discharge	10 (9–10)	10 (10–10)	.006
6MWD at hospital discharge, m	285 ± 112	384 ± 93	.004
6MWD at 3 months, m	541 ± 133	584 ± 67	.32
Discharge destination, n (%)			.11
Home	12 (85.7)	28 (100)	
In-patient rehabilitation	2 (14.3)	0 (0)	

Values are presented as mean ± SD, median (interquartile range), or as a number (%). P values represent the difference between ECMO versus no ECMO groups.
ECMO = extracorporeal membrane oxygenation
APACHE II = Acute Physiology and Chronic Health Evaluation II
LOS = length of stay
IMS = ICU mobility scale
6MWD = 6-min walk distance

levels (mean improvement MRC 11, 95% CI 7–15, $P < .001$). There was no significant difference in physical function outcomes between subjects who underwent ECMO before versus after lung transplantation.

Leg complications were observed in 50% of ECMO survivors (7 of 14 subjects), including vascular and sensory neurological injuries (Table 3). The vascular injuries occurred in 6 of 9 subjects who underwent femoral venoarterial ECMO, while the neurological injuries were seen in subjects who underwent femoral venoarterial or venovenous ECMO. The neurological injuries were confined to sensory deficits, with no motor deficits noted. There was no significant difference in 6MWD or SF-36 scores between subjects who had a leg complication compared to those who had no complication. All survivors who had a leg complication were able to complete the 12-week post-transplant rehabilitation program, with only minor modifications required; lower limb resistance exercises including squats and leg press exercises were removed for those with vascular complications.

Subjects undergoing ECMO had lower SF-36 scores at hospital discharge than Australian norms across all domains except role emotional (Fig. 2). The SF-36 physical component score was also lower in our cohort than Australian norms (mean difference = 24.07, $P = .003$), while there was no difference for the mental component score.

Table 3. Leg Complications After ECMO

Subject	ECMO Type	Leg Complication
1	Venoarterial	Left femoral artery thrombectomy and vein patch repair of false aneurysm
2	Venoarterial	Right femoral artery multiple vascular surgeries, ilio-popliteal bypass, ischemic right foot with ongoing infection leading to amputation of toes
3	Venoarterial	Left groin seroma with long-term drain in situ; dense paresthesia left thigh
4	Venoarterial	Right groin hematoma and infection; right femoral artery reconstruction and vein patch repair
5	Venoarterial	Stenosis of external iliac vein resulting in significant left leg edema, managed conservatively
6	Venovenous	Right leg paresthesia and neurogenic pain
7	Venoarterial	Right groin seroma and right thigh numbness, bilateral pins and needles

ECMO = extracorporeal membrane oxygenation

The majority of ECMO survivors (79%, 11 of 14 subjects) required hospital readmission within the first year after lung transplantation, with 39 readmissions in total,

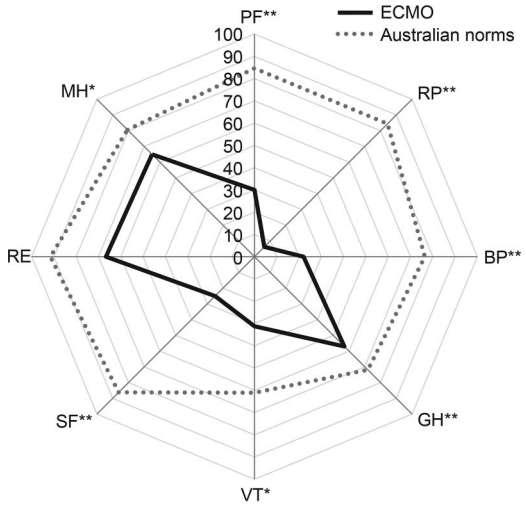

Fig. 2. Comparison of SF-36 scores in lung transplant subjects who received extracorporeal membrane oxygenation (ECMO, $n = 11$) versus Australian population norms (data from Reference 20, $N = 3{,}015$). SF-36, Short-Form General Health Survey (version 2); PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health. $^{**}P < .005$, $^{*}P < .05$.

including 8 subjects who required multiple readmissions. The median number of readmissions was 2 (IQR 1–4) with a median LOS of 7 d (IQR 4–17). The causes for readmission were chest infection (36%, 14 of 39 subjects), rejection (21%, 8 of 39 readmissions), lower limb vascular complications related to ECMO (10%, 4 of 39 readmissions), and miscellaneous (33%, 13 of 39 readmissions).

Discussion

To our knowledge, this is the first study to describe early physical function outcomes in subjects undergoing ECMO before or after lung transplantation, compared to those who did not require ECMO. The majority of the ECMO subjects demonstrated severe muscle weakness at ICU discharge, indicative of ICU-acquired weakness. The cause of this weakness is likely multifactorial, with an interplay between preexisting muscle weakness associated with chronic lung disease[22,23] and critical illness requiring ECMO. Pre-morbid weakness prior to ECMO may be a factor; however, only 1 subject was bed-bound in the 48 h prior to ECMO commencement, and the majority of subjects were ambulating independently. The grading of muscle weakness prior to the initiation of ECMO is unknown because this was not objectively assessed due to the acute presentation of subjects to ICU.

A number of factors have been associated with the development of ICU-acquired weakness[18] and may be related to the worse physical function in the ECMO group. These include differences between the groups in the use of steroids and neuromuscular blockers, presence of multiorgan dysfunction syndrome, sedation levels and muscle inactivity levels. The use of steroids post lung transplant was the same between the groups and therefore unlikely to be a contributory factor. Continuous neuromuscular blockade was not used in either group and is therefore unlikely to be a confounding factor and multiorgan dysfunction syndrome was not common in either group. Both groups had similar APACHE II scores at ICU admission, but the ECMO group required a longer period of sedation and mechanical ventilation and longer ICU LOS. A longer period of immobilization related to being on ECMO may have been a contributing factor to the lower functional level. Prolonged immobility is associated with decreased muscle protein synthesis and muscle atrophy,[24] while critical illness is associated with an increased catabolic state with up-regulation of pro inflammatory mediators and changes in muscle composition leading to muscle weakness.[25]

The majority of subjects requiring ECMO underwent femoral cannulation, which may have been a barrier to early mobilization. Only two subjects mobilized out of bed while on ECMO, both of whom had dual lumen cannula. The majority were sedated and mechanically ventilated for the duration of ECMO, including all subjects that required ECMO post lung transplant. Previous studies have reported that femoral cannulation, sedation and mechanical ventilation are barriers to the early mobilization of ECMO patients,[26,27] and there are no published studies to date describing the ambulation or out of bed rehabilitation of patients with femoral venoarterial ECMO. Over half of the subjects in our study underwent femoral venoarterial ECMO and required higher sedation levels than our protocol aims. Recent studies have reported higher levels of mobility while on ECMO in comparison to our study, but they included awake subjects that had upper body cannulation (dual lumen cannula) rather than femoral, venovenous rather than venoarterial ECMO, and not mechanically ventilated.[28-30] Whereas our study included both pre and post lung transplant ECMO patients, these recent studies consisted mostly of bridge to lung transplant subjects.[28-30]

With physiotherapy rehabilitation, our ECMO subjects showed improvements in muscle strength and mobility status over time, with near normal muscle strength and independent walking by hospital discharge. These results compared favorably with those of 18 survivors of ARDS that underwent venovenous ECMO,[31] in whom 83% described muscle weakness at hospital discharge and only 67% were ambulant. Our study cohort had similar APACHE II scores but a shorter ECMO duration [median 5 d (IQR 4–10) versus 11 d (IQR 4–16)]. The ARDS cohort may have experienced a longer period of immobilization as a result of the prolonged ECMO duration. Our study cohort also had a longer hospital LOS compared to the ARDS cohort (40.1 d vs 28.4 d). Discharge from ICU and hospital

is determined by medical readiness and is not reliant on the achievement of a specified functional status. If patients are medically ready for discharge but have not achieved premorbid level of function, they are transferred to another facility for in-patient rehabilitation. It may be that the lung transplant cohort had ongoing medical issues that were not present in the ARDS group and thus led to the increased hospital LOS. The longer hospital LOS in the lung transplant cohort may also have allowed for more rehabilitation once out of ICU, which may account for the higher level of physical function and higher discharge rate direct to home (86% vs 44%).

HRQOL in our ECMO survivors was impaired at hospital discharge compared to that of Australian norms, revealing problems with work or other daily activities because of physical health and pain. HRQOL was only measured at hospital discharge in our ECMO cohort, which may partly account for the lower scores. Other studies reporting on HRQOL in ECMO survivors[32] have reported significant improvements in HRQOL as time from hospital discharge increases, and longer-term follow-up is warranted in this population. HRQOL was not assessed in the non-ECMO lung transplant subjects, therefore comparison between the groups is not possible but is warranted in future studies.

Among the 14 survivors, 7 (50%) reported complications involving the lower extremity. Six subjects (43%) developed vascular complications, which occurred in over half of subjects (67%, 6 of 9 subjects) who had femoral venoarterial ECMO. This rate is higher than that reported in a study of 101 subjects requiring femoral venoarterial ECMO.[33] Aziz et al[33] reported a vascular complication rate of 18%, using cannulation techniques very similar to that described in our study. Our cohort was entirely composed of lung transplant patients, whereas the etiology of the subjects in the Aziz et al[33] study is unclear but appears to be a mix of cardiogenic shock and patients with ARDS. Impaired wound healing after lung transplant secondary to immunosuppression and the need for femoral artery surgical repair after ECMO arterial decannulation may be related to the higher complication rate seen in our lung transplant cohort.

Although our study showed no significant difference in 6MWD or HRQOL between subjects with a leg complication and those without, this may be due to the small sample size and warrants further investigation in a larger cohort of ECMO patients. The impact of leg complications on participation in post-transplant rehabilitation also was minimal, with only minor modifications to the exercise program required. A small percentage (10%) of readmissions in the year following lung transplantation was directly related to vascular complications related to ECMO. Longer-term monitoring of these leg complications is required to determine whether these complications persisted or lessened over time. In addition, the impact of early, more intensive rehabilitation during the ICU stay on physical function, HRQOL, and leg complications warrants further investigation.

Our study has several limitations. First, our study is a single-center retrospective study. Second, our population of subjects was a mixed cohort receiving both venoarterial and venovenous femoral and dual-lumen cannulation for a variety of medical and post–lung transplant causes. This was, however, representative of the population of patients requiring lung transplantation. Detailed evaluation of the different populations is warranted in larger trials. Although our study is the first to report on early physical function and lower limb complications in subjects before and after lung transplantation, the numbers are too small to draw definitive conclusions and preclude any detailed subgroup analyses. The multiple regression analysis is also limited by the small sample size, and results should be viewed as hypothesis-generating rather than generalizable to the wider ECMO population. HRQOL and strength were only assessed in the ECMO group and were not available for the non-ECMO subjects, so comparison could not be made between the groups for these measures. Finally, level of function prior to the implementation of ECMO was not objectively assessed as subjects often presented acutely or were transferred from other hospitals. However, a retrospective review of the medical history revealed that only 1 subject was bed-bound in the 48 h prior to ECMO initiation. Potential benefits from this study include new knowledge about the early physical function, leg complications, and HRQOL of subjects who have undergone ECMO before and after lung transplantation. Furthermore, this study identifies increased hospital LOS and worse physical function in lung transplant recipients requiring ECMO versus those who did not require ECMO. This may assist in the development of targeted treatment guidelines for this patient population, which currently do not exist.

Conclusion

This was the first study of early physical function after ECMO as a rescue therapy for subjects before or after lung transplantation, with comparison to non-ECMO lung transplant recipients. In this study population, subjects requiring ECMO had poor physical function at ICU discharge, but this improved by the time of hospital discharge, with the majority of subjects discharged directly to home. A longer period of mechanical ventilation and longer ICU and hospital LOS, along with lower physical function at ICU and hospital discharge, were observed in the ECMO group compared to the non-ECMO group; this may be related to the ECMO cannulation strategy and the level of sedation in the ECMO group. ICU LOS was the only

significant predictor of physical function at hospital discharge. HRQOL was poor at hospital discharge in the ECMO subjects and warrants further investigation with longer-term follow-up, as does the incidence and impact of complications involving the lower limb in subjects receiving femoral ECMO.

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Chapter 5: ACUTE SKELETAL MUSCLE WASTING AND RELATION TO PHYSICAL FUNCTION IN PATIENTS REQUIRING EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)

5.1. Declaration of authorship: Chapter 5

Student's declaration:

The nature and extent of contributions to Chapter 5 of this thesis are as follows:

Name	Nature of contribution	Contribution
Kate Hayes	Study concept and design, ethics application, data collection and analysis, manuscript preparation and revision for publication	75%
Anne Holland	Study concept and design, data analysis, drafting and revision of manuscript	8%
Vincent Pellegrino	Study design, revision of manuscript	3%
Sunita Mathur	Study design, data analysis, revision of manuscript	6%
Carol Hodgson	Study concept and design, data analysis, drafting and revision of manuscript	8%

Supervisor's declaration:

I hereby certify that the declaration above is a correct reflection of the extent and nature of contributions made toward Chapter 5 of this thesis by the student and all listed co-authors.

Name of supervisor	Signature
Anne Holland	

5.2. Preface to Chapter 5

Human Research Ethics Committee approvals for this study were granted from the Alfred Hospital Ethics Committee (Project number 516/16) and the La Trobe University Human Ethics Committee (UHEC). See Appendix 1 for the ethics approval forms.

The observational study presented in Chapter 5 was published in *Journal of Critical Care* and is presented in its published format.

Hayes K, Holland AE, Pellegrino VA, Mathur S, Hodgson CL. Acute skeletal muscle wasting and relation to physical function in patients requiring extracorporeal membrane oxygenation (ECMO). *J Crit Care.* 2018;48:1-8. doi:10.1016/j.jcrc.2018.08.002

See Appendix 2 for permission for inclusion in this thesis

Aspects of this study were presented at the following conferences:

Oral presentation:

International Society of Heart and Lung Transplantation (ISHLT) Annual Scientific Meeting in Nice, France, 12/04/2018.

Title: Acute skeletal muscle wasting and relation to physical function in patients requiring extracorporeal membrane oxygenation (ECMO).

Abstract: the abstract related to the oral presentation of this study was published as follows:

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extracorporeal membrane oxygenation (ECMO). *The Journal of Heart and Lung Transplantation.* 2018;37(4):S120. doi:10.1016/j.healun.2018.01.286

Poster presentation: Alfred Research Week June 18-22, 2018.

Title: Acute skeletal muscle wasting and relation to physical function in patients requiring extracorporeal membrane oxygenation

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Acute skeletal muscle wasting and relation to physical function in patients requiring extracorporeal membrane oxygenation (ECMO)☆

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ABSTRACT

Purpose: Muscle weakness is common in patients requiring extracorporeal membrane oxygenation (ECMO), but early identification is challenging. This study aimed to 1) quantify the change in quadriceps size and quality (echogenicity) from baseline to day 10 using ultrasound in patients requiring ECMO, 2) determine the relationship between ultrasound measures, muscle strength and highest mobility level.
Materials and methods: Prospective cohort study involving ultrasound measurement of quadriceps at baseline, days 10 and 20. Muscle strength and highest mobility level were assessed at days 10 and 20 using the Medical Research Council sum-score (MRC), hand-held dynamometry (HHD) and the ICU mobility scale (IMS).
Results: 25 patients (age 49 ± 14 years, 44% male) received ECMO. There was a significant reduction (−19%, $p < .001$) in rectus femoris cross-sectional area by day 10. Echogenicity did not change over time. There was a negative correlation between echogenicity and MRC at day 10 ($r = -0.66$) and HHD at day 20 ($r = -0.81$). At day 20, there was a moderate correlation between total muscle thickness and IMS (rho = 0.59) and MRC (rho = 0.56).
Conclusions: In patients requiring ECMO there was marked wasting of the quadriceps over the first 10 days. Ultrasound measures were related to muscle strength and highest mobility level.

1. Introduction

Survivors of a critical illness often suffer from profound muscle wasting and weakness, known as intensive care unit acquired weakness (ICUAW) [1, 2], which has been shown to occur early and rapidly within the first 10 days of the intensive care unit (ICU) admission [3, 4]. These complications are frequently severe and persistent, and are associated with increased hospital length of stay (LOS) and mortality [5-7], along with significant decrements in health-related quality of life and physical function persisting up to 5 years following ICU admission [8]. Patients requiring extracorporeal membrane oxygenation (ECMO) may have worse muscle wasting and weakness than other general ICU populations, but to date this has not been investigated. Extracorporeal membrane oxygenation (ECMO) is a form of temporary mechanical support of the heart and/or lungs with an extracorporeal circuit including a blood pump and gas exchange membrane. It is generally used in patients with the highest severity of illness, where there is refractory cardiac or respiratory failure despite optimal conventional therapy [9, 10]. There are two main types of ECMO; venovenous and venoarterial. Venovenous cannulation is used in patients with isolated respiratory failure, whereas venoarterial cannulation is used in patients with either isolated cardiac failure or combined cardiac and respiratory failure. ECMO may be associated with periods of bed rest secondary to medical instability, cannula positon and fear of cannula dislodgement [11, 12], which may further increase the risk of muscle wasting and weakness. Pre-existing frailty and comorbidities may have an additional deleterious impact on physical function but the impact of these factors on muscle wasting have not been investigated in patients requiring ECMO.

Muscle strength testing in the early stages of critical illness is limited, as it requires the patient to be awake, alert and cognitively intact. Diagnosis of ICUAW is therefore often delayed due to inability of patients to complete volitional muscle strength testing [13]. Consequently, there is growing interest in the utility of ultrasound imaging (USI) to monitor the trajectory of muscle wasting and inform development of targeted interventions in these critically ill patients [4, 14]. Ultrasound imaging

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(USI) of skeletal muscle is a painless, non-invasive and radiation free technique that is inexpensive and readily available in the ICU. It provides objective information about muscle size and quality (echogenicity), and is valid and reliable [15-18], making it an ideal technique for assessing longitudinal changes. To date, the use of USI to quantify change in skeletal muscle size and quality has not been investigated in patients requiring ECMO. Understanding the extent and impact of peripheral muscle wasting is vital for optimising clinical management, including development of better rehabilitative strategies to attenuate these devastating changes, improve recovery and optimise the risk/benefit profile of ECMO.

The primary aims of the study were to describe: 1) the change in quadriceps muscle size and echogenicity from day 1 to day 10 and 2) the relationship between the ultrasound measures and measures of muscle strength and highest level of mobility at day 10 and day 20. A secondary aim was to describe the relationship between the ultrasound measures and other factors including: premorbid frailty status and comorbidities, premorbid mobility level, and time to reach mobility milestones.

2. Materials and methods

2.1. Study design

This was a single-centre prospective cohort study conducted at a mixed medical/surgical ICU in a tertiary referral hospital for ECMO in Melbourne, Australia. This study received local ethics approval. Informed consent was sought from the patient's person responsible either in person or by telephone contact. Consent for ongoing participation was sought from patients when they became capable of providing informed consent.

2.2. Inclusion and exclusion criteria

Consecutive adult patients expected to be on ECMO for >24 h were included. Individuals were excluded if they had any of the following: >48 h on ECMO or 5 days in ICU prior to recruitment; any connective tissue disorders; a proven or suspected acute primary brain process that was likely to result in global impairment of conscious level or cognition; any neuromuscular conditions; any current cancer or chemotherapy; a pre-existing cognitive impairment that would impair capacity to follow verbal instructions; any current acute musculoskeletal injuries of hip, knee, and ankle; a pre-existing mobility impairment where the patient was unable to walk without assistance (use of a walking stick or frame was not an exclusion); a language barrier to patient comprehension, where death was deemed imminent and inevitable, or where the ultrasound assessor was away on leave.

2.3. Routine care on ECMO

Sedation breaks were routinely undertaken daily in patients that were stable on ECMO support. Patients with elevated respiratory drive that were requiring protective lung ventilation, and those that were hemodynamically unstable (life threatening arrhythmias or requiring high dose vasopressors) were sedated and were deemed not suitable to participate in active mobilisation. They received passive range of movement exercises only. Daily sedation targets were generally aimed at a Richmond agitation and sedation scale (RASS) [19] of between −1 and +1. Continuous neuromuscular blockers were not routine, however short-term paralysis was occasionally used to facilitate procedures where required. Volume state disorders are very common in severely ill patients considered for ECMO support of the heart or lungs. In general, ECMO support facilitates the removal of extra fluid acquired during critical illness. At our centre, volume state targets for patients on ECMO were to ensure the lowest volume state that allowed ECMO support and maintained organ function.

Our standard rehabilitation program for patients on ECMO was initiated as early as possible after commencement of ECMO, with the goal of achieving the highest level of mobility each day and progressing to ambulation where possible. Passive range of motion exercises for the upper and lower limbs were the only exercises provided to patients that were unstable or requiring sedation (with a RASS of < −1). When patients met the RASS target of −1 to +1, rehabilitation began with resistance and active range of motion exercises for the upper and lower limbs, progressing to sitting, standing, and, ultimately, ambulation, as medical stability allowed.

2.4. Outcome measures

2.4.1. Demographic and clinical characteristics

Demographic and clinical data were recorded from the medical history and included: age, gender, reason for ICU admission, ECMO type and configuration, ECMO duration (days), duration of mechanical ventilation (days), ICU and hospital LOS (days), discharge destination and in-hospital mortality. The acute physiology and chronic health evaluation II (APACHE II) score, a severity of illness score with higher scores corresponding to more severe illness, was calculated at ICU admission.

Pre-admission comorbidities were scored using the Functional Comorbidity Index (FCI) [20] from the ICU admission history, with additional information from the person responsible at the time of consent. The FCI is scored out of a maximum of 18, with higher scores corresponding to worse physical function outcomes and higher mortality [20-22]. Premorbid frailty was assessed at ICU admission using the Clinical Frailty Scale (CFS) which is scored from 1 to 9, with higher scores indicating worse frailty [23], and a score of ≥5 defining a patient as frail. Level of independence with activities of daily living (ADL) prior to admission was scored using the Katz Index of ADL [24]. The CFS and Katz score were completed from discussion with the patient's person responsible at time of consent, which is current usual clinical practice.

2.4.2. Ultrasonography imaging procedure and measures

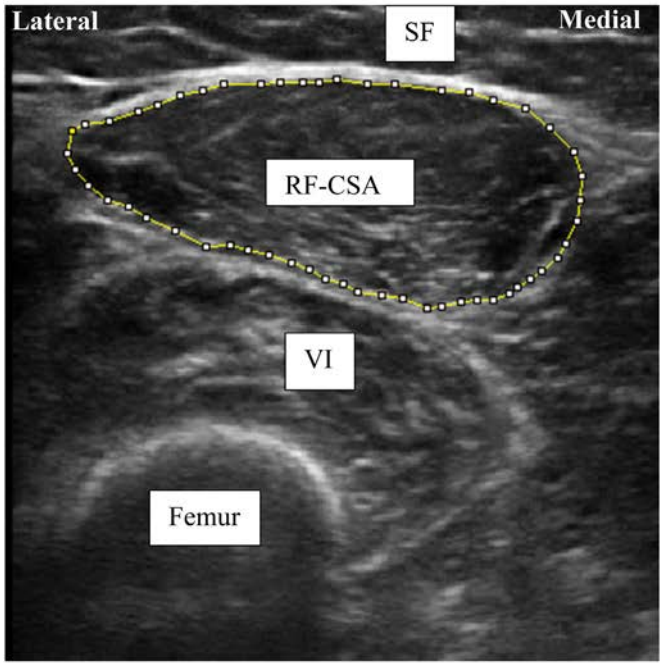
Ultrasound images were obtained at baseline (day 1), day 10 and day 20. All USI was done with a Sonosite Edge portable USI system using brightness mode by one trained investigator (KH). A two-dimensional, high frequency (6–15 MHz), 5.6 cm linear transducer was used for all measures. All ultrasound images were captured directly on the Sonosite system, and subsequently exported without any adjustments to a computer for further analysis. Image analysis was done using the image analysis software ImageJ (National Institutes of Health, Bethesda, Maryland; https://imagej.nih.gov/ij/). All measures were performed in triplicate, with the average of the scores used in the final analysis.

All sonograms were obtained with a standardized protocol of patient position for image acquisition, anatomic landmarks, and transducer placement (supplementary online material). Image analysis also followed a standardized protocol for measurement of muscle cross-sectional area, muscle thickness and muscle quality (echogenicity). Sonographic settings and order of imaging were kept constant between patients. To confirm the accuracy of technique and interpretation, the de-identified images of the first five patients were analysed separately by an expert in muscle ultrasound (SM), who was a co-investigator on the study.

The following measures of muscle size and echogenicity were obtained: Anterior thigh measures: rectus femoris (RF) echogenicity, rectus femoris cross-sectional area (RF-CSA) (Fig. 1A), RF thickness, vastus intermedius (VI) thickness, and total muscle thickness (RF + VI) (Fig. 1B). Lateral thigh measures: vastus lateralis (VL) thickness, VI thickness and total muscle thickness (VL + VI).

The intra-rater reliability of image acquisition and analysis of RF-CSA was calculated in the first 10 patients. All imaging and analysis was performed by one trained assessor (KH). Three consecutive images of RF-CSA were obtained. A further three images of RF-CSA were obtained

A.



B.

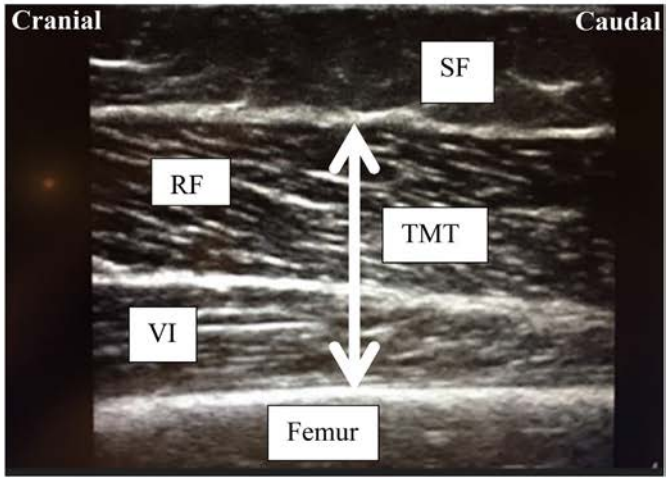


Fig. 1. Ultrasound imaging of the right quadriceps muscle. A. The ultrasound probe was positioned on the anterior thigh and oriented in the transverse plane at a point that was two thirds of the distance from the medial aspect of the anterior superior iliac spine to the superior patella border. RF-CSA, rectus femoris cross-sectional area; VI, vastus intermedius; SF, superficial fascia. The dotted line traces the inner echogenic line of the RF fascia and outlines the RF-CSA. B. The ultrasound probe was positioned on the anterior thigh and orientated in the sagittal plane at a point that was two thirds of the distance from the medial aspect of the anterior superior iliac spine to the superior patella border. RF, rectus femoris; VI, vastus intermedius; TMT, total muscle thickness (RF + VI); SF, superficial fascia. The solid white arrow represents total muscle thickness, measured from the inner most aspect of the superficial fascia to the femur.

after a period of at least 1 h had passed. There was a time delay of 1 week between image analyses of the two sets of measures for each patient to ensure the assessor was blinded to the previous set of measurements.

2.4.3. Muscle strength and mobility level

Measures of muscle strength and highest mobility level were obtained at day 10 and day 20 in order to determine the relationship between these volitional measures and the USI parameters. A detailed description of the measurement tools and study protocol are available in the supplementary online material. On each test day, the level of alertness and attention were assessed using the RASS [19] and Attention Screening Examination (ASE) [25] to ensure the patients had suitable attention to comply with volitional measures of muscle strength [1].

Muscle strength was assessed using the Medical Research Council sum-score (MRC) which has a maximum score of 60 [26]. A score of <48 is indicative of ICUAW [1, 27]. Peak isometric knee extension force was measured following a standardized protocol (supplementary online material) using the Nicholas Manual Muscle Tester (model 01165; Lafayette Instrument Company, Lafayette, Indianna).

The highest level of mobility was scored using the ICU Mobility Scale (IMS), which is scored from 0 to 10, with 10 being the best score [28]. The highest level of mobility achieved in the week prior to ICU admission and during ECMO was also recorded from a retrospective review of the medical histories using the IMS. Time taken in days to achieve mobility milestones, including time to first stand and time to first walk >5 m away from the bed, were also recorded.

2.5. Sample size and statistical analysis

A recent study reported that RF-CSA may decrease more significantly over time than quadriceps total muscle thickness in critically ill patients [29]. For this reason, change in RF-CSA over a 10 day period was the primary outcome measure. Previous studies have reported very large decreases in RF-CSA with effect sizes of up to −1.5 at 10 days [3]. We powered this study to find a more modest (but still large and clinically important) effect size of 0.8, which corresponded to a 15% reduction in RF-CSA over 10 days. To detect an effect size of 0.8 with 80% power and a two-tailed alpha of 0.05 required 20 participants. This assumed a standard deviation of 2.33 and a within-participant correlation between measures of 0.85 [15].

To detect a relationship between RF-CSA and peak quadriceps force with 80% power, a total sample size of 15 participants was required. This assumed a change in peak quadriceps muscle force of 0.10 kg per 1 mm^2 change in RF-CSA, with standard deviations of 9.9 kg and 78 mm^2 respectively [30] and a two-sided p value of 0.05.

It was anticipated that measures of RF-CSA may not be obtained in a small number of participants due to inability to visualise the entire inner echogenic line of the RF fascia. In addition, the high mortality in this patient group may also lead to missing data. Therefore, it was decided that a total of 25 participants would be recruited to ensure adequate power for the primary aims and to account for missing data.

Statistical analysis was performed using IBM SPSS Statistics Version 25 for Windows (IBM Corp., Armonk, New York, USA). Continuous variables were assessed for normality using the Shapiro Wilk test and expressed as mean ± SD (standard deviation), whilst non-normally distributed data as medians (interquartile ranges). Categorical variables were expressed as counts and proportions and analysed using the chi-square or fisher's exact test. To investigate a change over time, a paired t-test was used for continuous data or the Wilcoxon Signed Rank Test for nonparametric data. A one-way repeated measures ANOVA was conducted to investigate the change in ultrasound measures over the three-time points (day 1, day 10, day 20). A two-sided p value of ≤0.05 was considered to be statistically significant. Pearson's r or Spearman's rho (depending on the normality of the data) was used to assess the relationship between ultrasound and physical function measures. Coefficients were interpreted as little (0.00–0.25), fair (0.25–0.50), moderate (0.50–0.75) and strong (≥ 0.75) association [31]. Intra-rater reliability was assessed using coefficient of variation [32] and Intraclass correlation coefficient (ICC) with 95% confidence intervals (CI) using the Shrout and Fleiss Model 3 [33] (Two-way mixed average measures). An ICC value ≥0.75 reflects excellent agreement, 0.60–0.74 reflects good agreement, 0.40–0.59 reflects fair agreement and an ICC value <0.40 reflects poor agreement [34].

3. Results

Over an 8-month period, a total of 48 patients underwent ECMO support, of which 25 were recruited to the study (Fig. 2). Table 1 describes the baseline demographic and clinical characteristics of those patients. Time to baseline ultrasound measurement was a median of 26 h (IQR: 15 to 38 h) following ECMO commencement. The majority of patients underwent femoral vessel cannulation ($n = 20/25$, 80%), with only one patient having a dual lumen cannula and two patients undergoing central venoarterial ECMO. Patients were deeply sedated during ECMO, with a median RASS = −4 (IQR: −5 to −4), with only two patients having a RASS between −1 and + 1 during ECMO.

The majority of patients ($n = 22$, 88%) were independent with all activities of daily living prior to admission to hospital, with a score of Category A on the Katz Index of ADL. Eight patients (32%) were considered frail at ICU admission, with a CFS of ≥5, whilst the majority of patients were independent with mobility and not requiring a gait aide prior to ICU (Table 1).

Rectus femoris cross-sectional area (RF-CSA) significantly decreased from day 1 to day 10 (−19.2% [95% CI, −13.7 to −24.8%]; $p < .001$), and continued to decrease to day 20 (−30.5% [95% CI, −24.1 to −36.9]; $p < .001$)(Fig. 3). All other ultrasound measures of muscle size decreased significantly from day 1 to day 20 (Table 2). The percentage reduction in muscle size from day 1 to day 20 varied between 26.7% for VI thickness in the lateral thigh measurement and 34.9% for RF thickness (Table 2). There was no difference in the pattern of wasting between the different muscle groups. Echogenicity increased over the 10-day period but these changes were not statistically significant. There was excellent intra-rater reliability of measurement of RF-CSA in the first 10 patients ($ICC_{3,1} = 0.98$ [95% CI, 0.92 to 0.99]). The coefficient of variation was 4.3%.

Muscle strength was poor at day 10, with a median MRC score of 38 (Table 3), which is indicative of ICUAW. Knee extension force measured with HHD was also low at day 10. Both measures improved by day 20 but remained below normal levels (Table 3). There was no difference between the MRC strength score for the upper limb muscles versus the lower limb muscles at day 10 or day 20. Measures of muscle strength (MRC and HHD) were performed in less than half of patients alive on day 10 (Table 3) secondary to high levels of sedation or presence of delirium. The completion of HHD and MRC improved by day 20 as patients became more alert and orientated. Knee extension force measured with HHD at day 20 was performed slightly less often than completion of the MRC (Table 3). In three patients, knee extension was scored ≤2 in the MRC at day 20, such that HHD was not feasible.

The highest level of mobility at day 10 was low (IMS median 0), which translates to passive exercises in bed, however improved by day 20 to a level where patients were standing at the bedside (IMS median 4)(Table 3). The highest level of mobility achieved on ECMO was low (IMS median = 0, IQR: 0–1, Range 0–6), and was limited by sedation requirements in unstable patients. Only 2 patients stood and stepped on the spot at the bedside whilst on ECMO, both of whom were awaiting lung transplantation, were medically stable on ECMO and alert and cognitively intact. Time to achieve mobility milestones including time to first stand and first walk were median 12.3 days (IQR: 9 to 20) and 20.1 days (IQR: 15.5 to 33) respectively. Time to first stand was moderately correlated with the duration of ECMO (rho = 0.50, $p = .04$) and mechanical ventilation (rho = 0.61, p 0.007), whilst time to first walk was strongly correlated with ICU LOS (rho = 0.89, $p < .001$).

The relationship between the ultrasound measures and measures of muscle strength and highest level of mobility at day 10 and day 20 are described in Table 4. A higher echogenicity score (worse muscle quality) was associated with lower strength scores, whilst a smaller muscle size (total muscle thickness) was associated with both lower strength scores and mobility level. There was a moderate negative correlation between premorbid frailty (CFS) and day 1 ultrasound measures (RF-CSA: $r = −0.56$, $p = .004$; total muscle thickness in the anterior thigh: $r = −0.55$, p = .004; total muscle thickness in the lateral thigh: $r =$

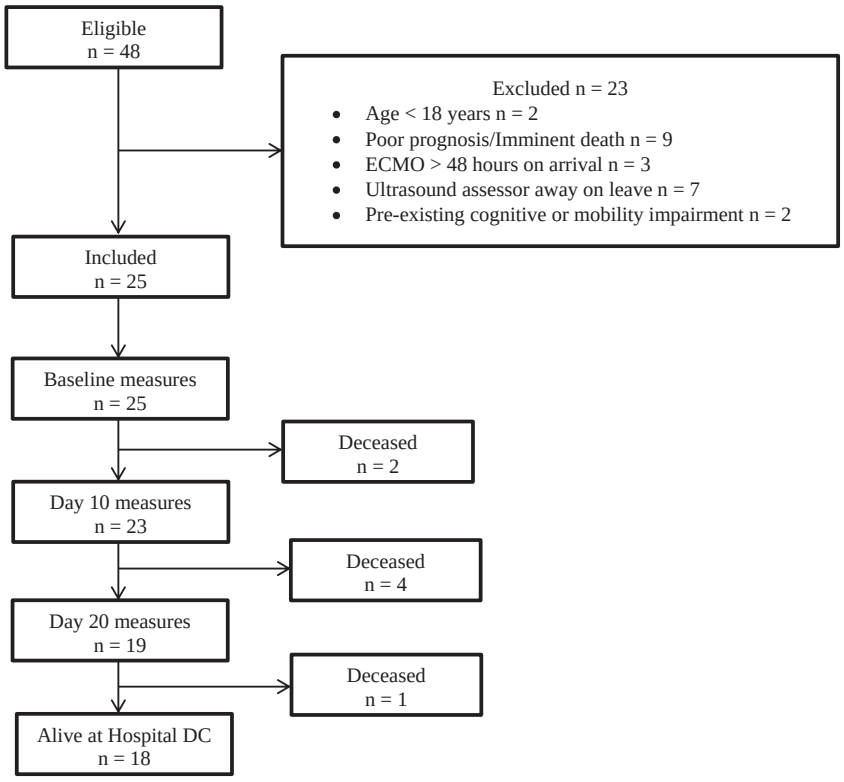


Fig. 2. Flow of subjects requiring ECMO. ECMO, extracorporeal membrane oxygenation; DC, discharge.

Table 1
Demographic and clinical characteristics of subjects on ECMO.

Characteristic	All ECMO ($n = 25$)
Age (years)	49.3 ± 14.4
Male n (%)	11 (44)
Hospital data	
APACHE II	23.9 ± 9.1
RASS on ECMO	−4 (−5 to - 4) Range (−5 to 0)
ECMO duration (days)	8.2 (5.8–14.9)
Ventilation (days)	9.9 ± 6.7
ICU LOS (days)	17.0 (12.5–24.1)
Hospital LOS (days)	30.3 (25–43)
Main diagnosis n (%)	
ARDS	6 (24)
Respiratory failure bridge to LTx	3 (12)
Post LTx primary graft failure	2 (8)
Pulmonary Hypertension post LTx	2 (8)
Cardiac failure/infarction	7 (28)
Cardiac arrest	4 (16)
Post HTx primary graft failure	1 (4)
ECMO type n (%)	
Venoarterial	14 (56)
Venovenous	11 (44)
Preadmission status	
IMS pre ICU (/10)	10 (10−10) Range (5–10)
Katz score (Category A)	22 (88)
Functional comorbidity index (/18)	2 (1–4)
Clinical frailty scale (/9)	3 (3–5) Range (2–7)
In-hospital mortality n (%)	7 (28)
Discharge destination of survivors n (%)	
Home	11/18 (61.1)
Inpatient rehabilitation	7/18 (38.9)

Values are presented as mean ± SD, median (interquartile range), or as a number (%). ECMO, extracorporeal membrane oxygenation; APACHE II, acute physiology and chronic health evaluation II score; RASS, Richmond agitation and sedation scale; ICU, intensive care unit; LOS, length of stay; ARDS, acute respiratory distress syndrome; LTx, lung transplantation, HTx, heart transplantation; IMS, ICU mobility scale;

−0.52, $p = .008$). Little correlation (rho <0.25) was seen between the ultrasound measures at day 10 and day 20 and premorbid frailty (CFS), premorbid comorbidities (FCI) or premorbid mobility level (IMS).

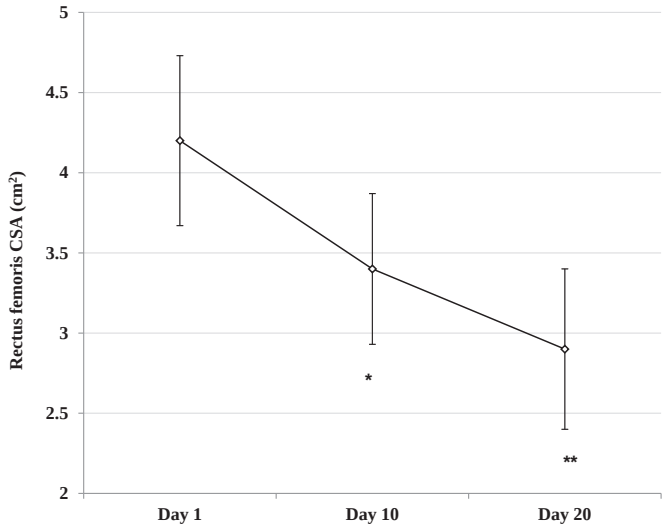


Fig. 3. Change in rectus femoris cross-sectional area from day 1 to day 20. Data are expressed as means and 95% confidence intervals. Rectus femoris CSA, rectus femoris cross-sectional area. * $P < .001$ for change from day 1 to day 10. This change represents −19.2% reduction in RF-CSA from day 1 to day 10. ** $P < .001$ for change from day 1 to day 20. This change represents −30.5% reduction in RF-CSA from day 1 to day 20.

4. Discussion

This is the first study to quantify the early change in quadriceps muscle size and quality (echogenicity) using USI in ECMO patients. This study demonstrated significant quadriceps muscle wasting in ECMO patients from day 1 to day 10, which continued to decline to day 20. In previous studies a 10% reduction in RF-CSA was considered as clinically relevant muscle wasting [4, 30]. Our study exceeded this threshold, with a 20% reduction in RF-CSA and total muscle thickness by day 10, and 30% reduction by day 20. There was no difference in the pattern of wasting between the different muscle groups. Ultrasound measures of muscle size were associated with impairments in muscle strength and mobility.

Other studies using USI in different populations have demonstrated significant reductions in quadriceps muscle size (cross-sectional area and thickness) over the first 10 days of admission to ICU [3, 4]. The percentage reduction in RF-CSA from day 1 to day 10 in the current study was similar to that reported in an earlier study involving ICU patients with similar age, APACHE II scores, duration of mechanical ventilation and ICU LOS [4]. This suggests that muscle wasting in ECMO patients is no worse than that of a more general ICU population. There was no information provided in the earlier study regarding sedation levels or the level of mobilisation performed to be able to compare to the current study, but given the similarities in severity of illness and requirements for mechanical ventilation it is likely that both groups had prolonged periods of bed rest.

In contrast, a 30% reduction in RF-CSA from day 1 to day 10 was reported in a study by Parry et al. [3], which included a general ICU population with similar APACHE II scores to our study but shorter duration of mechanical ventilation and ICU LOS. Similar to our study, patients were sedated for the majority of this early 10-day period suggesting minimal active mobilisation. It is unclear what mechanisms are responsible for this difference between the studies. There may have been a difference in the amount of lower limb muscle edema, however this was not measured in either study.

In the current study, the association between muscle size and muscle strength and mobility was not as strong as that reported in an earlier study [3]. This may be related to the timing of measurement, which was completed on day 10 and day 20 in our study, but on patient awakening and ICU discharge in the earlier study. The assessment of muscle strength was limited in our study, particularly at day 10, due to sedation requirements and patient delirium, highlighting the limitations of volitional strength testing in the early period of an ICU stay.

In the current study there was an increase in echogenicity (increased whiteness in the muscle) from day 1 to day 10 but it was not statistically significant. This is similar to the results of an earlier study of ICU patients with severe sepsis, which reported an increase in echogenicity from day 4 to 14 [35]. This higher echogenicity may be due to muscle necrosis and loss of the normally well-organised muscle architecture, along with increased intramuscular fibrosis and fatty tissue [35-37]. Muscle edema may also effect echogenicity by reducing it (making the image darker) thereby possibly impacting on the amount of change in echogenicity reported in both studies. Unfortunately, measures of total volume status and lower limb edema were not reported in either study.

In a later study involving general ICU patients, a significant increase in quadriceps echogenicity from day 1 to day 10 was reported and correlated with a reduction in physical function [3]. Our study also demonstrated an association between echogenicity and strength at day 10 and day 20. The greater increase in echogenicity reported in the study by Parry et al. [3] may be associated with the larger amount of muscle wasting that they found. As the total volume of the muscle fibre decreases, this may result in a relative increase in fibrous and fatty tissue, resulting in a net increase in whiteness of the image [35]. A further explanation may be that our cohort had a higher echogenicity at baseline and therefore reduced capacity to show further deterioration. We are unable to directly compare the baseline echogenicity values between

Table 2
Ultrasound measurement of quadriceps muscle size and quality in ECMO subjects.

Ultrasound muscle parameter	Day 1 (n = 25)	Day 10 (*n* = 23)	Day 20 (*n* = 19)	*p*-value	% change Day 1 – Day 10 (n = 23)	% change Day 1 – Day 20 (n = 19)
RF CSA (cm^2)	4.2 ± 1.3	3.4 ± 1.1	2.9 ± 1.0	<0.001	−19.2 ± 12.9	−30.5 ± 13.3
RF Thickness (cm)	1.1 ± 0.3	0.7 (0.6–1.0)	0.6 ± 0.2	<0.001	−25.4 ± 20.5	−34.9 ± 25.9
VI Thickness anterior view (cm)	0.9 ± 0.3	0.8 ± 0.2	0.7 ± 0.2	<0.001	−16.4 ± 22.4	−31.0 (−42.5 to −27)
VL Thickness (cm)	1.6 ± 0.3	1.4 ± 0.3	1.1 ± 0.3	<0.001	−16.4 ± 19.1	−32.5 ± 15.5
VI Thickness lateral view (cm)	1.2 ± 0.4	1.1 ± 0.5	0.9 ± 0.4	<0.001	−11.0 (−29.4 to 6.7)	−26.7 ± 23.9
Total muscle thickness anterior thigh = (RF + VI) (cm)	2.1 ± 0.6	1.7 ± 0.5	1.4 ± 0.4	<0.001	−20.0 ± 15.7	−30.3 ± 20.1
Total muscle thickness lateral thigh = (VL + VI) (cm)	2.9 ± 0.5	2.6 ± 0.7	2.2 ± 0.5	<0.001	−11.5 ± 18.8	−27.9 ± 13.6
RF Echogenicity	74.2 (64.0–86.4)	80.9 ± 21.1	79.6 ± 31.7	0.41	+4.7 ± 15.1	+1.6 ± 23.7

Values are presented as mean ± SD or median (interquartile range). *p*-value represents time effect from 1-way repeated measures ANOVA. ECMO, extracorporeal membrane oxygenation; RF, rectus femoris; CSA, cross-sectional area; VI, vastus intermedius; VL, vastus lateralis.

studies, as these values are dependent on the ultrasound device and settings.

Validity studies are lacking regarding echogenicity as a measure of muscle quality. However, in an earlier study in the critical care setting [38], echogenicity was correlated to muscle necrosis as seen on muscle biopsy. Previous studies have also reported echogenicity as a surrogate measure of muscle quality [3, 39] and in a recent review article of muscle ultrasound [40], echogenicity was recommended as a surrogate measure of muscle quality. In populations outside of the critical care setting, echogenicity has also been correlated with skeletal muscle pathology. Assessment of echogenicity using quantitative grey scale analysis was reported as a highly sensitive and specific method for detecting neuromuscular disorders in children [41], whilst muscle fibrosis and fatty infiltration as seen on muscle biopsy were associated with increased echogenicity. In a later study, experimentally induced skeletal muscle degeneration and histological changes were also associated with increased echogenicity [42].

In the current study muscle strength and mobility level improved from day 10 to day 20 (although still remained below normal levels) despite a reduction in muscle size over this time period. Although muscle size is a predictor of muscle strength, there are many other factors involved. Muscle strength depends not only on the size and quality of the involved muscles, but also upon the ability of the nervous system to appropriately recruit the muscles [43]. In addition to improved neural adaptation over time, there was likely a decrease in the pathological effects of critical illness on the muscle at a cellular level from day 10 to 20 [44]. Patients were also more likely to be off ECMO from day 10 to day 20, and not requiring sedation. This resulted in patients participating in higher levels of active exercise, including ambulation during the latter part of the study.

Thirty-two percent of patients in our study were classified as frail at ICU admission. This is similar to the prevalence of frailty reported in a surgical ICU cohort of patients (38%) [45]. Our study demonstrated that premorbid frailty was associated with muscle size at baseline, however by day 10 and 20 there was little correlation with the ultrasound measures. This suggests that premorbid frailty may not play a major role in predicting ECMO patients at risk of muscle wasting; rather that factors related to critical illness and/or the ICU stay are more important. An earlier study demonstrated a similar association between baseline frailty and RF-CSA measured using ultrasound in patients admitted to a surgical ICU [45]. The measurement of RF-CSA was not repeated in the earlier study, and therefore the correlation between premorbid frailty and quadriceps muscle size later in the ICU stay is unknown. It is important to note that our study was powered to detect a change in RF-CSA and not the relationship between premorbid frailty and muscle size, which requires further evaluation.

To our knowledge, this is one of the first studies to report the prevalence of premorbid frailty in patients requiring ECMO and the impact of frailty on muscle wasting warrants further investigation in a larger trial. In addition, the impact of total volume status whilst on ECMO and the relationship to muscle edema requires investigation. Our small sample size also prevented exploration of relationships between muscle wasting and ECMO type and cannulation strategy. A further limitation is that our study was a single centre study and so may not reflect ECMO practices at other centres in regards to sedation management and early mobilisation. We also excluded patients that were deemed unlikely to survive, and it may be possible that these patients have a different pattern of muscle wasting. In addition, day 1 ultrasound measures may not accurately reflect the first day of critical illness. Although we were able to undertake the ultrasound measures within 48 h of ECMO cannulation, patients may have been critically unwell prior to ICU admission. Finally, we were unable to include a matched control group that did not undergo ECMO, and therefore cannot comment on any causal relationship between ECMO and muscle wasting.

5. Conclusions and future directions

In patients requiring ECMO there was marked wasting of the quadriceps muscle over the first 10 days, and this continued to day 20. Ultrasound measures (muscle size and echogenicity) were associated with measures of muscle strength and highest mobility level, whilst premorbid frailty was associated with muscle size at baseline. Muscle ultrasound is a promising non-invasive method for the early assessment of muscle wasting in patients on ECMO and is associated with physical function. Larger studies, including a control group that does not have

Table 3
Physical function outcomes for ECMO subjects.

Outcome measures		Day 10 (n = 23)	Day 20 (n = 19)	*p*-Value
Strength	MRC (/60)	38 (20–51) (*n* = 11)	52 (43–56) (*n* = 18)	0.005
Knee extension muscle force	HHD (kg) Left	8.1 ± 3.4	12.0 ± 4.1	0.008
	HHD (kg) Right	10.7 ± 4.1 (*n* = 9)	13.3 ± 4.7 (*n* = 15)	0.06
Mobility level	IMS (/10)	0 (0–3) (n = 23)	4 (3–9) (n = 19)	<0.001

Values are presented as mean ± SD or median (interquartile range) and *p*-values are comparison between time points (Day 10 and Day 20). ECMO, extracorporeal membrane oxygenation; MRC, Medical Research Council sum-score; HHD, hand held dynamometry; IMS, ICU mobility scale.

Table 4
Correlation between ultrasound parameters and measures of muscle strength and mobility.

Ultrasound parameter	Comparator	Day 10		Day 20	
		Correlation coefficient	P value	Correlation coefficient	P value
RF CSA	MRC	$r = -0.06$	0.87	rho = 0.02	0.94
	IMS	rho = 0.24	0.28	rho = 0.21	0.39
	HHD	$r = 0.19$	0.62	$r = 0.23$	0.41
RF Thickness	MRC	$r = 0.07$	0.83	rho = 0.26	0.30
	IMS	rho = −0.14	0.51	rho = 0.25	0.30
	HHD	r = 0.19	0.62	$r = 0.45$	0.09
VI Thickness anterior thigh	MRC	$r = 0.33$	0.32	rho = 0.35	0.16
	IMS	rho = −0.01	0.98	rho = 0.58	0.01*
	HHD	$r = 0.21$	0.59	$r = 0.47$	0.08
Total muscle thickness anterior thigh = (RF + VI)	MRC	r = 0.19	0.58	rho = 0.35	0.15
	IMS	rho = −0.01	0.95	rho = 0.49	0.03*
	HHD	$r = 0.06$	0.88	$r = 0.53$	0.04*
VL Thickness	MRC	$r = 0.09$	0.78	rho = 0.44	0.07
	IMS	rho = 0.14	0.52	rho = 0.57	0.01*
	HHD	$r = 0.05$	0.90	$r = 0.16$	0.58
VI Thickness lateral thigh	MRC	$r = 0.43$	0.19	rho = 0.16	0.53
	IMS	rho = 0.06	0.78	rho = 0.24	0.32
	HHD	r = 0.09	0.82	$r = 0.51$	0.050*
Total muscle thickness lateral thigh = (VL + VI)	MRC	$r = 0.42$	0.20	rho = 0.56	0.02*
	IMS	rho = 0.01	0.97	rho = 0.59	0.007*
	HHD	$r = 0.13$	0.73	$r = 0.46$	0.09
RF Echogenicity	MRC	$r = -0.66$	0.03*	rho = −0.16	0.53
	IMS	rho = −0.19	0.39	rho = −0.28	0.24
	HHD	$r = -0.38$	0.32	r = −0.81	< 0.001*

Pearson correlation coefficient (r) or Spearman rank order correlation (rho) was used to determine correlations. * Significant results, $p < .05$. RF, rectus femoris; CSA, cross-sectional area; VI, vastus intermedius; VL, vastus lateralis; MRC, Medical Research Council sum-score; IMS, ICU mobility scale; HHD, hand-held dynamometry measuring peak knee extension force.

ECMO, are required to investigate the effect of ECMO on muscle wasting, and the impact of different cannulation approaches. Ultrasound imaging holds promise for investigating the effects of interventions on muscle wasting and weakness in patients requiring ECMO, such as increased early mobilisation or electrical muscle stimulation. Furthermore, it is well established that muscle size in only one factor associated with muscle strength. Therefore, future studies should include muscle ultrasound combined with electrophysiological studies and muscle biopsy to add valuable information to our knowledge of the pathological processes contributing to ICUAW in this population.

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Conflicts of interest

On behalf of all authors, the corresponding author states that there is no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2018.08.002.

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Supplementary Information

Materials and methods

1. Ultrasonography imaging procedure and measures:

Patients were positioned supine with a pillow under their head; hip and knee extended; leg in neutral rotation. The ultrasound probe was placed directly on the skin, perpendicular to the skin surface, and a water soluble transmission gel was used to aid acoustic coupling without depressing the dermal surface.

One leg was measured to avoid disturbing or needing to move the ECMO cannulae. As ECMO cannulation was predominantly femoral in this study, the cannulae were often overlying the quadriceps muscle on the anterior thigh. We chose to measure the non-cannulated leg, when only one leg was cannulated. When both legs were cannulated, we measured the leg with the venous cannula in venoarterial ECMO and we measured the leg with better access to the thigh in venovenous ECMO.

The investigator palpated anatomical landmarks to identify the image acquisition locations, which were then indicated with an indelible marker on the patient's skin. Firstly, the linear transducer was positioned on the anterior surface of the thigh in the transverse plane at a point that was two thirds of the distance from the medial aspect of the anterior superior iliac spine (ASIS) to the superior patella border, and 50% of the distance between the femoral epicondyles to measure rectus femoris cross-sectional area (RF-CSA). This location was the most proximal position in the thigh where the whole cross-sectional image of RF was within the field of view. In order to measure RF-CSA the entire border of RF needed to lie within the field of view of the transducer footprint, otherwise the image was excluded.

The transducer was then rotated to lie on the anterior thigh in the sagittal plane to measure thickness of rectus femoris (RF), vastus intermedius (VI) and total muscle thickness (RF + VI). The transducer was then moved laterally 6-12cm to measure vastus lateralis (VL) thickness, VI thickness and total muscle thickness (VL + VI). The final position of the transducer was determined by the best view of VL and VI and the lateral distance from the mid-point was recorded. To ensure consistency between measures, the same locations were used at each time point for each individual patient.

To date, there is no universal protocol for skeletal muscle ultrasound. Muscle thickness has been measured previously in the literature in both the sagittal plane [1-3] and the transverse plane [4, 5]. We wanted both the anterior and lateral thigh muscle thickness measures to be measured in the same plane, and VL is usually measured in the sagittal plane [2, 6] since it is difficult to capture it in the

transverse plane due to its size and architecture. In an earlier study [7], total muscle thickness was measured in both the sagittal and transverse planes, and they showed that the measurement in the transverse plane was strongly correlated with the corresponding measurement in the sagittal plane ($r = 0.97$, $p < 0.001$).

Finally, the transducer was placed in the transverse plane on the anterior thigh at a point that was 50% of the distance from the medial aspect of the ASIS and the superior patella border, and 50% of the distance between the femoral epicondyles. This position was used to measure RF echogenicity. This point was chosen as it provided a large enough image of RF to accommodate the region of interest for analysis. The same image acquisition locations and imaging order was used for each patient at each time point.

Muscle thickness parameters were calculated in centimeters in the middle of the ultrasound image at a 90-degree angle from the deep aponeurosis, as the distance between the superficial and deep aponeurosis of the muscle, or to the surface of the femur when measuring total muscle thickness. Cross-sectional area of RF was measured in centimeters squared, and was calculated by manually tracing the inner echogenic line of the RF fascia.

Echogenicity was determined using computer-assisted quantitative grayscale analysis as previously described by Cartwright et al [8]. The region of interest (ROI) was determined by a standard square (2 x 2 cm) within the muscle margins of RF and excluding bone or surrounding fascia. If the area to be analysed was smaller than 2 x 2 cm, the largest possible square within the anatomic boundaries of the muscle was examined. Mean and SD echogenicity of this ROI was calculated by using the histogram function of ImageJ software (National Institutes of Health, Bethesda, Maryland) and expressed in arbitrary units as a value between 0 (=black) and 255 (=white). The initial device settings were kept constant for gain and frequency and depth was set at 4.9 cm. The depth setting was only increased when a deeper view was required to view the femur for muscle thickness measures. To confirm the accuracy of technique and interpretation, the de-identified images of the first five patients were analysed separately by an expert in muscle ultrasound (SM), who was a co-investigator on the study.

2. Muscle strength and mobility level

Measures of muscle strength and highest mobility level were obtained at day 10 and day 20 in order to determine the relationship between these volitional measures and the USI parameters. On each test day, the level of alertness and attention were assessed using the Richmond Agitation-Sedation Scale (RASS) [9] and Attention Screening Examination (ASE) [10]. The RASS is a 10 point scale, ranging from -5 to +4, and has high reliability ($k = 0.73$, 95% CI 0.71 to 0.75) and validity in ICU patients [9].

Similarly, the ASE has been tested for validity and inter-rater reliability in ICU patients (Kappa of 0.79 to 0.95) and forms part of the assessment of inattention in the Confusion Assessment Method for ICU patients (CAM-ICU) [10]. Muscle strength was assessed only if the RASS was between -1 and +1 and the ASE ≥ 8/10, signifying that the patient had suitable attention to comply with volitional measures of muscle strength [11].

Muscle strength was assessed using the Medical Research Council sum-score (MRC). It involved an isometric strength assessment of three upper limb and three lower limb muscle groups bilaterally, with a score from 0 to 5 for each muscle group, and maximum score of 60 [12]. A score of less than 48 is indicative of intensive care unit acquired weakness (ICUAW) [11, 13]. Inter-rater reliability of the MRC is very good in critically ill patients (Pearson's r = 0.96) [14]. The minimal important difference is 2 to 3.6 points [15].

Peak isometric knee extension force was measured in the modified recumbent position with 30 degrees of knee flexion over 6-second intervals using the Nicholas Manual Muscle Tester (model 01165; Lafayette Instrument Company, Lafayette, Indianna). This hand held dynamometer (HHD) registers 0.0 to 199.9 kg with a precision of 0.1 kg. Three trials were completed on each leg with 1 minute rest in between each test. The best measure/peak force for each leg was used for analysis. Patients were not given warm-up exercises. Standardized instructions and encouragement were provided. A "Make" test protocol was used, where the examiner holds the dynamometer stationary while the patient exerts maximal force against it [16]. The dynamometer was placed perpendicular to the leg just proximal to the talocrural joint line. Test-retest agreement for bilateral knee extension force measured with dynamometry in critically ill patients is very good (ICC [95% CI]: 0.896 [0.706-0.963] to 0.909 [0.722-0.969] [17].

The highest level of mobility was scored using the ICU Mobility Scale (IMS), which is scored from 0 to 10, with 10 being the best score. It has good inter-rater reliability (Weighted Kappa of 0.83; 95% CI: 0.76 - 0.90) [18]. Highest level of mobility achieved in the week prior to ICU admission and during ECMO was also recorded from a retrospective review of the medical histories using the IMS. Time taken in days to achieve mobility milestones, including time to first stand and time to first walk more than 5 metres away from the bed, were also recorded.

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Chapter 6: EARLY REHABILITATION DURING EXTRACORPOREAL MEMBRANE OXYGENATION HAS MINIMAL IMPACT ON PHYSIOLOGICAL PARAMETERS: A PILOT RANDOMISED CONTROLLED TRIAL

6.1. Declaration of authorship: Chapter 6

Student's declaration:

The nature and extent of contributions to Chapter 6 of this thesis are as follows:

Name	Nature of contribution	Contribution
Kate Hayes	Study concept and design, ethics application, data collection and analysis, manuscript preparation and revision for publication	70%
Anne Holland	Study concept and design, data analysis, drafting and revision of manuscript	10%
Vincent Pellegrino	Study concept and design, revision of manuscript	3%
Meredith Young	Study concept, recruitment of subjects, revision of manuscript	3%
Eldho Paul	Data analysis, revision of manuscript	2%
Carol Hodgson	Study concept and design, ethics application, data analysis, drafting and revision of manuscript	12%

Supervisor's declaration:

I hereby certify that the declaration above is a correct reflection of the extent and nature of contributions made toward Chapter 6 of this thesis by the student and all listed co-authors.

Name of supervisor	Signature
Anne Holland	

6.2. Preface to Chapter 6

Human Research Ethics Committee approvals for this study were granted from the Alfred Hospital Ethics Committee (Project number 149/17) and the La Trobe University Human Ethics Committee (UHEC). See Appendix 1 for the ethics approval forms.

The randomised controlled trial presented in Chapter 6 was published in *Australian Critical Care* and is presented in its published format.

Hayes K, Holland AE, Pellegrino VA, Young M, Paul E, Hodgson CL. Early rehabilitation during extracorporeal membrane oxygenation has minimal impact on physiological parameters: A pilot randomised controlled trial. *Aust Crit Care.* 2020. doi:10.1016/j.aucc.2020.07.008

See Appendix 2 for permission for inclusion in this thesis

Aspects of this study were presented at the following conference:

Oral presentation:

World Congress of Intensive Care in Melbourne, Australia, 17/10/2019.

Title: Early intensive rehabilitation does not affect respiratory or haemodynamic parameters in patients requiring extracorporeal membrane oxygenation.

Poster presentation: Alfred Research Week June 2019.

Title: Early intensive rehabilitation does not affect respiratory or haemodynamic parameters in patients requiring ECMO.

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Research paper

Early rehabilitation during extracorporeal membrane oxygenation has minimal impact on physiological parameters: A pilot randomised controlled trial

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ABSTRACT

Background: Patients on extracorporeal membrane oxygenation (ECMO) often require prolonged periods of bed rest owing to their severity of illness along with the care required to maintain the position and integrity of the ECMO cannula. Many patients on ECMO receive passive exercises, and rehabilitation is often delayed owing to medical instability, with a high proportion of patients demonstrating severe muscle weakness. The physiological effects of an intensive rehabilitation program started early after ECMO commencement remain unknown.

Objectives: The primary objective of this study was to describe the respiratory and haemodynamic effects of early intensive rehabilitation compared with standard care physiotherapy over a 7-d period in patients requiring ECMO.

Methods: This was a physiological substudy of a multicentre randomised controlled trial conducted in one tertiary referral hospital. Consecutive adult patients undergoing ECMO were recruited. Respiratory and haemodynamic parameters, along with ECMO settings, were recorded 30 min before and after each session and continuously during the session. In addition, the minimum and maximum values for these parameters were recorded outside of the rehabilitation or standard care sessions for each 24-h period over the 7 d. The number of minutes of exercise per session was recorded.

Results: Fifteen patients (mean age = 51.5 ± standard deviation of 14.3 y, 80% men) received ECMO. There was no difference between the groups for any of the respiratory, haemodynamic, or ECMO parameters. The minimum and maximum values for each parameter were recorded outside of the rehabilitation or standard care sessions. The intensive rehabilitation group (n = 7) spent more time exercising per session than the standard care group (n = 8) (mean = 28.7 versus 4.2 min, $p < 0.0001$). Three patients (43%) in the intensive rehabilitation group versus none in the standard care group mobilised out of bed during ECMO.

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Conclusions: In summary, early intensive rehabilitation of patients on ECMO had minimal effect on physiological parameters.

1. Introduction

Extracorporeal membrane oxygenation (ECMO) is a form of extracorporeal life support that is used in patients with the most severe forms of cardiorespiratory failure, where conventional therapies have failed [1,2]. The extracorporeal circuit includes a blood pump, gas exchange membrane, and large cannula, which are often positioned in the femoral vessels or vessels of the neck. These patients are often the sickest cohort in the intensive care unit (ICU) and traditionally receive bed rest as part of their care. Duration of bed rest during critical illness has been reported as the only consistent factor associated with the development of severe prolonged neuromuscular weakness [3]. Described clinically as ICU-acquired weakness (ICUAW), it is associated with significant physical and cognitive deficits that may persist for years after the ICU stay [4]. Previous studies have demonstrated that a high proportion of patients requiring ECMO have ICUAW [5,6]. In an attempt to address this issue, there has been increasing interest in having patients awake and participating in active rehabilitation and ambulation whilst on ECMO[7–9]. However, this is still not commonly achieved [10]. The majority of patients on ECMO remain in bed and receive passive exercises [11], and rehabilitation is often started late in the ICU admission. Little is known about the respiratory and haemodynamic effects of a more intensive rehabilitation program, started early after ECMO commencement.

Early rehabilitation in the ICU is recognised as safe and feasible in other ICU populations [12]. Patients who receive rehabilitation early in their ICU stay have shown improved rates of returning to independent functioning, shorter ICU and hospital length of stay (LOS) and more days alive and out of hospital at 6 months [13]. The number of publications investigating rehabilitation of patients whilst on ECMO has increased over the past decade; however, the majority of studies are retrospective and mostly case series [14–16]. This new area of physiotherapy practice is both labour- and time-intensive owing to the severity of illness of patients along with the care required to maintain the position and integrity of the ECMO cannula. With the dramatic increase in the use of ECMO worldwide [17], a prospective study examining the effect of early intensive rehabilitation on physiological parameters in patients on ECMO is urgently needed. This will assist with the development of safe and effective rehabilitation guidelines for patients on ECMO.

The primary aims of this study were to describe the respiratory and haemodynamic effects of early intensive rehabilitation compared with standard care physiotherapy over a 7 d period in patients requiring ECMO. In addition, we aimed to determine if the minimum and maximum values of the physiological parameters were recorded outside of or during the rehabilitation or standard care physiotherapy sessions. A secondary aim was to describe the relationship between the physiological parameters and the highest level of mobility achieved during rehabilitation or standard care physiotherapy.

2. Materials and methods

2.1. Study design

This was a physiological substudy of a multicentre, phase II pilot randomised controlled trial of intensive rehabilitation in ECMO [18] conducted in one tertiary referral hospital for ECMO in Australia. The study was registered at ClinicalTrials.gov (NCT03328767). Local institutional ethics approval was obtained (Project 149/17). Data were reported in line with the CONSORT (CONsolidated Standards of Reporting Trials) 2010 statement and checklist [19]. Informed consent was sought from the patient's medical treatment decision-maker, with consent for ongoing participation being sought from patients when they became capable of providing informed consent. Group allocation was computer generated using a Web-based system and distributed in opaque envelopes. A permuted block randomisation method was used to allocate eligible patients to either the standard care or the intervention group in a 1:1 ratio. It was not feasible to blind treatment providers to group allocation. The methodology outlined pertains to the primary randomised controlled trial, with the exception of collection of physiological outcomes, which was specific to this substudy.

2.2. Inclusion and exclusion criteria

All consecutive patients who were aged 18 y or older with an anticipated ECMO duration of more than 24 h were included. Patients were excluded if they met any of the following criteria: more than 72 h on ECMO or 5 d in the ICU before recruitment, pre-existing musculoskeletal or neurological impairments, any current cancer or chemotherapy, pre-existing mobility impairment, pre-existing cognitive impairment, language barrier, where death was deemed imminent and inevitable, or where the physiotherapist providing the rehabilitation was unavailable.

2.3. Intervention

The early, intensive rehabilitation was provided by a senior physiotherapist who had specialised training in ECMO. Rehabilitation commenced on the day of randomisation and continued for a 7 d period. The intervention involved a progression of exercises with the objective of exercising the patient at the highest level of mobility that the patient could tolerate, based on the ICU Mobility Scale (IMS) [20]. Rehabilitation was conducted for up to an hour per day, with a minimum time of 20 min if passive exercise was performed and 30 min if active exercise was undertaken. This time could be continuous or intermittent throughout the day, depending on the individual physiological and perceived exertion response to rehabilitation. The intensity of rehabilitation was targeted at a perceived exertion level of 3–5 on the modified Borg scale of rating of perceived exertion, which represents a moderate to strong level of exertion [21]. Sessions were conducted if the patient was physiologically stable, defined by international expert consensus on mobilising ICU patients, including specific recommendations for patients on ECMO [22].

Daily sedation targets were aimed at a Richmond Agitation and Sedation Scale (RASS) score of between −1 and +1, which corresponds to the patient being drowsy but with sustained awakening to voice through to restless but not aggressive. The RASS is a 10-point scale that has discrete criteria for levels of sedation and agitation, ranging from −5 (unrousable) to +4 (combative) [23]. The RASS score was recorded during each intensive rehabilitation and standard care physiotherapy session. At least three staff members were available during active rehabilitation sessions out of bed, with the physiotherapist assisting the patient, the ECMO specialist nurse monitoring the ECMO cannula and circuit, and the primary nurse

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managing other lines and attachments. All other aspects of management were as per routine ICU practice.

The control group received care from physiotherapy staff not involved in the early, intensive rehabilitation program. Passive range of motion exercises for the upper and lower limbs were the only exercises provided to patients who were unstable or requiring sedation (with a RASS score of <-1). When the patients met the RASS target of -1 to $+1$, rehabilitation consisted of resistance and active range of motion exercises for the upper and lower limbs. The patients could progress to sitting on the edge of the bed, standing, and, ultimately, ambulation, if medical stability allowed. The expert consensus guidelines for mobilising ICU patients [22] were used to assess physiological stability and suitability to participate in standard care. The timing of commencement of rehabilitation was at the discretion of the treating physiotherapist, and there was no set frequency, duration, or intensity of rehabilitation provided.

2.4. Demographic and clinical characteristics

Demographic and clinical data were recorded from the medical history and included the following: age, gender, reason for ICU admission, ECMO mode [veno-venous (VV) or veno-arterial (VA)] and cannula configuration, ECMO duration (days), duration of mechanical ventilation (days), LOS in the ICU and hospital (days), discharge destination, and in-hospital mortality. The Acute Physiology and Chronic Health Evaluation) (APACHE II and III) scores; severity of illness scores with higher scores corresponding to more severe illness, were calculated at ICU admission.

Preadmission comorbidities were scored using the Functional Comorbidity Index (FCI) [24] from the ICU admission history, with additional information from the patient's medical treatment decision-maker. The FCI is scored out of a maximum of 18, with higher scores correlating to higher mortality and worse physical function [24–26]. Premorbid frailty was assessed at ICU admission using the Clinical Frailty Scale (CFS) which is scored from 1 to 9, with higher scores indicating worse frailty [27] and a score of ≥ 5 defining a patient as frail. The level of independence with activities of daily living (ADL) prior to admission was scored using the Katz Index of ADL [28]. The CFS and Katz score were completed from discussion with the patient's medical treatment decision-maker, with verification from the patient when they could provide consent for ongoing participation in the study.

2.5. Outcome measures

2.5.1. Physiological parameters

The primary physiological outcomes of interest were respiratory rate, oxygen saturation, heart rate, and mean arterial pressure. A detailed description of all the respiratory, haemodynamic, and ECMO parameters collected is available in the supplementary material (Supplementary Table 1). Respiratory and haemodynamic parameters, along with ECMO settings, were recorded 30 min before and after each rehabilitation or standard care session. In addition, the minimum and maximum values for each parameter were recorded outside of the rehabilitation or standard care sessions for each 24 h period over the 7 d. These parameters were also recorded continuously during the intensive rehabilitation or standard care sessions.

2.5.2. Highest mobility level, mobility milestones, and exercise duration

The highest level of mobility was scored using the ICU Mobility Scale (IMS), which is an ordinal scale ranging from 0 to 10, with 10 being the best score and representing walking independently without a gait aide and a score of 0 equal to lying in bed doing no active movement [20]. The number of minutes of exercise per session was recorded, along with the highest mobility level achieved during each of the early, intensive rehabilitation and standard care sessions over the 7 d period. The highest level of mobility achieved in the week before ICU admission was also recorded using the IMS, from a retrospective review of the medical histories and from discussion with the patient's medical treatment decision-maker. Time taken in days from recruitment to achievement of mobility milestones was recorded. Mobility milestones included time to first sit out of bed, time to first stand, and time to first walk more than 5 m away from the bed.

2.5.3. Safety events

Adverse safety events were defined in the primary randomised controlled trial [18] and included patient agitation, patient fall to the floor, ECMO cannula dislodgment, major bleeding at the ECMO cannula site, a requirement to increase ECMO blood flow or fresh gas flow, increased inotrope requirements, and arrhythmias. Adverse safety events were reported if they occurred during the exercise intervention, causing the session to cease, or if they occurred at any time but may have been related to the intervention.

2.6. Power calculations and sample size

This substudy was part of a larger multicentre phase II safety and feasibility pilot randomised controlled trial, and as such, no formal power calculation was performed. All 15 patients randomised at the one site were included in this physiological substudy.

2.7. Statistical analysis

All data were analysed using IBM SPSS Statistics, version 25, for Windows (IBM Corp., Armonk, New York, USA) or SAS software, version 9.4 (SAS Institute, Cary, NC, USA). Continuous variables were initially assessed for normality and expressed as mean ± standard deviation or medians (interquartile ranges), depending on the underlying distribution of the data. Categorical variables were expressed as counts and proportions. Comparisons between groups were carried out using independent t-tests for normally distributed continuous variables, the Mann–Whitney U test for non-normally distributed continuous variables, and the chi-square or Fisher's exact test as appropriate for categorical variables.

Analyses of the physiological outcome data over the 7 d period were performed using the PROC MIXED procedure in SAS software, with each patient treated as a random effect. The primary outcomes (respiratory, haemodynamic, and ECMO parameters) were assessed fitting main effects for group (intensive rehabilitation or standard care) and time and an interaction between group and time to determine if groups behaved differently over time. Linear mixed-effects modelling was also used to assess the association between the highest level of mobility achieved (IMS) and each of the outcome variables. All observed data were considered for analysis, with the mixed-effects models assuming noninformative dropout such that the probability of dropout may depend on a participant's previous response but not on current or future responses. Analyses were based on the intention-to-treat principle, which included data on all randomised participants with at least one outcome measure. Statistical significance was set at a two-sided p value of ≤ 0.05.

3. Results

Over a 6 month period, a total of 44 patients underwent ECMO support, of which 41 met the inclusion criteria (Fig. 1). All patients excluded for being on ECMO for more than 72 h were retrievals from other hospitals. Table 1 describes the baseline demographic

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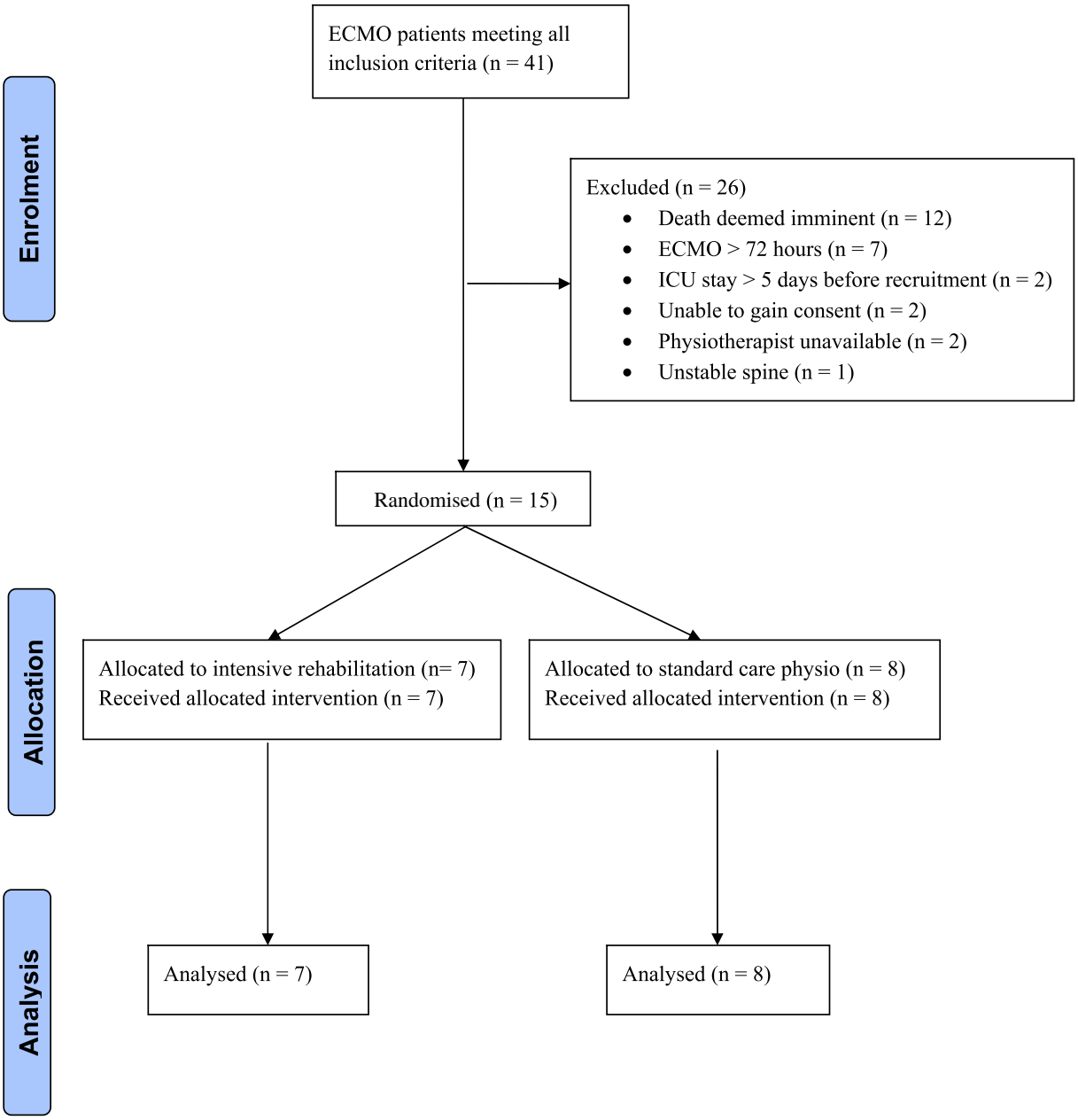

Fig. 1. CONSORT (CONsolidated Standards of Reporting Trials) diagram: design and flow of the participants through the study. ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit.

and clinical characteristics of the included patients. The time to recruitment was a median of 37 h (interquartile range: 27–47 h) after ECMO commencement. All patients had at least one femoral vessel cannulated for ECMO, with 13 of 15 (87%) having femoro-femoral cannulation.

There was no difference between the groups for the primary respiratory (Table 2) or haemodynamic parameters (Table 3). ECMO flow, fresh gas flow, and blender FiO_2 were not adjusted during any of the rehabilitation or standard care physiotherapy sessions. The minimum and maximum values for each of the primary respiratory and haemodynamic parameters were recorded outside of the rehabilitation or standard care sessions (Fig. 2). A detailed description for all the remaining respiratory, haemodynamic, and ECMO parameters is available in the supplementary material (Supplementary Tables 2–7). Although there was a statistically significant interaction effect for PEEP (Positive End Expiratory Pressure) and minimum tidal volume during physiotherapy (Supplementary Table 2) and for PEEP from before to after physiotherapy (Supplementary Table 4), the change was very small and related to a single episode in one patient.

The only physiological parameters associated with the highest level of mobility (IMS) were respiratory rate and maximum tidal volume during physiotherapy (Supplementary Table 8). Higher mobility levels (IMS) were also associated with lower noradrenaline dosage, less sedation, longer exercise duration, and lower ECMO fresh gas flow (Supplementary Table 8). The level of sedation over the 7 d study period was high for both groups (Supplementary Table 9) but reduced over time ($p < 0.0001$). There was no difference between the groups for sedation scores ($p = 0.51$).

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Table 1
Baseline demographic and clinical characteristics.

Characteristic	Intensive PT Group (n = 7)	Standard care PT Group (n = 8)
Age (years)	52.0 ± 13.3	51.1 ± 16.0
Male	6 (86)	6 (75)
Hospital data		
APACHE II score	24.3 ± 6.4	17.6 ± 3.4
APACHE III score	97.1 ± 30.7	71.3 ± 16.1
Main diagnosis		
ARDS	0 (0)	4 (50)
Post-LTx primary graft failure	1 (14.3)	0 (0)
Pulmonary hypertension after LTx	0 (0)	1 (12.5)
Cardiac failure/infarction	3 (42.9)	1 (12.5)
Cardiac arrest	2 (28.6)	1 (12.5)
Post-HTx primary graft failure	1 (14.3)	1 (12.5)
ECMO type		
Venoarterial	6 (85.7)	4 (50)
Venovenous	1 (14.3)	4 (50)
Preadmission status		
IMS pre ICU (out of 10)	10 (10–10)	10 (10–10)
Katz score (category A)	5 (71)	7 (88)
Functional Comorbidity Index (out of 18)	1.0 ± 1.2	2.8 ± 2.6
Clinical Frailty Scale (out of 9)	3 (3–5)	5 (3–5)

APACHE II, Acute Physiology and Chronic Health Evaluation II score; APACHE III, Acute Physiology and Chronic Health Evaluation III score; ARDS, acute respiratory distress syndrome; LTx, lung transplantation; HTx, heart transplantation; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IMS, ICU Mobility Scale; PT, physiotherapy; SD, standard deviation.
Values are presented as mean ± SD, as median (interquartile range), or as number (%).

The early intensive rehabilitation group spent more time exercising per session than the standard care group (mean = 28.7 [standard error {SE} = 2.5] versus 4.2 [SE = 2.2] minutes, $p < 0.0001$). Three patients (3/7, 43%) in the intensive rehabilitation group, versus none in the standard care group, mobilised out of bed whilst on ECMO. The respiratory and haemodynamic changes during the out of bed rehabilitation were small with no increase in inotropes, and all three patients were on VA ECMO. There was a significant increase in the highest mobility level (IMS) achieved over the 7 d period (mean = 0 [SE = 0.4] on day 1 versus mean = 2 [SE = 0.5] on day 7, $p = 0.03$), with no difference between the groups ($p = 0.14$). Patients in the intensive rehabilitation group achieved standing sooner than patients in the standard care group (Table 4). There were no differences in the time to achieve other mobility milestones, LOS in the ICU and hospital, or duration of mechanical ventilation (Table 4). There were no adverse events related to the intensive rehabilitation or standard care physiotherapy, as defined in the primary randomised controlled trial [18], and none of the sessions were interrupted or cancelled owing to safety concerns.

4. Discussion

This physiological study provides some important new findings in relation to early rehabilitation of patients on ECMO. Changes in respiratory, haemodynamic, and ECMO parameters within each intervention were small, and the minimum and maximum values of parameters were recorded outside of physiotherapy. This implies that the physiological impact was less than that with other aspects of patients' daily care, including nursing and medical procedures. The patients in the intensive rehabilitation group did spend significantly more time exercising than those in the standard care group, and they achieved standing 15 d earlier. Although there was no significant difference in the highest mobility level achieved between the groups, three of the patients in the intensive rehabilitation group versus none in the standard care group stood whilst on ECMO. It does raise the question of whether the intensity of the intervention could have been even higher. A low rate of potential safety events (2.6%) and even lower rate of consequences from those events (0.6%) were reported in a systematic review with meta-analysis of studies investigating early mobilisation in the general ICU population [12], suggesting that the intensity of rehabilitation in the ICU is perhaps too conservative. Further research is required to investigate dosage and intensity of rehabilitation and the impact on safety and efficacy in the ECMO population.

Sedation levels were high for most patients, especially in the initial days of the study owing to haemodynamic and respiratory instability, which precluded weaning of sedation. This is consistent with an international survey of sedation practices for patients on ECMO [11], in which 84% of respondents targeted a moderate to deep level of sedation. Not all patients on VV ECMO or VA ECMO are suitable for early intensive rehabilitation owing to respiratory or haemodynamic instability and concomitant high sedation requirements. We did follow a daily screening process to determine physiological suitability for participation in exercise training based on the expert consensus document for mobilising ventilated ICU patients [22] and similar to previous studies of patients on ECMO [10,14,15]. These earlier studies also reported a proportion of patients on ECMO who were unsuitable for active exercise owing to failure to meet screening criteria. The majority of patients in each of these studies received passive range of motion exercises in bed [10,14,15]. This is further supported by an international survey of mobilisation practices of patients on ECMO [11], in which the majority of respondents reported that passive exercises in bed were the most common exercise provided. The high proportion of passive exercises performed in the first few days of the present study may partly account for the lack of association between the highest mobility level (IMS) and the physiological parameters.

There is a paucity of studies describing the physiological effects of exercise in patients on ECMO, and most are in the form of case reports or retrospective cohort studies [14,15,29]. In a retrospective study of eight patients on ECMO, a significant increase in ECMO blood flow during standing or mobilisation was reported; however, the actual difference was only 0.09 L/min [14], which is unlikely to be clinically significant. ECMO fresh gas flow was not altered during any of the rehabilitation sessions. Similarly, the physiological changes observed in the present

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Table 2
Respiratory rate and oxygen saturation during physiotherapy as per allocation.

Physiological parameter	Time period	Standard care PT, mean (SE)	Intensive PT, mean (SE)	Time × group, p value[a]	Time, p value	Group, p value
RR maximum (breaths/min)	Day 1	12.50 (1.89)	14.57 (2.02)	0.67	0.001	0.42
	Day 2	12.38 (1.89)	14.00 (2.02)			
	Day 3	16.00 (1.89)	13.76 (2.15)			
	Day 4	16.55 (2.13)	17.94 (2.57)			
	Day 5	16.25 (1.89)	16.45 (2.16)			
	Day 6	17.25 (1.89)	19.17 (2.33)			
	Day 7	18.66 (1.99)	23.69 (2.57)			
RR minimum (breaths/min)	Day 1	12.13 (1.62)	13.29 (1.74)	0.15	0.006	0.15
	Day 2	12.25 (1.62)	13.43 (1.74)			
	Day 3	14.00 (1.62)	13.50 (1.84)			
	Day 4	14.52 (1.81)	16.66 (2.17)			
	Day 5	13.75 (1.62)	14.94 (1.85)			
	Day 6	13.75 (1.62)	16.80 (1.98)			
	Day 7	14.40 (1.71)	22.19 (2.17)			
SpO_2 maximum (%)	Day 1	95.75 (0.92)	99.57 (0.98)	0.13	0.38	0.26
	Day 2	97.12 (0.92)	98.71 (0.98)			
	Day 3	97.37 (0.92)	97.99 (1.02)			
	Day 4	98.75 (0.99)	99.69 (1.16)			
	Day 5	97.62 (0.92)	98.45 (1.03)			
	Day 6	97.87 (0.92)	98.11 (1.08)			
	Day 7	98.48 (0.95)	98.94 (1.16)			
SpO_2 minimum (%)	Day 1	93.25 (1.27)	98.14 (1.36)	0.14	0.93	0.48
	Day 2	95.00 (1.27)	96.57 (1.36)			
	Day 3	95.38 (1.27)	95.53 (1.42)			
	Day 4	96.83 (1.39)	96.33 (1.39)			
	Day 5	95.63 (1.27)	95.94 (1.43)			
	Day 6	94.75 (1.27)	95.55 (1.52)			
	Day 7	96.20 (1.32)	95.83 (1.65)			

PT, physiotherapy; RR, respiratory rate; SpO_2, peripheral oxygen saturation; SE, standard error.
[a] Linear mixed-model testing interaction between group allocation and time. Data are reported as mean (standard error).

Table 3
Haemodynamic parameters during physiotherapy as per allocation.

Physiological parameter	Time period	Standard care, mean (SE)	Intensive PT, mean (SE)	Time × group, p value[a]	Time, p value	Group, p value
HR maximum (beats/min)	Day 1	93.00 (6.96)	98.71 (7.44)	0.86	0.94	0.60
	Day 2	87.13 (6.96)	100.43 (7.44)			
	Day 3	92.88 (6.96)	95.67 (7.72)			
	Day 4	90.01 (7.48)	91.16 (8.70)			
	Day 5	91.50 (6.96)	95.72 (7.75)			
	Day 6	90.88 (6.96)	90.57 (8.15)			
	Day 7	89.60 (7.19)	93.41 (8.70)			
HR minimum (beats/min)	Day 1	89.00 (6.97)	95.43 (7.45)	0.99	0.78	0.49
	Day 2	82.88 (6.97)	93.57 (7.45)			
	Day 3	86.38 (6.97)	92.47 (7.69)			
	Day 4	83.15 (7.40)	85.99 (8.51)			
	Day 5	87.63 (6.97)	92.01 (7.71)			
	Day 6	84.00 (6.97)	89.25 (8.05)			
	Day 7	84.84 (7.16)	91.49 (8.51)			
MAP maximum (mmHg)	Day 1	78.63 (3.84)	72.43 (4.11)	0.77	0.19	0.41
	Day 2	77.38 (3.84)	77.00 (4.11)			
	Day 3	79.50 (3.84)	76.18 (4.38)			
	Day 4	82.54 (4.34)	85.48 (5.25)			
	Day 5	85.13 (3.84)	78.43 (4.39)			
	Day 6	83.25 (3.84)	83.74 (4.76)			
	Day 7	84.65 (4.06)	76.98 (5.25)			
MAP maximum (mmHg)	Day 1	75.25 (3.14)	66.57 (3.35)	0.57	0.32	0.40
	Day 2	70.00 (3.14)	69.71 (3.35)			
	Day 3	72.38 (3.14)	68.03 (3.58)			
	Day 4	70.76 (3.55)	71.20 (4.31)			
	Day 5	75.63 (3.14)	72.73 (3.59)			
	Day 6	74.50 (3.14)	77.56 (3.90)			
	Day 7	76.06 (3.32)	71.95 (4.31)			

PT, physiotherapy; HR, heart rate; MAP, mean arterial pressure; SE, standard error.
[a] Linear mixed-model testing interaction between group allocation and time. Data are reported as mean (standard error).

study were small and ECMO settings were not altered. The three patients on VA ECMO who did participate in out of bed mobility also demonstrated small changes in respiratory and haemodynamic parameters, with no increase in inotrope requirements. These results are further supported by an earlier study by Abrams et al. [15], in which no change in ECMO blood flow or fresh gas flow was reported in 35 patients participating in physiotherapy including ambulation. In a case report by Morris

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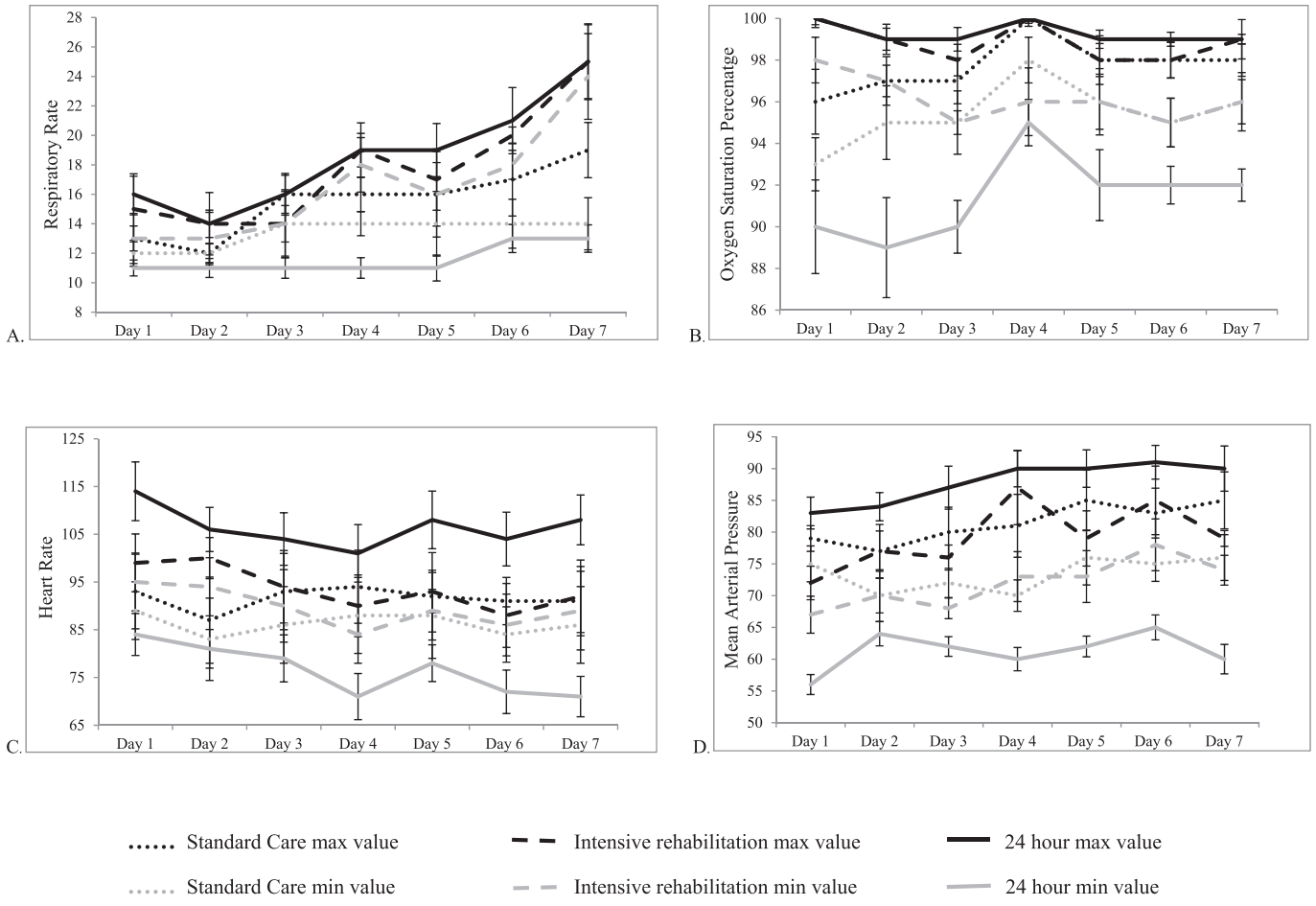

Fig. 2. Changes in respiratory and haemodynamic parameters during physiotherapy over 7 d. Data are expressed as means and standard error. (A) Respiratory rate in breaths per minute. (B) Peripheral oxygen saturation as a percentage. (C) Heart rate in beats per minute. (D) Mean arterial pressure in mmHg.

et al. [29], physiological parameters in a patient on VV ECMO were reported before, during, and after sitting on the edge of the bed. In contrast to the present study, the patient demonstrated a clinically significant increase in systolic blood pressure, heart rate, and ECMO blood flow whilst oxygen saturation reduced during the session. The ECMO fresh gas flow was unchanged, possibly resulting in an increased shunt fraction. In the present study, the majority of patients were on VA ECMO with minimal

Table 4
Clinical outcomes of patients requiring ECMO.

Outcome	Intensive PT	N	Standard care PT	N	p-value
Hospital outcomes					
In-hospital mortality	3 (42.9)	7	1 (12.5)	8	0.46
ECMO duration (days)	8.1 ± 4.9	7	10.9 ± 5.5	8	0.32
ECMO duration for survivors	10.5 ± 5.5	4	11.5 ± 5.7	7	0.78
Ventilation (days)	6.2 ± 2.5	7	9.2 ± 3.8	8	0.33
Ventilation for survivors	7.3 ± 2.8	4	9.4 ± 4.1	7	0.39
LOS in the ICU (days)	12.9 (7.2–16.7)	7	21.4 (15.5–38.5)	8	0.05
LOS in the ICU for survivors	16.7 (14.6–21.6)	4	22.2 (16.2–38.5)	7	0.45
LOS in the hospital for survivors	41.9 (34.3–56.4)	4	34.4 (29.3–87.2)	7	0.85
Mobility milestones					
Time to first SOOB (days)	12.6 ± 6.6	4	12.5 ± 7.7	8	0.98
Time to first stand (days)	5.5 ± 4.5	5	20.8 ± 12.3	7	0.03
Time to first walk (days)	16.1 (11.5–21.0)	4	21.9 (16.5–52.4)	7	0.35
Discharge destination of survivors					0.30
Home	4 (100)	4	3 (43)	7	
Inpatient rehabilitation	0 (0)	4	3 (43)	7	
Transfer to the local acute hospital	0 (0)	4	1 (14)	7	

ECMO, extracorporeal membrane oxygenation; PT, physiotherapy; ICU, intensive care unit; LOS, length of stay (in days); SOOB; sit out of bed; SD, standard deviation. Values are presented as mean ± SD, median (interquartile range), or as number (%).

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respiratory compromise, therefore the risk of increasing shunt fraction with exercise was less likely. Alterations to ECMO flow and fresh gas flow during exercise may be of greater importance in patients on VV ECMO and warrant further investigation in a larger trial.

The cannulation strategy used for ECMO may affect the delivery of rehabilitation. A number of earlier studies report upper body cannulation as being a facilitator to rehabilitation [30,31]. All of the patients in the present study underwent cannulation of at least one femoral vessel, and this may account for the longer time period to achieve sitting out of bed than standing, in an attempt to avoid prolonged hip flexion. Similar to an earlier study [10], we assessed the effect of hip flexion on ECMO blood flow as part of the daily screening. In addition, if there was oozing from the femoral cannula, we avoided hip flexion but still assessed for suitability for standing on a tilt table. Only eight patients on ECMO of a cohort of 254 (3%) ambulated in the earlier study by Wells et al. [10], five of whom had femoral cannulation. This demonstrates that ambulation of patients on ECMO with femoral cannulation is still uncommon, even in a high-volume ECMO centre with experienced rehabilitation staff.

This study has several limitations, including the small sample size, heterogeneous population, and single centre. However, this was a pilot study and the population was representative of the ECMO cohort at our centre. Any significant effects should be interpreted with caution, given the small sample size, and our results may not be generalisable to other ECMO centres. We also excluded patients who were deemed unlikely to survive, so there may be a selection bias. Not all patients on VV ECMO or VA ECMO are suitable for early intensive rehabilitation; however, owing to the small sample size, we were also unable to perform any subgroup analysis for ECMO type, and this is an area that would benefit from further research. Furthermore, the rehabilitation intensity may have been insufficient to show a significant difference from the standard care physiotherapy, although three patients mobilised out of bed. The effect of a higher intensity of exercise and a longer period of intensive rehabilitation, extending beyond the 7-d period, is unknown.

5. Conclusions

In summary, early intensive rehabilitation of patients on ECMO had minimal effect on respiratory and haemodynamic parameters or ECMO settings. The small changes in physiological parameters that occurred during rehabilitation were less than those observed outside of the rehabilitation sessions. The ideal timing, duration, frequency, and intensity of rehabilitation in patients on ECMO remain unclear; however, the positive effect on mobility milestones is promising and warrants further investigation.

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Conflict of interest

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CRediT authorship contribution statement

K. Hayes: Conceptualisation, Methodology, Formal analysis, Investigation, Data curation, Writing - original draft, Writing - review & editing, Visualisation. **A.E. Holland:** Conceptualisation, Methodology, Formal analysis, Writing - review & editing, Supervision. **V.A. Pellegrino:** Conceptualisation, Writing - review & editing. **M. Young:** Conceptualisation, Methodology, Investigation, Resources, Writing - review & editing. **E. Paul:** Formal analysis, Writing - review & editing. **C.L. Hodgson:** Conceptualisation, Methodology, Writing - review & editing, Supervision.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.aucc.2020.07.008.

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CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	Title page
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	Abstract
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	P1
	2b	Specific objectives or hypotheses	P2
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	P2
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	P2
	4b	Settings and locations where the data were collected	P2
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	P3-4
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	P4-5
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	P6
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	P2
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	P2
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	P2
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	P2
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	P2

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	P6
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	NA
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Fig 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Fig 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	P2
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Fig 1 and P6
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Fig 2, Tables 2-4, Supp Tables 2-9
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Table 4
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	NA
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	P8
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	P10
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	P10
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	P8-10
Other information			
Registration	23	Registration number and name of trial registry	P2 and title page
Protocol	24	Where the full trial protocol can be accessed, if available	Available on request
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	P11

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up to date references relevant to this checklist, see www.consort-statement.org.

Electronic Supplement:

Early rehabilitation during extracorporeal membrane oxygenation has minimal impact on physiological parameters: a pilot randomised controlled trial.

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Supplementary Table 1. Physiological parameters

Respiratory parameters	**Haemodynamic parameters**	**ECMO settings**
RR (breaths/min)	HR (beats/min)	Blood flow (L/min)
FiO_2 (%)	MAP (mmHg)	Fresh gas flow (L/min)
SpO_2 (%)	Inotrope requirements	ECMO FiO_2
Tidal volume (mls)		
PEEP (cmH_20)		
ABG (mmHg)		

ECMO, extracorporeal membrane oxygenation; RR, respiratory rate; FiO_2, fraction of inspired oxygen; SpO_2, peripheral oxygen saturation; PEEP, positive end expiratory pressure; ABG, arterial blood gas; HR, heart rate, MAP, mean arterial pressure

Supplementary Table 2. Tidal volume and PEEP during physiotherapy according to allocation

Physiological parameter	Time period	Standard care PT Mean (SE)	Intensive PT Mean (SE)	Time x Group P value[a]	Time P value	Group P value
Tidal Volume Maximum (mls)	Day 1	384 (97)	428 (107)	0.65	0.01	0.79
	Day 2	386 (97)	465 (107)			
	Day 3	488 (97)	579 (111)			
	Day 4	533 (102)	622 (125)			
	Day 5	494 (97)	562 (117)			
	Day 6	599 (102)	651 (127)			
	Day 7	696 (102)	513 (141)			
Tidal Volume Minimum (mls)	Day 1	272 (55)	356 (61)	0.01	0.66	0.93
	Day 2	292 (55)	392 (61)			
	Day 3	333 (55)	398 (63)			
	Day 4	430 (58)	291 (72)			
	Day 5	344 (55)	412 (67)			
	Day 6	402 (58)	304 (73)			
	Day 7	423 (58)	301 (81)			
PEEP (cmH_20)	Day 1	12 (1)	12 (1)	0.03	< 0.0001	0.22
	Day 2	12 (1)	11 (1)			
	Day 3	10 (1)	9 (1)			
	Day 4	11 (1)	12 (1)			
	Day 5	10 (1)	8 (1)			
	Day 6	10 (1)	6 (1)			
	Day 7	10 (1)	6 (2)			

[a]Linear mixed model testing interaction between group allocation and time. Data reported as mean (standard error). PT, physiotherapy; PEEP, positive end expiratory pressure.

Supplementary Table 3. ECMO parameters during physiotherapy according to allocation

Physiological parameter	Time period	Standard care Mean (SE)	Intensive PT Mean (SE)	Time x Group P value[a]	Time P value	Group P value
ECMO flow maximum (L/min)	Day 1	4.51 (0.33)	3.39 (0.35)	0.57	0.001	0.10
	Day 2	4.24 (0.33)	3.39 (0.35)			
	Day 3	3.69 (0.33)	3.37 (0.38)			
	Day 4	4.06 (0.35)	3.31 (0.43)			
	Day 5	3.74 (0.34)	3.08 (0.40)			
	Day 6	3.70 (0.35)	3.05 (0.43)			
	Day 7	3.28 (0.38)	2.51 (0.43)			
ECMO flow minimum (L/min)	Day 1	4.41 (0.34)	3.35 (0.37)	0.64	0.004	0.17
	Day 2	3.89 (0.34)	3.36 (0.37)			
	Day 3	3.60 (0.34)	3.31 (0.39)			
	Day 4	3.94 (0.36)	3.24 (0.45)			
	Day 5	3.59 (0.35)	3.04 (0.42)			
	Day 6	3.58 (0.36)	3.05 (0.45)			
	Day 7	3.15 (0.40)	2.45 (0.45)			
ECMO fresh gas flow (L/min)	Day 1	5.12 (1.03)	4.71 (1.10)	0.63	< 0.0001	0.64
	Day 2	4.87 (1.03)	4.14 (1.10)			
	Day 3	4.25 (1.03)	4.86 (1.15)			
	Day 4	3.70 (1.06)	2.90 (1.24)			
	Day 5	3.72 (1.05)	2.67 (1.19)			
	Day 6	3.79 (1.06)	2.73 (1.24)			
	Day 7	3.31 (1.12)	2.06 (1.24)			
ECMO FiO_2	Day 1	1.0 (0.1)	0.9 (0.1)	0.63	0.60	0.48
	Day 2	0.9 (0.1)	1.0 (0.1)			
	Day 3	0.8 (0.1)	0.9 (0.1)			
	Day 4	0.9 (0.1)	0.8 (0.1)			
	Day 5	0.8 (0.1)	0.9 (0.1)			
	Day 6	0.8 (0.1)	0.9 (0.1)			
	Day 7	0.8 (0.1)	1.0 (0.1)			

[a]Linear mixed model testing interaction between group allocation and time. Data reported as mean (standard error). ECMO, extracorporeal membrane oxygenation; PT, physiotherapy; FiO_2, fraction of inspired oxygen

Supplementary Table 4. Change in respiratory parameters pre to post physiotherapy according to allocation

Physiological parameter	Time period	Group		Time x Group P value[a]	Time P value	Group P value
		Standard care Mean (SE)	Intensive PT Mean (SE)			
Tidal Volume difference mls	Day 1	16.13 (22.46)	-6.50 (25.93)	0.20	0.052	0.11
	Day 2	0.62 (22.46)	2.67 (25.93)			
	Day 3	63.75 (22.46)	15.40 (28.41)			
	Day 4	-20.83 (25.93)	43.33 (36.67)			
	Day 5	41.13 (22.46)	-54.75 (31.76)			
	Day 6	10.00 (25.93)	-50.00 (36.67)			
	Day 7	-61.83 (25.93)	-80.00 (44.91)			
PEEP difference cmH_20	Day 1	0 (0.09)	0 (0.10)	0.009	0.009	0.06
	Day 2	0 (0.09)	0 (0.10)			
	Day 3	0 (0.09)	0 (0.11)			
	Day 4	0 (0.10)	-0.83 (0.15)			
	Day 5	0 (0.09)	0 (0.13)			
	Day 6	0 (0.10)	0 (0.15)			
	Day 7	0 (0.10)	0 (0.18)			
RR difference breaths/min	Day 1	-0.13 (1.21)	1.00 (1.29)	0.90	0.30	0.98
	Day 2	0.25 (1.21)	-0.29 (1.29)			
	Day 3	-1.13 (1.21)	-0.33 (1.39)			
	Day 4	0.83 (1.39)	0.75 (1.70)			
	Day 5	-0.63 (1.21)	0.17 (1.39)			
	Day 6	3.63 (1.21)	1.40 (1.52)			
	Day 7	1.00 (1.29)	1.25 (1.70)			
SpO_2 difference %	Day 1	-0.87 (0.88)	-0.71 (0.94)	0.44	0.35	0.19
	Day 2	-0.25 (0.88)	-1.57 (0.94)			
	Day 3	-1.25 (0.88)	-1.72 (1.01)			
	Day 4	-0.44 (1.01)	0.52 (1.24)			
	Day 5	0.13 (0.88)	0.34 (1.01)			
	Day 6	-0.38 (0.88)	-3.18 (1.11)			
	Day 7	0.40 (0.94)	-1.98 (1.21)			

[a]Linear mixed model testing interaction between group allocation and time. Data reported as mean (standard error). PT, physiotherapy; PEEP, positive end expiratory pressure; RR, respiratory rate; SpO2, peripheral oxygen saturation

Supplementary Table 5. Change in arterial blood gas parameters pre to post physiotherapy according to allocation

Physiological parameter	Time period	Group		Time x Group P value[a]	Time P value	Group P value
		Standard care Mean (SE)	Intensive PT Mean (SE)			
FiO_2 difference	Day 1	0.04 (0.02)	0.01 (0.02)	0.92	0.56	0.19
	Day 2	0 (0.02)	0 (0.02)			
	Day 3	0 (0.02)	0 (0.02)			
	Day 4	0 (0.02)	-0.04 (0.02)			
	Day 5	0 (0.02)	0 (0.02)			
	Day 6	0.01 (0.02)	0 (0.02)			
	Day 7	0.01 (0.02)	-0.01 (0.02)			
pH difference	Day 1	0.01 (0.19)	0 (0.20)	0.67	0.69	0.48
	Day 2	-0.02 (0.19)	0.01 (0.20)			
	Day 3	0 (0.19)	0.01 (0.22)			
	Day 4	0 (0.22)	0.03 (0.26)			
	Day 5	0.62 (0.19)	0 (0.22)			
	Day 6	-0.01 (0.19)	0 (0.24)			
	Day 7	0.02 (0.20)	0 (0.26)			
$PaCO_2$ difference (mmHg)	Day 1	-0.88 (1.92)	-1.97 (2.05)	0.99	0.66	0.29
	Day 2	-0.20 (1.92)	-1.50 (2.05)			
	Day 3	2.44 (1.92)	0.08 (2.21)			
	Day 4	-0.87 (2.21)	-3.15 (2.71)			
	Day 5	0.45 (1.92)	1.35 (2.21)			
	Day 6	-0.81 (1.92)	-1.24 (2.43)			
	Day 7	-0.54 (2.05)	-2.73 (2.71)			
PaO_2 difference (mmHg)	Day 1	15.50 (14.16)	18.63 (15.14)	0.59	0.09	0.78
	Day 2	-43.10 (14.16)	-9.66 (15.14)			
	Day 3	8.86 (14.16)	21.40 (16.34)			
	Day 4	1.49 (16.34)	16.42 (20.01)			
	Day 5	6.61 (14.16)	-0.93 (16.35)			
	Day 6	10.26 (14.16)	-9.04 (17.90)			
	Day 7	14.16 (15.13)	-5.05 (20.01)			

[a]Linear mixed model testing interaction between group allocation and time. Data reported as mean (standard error). PT, physiotherapy; FiO_2, fraction of inspired oxygen; pH, potential of hydrogen; $PaCO_2$, partial pressure of carbon dioxide in arterial blood; PaO_2, partial pressure of oxygen in arterial blood

Supplementary Table 6. Change in haemodynamic and ECMO parameters pre to post physiotherapy according to allocation

Physiological parameter	Time period	Group		Time x Group P value[a]	Time P value	Group P value
		Standard care Mean (SE)	Intensive PT Mean (SE)			
HR difference (beats/min)	Day 1	3.13 (2.90)	0.14 (3.10)	0.33	0.17	0.91
	Day 2	-5.13 (2.90)	2.29 (3.10)			
	Day 3	5.75 (2.90)	2.00 (3.35)			
	Day 4	-5.33 (3.35)	-6.25 (4.10)			
	Day 5	-0.88 (2.90)	1.33 (3.35)			
	Day 6	1.50 (2.90)	-5.20 (3.67)			
	Day 7	-1.14 (3.10)	2.25 (4.10)			
MAP difference (mmHg)	Day 1	1.13 (3.23)	-2.14 (3.46)	0.56	0.80	0.71
	Day 2	-2.88 (3.23)	3.57 (3.46)			
	Day 3	-4.50 (3.23)	-2.86 (3.73)			
	Day 4	-2.69 (3.72)	3.91 (4.55)			
	Day 5	-0.63 (3.23)	-0.84 (3.73)			
	Day 6	3.88 (3.23)	-1.31 (4.08)			
	Day 7	1.61 (3.45)	1.66 (4.55)			
ECMO flow difference (L/min)	Day 1	0.03 (0.04)	0 (0.05)	0.36	0.79	0.89
	Day 2	0.06 (0.04)	-0.03 (0.05)			
	Day 3	-0.01 (0.04)	-0.01 (0.06)			
	Day 4	0 (0.05)	0.12 (0.07)			
	Day 5	0.02 (0.05)	0.05 (0.06)			
	Day 6	-0.04 (0.05)	0.06 (0.07)			
	Day 7	0.01 (0.06)	-0.08 (0.07)			
ECMO FGF difference (L/min)	Day 1	0 (0.04)	0 (0.04)	0.60	0.60	0.46
	Day 2	0 (0.04)	-0.14 (0.04)			
	Day 3	0 (0.04)	0 (0.05)			
	Day 4	0 (0.05)	0 (0.07)			
	Day 5	0 (0.04)	0 (0.06)			
	Day 6	0 (0.05)	0 (0.07)			
	Day 7	0 (0.06)	0 (0.07)			

[a]Linear mixed model testing interaction between group allocation and time. Data reported as mean (standard error). PT, physiotherapy; HR, heart rate; MAP, mean arterial pressure; ECMO, extracorporeal membrane oxygenation; FGF, fresh gas flow.

Supplementary Table 7. Change in inotropic requirements pre to post physiotherapy according to allocation

Physiological parameter	Time period	Group		Time x Group P value[a]	Time P value	Group P value
		Standard care Mean (SE)	Intensive PT Mean (SE)			
Noradrenaline difference (mcg/min)	Day 1	0.25 (0.48)	-0.29 (0.52)	0.92	0.04	0.86
	Day 2	-0.50 (0.48)	-0.14 (0.52)			
	Day 3	0 (0.48)	0.50 (0.56)			
	Day 4	-1.33 (0.56)	-2.00 (0.68)			
	Day 5	0.13 (0.48)	0 (0.56)			
	Day 6	-0.25 (0.48)	0 (0.61)			
	Day 7	0.14 (0.52)	0 (0.68)			
Adrenaline difference (mcg/min)	Day 1	0 (0.37)	0 (0.40)	0.63	0.63	0.44
	Day 2	1.25 (0.37)	0 (0.40)			
	Day 3	0 (0.37)	0 (0.43)			
	Day 4	0 (0.43)	0 (0.43)			
	Day 5	0 (0.37)	0 (0.43)			
	Day 6	0 (0.37)	0 (0.47)			
	Day 7	0 (0.40)	0 (0.53)			

[a]Linear mixed model testing interaction between group allocation and time. Data reported as mean (standard error). PT, physiotherapy.

Supplementary Table 8. Association between highest mobility level and different variables during intensive rehabilitation or standard care physiotherapy

Outcome variable	Regression coefficient	Standard error	P value
RR max (breaths/min)	1.4	0.35	<0.0001
RR min (breaths/min)	0.9	0.30	0.002
TV max (mls)	137.34	38.90	0.001
TV min (mls)	-11.85	24.50	0.63
SpO_2 max	0.01	0.15	0.90
SpO_2 min	-0.33	0.21	0.12
PEEP (cmH_20)	-0.5	0.5	0.32
FiO_2	-0.02	0.01	0.15
HR max (beats/min)	0.30	0.97	0.76
HR min (beats/min)	-0.39	0.89	0.66
MAP max (mmHg)	1.25	0.71	0.08
MAP min (mmHg)	1.07	0.58	0.07
Adrenaline dose	-0.18	0.09	0.06
Noradrenaline dose (mcg/min)	-1.49	0.50	0.004
RASS	0.75	0.09	<0.0001
Exercise duration (minutes)	4.20	0.39	<0.0001
ECMO flow max (L/min)	-0.12	0.09	0.20
ECMO flow min (L/min)	-0.12	0.09	0.19
ECMO FGF (L/min)	-0.64	0.22	0.004
ECMO FiO_2	0.02	0.03	0.57

Effect of Highest mobility level (IMS) on each of the outcome variables was assessed using linear mixed modelling. RR, respiratory rate; TV, tidal volume; SpO_2, peripheral oxygen saturation; PEEP, positive end expiratory pressure; FiO_2, fraction of inspired oxygen; HR, heart rate, MAP, mean arterial pressure; RASS, Richmond agitation and sedation scale; ECMO, extracorporeal membrane oxygenation; FGF, fresh gas flow.

Supplementary Table 9. Sedation levels over the 7-day study period and number of patients meeting the sedation target

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Intensive PT	-4 (-5 to -4)	-4 (-5 to -2)	-4 (-5 to -2)	-3 (-5 to -1)	-2 (-5 to -1)	-2 (-3 to 0)	-1 (-3 to +1)
RASS -1 to +1	1/7 (14)	2/7 (29)	1/7 (14)	2/4 (50)	2/6 (33)	2/5 (40)	2/4 (50)
Standard Care PT	-5 (-5 to -5)	-5 (-5 to -4)	-4 (-5 to -4)	-3 (-3 to -2)	-3 (-4 to -1)	-2 (-3 to -1)	-2 (-2 to -1)
RASS -1 to +1	0/8 (0)	0/8 (0)	0/7 (0)	1/6 (17)	3/8 (38)	3/8 (38)	3/7 (43)

Values are presented as median (range) or as number of patients (%). RASS, Richmond agitation and sedation scale; PT, physiotherapy. The RASS was not recorded on days when physiotherapy sessions were missed due to medical instability or death.

Chapter 7: CONCLUSIONS AND FUTURE DIRECTIONS

7.1. Key findings of the thesis

The overall aim of this thesis was to optimise early rehabilitation delivered to patients on ECMO, in order to improve physical function outcomes. The studies in this thesis present a body of work that described the current knowledge and gaps in rehabilitation for patients on VA and VV ECMO and investigated the physiological effects of early rehabilitation in this cohort. Physical function outcomes and lower limb complications were described, along with changes in skeletal muscle size and quality. The key findings of this thesis are outlined below.

1. Rehabilitation of patients on ECMO was safe and feasible; however, there was incomplete reporting of intervention characteristics and patient outcomes

The scoping review in Chapter 2 comprehensively described the literature on rehabilitation of adult patients on ECMO, and to our knowledge was the first scoping review completed on this topic. Rehabilitation on ECMO was reported in 152 original studies, predominantly retrospective single-centre studies based in North America. Rehabilitation on ECMO was feasible and appeared to be safe; however, screening for eligibility was infrequently reported with over a third of patients not meeting inclusion criteria. This review identified that physical function outcomes were rarely reported, and there was heterogeneity in the type and timing of outcome measures utilised. These issues underpin the difficulty of comparing or aggregating results across studies in systematic reviews. Comprehensive reporting of the intervention, to facilitate replication and comparison with other studies was also identified as an important gap in the current evidence. Most importantly, more robust methodological designs,

specifically a randomised controlled trial of early rehabilitation on ECMO was identified as a priority to progress this field and guide clinical practice.

2. *Physical function was poor at ICU discharge in patients requiring ECMO, and although it improved was still below normal levels at hospital discharge.*

The lack of data on physical function outcomes identified in the scoping review was addressed in Chapter 3. In the first study of early physical function following ECMO pre or post heart transplantation, this retrospective single centre study of 25 patients described poor strength and mobility levels at ICU discharge, with 70% of patients having severe muscle weakness consistent with ICUAW and patients requiring assistance of two or more people to walk. This did not appear to be related to pre-existing deficits as all patients were independently walking without assistance prior to the ICU admission. Previous work has shown an association between the presence and severity of ICUAW at ICU discharge and increased 1-year mortality.[28] Survival to hospital discharge was 80%; however, longer-term mortality out to 1 year was not reported. Although physical function improved by the time patients were discharged, muscle strength and mobility levels remained below normal levels. There was no significant difference in physical function outcomes between patients who received ECMO pre versus post heart transplant.

Chapter 4 added to the knowledge on early physical function outcomes in patients requiring ECMO. In a retrospective study of 17 patients requiring ECMO as a bridge to or following lung transplant, physical function was similarly shown to be poor at ICU discharge. ICUAW was reported in 64% of patients and the median highest level of mobility at ICU discharge was limited to stepping on the spot at the bedside. Physical function improved over the hospital stay to the level

where patients were mobilising independently without a gait aid, but strength and mobility distance were still below normal levels at hospital discharge. Survival to hospital discharge was 82%, with all patients alive 1 year after lung transplant. This study also compared early physical function of the patients requiring ECMO with a matched cohort who did not require ECMO. Lung transplant recipients requiring ECMO had significantly worse physical function at ICU and hospital discharge, took longer to reach mobility milestones and required longer periods of mechanical ventilation and had a longer stay in ICU and hospital than those not requiring ECMO. The duration of ICU stay was the only significant predictor of physical function at ICU discharge.

3. *Vascular and neurological complications of the lower limb were common in patients requiring femoral cannulation for ECMO.*

Lower limb complications were reported in the studies presented in Chapters 3 and 4. The majority of patients included in these two studies underwent femoral vessel cannulation for ECMO. Chapter 3 included patients requiring ECMO pre or post heart transplantation, with the majority (n=21/25, 80%) undergoing femoral VA ECMO. Patients included in the study presented in Chapter 4 were on ECMO as a bridge to or following lung transplant, with 88% (n=15/17) having femoral cannulation. Vascular and neurological complications involving the lower limb were recorded from the time of ECMO insertion to hospital discharge in both studies. Vascular complications included multiple vascular surgical repairs or debridement, fasciotomy, thrombectomy, seroma requiring repeated drainage or surgical intervention, vessel stenosis requiring angioplasty/stenting and limb amputation during or after ECMO. Neurological complications included motor or sensory deficit on neurological exam, abnormal nerve conduction study and/or magnetic resonance imaging. Lower limb complications were common (n=11/25,

44%) in patients on ECMO prior to or following heart transplant. Of note, three patients had profound generalised lower limb weakness consistent with spinal cord ischaemia or infarct, which was confirmed with neurological exam, electrophysiological studies, and magnetic resonance imaging. Those that had a lower limb complication had worse HRQOL related to physical health and a 6-minute walk distance that was lower than those with no complication, with a mean difference that was clinically significant (mean difference of 64m).

A similar finding was reported in patients requiring ECMO pre or post lung transplant, with 50% of survivors having a lower limb complication. In this cohort there was no difference in HRQOL or 6-minute walk distance in those with a complication versus those without; however, this may have been due to the small sample size and warrants investigation in a larger trial. Longer term follow-up of these complications is required to determine the trajectory of recovery and impact on long term patient outcomes.

4. Patients requiring ECMO had profound wasting of the quadriceps muscle over the first 10 days, and greater muscle wasting was associated with worse physical function.

Using ultrasound imaging to quantify early changes in skeletal muscle size and quality (echogenicity), the prospective cohort study in Chapter 5 demonstrated that patients requiring ECMO had marked wasting of the quadriceps muscle over the first 10 days (20% reduction), and continued to decline to day 20 (30% reduction). This percentage reduction in muscle size was comparable to that reported in an earlier study involving general ICU patients of a similar age, severity of illness, duration of mechanical ventilation and length of stay in ICU.[49] This result suggests that muscle wasting in patients on ECMO, although severe,

is no worse than that reported in the general ICU population. Ultrasound measures (muscle size and echogenicity) were associated with measures of muscle strength and highest mobility level. This study demonstrated that ultrasound imaging of skeletal muscle in patients on ECMO is feasible and may assist in early identification of patients at risk of poor functional outcomes.

5. In patients on ECMO, the impact of early rehabilitation on respiratory and haemodynamic parameters was minimal and less than that observed outside of the rehabilitation sessions.

The pilot randomised controlled trial of early intensive rehabilitation versus standard care over a 7-day period on physiological parameters in patients on ECMO was presented in Chapter 6. This was a physiological sub-study performed in one site of a larger multi-centre feasibility and safety pilot randomised controlled trial, the first on early rehabilitation during ECMO. This study demonstrated that there was no difference between the two groups in terms of respiratory or haemodynamic effects, and the small changes in physiological parameters that occurred in both groups were less than that observed outside of the rehabilitation sessions. Importantly it showed separation between the groups in terms of dosage of rehabilitation delivered. Patients in the early intensive rehabilitation group achieved mobility milestones significantly earlier than the standard care group. This was a small pilot study but provided some important safety data for a future large multi-centre randomised controlled trial on rehabilitation on ECMO.

7.2. Strengths and limitations

A range of different study designs were employed in this thesis, including retrospective and prospective observational studies, a scoping review, and an

interventional study in the form of a pilot randomised controlled trial. A major strength of this thesis was the inclusion and rigorous methodology employed for the randomised controlled trial in Chapter 6 and scoping review in Chapter 2. Prior to the commencement of these studies, there were no published randomised controlled trials or scoping reviews on rehabilitation of patients on ECMO.

A comprehensive search strategy and inclusion of grey literature, along with rigorous methodology as recommended in the PRISMA ScR guideline (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews)[103] were employed for the scoping review presented in Chapter 2. This resulted in a more extensive review of the literature on rehabilitation during ECMO than reported in previous systematic reviews.[74,75] The pilot randomised controlled trial presented in Chapter 6 also adhered to the guidelines for controlled clinical trials as set out in the CONSORT 2010 statement and checklist[104] to ensure robust methodological design.

This thesis identified key gaps in the knowledge of early rehabilitation of patients on ECMO and provided novel data on physical function outcomes and physiological responses to early rehabilitation during ECMO. This information may aid in future trial planning as well as assist with the development of clinical practice recommendations and rehabilitation guidelines for patients on ECMO, which currently do not exist nationally or internationally. Detailed demographic and clinical data were presented in all studies, which will facilitate comparison with other ECMO sites and other studies.

The studies presented in this thesis focused on patient-centred outcomes, specifically physical function, rather than the focal point being hospital outcomes

such as length of stay and mortality. The findings demonstrate that physical function is an important problem for patients requiring ECMO, but consensus on the best measure to use and the timing of measurement is lacking.

There are some important limitations in the research included in this thesis. The retrospective and prospective studies and randomised controlled trial included small samples sizes from a single centre. The scoping review in Chapter 2 highlighted this as a common issue in research on rehabilitation on ECMO, with the majority of included studies being small single centre studies. This limits the generalizability of our findings to other ECMO sites. The small sample sizes have prevented any detailed sub-group analysis to determine if there were statistically significant differences between sub-groups that could be clinically relevant. ECMO is used in the sickest of ICU patients, and therefore numbers in each individual centre are low. Accumulating enough patients to answer research questions regarding efficacy and safety of rehabilitation on ECMO will most likely require extensive national and international collaboration.

The scoping review and randomised controlled trial included patients on both VA and VV ECMO with a wide range of admission diagnoses. This may limit the validity of results as the response to rehabilitation and the trajectory of recovery may vary between different types of ECMO and specific diagnostic groups. Detailed evaluation of the different patient groups and modes of ECMO is warranted in future, larger studies.

The observational studies presented in Chapters 3, 4 and 5 have limitations inherent to all studies of this type; being more prone to bias and confounding and unable to determine causality. However, the data from these studies may inform

the design of future definitive robust trials investigating early rehabilitation during ECMO.

A further limitation involved the lack of objective measurement of physical function prior to commencement on ECMO. This was due to the acute presentation of patients requiring ECMO. The lack of an objective baseline measurement makes it difficult to accurately determine the degree of deterioration in physical function over the course of the ICU stay. This is a common issue in studies involving critically ill patients admitted to ICU. A retrospective review of the medical histories and discussion with the patient's medical treatment decisionmaker were undertaken to determine premorbid physical function, with confirmation from the patient upon awakening; however, it is important to note that subjective measures of physical function may present issues with poor reliability and patient recall bias. Detailed limitations relevant to each of the individual studies are presented in each chapter.

7.3. Recommendations for future research

The major pressing issue for rehabilitation during ECMO is to determine the efficacy of this intervention in improving patient-centred outcomes, such as physical function, and to identify which sub-groups may benefit most from rehabilitation. A definitive multi-centre international randomised controlled trial to assess the short-term and long-term effect of early rehabilitation in patients on ECMO is required. Conducting controlled clinical trials investigating rehabilitation of patients on ECMO has been challenging and is evidenced by the paucity of randomised controlled trials in the area. Some of the challenges have already been alluded to, including the small number of patients suitable for ECMO therapy, of which only a proportion may meet eligibility requirements for inclusion

in a clinical trial. This will need to be considered when planning the time required to recruit suitable participants. In addition, comprehensive screening of potential candidates with reporting of eligibility is needed.

ECMO research has traditionally focused on short-term hospital outcomes, such as hospital mortality. However, it is becoming clear that patients that survive ECMO have significant morbidity. The scoping review in Chapter 2 highlighted the lack of reporting of patient-centred outcome measures in research on rehabilitation during ECMO. There was also heterogeneity in the type of outcomes and measurement tools utilised and the timing of measurement. Standardisation of outcome measures will be important when planning future studies and systematic reviews. Recent development of a core outcome set to standardise the reporting of ECMO studies have been published.[84] This core set of outcomes include disability, activities of daily living, HRQOL, neurologic recovery, and return to work. Incorporating ultrasound imaging of skeletal muscle as an early measure of impairment, where other outcomes are not viable should be considered. Ideally, a definitive randomised controlled trial on rehabilitation during ECMO would include a measure of muscle strength that could identify patients with ICUAW in the early stages of their ICU stay and be feasible to repeat throughout the hospital stay to determine the trajectory of recovery. In addition, a measure of mobility and performance of activities of daily living at both ICU and hospital discharge would provide important information regarding the level of disability in the acute phase of recovery. However, understanding the impact of early rehabilitation in patients on ECMO needs to extend beyond the hospital stay and include long-term follow up of physical function and HRQOL to determine whether patients have returned to their baseline level of function.

More work still needs to be done on determining the optimum measurement tools for each of the core outcomes and when they should be completed.

Future trials should include detailed reporting of intervention characteristics, ideally using standardised guidelines and checklists, such as the Consensus on Exercise Reporting Template (CERT)[105] or the Template for Intervention Description and Replication (TIDieR) checklist.[106] The use of these tools would improve the completeness of reporting of rehabilitation interventions and allow replication and comparison of studies. In addition, any modification to ECMO settings during rehabilitation and the effect on exercise capacity and cardiorespiratory tolerance should be reported.

The impact of antecedent factors such as frailty on physical function require further investigation. The results from our prospective cohort study in Chapter 5 demonstrated an association between frailty at ICU admission and baseline quadriceps muscle size; however, frailty was not associated with quadriceps measures taken later in the ICU stay. Of note, this study was not powered to detect a relationship between frailty and quadriceps muscle size or quality and therefore requires investigation in a larger trial.

The optimal selection of patients and timing of rehabilitation remains unclear. Questions such as when to initiate rehabilitation, how long should it be delivered and in what dosage and intensity remain unanswered. In addition, there may be specific sub-groups of patients on ECMO that respond better to rehabilitation than others, such as different diagnostic groups or patients on different modes of ECMO. There has previously been a focus on rehabilitation of patients on VV ECMO, in particular as a bridge to lung transplant.[5,62,66,73,91,107] More controlled trials are needed to determine the feasibility, safety, and efficacy of rehabilitation

of patients with cardiac failure on VA ECMO. Future studies need to focus on determining the optimal patients, timing, dosage, and intensity of rehabilitation for patients on ECMO.

7.4. Implications for clinical practice

The studies in this thesis have shown that it is safe and feasible to implement early rehabilitation to patients on ECMO; however, not all patients are suitable for participation in early rehabilitation, and more data are needed on the feasibility of both selection for and delivery of the intervention. Early physical function was poor in patients requiring ECMO, with ICUAW commonly reported and severe muscle wasting occurring in the first 10 days. Vascular and neurological lower limb complications associated with femoral cannulation for ECMO were common; however, the effect on physical function and HRQOL is unclear and warrants further investigation.

Based on these findings, a number of recommendations can be made for clinical practice:

i. Rehabilitation should be considered for all patients on ECMO, with screening for inclusion using criteria set out in general guidelines available for mobilising critically ill patients in ICU,[52,53,55] until such time as ECMO specific guidelines have been developed. The international expert consensus guideline on mobilising critically ill mechanically ventilated patients includes specific recommendations for patients on ECMO.[54] In addition, a consensus agreement for physiotherapy best practice has been developed for physiotherapists delivering respiratory and rehabilitation interventions to patients on VV ECMO.[76] To date there are no published guidelines specific to patients on VA ECMO.

ii. The implementation of rehabilitation to patients on ECMO may require a culture shift in ICU, to view rehabilitation as a priority for this cohort of patients and equip a multi-disciplinary team with appropriate skill and training to deliver the intervention. What that training involves is still not clear, but expert opinion supports staff undertaking training specific to ECMO. Out-of-bed rehabilitation typically requires an experienced, multi-disciplinary team of three to five staff,[46,47,70] which will need to be considered in future workforce planning.

iii. The implementation of rehabilitation to patients on ECMO should be considered early after ECMO commencement, as the decrements in physical function have been shown to occur early and rapidly.

iv. To facilitate the implementation of early rehabilitation in patients on ECMO, sedation levels need to be optimised to allow patient engagement in therapy. Currently, patients on ECMO typically receive heavy sedation particularly in the first few days on ECMO, and it would require a culture shift in ICU to reduce sedation levels in these patients.

v. Physical function should be measured early and throughout the ICU stay. Functional measures that are quick and easy to implement in the clinical setting, such as the IMS, need to be considered. The optimum frequency that these measures are completed has not yet been determined. Consensus from key stakeholders about how often these measurements should be collected would allow for benchmarking across different ECMO centres and comparison between different patient populations requiring ECMO. Skeletal muscle ultrasound may provide an early measure of muscle size and quality that can be completed within the first 48 hours following cannulation, but this does require specialised training.

Ultrasound measures may help to identify patients with more profound muscle wasting, and these measures have been associated with muscle strength and mobility level.

vi. Rehabilitation on ECMO was associated with a low number of adverse events with few sessions needing to be ceased. Of note, these results are from clinical research involving strict inclusion and exclusion criteria, protocols for delivering the intervention, and criteria for ceasing the intervention. To ensure patient safety in clinical practice it will be imperative to have local guidelines in place for early rehabilitation on ECMO, until such time as international consensus guidelines are developed.

vii. There was a signal for reduced ICU and hospital length of stay and cost in patients on ECMO that received rehabilitation versus no rehabilitation, but these data are from uncontrolled trials and so this needs further investigation.

viii. Vigilance in the early detection and management of lower limb complications associated with femoral vessel cannulation is recommended, along with assessment of the impact of these complications on HRQOL and physical function. Long-term surveillance of these complications after discharge from hospital would assist in determining if there are persistent and significant sequelae associated with these complications and whether additional interventions are required to optimise recovery.

7.5. Conclusion

The research in this thesis has shown that patients requiring ECMO often have severe muscle weakness consistent with ICUAW, poor mobility levels and

reduced HRQOL in the acute period following ECMO. Vascular and neurological lower limb complications are common in patients that undergo femoral cannulation for ECMO; however, the early impact on physical function and HRQOL remains unclear. The long-term sequelae of these complications are unknown and follow up after hospital discharge to determine the trajectory of recovery would be of benefit. Early severe muscle wasting and deterioration in muscle quality was described in patients on ECMO and these changes were associated with reductions in strength and mobility. Importantly, the early initiation of rehabilitation to patients on ECMO was shown to be feasible and safe, with minimal impact on haemodynamic and respiratory parameters and no serious adverse events, along with a positive impact on achievement of mobility milestones. This thesis will form the basis of important ongoing work designed to improve the functional outcomes of ECMO patients. It has provided data to inform a large, definitive randomised controlled trial to investigate the short and long-term impact of early rehabilitation delivered to patients on ECMO, and to identify patients that will derive the most benefit.

APPENDICES

Appendix 1: Ethics Approvals

Chapters 3 and 4

Alfred Health Human Research Ethics Committee: Project Number 314/14

La Trobe University, Faculty of Health Sciences Ethics Committee: FHEC14/253

Chapters 3 and 4 were considered in the same ethics approval statement.

ETHICS COMMITTEE CERTIFICATE OF APPROVAL

This is to certify that

Project No: 314/14

Project Title: The effect of extracorporeal membrane oxygenation (ECMO) support on physical function and quality of life in thoracic transplant patients

Principal Researcher: Ms Kate Hayes

was considered for Low Risk Review and ***APPROVED*** *on* **14 July 2014**

It is the Principal Researcher's responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved.

The Principal Researcher is required to notify the Secretary of the Ethics Committee, via amendment or report, of

- Any significant change to the project and the reason for that change, including an indication of ethical implications (if any);
- Serious adverse effects on participants and the action taken to address those effects;
- Any other unforeseen events or unexpected developments that merit notification;
- The inability of the Principal Researcher to continue in that role, or any other change in research personnel involved in the project;
- A delay of more than 12 months in the commencement of the project; and,
- Termination or closure of the project.

Additionally, the Principal Researcher is required to submit

- A Final Report on completion of the project.

Approval covers the project as described in the application (including any modifications made prior to approval). Low Risk projects are subject to audit and ethical approval may be withdrawn if the project deviates from that proposed and approved.

SPECIAL CONDITIONS

None

SIGNED:

R Frew
Secretary, Ethics Committee

Please quote project number and title in all correspondence

FACULTY OF HEALTH SCIENCES

MEMORANDUM

To: **Associate Professor Anne Holland**

Student: **Ms Kate Hayes**

From: **Chair, La Trobe University Faculty Human Ethics Committee**

Subject: **FHEC acceptance of The Alfred HREC approved project – 314/14. FHEC14/253**

Title: **The effect of extracorporeal membrane oxygenation (ECMO) support on physical function and quality of life in thoracic transplant patients**

Date: **13/11/2014**

Thank you for submitting the above protocol to the Faculty Human Ethics Committee (FHEC). Your material was forwarded to the FHEC Chair for consideration. Following evidence of a full review and subsequent final approval by the **The Alfred HREC**, the FHEC Chair agrees that the protocol complies with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and is in accordance with La Trobe University's *Human Research Ethics Guidelines*.

Endorsement is given for you to take part in this study in line with the conditions of final approval outlined by The Alfred HREC.

Limit of Approval. La Trobe FHEC endorsement is limited strictly to the research protocol as approved by The Alfred HREC.

Variation to Project. As a consequence of the previous condition, any subsequent modifications approved by The Alfred HREC for the project should be notified formally to the FHEC.

Annual Progress Reports. Copies of all progress reports submitted to The Alfred HREC are to be forwarded to the FHEC. Failure to submit a progress report will mean that endorsement for your involvement in this project will be rescinded. An audit related of your involvement in the study may be conducted by the FHEC at any time.

Final Report. A copy of the final report is to be forwarded to the FHEC within one month of it being submitted by The Alfred HREC.

If you have any queries related to the information above or require further clarifications, please fhechealth@latrobe.edu.au. Please quote FHEC application reference number FHEC14/253.

On behalf of the Faculty Human Ethics Committee, best wishes with your research!

Owen M Evans, PhD
Chair
Faculty Human Ethics Committee
Faculty of Health Sciences

Chapter 5

Alfred Health Human Research Ethics Committee: Project Number 516/16

La Trobe University, University Human Ethics Committee (UHEC): acceptance letter of project 516/16

ETHICS COMMITTEE CERTIFICATE OF APPROVAL

This is to certify that

Project No: 516/16

Project Title: Acute skeletal muscle wasting and relation to physical function in patients requiring extracorporeal membrane oxygenation (ECMO)

Principal Researchers: Professor Anne Holland & Dr Carol Hodgson

Protocol Version 2 **dated:** 21-Nov-2016

Participant Information and Consent Form (Person Responsible) Version 2 **dated:** 21-Nov-2016
Participant Information and Consent Form (Continuing after Person Responsible) Version 2 **dated:** 21-Nov-2016

*was considered by the Ethics Committee on **24-Nov-2016**, meets the requirements of the National Statement on Ethical Conduct in Human Research (2007) and was **APPROVED** on **14-Dec-2016***

It is the Principal Researcher's responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved.

The Principal Researcher is required to notify the Secretary of the Ethics Committee, via amendment or progress report, of

- Any significant change to the project and the reason for that change, including an indication of ethical implications (if any);
- Serious adverse effects on participants and the action taken to address those effects;
- Any other unforeseen events or unexpected developments that merit notification;
- The inability of the Principal Researcher to continue in that role, or any other change in research personnel involved in the project;
- Any expiry of the insurance coverage provided with respect to sponsored clinical trials and proof of re-insurance;
- A delay of more than 12 months in the commencement of the project; and,
- Termination or closure of the project.

Additionally, the Principal Researcher is required to submit

- A Progress Report on the anniversary of approval and on completion of the project *(forms to be provided)*;

The Ethics Committee may conduct an audit at any time.

All research subject to the Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Hospital Ethics Committee is a properly constituted Human Research Ethics Committee in accordance with the National Statement on Ethical Conduct in Human Research (2007).

SPECIAL CONDITIONS

None

SIGNED:

Professor John J. McNeil
Chair, Ethics Committee

Please quote project number and title in all correspondence

LA TROBE UNIVERSITY

University Human Ethics Committee

RESEARCH OFFICE

MEMORANDUM

To: **Professor Anne Holland, La Trobe University Clinical School, RAH Health**

From: **Senior Human Ethics Officer, Ethics and Integrity**

Subject: **UHEC acceptance of The Alfred HREC approved project - 516/16**

Title: **Acute skeletal muscle wasting and relation to physical function in patients requiring extracorporeal membrane oxygenation (ECMO)**

Date: **16 December 2016**

Thank you for submitting the above protocol to the University Human Ethics Committee (UHEC). Your material was forwarded to the UHEC Chair for consideration. Following evidence of a full review and subsequent final approval by the **The Alfred HREC**, the UHEC Chair agrees that the protocol complies with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and is in accordance with La Trobe University's *Human Research Ethics Guidelines*.

Endorsement is given for you to take part in this study in line with the conditions of final approval outlined by **The Alfred HREC.**

Limit of Approval. La Trobe UHEC endorsement is limited strictly to the research protocol as approved by **The Alfred HREC**.

Variation to Project. As a consequence of the previous condition, any subsequent modifications approved by **The Alfred HREC** for the project should be notified formally to the UHEC.

Annual Progress Reports. Copies of all progress reports submitted to **The Alfred HREC** must be forwarded to the UHEC. Failure to submit a progress report will mean that endorsement for your involvement this project will be rescinded. An audit related to your involvement in the study may be conducted by the UHEC at any time.

Final Report. A copy of the final report is to be forwarded to the UHEC within one month of it being submitted to **The Alfred HREC.**

If you have any queries on the information above please e-mail: humanethics@latrobe.edu.au or

contact me by phone.

On behalf of the La Trobe University Human Ethics Committee, best wishes with your research!

Kind regards,

Sara Paradowski
Senior Human Ethics Officer
Executive Officer – University Human Ethics Committee
Ethics and Integrity / Research Office
La Trobe University Bundoora, Victoria 3086
P: (03) 9479 – 1443 / F: (03) 9479 - 1464
http://www.latrobe.edu.au/researchers/ethics/human-ethics

Chapter 6

Alfred Health Human Research Ethics Committee: Project Number 149/17

La Trobe University, University Human Ethics Committee (UHEC): acceptance letter of project 149/17

ETHICS COMMITTEE CERTIFICATE OF APPROVAL

This is to certify that

Project Number: HREC/17/Alfred/49 (Local Reference: Project 149/17)

Project Title: A pilot randomised controlled trial in Extracorporeal Membrane Oxygenation Physical Training (ECMO-PT)

Coordinating Principal Investigator: Associate Professor Carol Hodgson

*was considered under the National Mutual Acceptance (NMA) scheme by the Ethics Committee on **1-Jun-2017**, meets the requirements of the National Statement on Ethical Conduct in Human Research (2007) and was **APPROVED** on **7-Aug-2017**.*

It is the Coordinating Principal Investigator's responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved.

The Coordinating Principal Investigator is required to notify the Secretary of the Ethics Committee, via amendment or progress report, of

- Any significant change to the project and the reason for that change, including an indication of ethical implications (if any);
- Serious adverse effects on participants and the action taken to address those effects;
- Any other unforeseen events or unexpected developments that merit notification;
- The inability of the Coordinating Principal Investigator to continue in that role, or any other change in research personnel involved in the project;
- Any expiry of the insurance coverage provided with respect to sponsored clinical trials and proof of re-insurance;
- A delay of more than 12 months in the commencement of the project; and,
- Termination or closure of the project.

Additionally, the Coordinating Principal Investigator is required to submit

- A Progress Report on the anniversary of approval and on completion of the project.

The Ethics Committee may conduct an audit at any time.

All research subject to the Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Hospital Ethics Committee is a properly constituted Human Research Ethics Committee in accordance with the National Statement on Ethical Conduct in Human Research (2007).

SPECIAL CONDITIONS

None

The HREC notes that it is the responsibility of the researchers to ensure that they and any other people or entities involved in the conduct of the study comply with all applicable laws regarding the conduct of the study, including laws regarding the recruitment of participants who lack the capacity to provide informed consent, of the jurisdiction in which the study will be conducted.

APPROVED DOCUMENTS

Documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Protocol	1	1-May-2017
MASTER Person Responsible Information Sheet & Consent Form	2	8-Jun-2017
MASTER Participant Information Sheet & Consent Form (Consent to continue after Person Responsible consent)	2	8-Jun-2017
Person Responsible Checklist (on template dated 25-Sep-2012)	-	-
NSW Privacy Form	-	-

APPROVED SITES

Approval is given for this research project to be conducted at the following sites and campuses:

- Alfred Health (The Alfred), VIC
- The Prince Charles Hospital, QLD
- St Vincent's Hospital, NSW
- Royal Prince Alfred Hospital, NSW
- Monash University

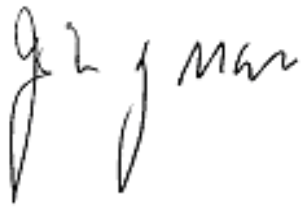
The Alfred Hospital Ethics Committee has approved the study but does not take responsibility for research governance processes at the participating sites. It is the responsibility of each participating site to create and implement research governance practices to adequately authorise, monitor and oversee the conduct of the study at their site.

Site-Specific Assessment (SSA)
SSA authorisation is required at all sites participating in the study. SSA must be authorised at a site before the research project can commence.

The completed Site-Specific Assessment Form and a copy of this ethics approval letter must be submitted to the Research Governance Officer for authorisation by the Chief Executive or delegate. This applies to each site participating in the research.

The HREC wishes you and your colleagues every success in your research.

SIGNED:



Chair, Ethics Committee (or delegate)

Please quote project number and title in all correspondence

LA TROBE UNIVERSITY

University Human Ethics Committee

RESEARCH OFFICE

MEMORANDUM

To: **Professor Anne Holland, School of Allied Health, College of SHE**

From: **Senior Human Ethics Officer, Ethics and Integrity**

Subject: **UHEC acceptance of The Alfred HREC approved project – 149/17**

Title: **A pilot randomised controlled trial in Extracorporeal Membrane Oxygenation Physical Training (ECMO-PT)**

Date: **3 October 2017**

Thank you for submitting the above protocol to the University Human Ethics Committee (UHEC). Your material was forwarded to the UHEC Chair for consideration. Following evidence of a full review and subsequent final approval by the **The Alfred HREC**, the UHEC Chair agrees that the protocol complies with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and is in accordance with La Trobe University's *Human Research Ethics Guidelines*.

Endorsement is given for you to take part in this study in line with the conditions of final approval outlined by **The Alfred HREC.**

Limit of Approval. La Trobe UHEC endorsement is limited strictly to the research protocol as approved by **The Alfred HREC**.

Variation to Project. As a consequence of the previous condition, any subsequent modifications approved by **The Alfred HREC** for the project should be notified formally to the UHEC.

Annual Progress Reports. Copies of all progress reports submitted to **The Alfred HREC** must be forwarded to the UHEC. Failure to submit a progress report will mean that endorsement for your involvement this project will be rescinded. An audit related to your involvement in the study may be conducted by the UHEC at any time.

Final Report. A copy of the final report is to be forwarded to the UHEC within one month of it being submitted to **The Alfred HREC.**

If you have any queries on the information above please e-mail: **humanethics@latrobe.edu.au** or

contact me by phone.

On behalf of the La Trobe University Human Ethics Committee, best wishes with your research!

Kind regards,

Sara Paradowski
Senior Human Ethics Officer
Executive Officer – University Human Ethics Committee
Ethics and Integrity / Research Office
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http://www.latrobe.edu.au/researchers/ethics/human-ethics

Appendix 2: Copyright Approvals

Chapter 1

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Permission to reuse Figure 3, page 2771 in Abrams et al.[4]

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The paper from Chapter 3 was published in *Heart & Lung* in 2016 and the citation is as follows:

Hayes K, Holland AE, Pellegrino VA, Leet AS, Fuller LM, Hodgson CL. Physical function after extracorporeal membrane oxygenation in patients pre or post heart transplantation - An observational study. *Heart Lung.* 2016;45(6):525-531. doi:10.1016/j.hrtlng.2016.07.007

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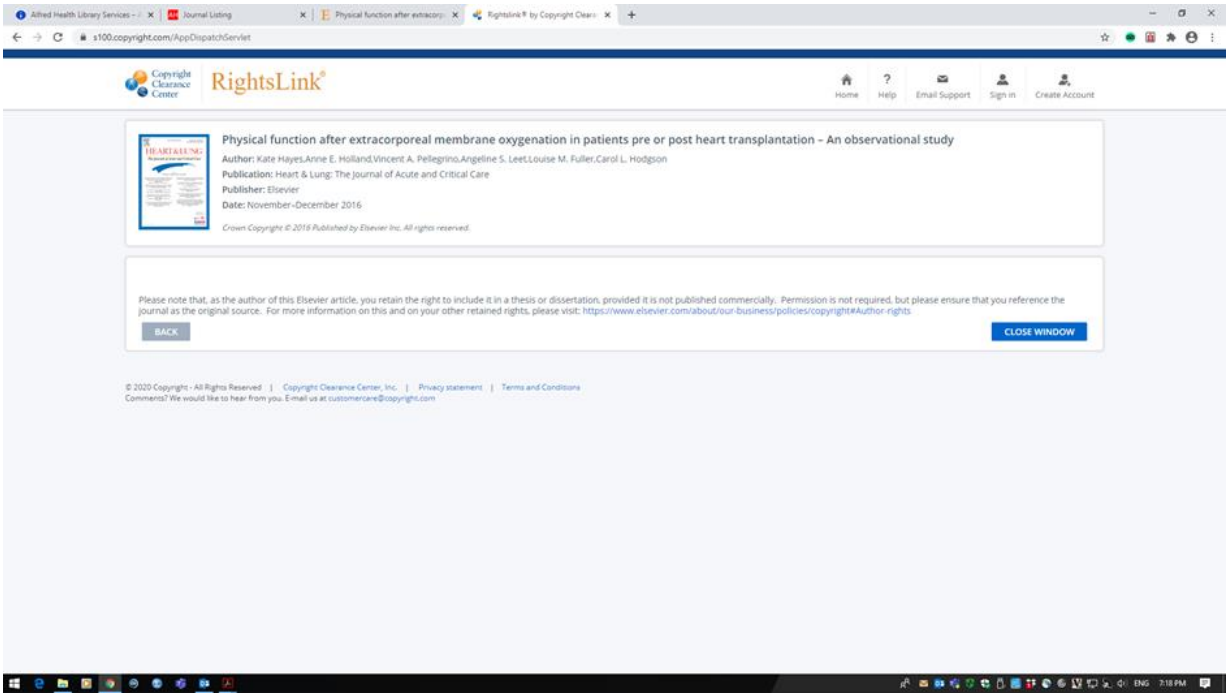
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Chapter 4

The paper from Chapter 4 was published in *Respiratory Care* in 2018 and the citation is as follows:

Hayes K, Hodgson CL, Pellegrino VA, Snell G, Tarrant B, Fuller LM, Holland AE. Physical function in subjects requiring extracorporeal membrane oxygenation before or after lung transplantation. *Respir Care.* 2018;63(2):194-202. doi:10.4187/respcare.05334

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Kindest regards,

Kate Hayes

Chapter 5

The paper from Chapter 5 was published in *Journal of Critical Care* in 2018 and the citation is as follows:

Hayes K, Hodgson CL, Pellegrino VA, Snell G, Tarrant B, Fuller LM, Holland AE. Physical function in subjects requiring extracorporeal membrane oxygenation before or after lung transplantation. *Respir Care.* 2018;63(2):194-202. doi:10.4187/respcare.05334

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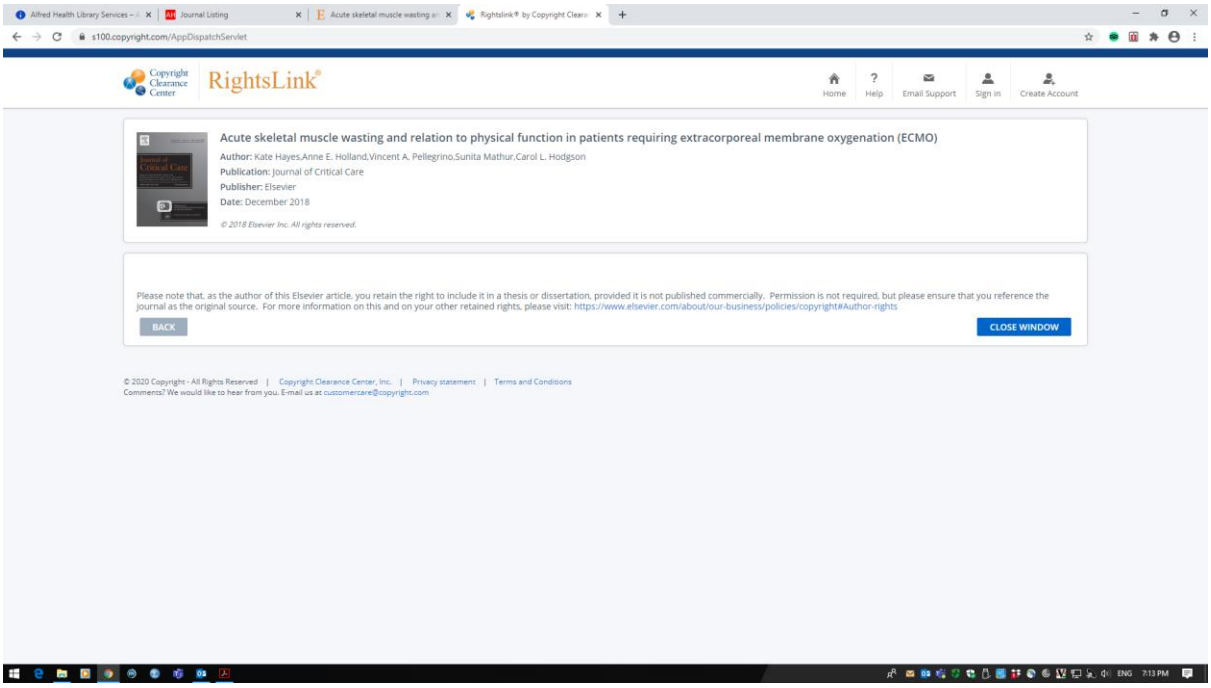
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Chapter 6

The paper from Chapter 6 was published in *Australian Critical Care* in 2020 and the citation is as follows:

Hayes K, Holland AE, Pellegrino VA, Young M, Paul E, Hodgson CL. Early rehabilitation during extracorporeal membrane oxygenation has minimal impact on physiological parameters: A pilot randomised controlled trial. *Aust Crit Care.* 2020. doi:10.1016/j.aucc.2020.07.008

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