From the Department of Physiology and Pharmacology, Section for anesthesiology and intensive care

Karolinska Institutet, Stockholm, Sweden

LIFE AFTER EXTRACORPOREAL MEMBRANE OXYGENATION - LONG-TERM SURVIVAL AND QUALITY OF LIFE

Viktor von Bahr, MD

Karolinska Institutet

Stockholm 2019

Published by Karolinska Institutet.

ISBN 978-91-7831-337-2
Printed by Eprint AB 2019.

Life after extracorporeal membrane oxygenation - long-term survival and quality of life

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Viktor von Bahr

Principal Supervisor:
Jan Hultman
Karolinska Institutet
Department of physiology and pharmacology
Section for anesthesiology and intensive care medicine

Co-supervisors:
Björn Frenckner
Karolinska Institutet
Department of women's and children's health
Division of paediatric surgery

Bernhard Holzgraefe
Landstinget Värmland
Centrum för klinisk forskning

Staffan Eksborg
Karolinska Institutet
Department of women's and children's health
Childhood cancer research unit

Opponent:
Matthias Lubnow
University medical center Regensburg
Department of internal medicine II

Examination Board:
Jan van der Linden
Karolinska Institutet
Department of molecular medicine and surgery

Fredrik Lennmyr
Uppsala University
Department of surgical sciences

Johan Petersson
Karolinska Institutet
Department of physiology and pharmacology

A simple hello could lead to a million things.

To my family.

ABSTRACT

Background:

The use of Extracorporeal membrane oxygenation (ECMO) has steadily increased in the last decades and has evolved in several ways. From originally being a means to support the neonatal patient with respiratory or circulatory failure for days to weeks, ECMO is now mainly used in paediatric and adult patients.

Survival after ECMO varies depending on the underlying condition, and survival to discharge and 6-12 months has been readily reported in the literature. Likewise, quality-of-life and health status are well-investigated in the 3-24-month period after discharge. However, there is a paucity of data concerning long-term outcomes several years after ECMO treatment.

Aim:

To identify long-term survival and causes of death in ECMO treated patients (study I and II), and to investigate the long-term health and mental status after treatment, including cognitive functions and brain radiographic findings (study III), pulmonary function, pulmonary morphology, mood disorders and quality of life (study IV).

Overview of methods:

Using the Swedish national causes of death registry, study I and II attained survival status and causes of death in all commonly treated patient groups at the ECMO Centre of the Karolinska University Hospital. Survival was depicted using the Kaplan-Meier technique. For study III and IV, a retrospective cohort was created by contacting consecutive long-term adult survivors, starting with the first adult survivor treated at the centre. Thirty-eight patients treated with ECMO for respiratory failure were investigated. This included magnetic resonance imaging of the brain and extensive neurocognitive tests (study III), followed by computed tomography of the lungs, spirometry, a six-minute walk test and self-reported forms of quality of life and mood symptoms (study IV, including Short form 36, St George's respiratory questionnaire, Hospital anxiety and depression scale and Trauma screening questionnaire).

Summary of research results:

Survival status in 255 adults was investigated in median 4.4 years after treatment (study I). The mortality was high in the first three months after treatment (17% of the ECMO survivors died in the first 90 days). This time point served as a cut-off to define late survival. In patients who were alive at 90 days, 87% were alive five years later. Long-term survival differed between groups and was highest in patients treated for a known or suspected infectious disease. In study II, 400 children were investigated in median 7.2 years after treatment. Similar to the results in adults, there was high 90-day mortality, and 93% of neonates and 89% of paediatric patients were alive 10 years later in the group who survived to this time

point. Patients who died generally had severe comorbidities or an underlying disease which caused deterioration later in life.

Brain lesions were seen in 37% of the long-term survivors (14/38, study III). In the group treated with venoarterial ECMO, 64% had signs of brain lesions. General intelligence depicted as the full-scale intelligence quotient (normal mean 100, SD 15) was 97 in median (IQR 86-104). In patients with brain lesions, the median full-scale intelligence quotient was 88, compared to 102 in patients with normal brain imaging ($p=0.28$). Memory functions and executive functions, also reported as indices with a normal mean of 100 and a SD of 15, were significantly reduced in patients with brain lesions ($p=0.03$ and 0.02, respectively). Patients with hypoxaemia during ECMO treatment, defined as <93% pulse oximetry haemoglobin saturation in median during ECMO treatment (or the first 10 days if treated for a long time) had similar intelligence as patients with normoxaemia.

Quality of life was reduced in the present cohort, but the results were similar to previously published data on patients with acute respiratory distress syndrome not treated with ECMO. A reduction in diffusion capacity was seen in 47% of the patients, and lung function varied greatly between patients. Lung parenchymal damage was common, in mean 7% of the parenchyma was damaged (range 0-44%). In 50% of the patients, this damage was predominantly localised anteriorly, possibly indicating ventilator-induced lung injury. Parenchymal damage correlated with time on ECMO and time with mechanical ventilation, and with reductions in quality of life and diffusion capacity.

LIST OF SCIENTIFIC PAPERS

I. **Long-term survival in adults treated with extracorporeal membrane oxygenation for respiratory failure and sepsis.**
von Bahr V, Hultman J, Eksborg S, Frenckner B, Kalzén H.
Crit Care Med. 2017 Feb;45(2):164–70.

II. **Long-term survival and causes of late death in children treated with extracorporeal membrane oxygenation.**
von Bahr V, Hultman J, Eksborg S, Gerleman R, Enstad Ø, Frenckner B, Kalzén H.
Pediatr Crit Care Med. 2017 Mar;18(3):272-280.

III. **Long-term cognitive outcome and brain imaging in adults after extracorporeal membrane oxygenation.**
von Bahr V, Kalzén H, Hultman J, Frenckner B, Andersson C, Mosskin M, Eksborg S, Holzgraefe B.
Crit Care Med. 2018 May;46(5):e351-e358.

IV. **Long-term pulmonary function and quality of life in adults after extracorporeal membrane oxygenation for respiratory failure.**
von Bahr V, Kalzén H, Frenckner B, Hultman J, Frisén G, Lidegran M, Diaz S, Malfertheiner M, Millar JE, Dobrosavljevic T, Eksborg S, Holzgraefe B.
Perfusion 2019. Accepted for publication. DOI: 10.1177/0267659119830244.

CONTENTS

LIST OF ABBREVIATIONS

6MWD	Six-minute walk test (distance)
ARDS	Acute respiratory distress syndrome
CD	Cognitive dysfunction
CDH	Congenital diaphragmatic hernia
CMV	Conventional mechanical ventilation (as opposed to ECMO treatment)
CPB	Cardiopulmonary bypass
CPR	Cardiopulmonary resuscitation
CVL	Cerebrovascular lesion
DLCO	Diffusing capacity of the lungs for carbon monoxide
ECK	ECMO Centre Karolinska
ECMO	Extracorporeal membrane oxygenation
ECPR	Extracorporeal cardiopulmonary resuscitation
ELSO	Extracorporeal life support organization
FiO_2	Fraction of inspired oxygen
FSIQ	Full-scale intelligence quotient
HADS	Hospital anxiety and depression scale
HFOV	High-frequency oscillatory ventilation
HRCT	High-resolution computed tomography
ICU	Intensive care unit
IQR	Interquartile range
MAS	Meconium aspiration syndrome
MRI	Magnetic resonance imaging
OI	Oxygenation index
PaO_2	Arterial partial pressure of oxygen
PEEP	Positive end-expiratory pressure
PF ratio	PaO_2/FiO_2
PTSD	Post-traumatic stress disorder
RCT	Randomised controlled trial

SaO_2	Haemoglobin oxygen saturation in arterial blood (measured by blood analysis)
SD	Standard deviation
SF-36	Short form 36 (36-item health survey)
SGRQ	St George's Respiratory Questionnaire
SpO_2	Haemoglobin oxygen saturation in arterial blood (measured by pulse oximetry)
SvO_2	Haemoglobin oxygen saturation in venous blood (measured by blood analysis)
TSQ	Trauma screening questionnaire
VA ECMO	Venoarterial ECMO
VILI	Ventilator-induced lung injury
VV ECMO	Venovenous ECMO

1 INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) supports the heart and lungs in cases of severe circulatory or respiratory failure, refractory to conventional treatment methods. Since its introduction in the 1970s, more than 100,000 patients have been reported to the international extracorporeal life support organization (ELSO) registry (1). The use of ECMO in adults is increasing, aided by new indications such as ECMO for cardiopulmonary resuscitation (ECPR; [2]) and favourable outcomes in randomised controlled trials (3-4) and the pandemic H1N1 influenza (5). ECMO is an invasive and costly procedure, associated with potentially severe side effects. It is therefore natural to ask what the long-term effects are. In other words: how is life after ECMO? What is the long-term survival and survivorship? These questions were addressed in my doctoral thesis.

2 BACKGROUND

2.1 WHAT IS ECMO?

Extracorporeal membrane oxygenation is a modified heart-lung machine which oxygenates the blood through a membrane lung outside of the body (extracorporeally). In this way, ECMO may help or fully replace the major functions of the lungs (oxygenation, decarboxylation) and heart (circulate the blood and maintain adequate organ perfusion) when these organs are failing, for short or extended periods of time. ECMO is used in specialised intensive care units (ICUs) and is not a treatment in itself but provides life-support while other treatments such as antibiotics or surgery, or the immune system itself, heals the underlying condition. ECMO is an invasive and resource intense treatment option and is normally only instituted when the patient's prognosis is considered poor despite maximal intensive care treatment. Terminology wise, ECMO and ECLS (extracorporeal life support) are used synonymously, and there are several modified techniques available, such as extracorporeal carbon dioxide removal ($ECCO_2R$), which uses low-flow ECMO for decarboxylation. (6)

2.1.1 The ECMO circuit

The ECMO circuit is illustrated in Figure 1. In short, a suction cannula is inserted in one of the great veins, usually the femoral or internal jugular vein. The blood is circulated with a pump in large tubing through the oxygenator, warmed, and then returned to the body. For respiratory failure without heart failure, ECMO is usually used in a venovenous (VV) configuration. In VV ECMO, the return cannula is inserted into one of the great veins, leaving oxygenated and decarboxylated blood for the patient's own heart to circulate through the native lungs and then further out to the body through the aorta. When heart failure is present or imminent, venoarterial (VA) ECMO is used, i.e. the return cannula is inserted in one of the great arteries, usually the femoral artery (called peripheral cannulation as opposed to central cannulation in the aorta, which demands a thoracotomy).

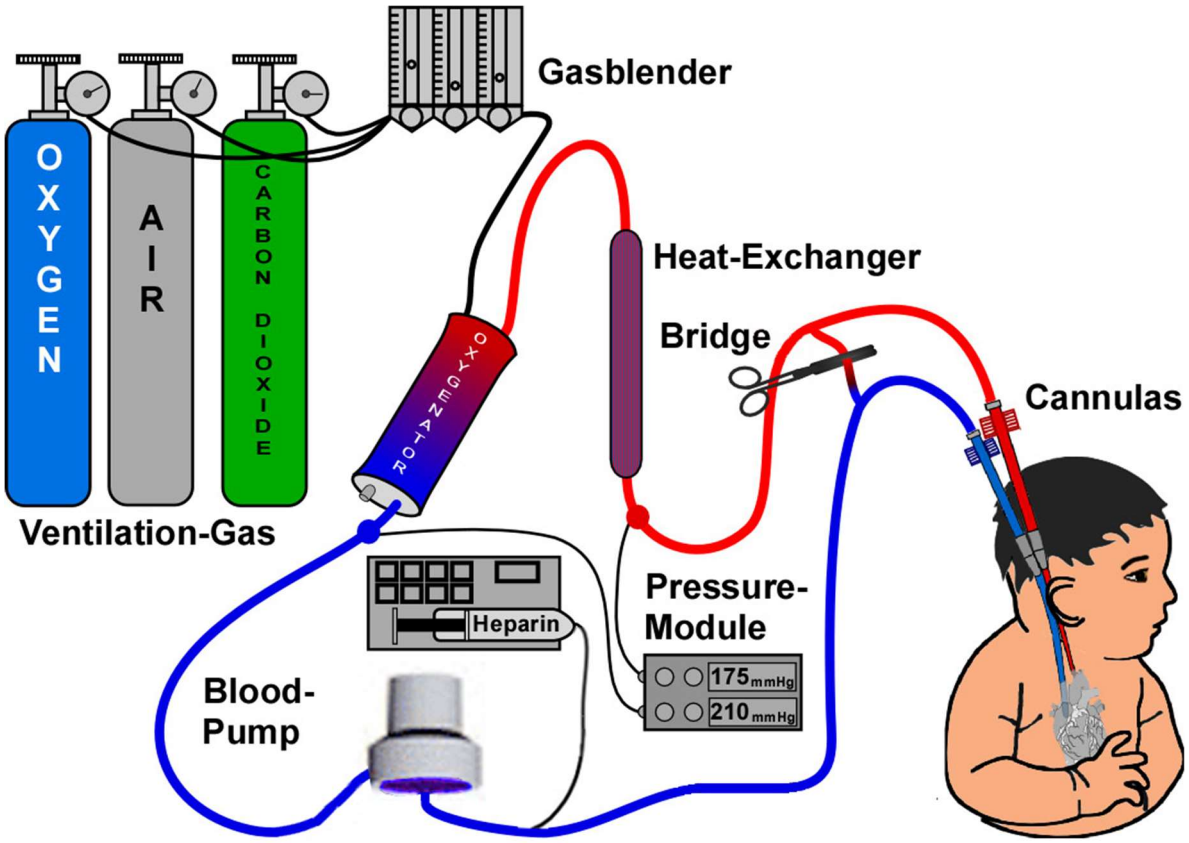

Figure 1. Schematic illustration of an ECMO circuit, showing the suction cannula with deoxygenated venous blood (blue), the ECMO system and the return cannula with oxygenated blood (red) which can be inserted into a major vein (venovenous or "VV ECMO") or artery (venoarterial or "VA ECMO"). Image by Jürgen Schaub downloaded from Wikipedia Commons, modified by the author. https://commons.wikimedia.org/wiki/File:Ecmo_schema-1-.jpg

2.1.2 Mechanical ventilation

During ECMO, the patients receive mechanical ventilation, sedation, analgesia and other intensive care as needed. Mechanical ventilation pressures, often needed in potentially harmful levels before ECMO is started, are reduced significantly after ECMO cannulation to allow the lungs to rest and to minimise ventilator-induced lung injury (7-8).

2.1.3 Altered physiology and side effects

Anticoagulation (usually heparin) is used to reduce the risk of blood clots due to the introduction of foreign surfaces and altered blood flow (9). The body's normal physiology is also altered, namely with great local changes in blood flow where cannulas are inserted, and a continuous as opposed to pulsatile flow. Cannula positioning is of vital importance to avoid recirculation of blood between the return and drainage cannulas (which may cause hypoxaemia in VV ECMO) and to enable a high flow through the circuit. In peripheral VA ECMO with the return cannula in the femoral artery, the blood flow in the aorta is retrograde (oxygenated blood from the ECMO system), which may meet and mix with an anterograde

blood flow if the patient has an intrinsic cardiac output (usually with poor oxygenation through failing lungs). In this case, turbulence is created, and some parts of the body (typically the right subclavian and the carotid arteries) may receive blood with lower oxygen saturations (termed "harlequin syndrome" or differential hypoxia). If a gas bubble or blood clot accidentally leaves the ECMO machine, the lungs usually filter these with no or little harm in VV ECMO, but with potentially detrimental effects in VA ECMO since the lungs are bypassed. (10)

Major side effects include blood thrombus formation and air embolism, but also bleeding due to the anticoagulation used and the invasiveness of the technique (11). Bleeding and ischemic lesions within the central nervous system are among the most feared complications since they are hard to treat and may cause life-long disabilities if not lethal (12). Due to the introduction of foreign surfaces through the skin, infections are common. As with all long-term treatment in the ICU, the effects of systemic inflammation, catabolism and drugs may cause short and long-term problems, including muscle weakness, nerve damage, delirium, cognitive dysfunction, post-traumatic stress disorder (PTSD) and anxiety (13-14).

2.1.4 Economic considerations

A large international study reported mean ECMO treatment health care costs of approximately £74,000 in 2006 (~50,300 € with the average exchange rate of the time) compared to £33,400 (~22,700 €) for conventionally treated patients (3).

2.2 HISTORY OF ECMO

In the 1930s, a young surgeon named John Heysham Gibbon Jr was asked to watch over a patient with massive pulmonary embolism. At the time, a surgical embolectomy was the only definite treatment option but constituted a high risk for the patient, and doctor Gibbon was assigned to follow the vital signs of the patient and to call in a senior colleague if the situation deteriorated. In his own words:

"During that long night, helplessly watching the patient struggle for life as her blood became darker and her veins more distended, the idea naturally occurred to me that if it were possible to remove continuously some of the blue blood from the patient's swollen veins, put oxygen into that blood and allow carbon dioxide to escape from it, and then to inject continuously the now-red blood back into the patient's arteries, we might have saved her life. We would have bypassed the obstructing embolus and performed part of the work of the patient's heart and lungs outside the body." (15)

The story of ECMO cannot be described without mentioning the heart-lung machine or cardiopulmonary bypass (CPB). The anecdote above was the spark that later developed into years of research and finally doctor Gibbon's screen oxygenator CPB, with which an atrial septum defect was successfully operated at Jefferson Hospital in Philadelphia USA in 1953. As the technique evolved, mortality during heart surgery declined from 50% in 1955 to 20%

in 1957, and in 1967, the CPB enabled doctor Christiaan Barnard to perform the first human heart transplant (16). The problem with the early CPB was that it caused haemolysis, thrombocytopenia, and bleeding after short periods of time, much due to the direct contact between oxygen and blood, which precluded it from long-term support. In the 1960s, a membrane lung oxygenator was developed which used a silicon rubber membrane to separate the gas and fluid elements. This enabled the apparatus to be used for days to weeks before major complications arose. The technique came to be called "extracorporeal membrane oxygenation", to differ it from non-membrane oxygenators (17). In 1971, the first successful case of adult ECMO treatment was described, in a man with acute respiratory distress syndrome (ARDS) after a traffic accident (18-19). In 1975, the first successful neonatal patient with respiratory failure was treated by doctor Robert Bartlett, a man many people has come to refer to as "the father of ECMO" (20). The patient, an orphan to a Mexican mother, was named "Esperanza" (Spanish for "hope"; [21]). Similar to doctor Gibbon's original thoughts in the 1930s, ECMO bought time in severe but treatable conditions that caused the heart or lungs to fail. The main differences between ECMO and a modern CPB are outlined in Table 1 below.

Aspect	CPB	VV ECMO	VA ECMO (peripheral)
Cardiac bypass	Full	None	Partial to full
Heparin dose	High	Low	Low
Pump flow	High	As needed: low for decarboxylation, high for oxygenation	As needed: low for decarboxylation, high for oxygenation
Haematocrit	Low	Normal	Normal
Hypothermia	Yes	No (if needed)	No (if needed)
Haemodynamics	Affected	Minimally affected	Affected
Risk of side effects	High (time dependant)	Low	Medium
Body part with risk of low O_2 saturation	-	-	Possibly in the right upper body (differential hypoxia) and the cannulated leg (if no extra perfusion cannula is used).

Table 1. Main differences between ECMO and a modern cardiopulmonary bypass.

2.3 MODERN ECMO TREATMENT

Early ECMO devices carried a significant risk for thrombocytopenia and bleeding and required a high pressure to generate flow due to a high blood flow resistance (22). Roller pumps (as opposed to centrifugal pumps) were generally used, before modern non-porous hollow fibre devices with low flow resistance were introduced, safely allowing a centrifugal technique for prolonged periods of time (although different brands use slightly different techniques). Modern devices also use new materials and antithrombogenic surfaces such as heparin coating, further decreasing the risk of thrombosis and the need for anticoagulation. Most improvements have been gradual and differ between centres, which makes a distinct cut-off in time when ECMO has evolved into something new difficult. Modern ECMO treatment involves less sedation, spontaneously breathing patients (usually with mechanical pressure support or continuous positive airway pressure), extubated patients with a tracheostomy often able to communicate with the staff, increased mobilisation and less lung recruitment manoeuvres (23). This has altogether contributed to the relatively safe ECMO treatment we are familiar with today, with 15-35% mortality for severe respiratory failure (1, 4).

It is currently unknown whether the minimal ventilatory settings seen during ECMO treatment may reduce ventilator-induced lung injury and patient morbidity and mortality (8, 24-25). It is further debated whether modern ECMO treatment reduces or increases net inflammation in the body (26-27) and what role inflammation plays in survival and long-term outcomes (13, 28).

2.4 SCIENTIFIC EVIDENCE IN RESPIRATORY FAILURE

In a 1979 randomised controlled trial (RCT), a 90% mortality was reported for ECMO in adult respiratory failure (29). Favourable results from the neonatal and paediatric world and the numerous case reports where ECMO was used as rescue therapy in severely hypoxaemic patients kept ECMO going over the years, despite the lack of high-quality studies (30). It was not until the CESAR RCT in 2009 and the H1N1 influenza pandemic 2009-2010 that the interest for ECMO in adults with respiratory failure renewed, with early reports of a convincing 71-76% survival (3, 5, 31). Since then, the use of ECMO has increased steadily, especially in the adult population (1). In 2018 a new RCT was published (EOLIA trial; [4]). The trial was designed to test the benefit of early ECMO vs conventional treatment in severe ARDS. The study failed to show a significantly better 60-day mortality rate (hazard ratio 0.70 compared to conventional treatment, 95% CI 0.47 -1.04, P=0.07). Crossover from the conventional treatment group was high (28% of patients randomised to conventional treatment), and it has been questioned whether the goal to show an absolute mortality reduction of 20% was possible, given the low recruitment rate (32). Therefore, it remains controversial whether ECMO should be used early in ARDS, but its role as a salvage therapy in refractory cases is relatively well mounted (33).

2.5 ARDS AND CONVENTIONAL TREATMENT OPTIONS

A common and feared clinical situation is acute respiratory distress syndrome (ARDS), characterised by refractory hypoxaemia with bilateral pulmonary infiltrates, not explained by left heart failure (34-35). ARDS accounts for 10% of ICU admissions globally and has a mortality of 40-50% in severe cases (36). ARDS may be triggered by several conditions, both pulmonary (e.g. pneumonia, aspiration) and non-pulmonary (e.g. sepsis, pancreatitis, blood transfusions, and trauma). Supplemental oxygen and mechanical ventilation (MV) are the cornerstones in the treatment of ARDS, but carry inherent adverse effects, such as oxygen toxicity and ventilator-induced lung injury (VILI). VILI is caused by oxygen toxicity and the unnatural mechanical power working on the lungs (barotrauma), and an increased inflammatory reaction in the lungs (37). In ARDS, so-called lung-protective ventilation is recommended with low tidal volumes and inspiratory pressures (38-39). This is however limited by how much hypercapnia, respiratory acidosis, and hypoxaemia the patient can tolerate.

Further ventilatory options include high peak end-expiratory pressures (PEEP), recruitment manoeuvres and high-frequency oscillatory ventilation (HFOV). HFOV is a form of low-tidal volume ventilation which aims to prevent lung injury from overdistension and loss of recruitment. HFOV is sometimes used as a rescue therapy, especially in neonates, but has failed to improve survival on a group level in adults with moderate to severe ARDS (40-41). To enable controlled mechanical ventilation, patients are usually deeply sedated, and a neuromuscular blocking agent is commonly used. Other possible medical treatments include inhaled nitric oxide, inhaled prostacyclin and intravenous almitrine (4, 39).

Another complementary approach is prone positioning, which improves ventilation/perfusion matching by addressing the heterogenous (dorsal) atelectasis and consolidation seen in ARDS (39). Prone positioning decreases mortality in moderate to severe ARDS and is not associated with any direct costs but is cumbersome for the hospital staff, which may explain why as few as 31% of patients receiving ECMO have had a trial with prone positioning (42).

2.6 FOR WHOM IS ECMO USED?

The principal indication for ECMO treatment is severe circulatory or respiratory failure refractory to the conventional treatment options mentioned above. After its introduction in the 1970s, ECMO was primarily used in newborns with severe respiratory failure (e.g. persistent foetal circulation, congenital diaphragmatic hernia [CDH], meconium aspiration syndrome [MAS]) and subsequently in older children (22, 43). As described above, ECMO has become standard of care for respiratory failure in adults in many centres despite a lack of sound evidence (30, 39).

Venoarterial ECMO is used as temporary support in severe circulatory failure, including when right heart failure develops during venovenous ECMO. In adults, severe cardiac failure after e.g. myocardial infarction or heart surgery is another common indication, to stabilise the haemodynamic situation until cardiac vessel catheterisation can be performed or as a bridge to recovery, mechanical assist device or transplant (22). ECMO for cardiopulmonary resuscitation (ECPR) has evolved as an alternative in refractory cardiac arrest, e.g. in cases with a witnessed cardiac arrest and bystander CPR, with a suspected reversible cause (e.g. myocardial ischemia). Several centres also treat patients with septic shock (1, 44) and perform ECMO in the pre-hospital setting, which anecdotally includes a French centre which has cannulated patients in the subway, on the streets of Paris and even in the Louvre museum (google “ECMO Louvre” for pictures).

Other uses include ECMO as a bridge to lung transplant, ECMO to keep organs viable for donation after cardiac death and experimental uses such as ECMO as an artificial placenta in prematurity (45-46).

A large registry held by the Extracorporeal Life Support Organization (ELSO) based in Ann Arbour, Michigan, USA, keeps track of North American and most international ECMO cases since 1990. To date (December 2018) more than 100,000 cases have been reported (1), and the evolution of the case mix can be seen in Figure 2. ELSO also publishes treatment guidelines to aid clinical decision making in patients receiving or being considered for ECMO treatment (47).

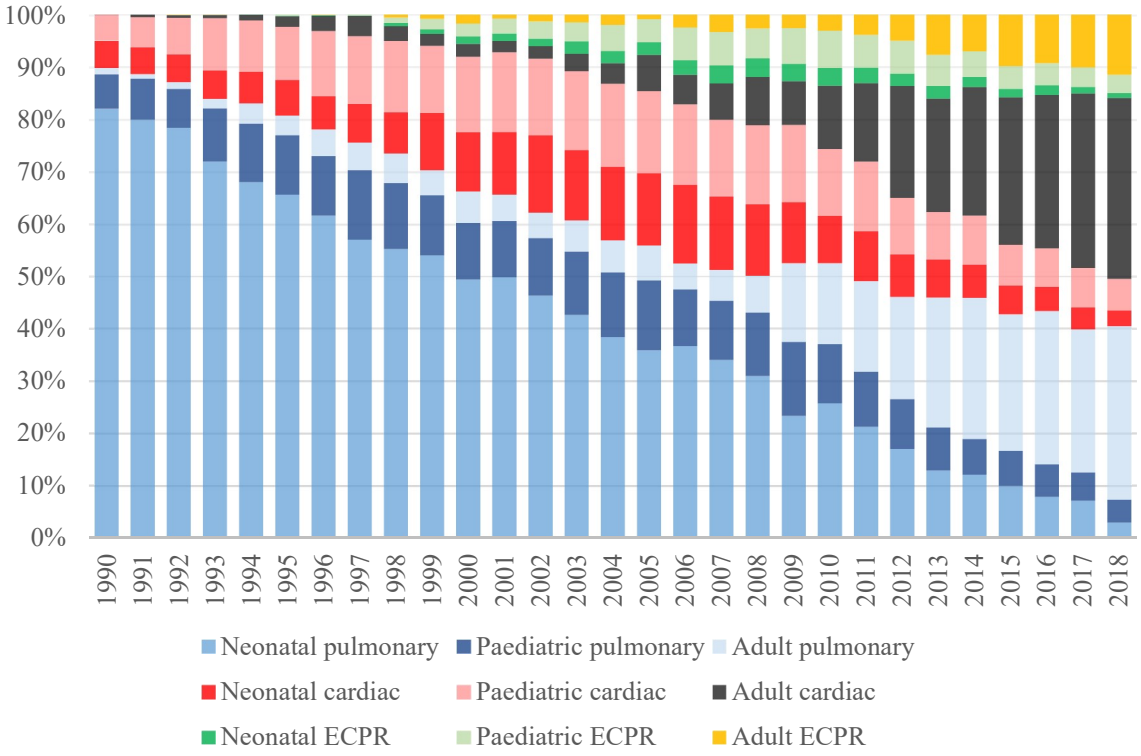

Figure 2. Proportional ELSO Registry case mix 1990-2018. Reprinted with permission (1). Note the proportional increase in adult patients starting around 2009.

In neonates, the Oxygenation Index (OI) represents the level of hypoxaemia in the light of ventilatory support and is used as a help to identify patients eligible for ECMO treatment (typically patients with an OI >40 for >4 hours). OI is defined as FiO_2 x 100 x mean airway pressure in cm H_2O / post-ductal PaO_2 in mmHg. In paediatric patients and adults, the ratio PaO_2/FiO_2 (PF ratio) is used in a similar way and represents the level of hypoxaemia. The PF ratio is used in the grading of ARDS according to the Berlin definition (35), with 200-300 representing mild, 100-200 moderate and <100 severe ARDS (PaO_2 in mmHg). The Murray score is another parameter commonly used to decide whether a patient is eligible for ECMO treatment, including four parameters: the degree of consolidation on chest x-ray findings, PF ratio, PEEP and lung compliance (3, 48). All three indices are clinical parameters from one or a few tests taken before or upon referral and sticks with a patient in many registries and databases. In reality however, they represent only a split-second view of the patient condition and cannot be used alone to describe a patient's severity of disease.

2.7 ECMO CENTRE KAROLINSKA

The ECMO Centre of the Karolinska University Hospital (ECK) treated its first patient in 1987 and has since treated more than 1,000 patients. It's considered a high-volume centre (49), with more than 30 cases annually since 2003 and ≥ 80 cases annually since 2010 (Figure 3). Initially, the ECK only treated neonatal and paediatric patients. The first adult patient was treated in 1995, and since 2007 adult patients constitute the most numerous age group.

The ECK differs somewhat to most other centres, most notably by being a dedicated ECMO ICU, i.e. only patients on ECMO are treated (most centres use ECMO on an "as needed" basis, in conjunction with other ICU patients), and the centre is a nation-wide referral centre for this indication. This has implications on staff training and experience since the whole ward is dedicated to the technology. The ECK has used minimal sedation and awake ECMO since the 1990s, and many patients were treated for long periods of time when ECMO internationally was seldom used more than 10-15 days (50-52). Cannulation is performed by a paediatric, vascular or cardiothoracic surgeon. The strategy for ventilator pressures, tidal volumes and fraction of inspired oxygen have been largely unchanged since the mid-1990s and includes a general reduction of inspiratory pressures within 3 hours from the commencement of ECMO in order to prevent further ventilator-induced lung injury. These settings are maintained until ECMO discontinuation. At this stage, the patients are ventilated conventionally with as low pressures and inspired fraction of oxygen as possible until breathing spontaneously (7, 50).

Approximately 90% of the patients treated at the ECK suffer from respiratory failure or sepsis. No developed program for ECPR exist, and by tradition, another ICU at the hospital (the thoracic ICU) treats most adult patients with cardiac indications, primarily with perioperative cardiac failure. When paediatric or adult patients are treated for cardiac failure or ECPR at the ECK, ECMO is often used as a last-resort rescue therapy. Neonatal cardiac patients are however common, where ECMO is used as a bridge to surgery.

Another aspect which may differ compared to other centres is the view on permissive hypoxaemia. The ELSO guidelines accept lower arterial haemoglobin oxygen saturations ($SaO_2 \geq 80\%$) than those recommended by the ARDSnet for conventional mechanical ventilation (≥88%). At the ECK, values as low as 70% have been accepted for prolonged periods of time in selected patients (pulse oximetry measurements [SpO_2] from the right ear, finger or nose complemented by arterial blood gas measurements; [38, 53-54]).

This permissive hypoxaemia approach is accepted if no signs of tissue hypoxia are seen (i.e. inadequate oxygen delivery to the tissues). At the ECK, the protocol is generally to monitor lactate and pre-oxygenator venous oxygen saturation (SvO_2) as rough measures of adequate tissue oxygenation. If lactate rises above 2.0 or SvO_2 falls below 65%, with no other apparent explanation, this is considered a marker of possible tissue hypoxia and compensated by increasing ECMO flow, optimising cannula positioning and haemoglobin concentration (i.e.

red blood cell transfusions). The rationale for this is the oxygen delivery equation $D'O_2 = Q$ x (haemoglobin concentration x SaO_2 x 1.34), where $D'O_2$ is the oxygen delivery rate in mL/min, Q is the cardiac output in L/min (partly or fully substituted with extracorporeal circuit flow in VA ECMO) and SaO_2 is the arterial oxyhaemoglobin saturation. Physically dissolved oxygen in the blood is neglected in the above equation.

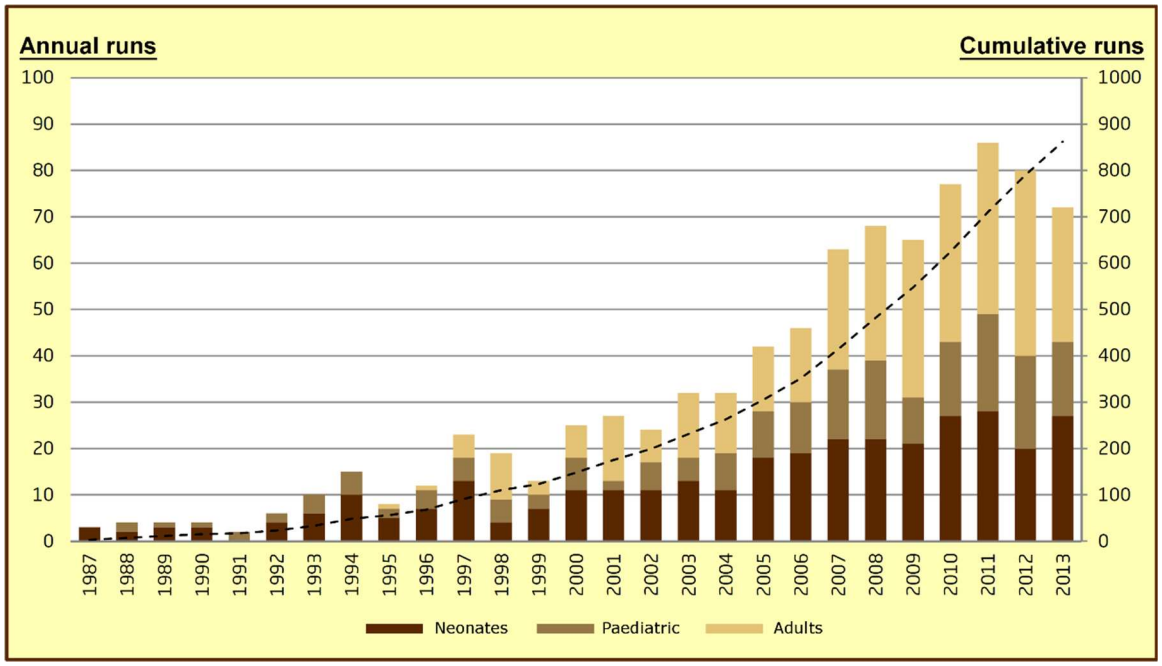

Figure 3. Patients treated at the ECMO Centre Karolinska from 1987 to 2013.

2.8 SURVIVAL AFTER ECMO

Since ECMO is a life support technique, survival is the main outcome parameter. The knowledge of short-term survival after ECMO is well-documented due to the ELSO registry (Table 2). It is well recognised that in-hospital survival outcomes vary according to diagnoses or indications for ECMO. For instance, the mean survival after ECMO for neonatal respiratory failure is 84% and within this group patients treated for meconium aspiration syndrome has a 3-month survival of 90% (55). In the other end of the spectrum, ECMO for cardiopulmonary resuscitation (ECPR) in adults has a mean survival to discharge of 29% (1). Furthermore, like many complex, resource-intensive therapies, ECMO patients have better outcomes at centres which perform more cases annually (49).

Few publications have reported data on long-term survival, and those that existed prior to this doctoral project had, for the most part, had short time horizons, small study groups or focused on cardiac disease (3, 56-58). Iguchi and colleagues presented a study on long-term survival and causes of late death in ECMO-treated children, 39% of whom were cardiac patients (as opposed to <10% at the ECK; [55]). They reported high mortality within the first 90 days after ECMO and suggested a cut-off at this point in time to define late survival. Patients who

were alive at this stage generally had a very good long-term survival, if treated for a reversible condition such as infectious disease or meconium aspiration syndrome. For MAS, Iguchi reported a "conditional" 5-year survival rate of 98%, i.e. 98% of the patients who were alive at 90 days, were alive after 5 years. Hsu and colleagues presented epidemiological data from the use of ECMO in Taiwan 2000-2010 (56). 3,969 patients were included, and the overall survival to discharge was 33% (compared to the overall reported ELSO survival of 56%). Furthermore, patients had ongoing mortality after discharge, and less than 70% of the survivors treated for respiratory failure were alive 5 years after treatment.

Patient group	Total runs	Survived treatment	Survived to discharge or transfer
Neonatal	**40,446**		
Pulmonary	30,934	84%	73%
Cardiac	7,794	64%	42%
ECPR	1,718	66%	41%
Paediatric	**23,228**		
Pulmonary	8,820	67%	58%
Cardiac	10,462	68%	52%
ECPR	3,946	57%	42%
Adult	**37,231**		
Pulmonary	16,337	66%	59%
Cardiac	15,942	55%	42%
ECPR	4,952	38%	29%
TOTAL	**100,905**	68%	56%

Table 2. ELSO Registry International Summary July 2018 (1).

2.9 COGNITIVE FUNCTIONS AFTER ECMO

Critical illness may result in significant long-term cognitive dysfunction (CD). 9-56% of patients have been reported to have some form of CD 2-8 years after ICU care (59). There are many risk factors for this, including multi-organ failure, inflammatory cytokines, hypotension, brain hypoxia, and blood glucose abnormalities. Furthermore, anaesthesia and sedating drugs have been reported as possible risk factors for delirium and long-term CD (60).

Patients treated with ECMO have several risk factors for CD from both the pre-ECMO period (with severe cardiac or respiratory failure and a failing conventional treatment) and the ECMO period itself. In children, neurodevelopmental disabilities and an increased need for special aid in school have been reported (61). ECMO specific risks include altered

coagulation, haemodynamics, and prolonged immobilisation and hospitalisation (62). Regional oxygen and blood flow imbalance and direct embolisation to the brain may constitute specific risks during VA ECMO. Moreover, many patients treated with ECMO are exposed to permissive hypoxaemia, which by several authors has been linked to CD (63-64). Meanwhile, ECMO treated patients may benefit from a more lung-protective ventilation and minimal sedation, possibly reducing the systemic inflammatory response (27, 54, 62).

Improved cognitive functions have been reported at least during the first year after discharge from the ICU, but little data exist over time periods longer than two years (13). One study showed attention, concentration, and memory deficits in 24% of ARDS patients six years after treatment (6 of 46 patients were treated with ECMO, but their results were not reported specifically; [65]). When investigating the same cohort two years later, 9% had mild to moderate cognitive impairment (66). In another study, neurologic outcomes in 28 ECMO-treated patients were presented on average 5 years after treatment (12). Clinical impairment was seen in 43%, and patients with intracranial lesions had worse cognitive outcomes. Researchers from the ECMO Centre Karolinska investigated seven H1N1 influenza survivors three years after discharge and found no evidence of cognitive dysfunction (54). Although the cohort was small, no association between hypoxaemia during ECMO and cognitive dysfunction was found.

2.10 QUALITY OF LIFE AND LONG-TERM SIDE EFFECTS AFTER ECMO

In patients with a history of ARDS, the long-term burden is prominent and well-described (13, 62, 67). This involves several organ systems, including the lungs, the muscular system, and the central and peripheral nervous systems. Many deficits improve in the first years after discharge, but some degree of pulmonary dysfunction, mood disorders, and muscle weakness seem to prevail even five years after treatment (14, 67-68).

In the ECMO population, most studies published prior to the present doctoral project had median follow-up times of 6-17 months after treatment (14), and a single study (also conducted at the ECK) investigated patients after 26 months (50).

Although comparing studies is cumbersome, ECMO treated patients seem to score similarly on the physical and the mental component scores of the well-validated quality-of-life questionnaire Short form 36 as conventionally treated patients (SF-36; [14]). Furthermore, the incidence of mood symptoms may be lower in ECMO treated patients and pulmonary function, namely a reduced diffusion capacity for carbon monoxide (DLCO), has been reported with similar results for both groups (14).

3 AIMS

The overall intention of this doctoral project was to evaluate life after ECMO. What is the *survival* and *survivorship* ≥ 3 years after leaving the ECMO unit?

The specific aims were:

1. To evaluate the long-term survival and causes of death after treatment with ECMO for respiratory failure and sepsis in adults (≥18 years).

2. To evaluate the long-term survival and causes of death after treatment with ECMO in children (<18 years).

3. To investigate the long-term cognitive functions and frequency of cerebrovascular lesions in adult ECMO survivors treated for respiratory failure.

4. To assess the long-term quality of life, pulmonary morphology and function, walking capacity and level of post-traumatic stress, anxiety, and depression after ECMO treatment for respiratory failure in adults.

4 ETHICAL CONSIDERATIONS

Full ethical approval was granted for this doctoral project (Stockholm regional ethical review board no. 2013/2259-31/4 for study I and II, 2013/2258-31/1 for study III and IV). The follow-up investigations (study III and IV) were registered at clinicaltrials.gov (NCT03031275).

The survival analyses (study I and II) were conducted as retrospective registry studies, with no involvement or contact with the patients. The main concern was that sensitive patient data would leak to a third party. Personal identification data were for this reason deidentified, and all results were presented on a group basis except when causes of death were presented in study I (supplemental digital content 2). In this case, to minimise the possibility of backtracking, the patients' ages were grouped by decades.

The follow-up investigations underlying study III and IV required more careful reflection and were performed after collecting each patient's individual written consent, according to the guidelines presented by the Swedish Data Protection Authority 1998:204 (Datainspektionen, "Personuppgiftslagen"). The database was deidentified in the same way as the survival analyses, and results were generally presented on a group basis. When publishing study III, individual results were included in supplementary digital content 3. This was in line with the written consent we had from patients (freely translated to "either fully anonymised on a group basis or fully deidentified") but was not stated explicitly in the ethical application. To minimise the risk of identifying individuals, the data was decoded with age groups (≤40 or >40 years old), diagnosis (pneumonia vs non-pneumonia) and follow-up time (<10 or ≥10 years). Another risk for the individual patient was radiation from the computed tomography, which the patients were informed about and consented to. It is my sincere hope that each patient felt they were given the chance to, as far as reasonably possible, understand and contemplate the risks and benefits of participating before deciding. Possible benefits included the thorough investigations made (with both personal and group results presented to the patients) and an opportunity to talk about and increase their understanding of ECMO and the experiences they had been through.

5 METHODS

5.1 OVERVIEW OF METHODS

An overview of the study methods is presented in Table 3 below.

Study	Design	Study population	Aim	No. of participants	Statistical methods
I	Retrospective registry study	Adult patients (≥18 yrs) with respiratory failure or sepsis treated 1995 – 2013	To study the long-term survival and causes of death	255	Kaplan-Meier method, Log-rank (Mantel-Cox) test, Cox-proportional-hazards model
II	Retrospective registry study	Neonatal patients (cardiac/respiratory) and paediatric patients (-17 yrs, respiratory) treated 1987 – 2013	To study the long-term survival and causes of death	400	Kaplan-Meier method, Log-rank (Mantel-Cox) test
III	Retrospective cohort	Long-term adult survivors (respiratory failure) treated 1995 - 2009	To evaluate long-term cognitive dysfunction and brain lesions	38	Mann-Whitney U test
IV	Retrospective cohort	Long-term adult survivors (respiratory failure) treated 1995 - 2009	To describe the long-term quality of life, mood disorders, lung function and morphology, and 6-minute walk distance	38	Descriptive statistics (mean, SD and median, IQR), Spearman's rank correlation test

Table 3. Overview of study methods.

5.2 STUDY DESCRIPTIONS

Study I and II were retrospective registry studies using the Swedish causes of death registry (69). All patients with a Swedish personal identification number treated at the ECMO Centre Karolinska from the centre's foundation in 1987 to December 2013 were cross-matched with the registry, and emigration status was obtained from the population registry (Swedish Tax Agency). Study I (adults) included patients with respiratory failure or sepsis since these indications constitute 90% of the patients treated at the centre. Cardiac (n=5) and ECPR (n=28) cases were excluded, as were non-Swedish citizens treated at the centre (no personal identification number, n=25). Study II (children 0-17 years old) excluded paediatric cardiac patients (n=8) and ECPR patients (n=40) for the same reason as described above, while neonatal cardiac patients (n=17) were included since this group has historically been common at the centre (usually treated while awaiting cardiac surgery). Non-Swedish citizens were also excluded (n=85).

The Kaplan-Meier method was used for survival calculations, and patients were grouped according to modified ELSO criteria. In study I, new groups were created altogether, while minor modifications were done in study II. Survival status and causes of death were obtained. Causes of death were registered according to ICD-9 or ICD-10[1] and were written by the physician in charge either at the hospital or in general practice for patients who died at home. A 90-day cut off was used to define late death, based on a previous study which showed high mortality in the first 90 days after treatment (55). Conditional survival rates were calculated (i.e. survival rates in patients who were alive 90 days after decannulation) to describe long-term survival in the group that survived the first critical period. In Study I, individual factors' influence on the patients' survival were evaluated using the Cox proportional-hazards model.

The general hypothesis for study I and II was that patients with a fully reversible condition who survived the initial critical months after treatment would have excellent long-term survival.

Study III and IV were follow-up investigations in a cohort of adult survivors. The first adult patient was treated in 1995, and consecutive survivors living in Sweden were contacted by mail and phone. Eligible survivors were approached (January 2014), and patients who agreed to participate were investigated during a day at the hospital, including magnetic resonance imaging (MRI) of the brain, neurocognitive tests[2] (70-75), high-resolution computed tomography (HRCT) of the lungs, pulmonary function testing (static and dynamic spirometry) and the 6-minute walk test (6MWD). Furthermore, patients were interviewed, and self-report forms were filled out to evaluate general quality of life (Short form 36; [76]),

[1] ICD = international classification of diseases, World Health Organisation. In Sweden, ICD-10 replaced ICD-9 in January 2011.
[2] Cognitive tests consisted of the Wechsler Adult Intelligence Scale 4th edition, the Wechsler Memory Scale 3rd edition (subtests), Rey Auditory Verbal Learning and Complex Figure Test, Free and Cued Selective and Reminding test, and the Delis–Kaplan Executive Function System (70-75).

respiratory-specific quality of life (St George's Respiratory questionnaire; [77]), symptoms of anxiety and depression (Hospital Anxiety and Depression Score [HADS]; [78]) and symptoms of post-traumatic stress disorder (PTSD, Trauma Screening Questionnaire [TSQ]; [79]). After investigating 35 patients, it was clear that the group was quite heterogeneous, and it was decided that patients treated for non-respiratory conditions and patients with a congenital mental disability should be excluded (n=4/35, resulting in 31 included and investigated patients). At this stage, the next survivors in line to be asked had already been investigated by a colleague three years after treatment (unpublished data at the time, cognitive results were later published separately; [54]). These patients were approached, and seven patients were added to the present cohort, with missing investigations completed when possible. In this way, the final cohort size became 38 patients.

Patient selection and investigation coherence are presented in Figure 4 based on the final inclusion and exclusion criteria (n=31+7=38).

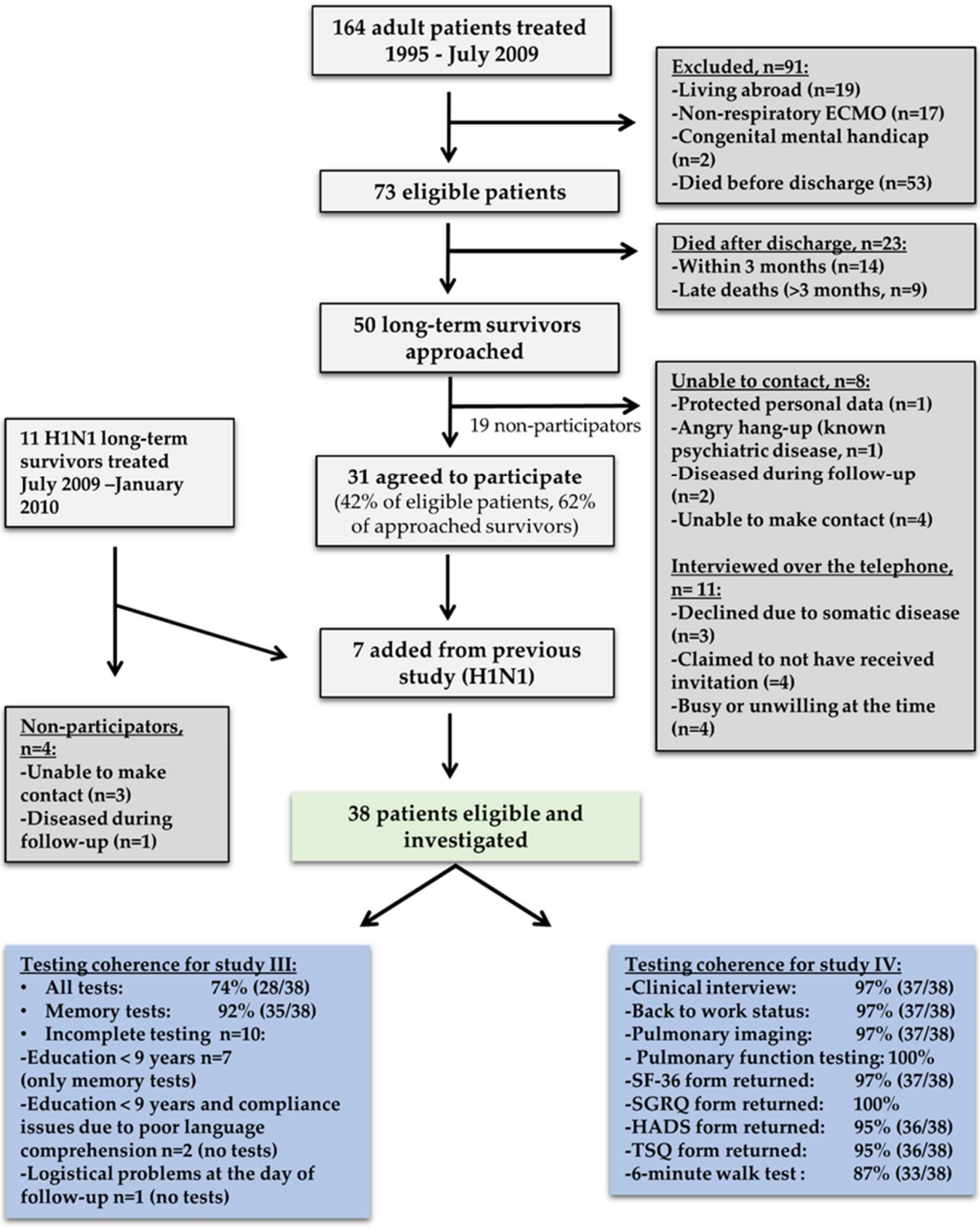

Figure 4. Flowchart showing patient inclusion and exclusion, patients lost to follow-up and testing coherence for study III and IV. Reproduced from study III and IV.

Interpretations of individual investigations were done by trained specialists (e.g. radiologists, neuropsychologists, a physiotherapist for the 6MWD, a nurse certified in SF-36 and SGRQ interpretation) and disagreements were generally resolved by consensus between specialists.

All investigators were blinded from any patient details but were aware of the presence of ECMO treatment. Patient charts were reviewed for clinical information, including hourly registered individual parameters (e.g. pulse oximetry oxygen saturations, mean arterial pressures, lactate levels, and the PEEP and FiO_2 used during ECMO treatment). Since some patients were treated for long periods of time, a ten-day observation period was decided upon to represent the ECMO treatment period (if treated <10 days, the whole treatment period was included). Pulse oximetry oxygen saturation values (SpO_2) defined hypoxaemia as a median SpO_2 <93% during the observation period (measured by peripheral pulse oximetry from the right ear, nose, or finger). This was in line with the methods used in the H1N1 cohort (54). Patients who, according to this definition, were hypoxaemic during the ECMO observation period were analysed separately in study III.

The main outcome parameters in **study III** were three indices representing global cognitive function (full-scale intelligence [FSIQ]), memory function (memory index) and executive function (executive index). The indices were created by comparing individual scores with age-matched healthy populations. These were presented using the IQ standard scale (normal mean = 100; SD 15). We did not use a strict definition of cognitive dysfunction since no widely accepted definition exists (59). Instead, group medians (IQR) and the number of patients with scores 1 and 2 SD below the group mean were presented. The hypothesis was that cognitive functions would generally be normal in ECMO treated patients, on par with a healthy normal population, and that hypoxaemia per se would not be associated with cognitive dysfunction if tissue hypoxia was avoided.

In **study IV** numerous outcome parameters were investigated. The main parameters of interest were the SF-36 physical and mental component scores, the SGRQ total score, diffusion capacity for carbon monoxide (DLCO, presented in % of expected normal value) and the extent of lung parenchyma pathology (presented in % of total lung parenchyma). The hypothesis was that quality of life, pulmonary function, mood levels and diffusion capacity (DLCO) after ECMO treatment would be reduced but similar to conventionally treated ARDS patients.

5.3 STATISTICAL METHODS

Survival was depicted using the Kaplan-Meier method, and the Log-rank (Mantel-Cox) test and Log-rank test for trend were used for the comparison of survival curves (study I and II). The Cox proportional-hazards model was used to evaluate the influence of covariates on survival in study I.

In study III, Mann-Whitney U tests were used to compare the IQ index scores between groups. In study IV Spearman's rank correlation test was used for evaluation of the correlation between outcome parameters of interest. Median or mean values for lung volumes, used in previous reports (3, 62, 67), were not calculated due to the heterogeneity of the data since the mean of mixed pathologically high and low values can be a normal value. Due to the methodological limitations of study III and IV and the small cohort size, we chose not to statistically test the reported findings further. P-values less than 0.05 were considered statistically significant.

Unless otherwise stated data were expressed as median (IQR).

Statistics were evaluated by Graph Pad InStat version 3.10 (Graph Pad Software, San Diego, USA) for study I, II, and IV. R software version 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org) was used for all statistical analyses in study III.

6 RESULTS

The most important findings are presented here. For all results, please refer to the full-text manuscripts with appendices enclosed at the end of this book.

6.1 SURVIVAL

In the survival studies (study I and II), there was no loss to follow-up. Median follow-up times were 7.8 years (mean 9.3) in neonatal patients, 5.6 years (mean 7.6) in paediatric and 4.4 years (mean 6.0) in adults. Median age was 2 days, 3 years and 46 years, respectively, and median EMCO treatment time was 6, 7 and 8 days, respectively.

Immediate survival after ECMO treatment was 84% in neonates, 74% in paediatric patients and 66% in adults (Table 4). Some patients, however, diseased shortly after decannulation[3] or before discharge to another hospital. 76%, 66%, and 55% respectively survived to 90 days after treatment, meaning that 9% of neonatal (21/222), 10% of paediatric (10/100) and 17% of adult survivors (29/168) died in the first 90 days after treatment. For most diagnostic groups, the survival curves plateaued after this point in time (Figure 5 A-B), indicating a high survival in the group that survived the first 90 days after treatment. Meconium aspiration syndrome and congenital diaphragmatic hernia were the most common neonatal diagnostic groups, while infections, namely pneumonia, were most common in paediatric patients and adults.

[3] Decannulation = discontinuation of ECMO by turning off the pump and retracting the cannulas from the vessels.

Patient group	Survived treatment	Survived to discharge	90-day survival	5-year survival	5-year survival if alive at 90d
Neonatal	**84%**	**80%**	**76%**	**72%**	**94%**
MAS	100%	100%	99%	99%	100%
CDH	83%	70%	68%	55%	77%
Congenital heart disease	67%	67%	58%	50%	86%
Paediatric	**74%**	**68%**	**66%**	**61%**	**91%**
Bacterial pneumonia	83%	70%	66%	54%	82%
Viral pneumonia	76%	76%	76%	76%	100%
Other respiratory	63%	63%	63%	58%	92%
Adult	**66%**	**64%**	**55%**	**47%**	**87%**
Bacterial pneumonia	69%	66%	58%	51%	88%
Viral pneumonia	65%	65%	61%	3YS: 57%	3YS: 93%
Other respiratory	73%	73%	47%	40%	86%

Table 4. Survival numbers for the three age categories and selected diagnoses after ECMO treatment (i.e. decannulation), after discharge from the Karolinska University Hospital, 90 days and 5 years later. For adult patients with viral pneumonia, the follow-up time was <5 years, and 3-year survival (3YS) is therefore presented. MAS = meconium aspiration syndrome; CDH = congenital diaphragmatic hernia. Reproduced from study I and II.

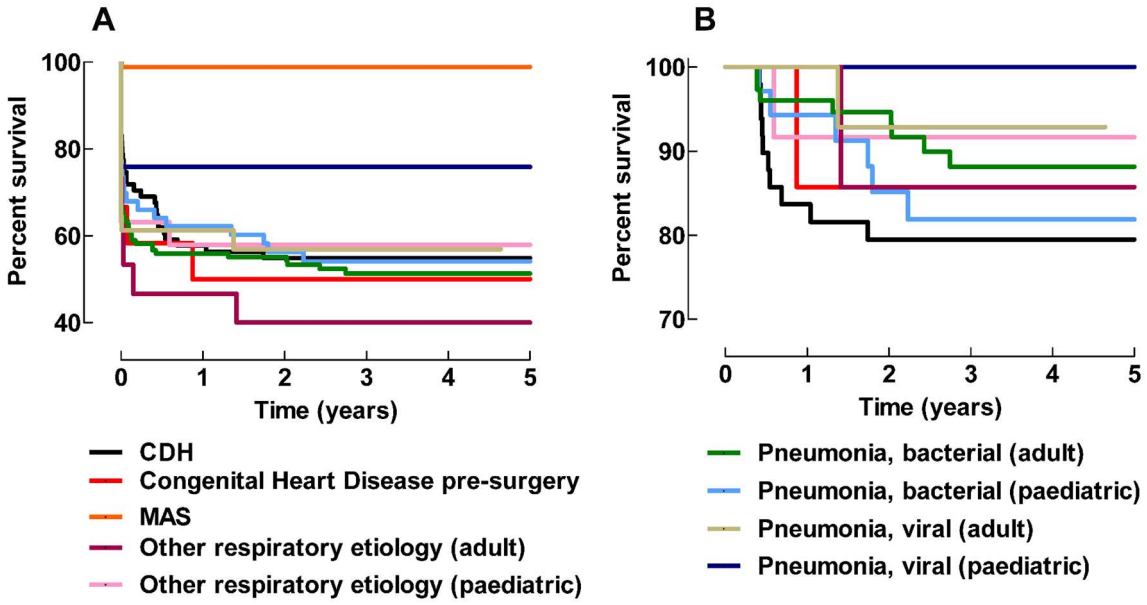

Figure 5. Kaplan–Meier survival estimates for selected diagnostic groups. In A, the initial descending part represents deaths during treatment (t0 = decannulation from ECMO treatment, diseased or alive). Panel B shows survival in patients who were alive at 90 days (i.e. t0 = 90 days after decannulation). Note that the curve for meconium aspiration syndrome (MAS) is hidden at 100% in panel B. CDH = congenital diaphragmatic hernia. Reproduced from study I and II.

Twenty-three late deaths (>90 days after treatment) appeared in the neonatal and paediatric cohorts (Table 5). Of these, 78% occurred within the first 3 years after treatment, and 12/14 neonatal patients had CDH (died from severe underlying main disease n=9, never recovered n=1, unknown n=2). In adults, 17 late deaths occurred, 94% of which occurred within 3 years after decannulation.

Cause	n, neonatal/paediatric	n, adults	Comment
Never recovered	2	1	
Died from severe underlying main disease	9	3	Congenital diaphragmatic hernia (CDH; n=9), cystic fibrosis (n=2), interstitial lung disease (n=1).
Malignancy	3	-	All known when ECMO was initiated.
Sepsis	1	-	Aspiration tendency.
Intoxication	-	3	Two had a known intoxication history.
Common societal causes	-	6	Metastatic Cancer (n=1), ischemic heart disease (n=1), stroke (n=1), pancreatitis (n=1), sepsis (n=2; one acquired influenza with a complicating pneumonia).
Miscellaneous	3	2	Children: encephalitis (n=1), persistent foetal circulation (n=1), immunodeficiency (n=1). Adults: immune disease (n=1), unspecified kidney failure (n=1).
Unknown	5	2	

Table 5. Causes of late death (>90 days after treatment). Reproduced from study I and II.

6.2 SURVIVORSHIP

In study III and IV, 38 patients were investigated in median 9.0 years after treatment (mean 9.6, range 3.1-17.1). Demographic data and clinical characteristics are shown in Tables 6 and 7.

Variable	All patients (n=38)
Age (yrs)	39 (24-52)
Sex, male / female	63% / 37%
Pre-existing condition	
None	26% (10/38)
BMI>30	50% (17/34)[a]
Cardiovascular disease	8% (3/38)
Pulmonary disease	18% (7/38)[b]
Diabetes mellitus	8% (3/38)
Immunodeficiency	5% (2/38)[c]
Other	13% (5/38)[d]
Smoking exposition	
Never smoker	55% (21/38)
<20 pack years	26% (10/38)
>20 pack years	18% (7/38)
Smoking at follow-up	11% (4/38)

Table 6. Demographic data at the time of ECMO treatment on patients included in study III and IV. Results are expressed as median (IQR) or % (n). Reproduced from study III and IV.

a Note that a high BMI in some cases may represent excess fluids from severe illness and its treatment. Median BMI (IQR): 30 (25-31). n (total) = 34 due to missing data.

b 5 asthma, 1 granulomatosis with polyangiitis (Wegener's, undiagnosed prior to ECMO treatment), 1 had undergone a curative lobe resection for small-cell lung cancer.

c 1 common variable immunodeficiency (CVID) with IgA deficiency, 1 suspected but unknown immunodeficiency.

d 1 Crohn's disease, 1 ulcerous colitis, 2 severe depression/anxiety, 1 pregnancy.

Variable	All patients (n=38)
Diagnosis	
Bacterial Pneumonia	63% (24/38)
Viral Pneumonia (H1N1)	18% (7/38)
Other pulmonary indication	8% (3/38)[a]
Non-pulmonary	11% (4/38)[b]
Durations (days)	
Mechanical ventilation	
before ECMO	2 (1-6)
ICU before ECMO	3 (1-7)
ECMO treatment	11 (7-23)
Mechanical ventilation, total	31 (15-44)
ICU, total	37 (23-57)
Hospital time, total	54 (30-114)
ECMO mode	
Venovenous (VV)	71% (27/38)
Venoarterial (VA) anytime[c]	29% (11/38)
Pre ECMO PaO_2/FiO_2	mmHg: 51 (43-58)
	kPa: 7 (5-8)

Table 7. Clinical characteristics of patients included in study III and IV. Results are expressed as median (IQR) or % (n). Reproduced from study III and IV.

a 1 lung bleed due to granulomatosis with polyangiitis (Wegener's, VV/hypoxaemia), 1 aspiration pneumonia after oral drug intoxication (VV/hypoxaemia), 1 asthma exacerbation (VV/hypercapnia).

b 1 developed ARDS after severe eclampsia and post-caesarean section bleed (VA ECMO, indication: hypoxaemia), 1 ARDS after septic abortion (initially VV, converted to VA ECMO, hypoxaemia), 1 multiple trauma (VV/hypoxaemia), 1 septic shock after neck infection (VV/hypoxaemia).

c Includes patients initially treated with venovenous ECMO, and later converted (n=4) and vice versa (VA-VV, n=2).

6.2.1 Study III

Twenty-eight patients had full testing performed, while seven patients were tested for memory functions only (due to a short formal education <9 years; Figure 4). Three patients were not tested whatsoever (logistical problems n=1, inadequate language comprehension n=2). The median FSIQ was 97 (IQR 86–104) and was within 1 SD in 79% (22/28 tested patients). Median memory function index was 101 (IQR 89–109), with one patient below 1 SD from the mean, and the median score on the executive function index was 104 (IQR 99–108), with two patients below 1 SD from the mean. Cerebrovascular lesions (CVL) were present in 37% (14/38; 64% in patients treated with VA ECMO). In the group with CVL, IQ scores were lower in all three domains, with significantly lower memory index (p=0.03) and executive index (p=0.02). No significant differences were found in either domain between patients with hypoxaemia during ECMO and patients without (Figure 6), including when testing an alternative definition of hypoxaemia post-hoc (defined as ≥12 hourly registrations or whole observation period median SpO_2 ≤85%).

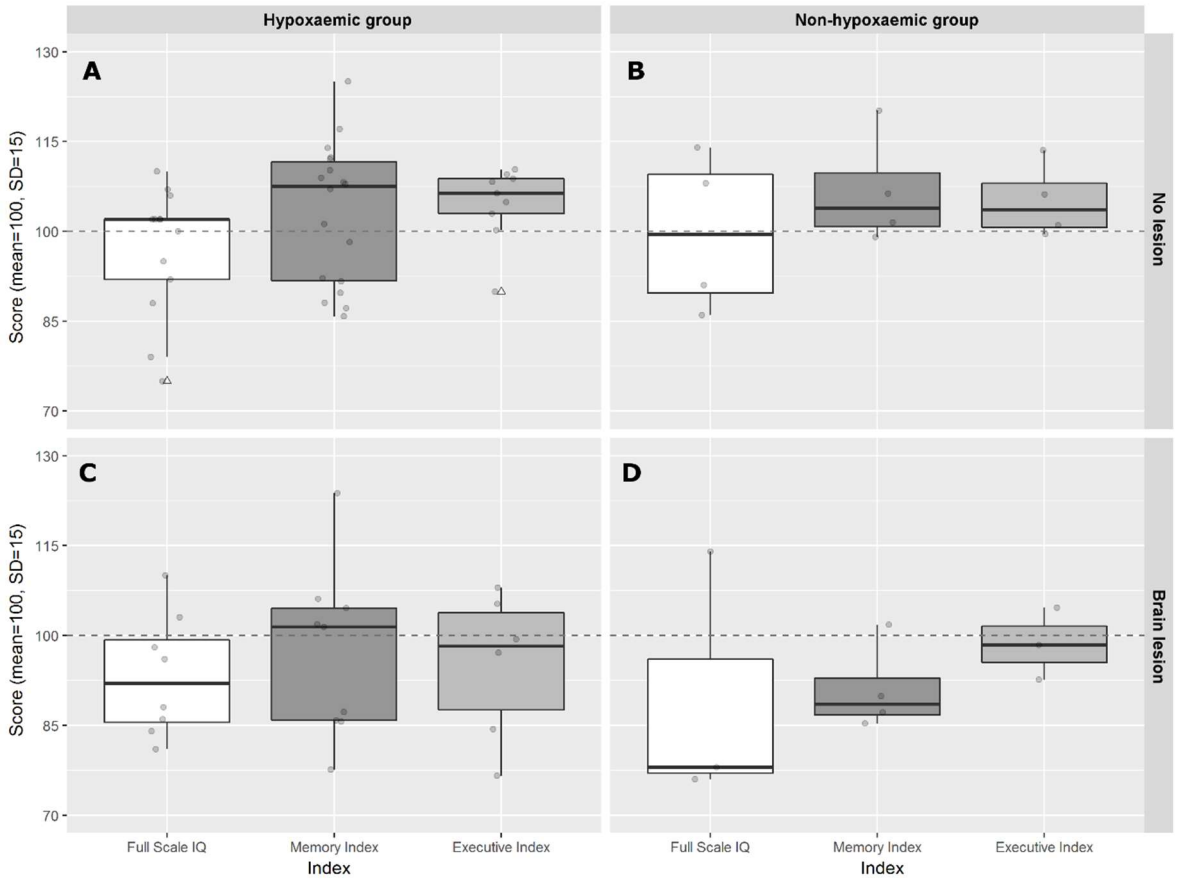

Figure 6. Neurocognitive test results from study III representing different cognitive domains based on MRI findings and hypoxaemia status during the ECMO observation period. Normal mean is 100 and 1 SD is 15 according to the intelligence quotient (IQ) standard scale. Note that only memory function was tested in some patients and the low sample size in B and D. Individual results are plotted as faded grey dots, and outliers are presented as triangles. The figure was created using ggplot2 for R statistics (Wickham, Ggplot2, Elegant Graphics for Data Analysis. New York, NY, Springer-Verlag, 2009).
A, Hypoxaemic group, no brain lesion; n = 19, full testing: n = 13.
B, Non-hypoxaemic group, no brain lesion; n = 5, full testing: n = 4.
C, Hypoxaemic group, brain lesion; n = 9, full testing: n = 8.
D, Non-hypoxaemic group, brain lesion; n = 5, full testing: n = 3.
Mann-Whitney U tests were performed to test the statistical difference between the groups for each cognitive domain. For patients with no lesions (A vs B), p values were 0.69 (full-scale IQ), 0.77 (memory index), and 0.83 (executive index). For patients with brain lesions (C vs D), p values were 0.50 (full-scale IQ), 0.50 (memory index), and 1.0 (executive index). Reproduced from study III.

6.2.2 Study IV

Quality of life was tested in 37/38 patients and was reduced in most domains of the SF-36, and all domains of the SGRQ, but comparable to conventionally treated ARDS patients (Figure 7 A-B). Symptoms of post-traumatic stress were seen in 14% (5/36). Possible anxiety and depression were seen in 22% (8/36) and 14% (5/36), respectively. Approximately half of the patients (19/36) had a normal quality of life and no self-reported depression or anxiety any time after discharge. Patients treated with ECMO ten days or more were overrepresented in the lower ends of SF-36, SGRQ and anxiety/depression scores. 51% of patients were back to work or studies one year after discharge (median time 6 months), and 22% (8/37) were not working or studying at follow-up (two of whom were not working before ECMO).

Lung function was normal in 37% of patients (14/38), primarily obstructive in 13% (n=5) and primarily restrictive in 21% (n=8). Many patients had non-ECMO-related risk factors for obstructive or restrictive disease (5/5 with signs of obstructive disease and 3/8 with signs of restrictive disease). Diffusion across the blood-gas barrier, assessed using the diffusing capacity for carbon monoxide (DLCO), was reduced in 47% of the patients.

In 82% of patients, some degree of residual pathology was seen on HRCT of the lungs (>1% parenchymal damage), and the mean damage was 7% (range 0–44%). Parenchymal damage correlated (Figure 8 A-B) with days on ECMO and total days with mechanical ventilation ($r=0.55$, $p<0.001$ and $r=0.72$, $p<0.001$), and with SF-36 physical component score ($r=-0.47$, $p=0.004$), SGRQ total score ($r=0.57$, $p<0.001$) and DLCO ($r=-0.57$, $p<0.001$).

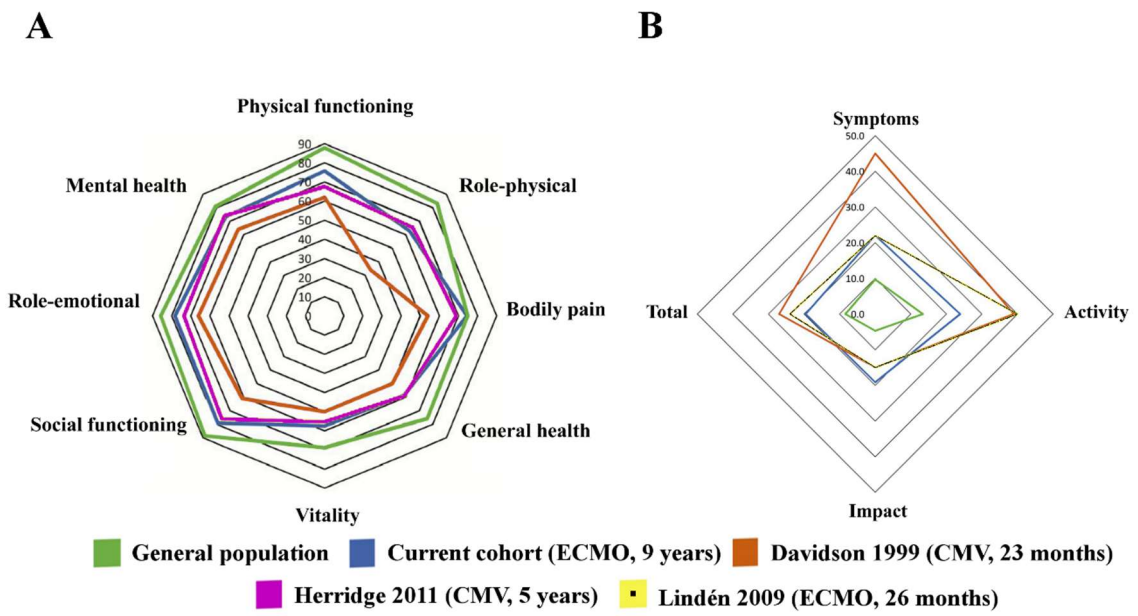

Figure 7. Quality of life results in comparison. A: Short form 36, B: St George's Respiratory Questionnaire. CMV = conventional mechanical ventilation (i.e. not ECMO). Reproduced from study IV.

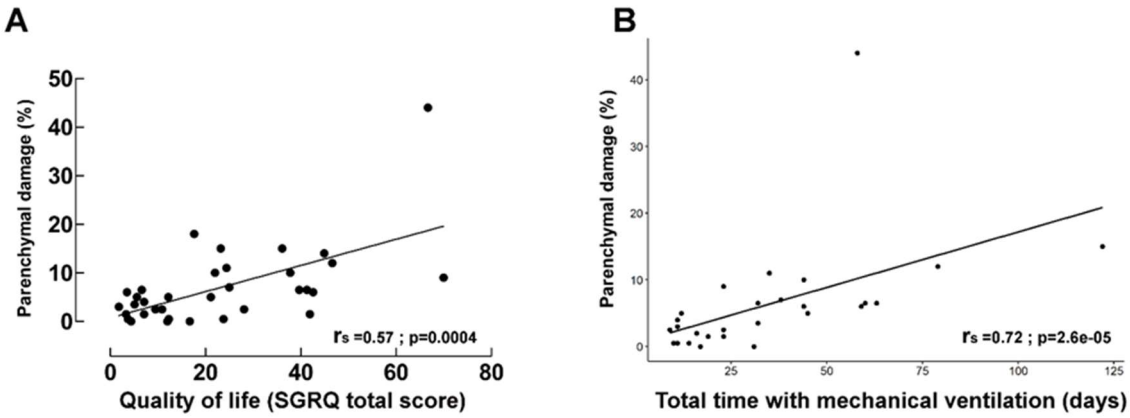

Figure 8. Spearman's rank correlations of lung parenchymal damage and quality of life (A) and time with mechanical ventilation (B). Reproduced from study IV.

7 DISCUSSION

In this thesis, long-term survival and survivorship were investigated with registry studies (study I and II) and follow-up investigations (study III and IV).

7.1 GENERAL DISCUSSION

7.1.1 Study I and II

There was high initial mortality, especially in the first three months after ECMO treatment. This is in line with the general ICU population and previous studies (55, 80-81), but is nevertheless important since many centres and the ELSO registry report survival to discharge only. If on the other hand, a patient survives to 90 days after treatment and was treated for a reversible condition such as meconium aspiration syndrome or an infection, long-term survival was good, with a principally plateaued survival curve. There was no unexplained accumulation of deaths years after treatment which would indicate an ECMO caused mortality. For most groups, survival to the 90-day endpoint was prognostic of 5 and 10-year survival, similar to what has been found in ICU treated patients in general (80, 82).

Not surprisingly, survival differed between diagnoses and was poor in patients with severe co-morbidities (e.g. CDH patients and paediatric patients with cancer). In study I, age and cannulation group were linked to overall mortality in adults, but not to mortality in patients who survived to 90 days after treatment. Cannulation itself was probably not the main cause for this. Rather, a venoarterial cannulation and especially the need to convert from VV to VA ECMO represents a more severe cardiorespiratory failure not sufficing with or failing to improve despite venovenous ECMO. Age was linked to mortality only when the group with full data (PF ratio available) was analysed ($p=0.04$), and not when all 255 patients were analysed ($p=0.10$). Since missing PF ratio data was arbitrary, we consider the latter non-significant result more reliable since it's based on more patients.

Causes of death, although a rough measure (see section 7.2.1), indicated that patients mainly died from a severe underlying disease, common societal causes or that the patient never fully recovered from the condition requiring ECMO treatment. It was however worrisome that three patients died from intoxications. Two of these patients had a history of self-incurred intoxications (one patient had an alcohol/drug dependence and one suffered from paranoid schizophrenia), but it is nevertheless sad that society, after long periods of intensive care treatment and rehabilitation, could not help these individuals with their underlying issues.

When interpreting reports from the ELSO registry, one must remember that it constitutes data from many centres, which in turn may differ in size, experience, case mix etcetera. Moreover, the meaning of "survival to discharge" may differ vastly between centres. At the ECK, survival to discharge indicates discharge from the Karolinska University Hospital, which in turn means different things depending on the patient's home city. For patients admitted from other hospitals outside Stockholm, discharge often meant that they were sent back to the ICU they were admitted from, while local patients were generally discharged from a normal ward

within the hospital to a rehabilitation unit or even home. Needless to say, the 3-month prognosis was probably inferior in the former group.

Comparing survival between centres needs careful consideration. Among other things, the mix of patients (age, diagnosis, severity of disease, contraindications), timing of ECMO institution (and decannulation), centre experience, volume and coherence with ELSO guidelines may differ. Furthermore, as ECMO, ventilator and general ICU management have evolved over the years, it may be misleading to compare a cohort treated in the 1990s with patients treated today. We chose not to compare e.g. pre and post-millennial survival mainly since the changes in equipment and approaches to ECMO treatment have been gradual and during periods there has been a significant overlap. Furthermore, the general mix of patients at the ECMO Centre Karolinska may have differed over time. It is reasonable to believe that the number of patients where ECMO was tried as a last resort salvage therapy was higher during the early years of ECMO. This was a time when the technology was still considered experimental by many, and ELSO guidelines were less explicit and evidence-based.

7.1.2 Study III and IV

The follow-up investigations indicated problems in life years after ECMO on par with what has been described in conventionally treated ARDS patients, although the studies were not designed to compare ECMO to CMV (see section 7.2.2).

Normal cognition was seen in the group with normal brain imaging (study III), although we could not present pre-illness cognitive functions. It is possible (but unlikely) that included patients' baseline IQ could have been above the general average, meaning that a median IQ of 100 actually represented a reduction in the present cohort. Memory and executive functions were significantly reduced in patients with brain lesions, as previously reported (12). Brain lesions were common, especially in the VA ECMO group. In the published literature, there's a large discrepancy between reported CVL prevalence when brain radiography is used when symptoms occur (5.3-5.4%; [83-84]) and routinely screened patients (16.4% in ECMO patients vs 7.6% in conventionally managed patients; [85]). The latter was supported in a recent study which reported CVL in 10.7% of ECMO patients upon admission, and a further 5.2% during ECMO treatment (86). Interestingly, the recent EOLIA RCT reported a similar haemorrhagic stroke prevalence in the ECMO (2%) compared to the non-ECMO group (4%), and significantly fewer ischemic strokes in the ECMO group (absolute risk reduction −5%, 95% CI −10% to -2%; [4]). No screening protocol was used in this trial (i.e. CT was used only if symptoms occurred).

Hypoxaemia may cause tissue hypoxia, including hypoxic brain damage resulting in cognitive dysfunction (54). At the ECMO Centre Karolinska, arterial blood oxygen saturations (SaO_2) of 70-80% have been accepted for long periods of time, as long as lactate stays low and pre-oxygenator mixed venous saturations high (i.e. permissive hypoxaemia with the assumption of no tissue hypoxia). Due to the inherent limitations in study III, including how hypoxaemia was defined (see section 7.2.2), the effects of hypoxaemia on

cognitive function remain unclear, although we have shown that patients with prolonged hypoxaemia may have normal cognitive functions years after treatment.

The reductions in quality of life spanned across most domains but were similar to reported findings in conventionally treated ARDS survivors (study IV). Patients treated with ECMO ten days or more were over-represented in the worse ends of SF-36, SGRQ and mood symptom scores, which is expected since these patients probably represent more complex cases needing long treatment times to get better. The level of lung parenchymal damage correlated with a reduced quality of life and DLCO, and with time on ECMO and mechanical ventilation. Although perhaps not overly surprising, this may constitute a factor worthy of future evaluation as a marker for long-term sequelae after treatment. It is possible that the correlation with mechanical ventilation time represents VILI, which is supported by the 50% anterior location of parenchyma damage, but this remains speculative.

Although not directly comparable, the present findings support the notion that ARDS survivors irrespective of CMV or ECMO treatment have a reduced quality of life even 3-17 years after treatment. When weighing the results of three comparative studies, quality of life was similar or slightly better after ECMO vs CMV (14). Comparing ECMO patients with CMV is cumbersome since the “perfect” RCT has yet to be done. Problems include very low recruitment rates and that many clinicians believe it is unethical to keep a patient randomised to CMV when the patient is dying and could possibly be saved with ECMO treatment. The latter aspect results in a high crossover from the CMV to the ECMO group (28% in the recent EOLIA trial). In the aftermath of the EOLIA trial, it has even been questioned whether another large RCT of ECMO for severe ARDS will ever happen (32, 87).

7.2 WEAKNESSES AND DIFFICULTIES

A general weakness of all four studies was their retrospective nature and lack of matched control groups.

7.2.1 Study I and II

In study I and II, the majority of patients were treated many years ago with intensive care and ECMO treatment of the time and may not be fully representative of patients treated today. Median (IQR) treatment dates for adult patients (study I) was February 2005 (November 2001 – December 2007) and in children (study II) September 2006 (June 2000 – October 2010). The lack of severity of illness scores such as APACHE[4] or SOFA[5] and comorbidity index scores hamper comparison with other studies.

Moreover, patients were grouped using modified ELSO guidelines (47, 53) which may also hinder cohort comparison. Categorisation of patients is inherently problematic but necessary to create order and to enable comparison and research. The perfect, utopian grouping with unambiguously clear instructions creating fully homogenous groups does not exist. Upon inspection, many patients treated at the ECMO Centre Karolinska were categorised in vague groups such as "ARDS, other", "Other respiratory failure" or simply "Other", and many cases were open for subjective interpretation. For example, how should a patient with septic shock with an unknown cause be categorised (non-pulmonary infections)? And should a patient with pneumothorax, aspiration, and ARDS after falling into the water be classified as aspiration pneumonia or ARDS post-op/trauma? We suggested a grouping based on the main aetiology of respiratory failure, except in neonates, where the cause for ECMO treatment is more often based on a clear diagnosis, e.g. congenital diaphragmatic hernia or meconium aspiration syndrome.

The national causes of death registry is valuable to researchers and provides two pieces of vital information: whether the patient is alive and which causes of death were reported. The latter is based on a form that must be sent by the physician in charge within three weeks after the patient's death. In the vast majority of cases, this report is not based on autopsy reports but rather on the physicians best-informed guess after clinical examination. In 2012, only 11% of deaths were subject to an autopsy in Sweden (88). For patients who die at home, a general practitioner is in charge of reporting the cause of death, if natural causes are expected (i.e., no forensic autopsy is deemed required). When extracting the data, it was unclear to us who diagnosed the cause of death and by what means.

7.2.2 Study III and IV

When designing the follow-up investigations, little was known about long-term life after ECMO, and the ECMO Centre Karolinska approved to finance 35-40 patients. Hence, the

[4] Acute physiology and chronic health evaluation
[5] Sequential organ failure assessment

cohort size was not based on statistical power calculations, and the design was retrospective, descriptive and without a matched control group. In a way, the studies, therefore, fall somewhere in between a case series and a cohort study.

Selection bias is a noteworthy limitation in study III and IV. Indeed, only 62% of eligible long-term survivors (42% of eligible patients) were investigated. It is possible that the patients who died after discharge, rejected participation or did not respond to our mails and phone calls were indeed the patients who were struggling the most with cognitive, pulmonary or quality of life sequelae. The present findings should be interpreted with this in mind.

The inclusion of H1N1 patients was widely discussed (see the supplemental digital content 1 of study III), as was the exclusion of patients who stood out, either because of the reason for ECMO treatment (e.g. a patient treated <24 hours as a re-warming procedure after a drowning accident) or due to co-morbidities (e.g. a patient with a congenital mental and physical handicap who could only participate in the radiographic examinations). We also discussed how much the language barrier for non-native speakers would affect the self-report forms and cognitive tests. When applying for ethical approval, we sought to exclude patients who did not have "at least seven years of European or North American education". This cut-off was very rough, and the ethical committee asked us to remove this geographical limitation before approving the application. We, therefore, decided to investigate all consecutive survivors and to report the results to the individual patients but to exclude some patients' findings from the final articles.

There are several limitations when comparing patients with median SpO_2 <93% to "normoxaemic" patients (i.e. ≥93%). First, SpO_2 was registered in the patient charts hourly, meaning they could represent transient high (or low) values and important events may have been missed. Second, the definition allowed a patient who was severely hypoxaemic for the first 36 hours followed by a normoxaemic four-day period and then decannulated, to be classified as normoxaemic. An alternative would be to define hypoxaemia as a certain number of hours with a low saturation, which was done as a post-hoc analysis. Third, the hypoxaemia limit was possibly too high, since most clinicians are comfortable having a SpO_2 of 90-92% (~PaO_2 8-9 kPa) for days but are far less prone to allow an SpO_2 of e.g. 80%. Four, the groups (hypoxaemic vs non-hypoxaemic) were not matched, meaning there could be unevenly distributed confounders. We tested an alternative definition post-hoc and could have redefined hypoxaemia further, but the more statistical tests performed, the higher the risk of having a type 1 error. In conclusion, we may have found no statistical reason to reject the null hypothesis, but the methodology of this can be questioned for several reasons as per the discussion above.

When interpreting the self-reported findings in study IV, namely quality of life, PTSD, anxiety, and depression, one must bear in mind that they may both reflect an actual improvement over the years and an adaptation by patients to the situation over time.

7.3 CLINICAL IMPLICATIONS

- Survival after ECMO treatment should if possible be presented as survival to decannulation and survival to 90 days. If survival to discharge is used, this should be clearly defined.

- Although the high mortality in the first months after decannulation is probably often expected, a high level of vigilance should reside with clinicians and caretakers responsible for ECMO treated patients.

- There is a high risk of cerebral lesions in ECMO treated patients, and silent lesions are probably common. Efforts should be made to monitor patients' cerebral functions, especially in the setting of VA ECMO, and a routine for cerebral imaging during and after ECMO treatment should be considered.

- Permissive hypoxaemia with an SaO_2 as low as 70% may be safe if tissue hypoxia is avoided, but there is a paucity of data in this area.

- Long-term sequelae, including cognitive functions, quality of life and pulmonary functions, may take years to improve, and some dysfunction seems irreversible. Follow-up clinics should be considered for all age groups to early identify treatable problems. Patient information based on this knowledge is vital to avoid unnecessary suffering and misunderstanding.

7.4 FUTURE RESEARCH

- To aid future patient selection, patient and treatment-specific factors which influence 90-day survival (short-term) and 5-year survival in the group that survives to 90 days (long-term) should be further investigated.

- It would be interesting to investigate ECMO patients' long-term health status in a longitudinal fashion, e.g. 1, 3 and 5 years after discharge, since there seems to be a large recovery potential in the first years after treatment.

- The damaging effects of hypoxaemia without hypoxia and whether it may cause cognitive dysfunction and increased mortality should be further studied. These studies should include measurements of oxygen delivery to the brain to account for regional flow characteristics and autoregulation.

- The occurrence of brain lesions during and after ECMO should be further investigated using a screening protocol rather than a radiography-when-symptoms-occur-approach. These studies should include investigations after discharge, since silent lesions are probably common, and preferably compare to conventionally treated matched patients.

- Whether lung parenchymal damage is caused by VILI and may serve as an early predictor for long-term dysfunction is worthy of further studies. Furthermore, it is currently unknown whether even lower pressures and tidal volumes than recommended by the ARDSnet ("ultra-protective ventilation") could reduce VILI further.

7.5 REFLECTIONS CONCERNING LEARNING OUTCOMES

During the five years it took to complete this doctoral thesis, learning has come from a multitude of sources. Academic courses have laid the groundwork for scientific thinking and understanding, and the process of working on a project from methodological planning to revising manuscripts with help from reviewers, supervisors, and co-authors has been invaluable. Study I and II constituted good introductions to research thinking, with relatively few methodological challenges. Still, they required careful ethical considerations in a time when IT system security and patient integrity were lively debated. The process of working on the first manuscript took much time and effort, and the initial submission was turned down by two journals before eventually being accepted for publication by a third journal after two major revisions. This process was in retrospect highly valuable, as it helped me to consider study limitations, alternative explanations for our results and how the presentation of the findings could be improved. Study II, conceived with the same methods and with similar results as study I, was accepted after one round of minor revision, probably reflecting the steep learning curve from study I. This process was repeated with study III and IV, where study III took many revisions before being accepted, while study IV, when writing this summary chapter, has been accepted without revision by a peer-reviewed journal.

In 2017, I joined the Critical Care Research Group in Brisbane Australia as an international research fellow for a year, focusing on projects outside this dissertation while simultaneously working on study 3. I cannot overstress the value of spending time in an environment with fellow PhD students from other universities and cultures, discussing current and future projects and research in general on a daily basis. During my time in Australia, among other things, I got acquainted with planning and conduction of large animal and ex-vivo laboratory studies, statistical calculations using R statistics, writing literature reviews, supervising students and organising a medical conference.

Another great source of learning has come from the numerous academic meetings where I've been fortunate to be given the opportunity to present my research, either as abstract posters or invited faculty. In my experience, when preparing to present your research in such an environment, you reflect about it on a deeper level, trying to anticipate what weaknesses may be brought up and how to meet both valid and less relevant criticism.

All-in-all, as a medical doctor spending most of my time with patients, the above and the invaluable help from my supervisors has helped me to grow as a scientist, not necessarily always on a very detailed level but as a generalist with a broad understanding of basic research concepts, which I'm sure will aid me both clinically and academically in the future.

8 CONCLUSION

Life after ECMO can take many forms, and each patient's destiny is affected by numerous factors.

Long-term survival after treatment with ECMO was generally good in patients who

- Survived the first critical months after decannulation
- Were treated for a fully reversible condition
- Did not have a severe comorbidity

After treatment with ECMO for respiratory failure in adults, the present results suggest that

- Cerebrovascular lesions are common, especially if venoarterial ECMO is used
- Long-term cognitive functions may be good if the patient has not suffered from a cerebrovascular lesion.
- Patients treated with a permissive hypoxemia approach may have normal long-term cognitive functions, but this needs to be further studied.
- Reduced quality of life, depression, anxiety, and pulmonary dysfunction are common many years after treatment, but in line with conventionally treated patients.

Given the severity of illness and risk of death when admitted for ECMO, these results are promising but need further evaluation. It is my hope that this thesis may inspire further research on the topic and help health care professionals when discussing life after ECMO with patients and relatives.

9 SUMMARY OF THESIS IN SWEDISH

ECMO betyder Extracorporeal (utanför kroppen) MembranOxygenering (syresättning genom ett membran) och är en slags hjärt-lung-maskin som används inom intensivvården vid allvarlig hjärt- eller lungsjukdom. ECMO botar inte sjukdomen som orsakar problemet, men kan hålla patienten vid liv de dagar till veckor (ibland månader) som behövs för att kroppen ska återhämta sig. Vanlig intensivvård och behandling av sjukdomen ges parallellt. Vid t.ex. allvarlig lunginflammation är första behandlingen att ge extra syrgas och mekanisk ventilation. När 100% syrgaskoncentration och höga tryck i respiratorn inte räcker kan ECMO vara ett alternativ. Med ECMO sugs det icke syresatta blodet ut från kroppen, leds genom membranlungan som syresätter blodet som sedan pumpas tillbaka till kroppen igen. Eftersom att ECMO är ett stort avsteg från den vanliga fysiologin, och både är kostsamt och behäftat med flera biverkningar, är det viktigt att veta hur det går för dessa patienter senare i livet. Detta har undersökts i fyra studier som ligger till grund för den här doktorsavhandlingen.

I studie I och II undersöktes långtidsöverlevnaden för nyfödda, äldre barn och vuxna som behandlats med ECMO. Det visade sig att många dör de första tre månaderna efter behandling, men att de som överlevt denna kritiska tid ofta har en god överlevnad på sikt, förutsatt att de inte har någon allvarlig grundsjukdom som påverkar deras överlevnad (t.ex. cancer eller medfödda lungsjukdomar) och att den sjukdom som de behandlats för är reversibel (går över, t.ex. en infektion som behandlas lyckosamt med antibiotika).

I studie III och IV undersöktes 38 vuxna överlevare som vårdats för lungsvikt, i genomsnitt 9 år efter ECMO-behandling, med magnetkameraundersökning av hjärnan och IQ-tester av en psykolog (studie III). Det visade sig att dessa patienter hade en IQ-nivå liknande normalbefolkningens, men att tecken till tidigare stroke (antingen från ECMO-tiden eller från innan eller efter) var vanligt och att de patienter som haft stroke hade signifikant sämre minnes- och exekutiva funktioner. Samma patienter undersöktes även med självskattningsformulär för livskvalité, ångest, depression och posttraumatisk stress, samt skiktröntgenundersökning av lungorna och lungfunktionsundersökningar. Patienterna hade sämre livskvalité och oftare psykologiska besvär än en frisk normalbefolkning, men resultaten var på en nivå som motsvarar andra patienter som haft svår lungsvikt och vårdats med respirator men utan ECMO. Dock är det svårt att jämföra våra 38 patienter med andra studerade grupper, då de kan skilja sig på flera viktiga punkter, och det är också diskutabelt om dessa 38 överlevare representerar ECMO-behandlade i stort.

Sammanfattningsvis tycks ECMO-överlevare som i övrigt är friska ha en god långtidsöverlevnad om de överlever den första kritiska tiden efter ECMO-behandlingen. Dessa patienter kan ha flertalet problem senare i livet, med sänkt livskvalité och påverkad lungfunktion. Det är därför viktigt att dessa patienter följs upp av vården på ett strukturerat sätt. Det är också viktigt att övervaka hjärnans funktioner under ECMO-vård, och forska mer kring vad man kan göra för att förhindra stroke, eftersom att det kan ge kognitiva besvär senare i livet.

10 ACKNOWLEDGEMENTS

Jan Hultman, for being an inspirational supervisor and mentor. Always with a laugh that cuts through any concern or doubt, mixed with straight-to-the-point tips for efficient working.

Björn Frenckner, for a humble, humorous, and knowledgeable supervision, with a sharp eye for details and high-quality scientific writing, and for bringing ECMO to Stockholm.

Håkan Kalzén, for opening my eyes to the world of extracorporeal life support. With a big smile, lots of ideas and prestigelessness both in life and in research.

Tanja Dobrosavljevic, for invaluable help, without which this doctoral project could not have happened. One of the brightest and most service minded persons I know.

Palle Palmér, for bringing ECMO Center Karolinska to life, for thinking outside the box (outside anyone's box for that matter) and for connecting me with the ECMO community.

Bernhard Holzgraefe for adding fingerspitzengefühl and German effectiveness to my research, always attentive and helpful.

Staffan Eksborg for a curious and cheerful view on statistics and imaging and for faithful safeguarding against cherrypicking results.

Michael Runold, for inspiring a young doctor to never forget to have a big heart, no matter how busy you get.

Daniel Brodie, for building bridges and overseeing my first article.

John Fraser, for opening the doors to an inspiring and highly productive international research environment.

Max, Johnny, Obonyo and Jacky, for bringing fun, inspiration and creativity to research.

Finally, thanks:

- To all patients who participated in the investigations.
- To all staff at the ECMO Centre Karolinska, for your life-saving work and help.
- To my generous funders over the years, including Stiftelsen Axel Tielmans minnesfond, SECMO, Sällskapet barnavård, Samariterorden, Stiftelsen Sigurd och Elsa Goljes Minne and Svenska Läkaresällskapet.
- To Ebba, my loving wife, for your patience and for bringing love, play, and balloons to my life.
- To Bob Bartlett, for devoting your life to this life-saving technology.

11 REFERENCES

1. Extracorporeal Life Support Organization Registry Report. International Summary July 2018 [Internet]. [cited 2018 Dec 9]. Available from: www.elso.org

2. Kim SJ, Kim HJ, Lee HY, Ahn HS, Lee SW. Comparing extracorporeal cardiopulmonary resuscitation with conventional cardiopulmonary resuscitation: A meta-analysis. Resuscitation. 2016;103:106–16.

3. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. Lancet. 2009 Oct 17;374(9698):1351–63.

4. Combes A, Hajage D, Capellier G, Demoule A, Lavoué S, Guervilly C, et al. Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome. New England Journal of Medicine. 2018 May 24;378(21):1965–75.

5. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators, Davies A, Jones D, Bailey M, Beca J, Bellomo R, et al. Extracorporeal Membrane Oxygenation for 2009 Influenza A(H1N1) Acute Respiratory Distress Syndrome. JAMA. 2009 Nov 4;302(17):1888–95.

6. Bartlett RH, Deatrick KB. Current and future status of extracorporeal life support for respiratory failure in adults. Curr Opin Crit Care. 2016 Feb;22(1):80–5.

7. Malfertheiner MV, Broman LM, Belliato M, Venti A, Bader A, Taccone FS, et al. Management strategies in venovenous extracorporeal membrane oxygenation: a retrospective comparison from five European centres. Crit Care Resusc. 2017;19(Suppl 1):76–81.

8. Bein T, Weber-Carstens S, Goldmann A, Müller T, Staudinger T, Brederlau J, et al. Lower tidal volume strategy (≈3 ml/kg) combined with extracorporeal CO2 removal versus "conventional" protective ventilation (6 ml/kg) in severe ARDS: the prospective randomized Xtravent-study. Intensive Care Med. 2013 May;39(5):847–56.

9. Malfertheiner MV, Pimenta LP, Bahr V von, Millar JE, Obonyo NG, Suen JY, et al. Acquired von Willebrand syndrome in respiratory extracorporeal life support: a systematic review of the literature. Crit Care Resusc. 2017 Oct;19(Suppl 1):45–52.

10. Napp LC, Kühn C, Hoeper MM, Vogel-Claussen J, Haverich A, Schäfer A, et al. Cannulation strategies for percutaneous extracorporeal membrane oxygenation in adults. Clinical Research in Cardiology. 2016 Apr;105(4):283–96.

11. Gray BW, Haft JW, Hirsch JC, Annich GM, Hirschl RB, Bartlett RH. Extracorporeal Life Support: Experience with 2,000 Patients. ASAIO Journal. 2015;61(1):2–7.

12. Risnes I, Wagner K, Nome T, Sundet K, Jensen J, Hynås IA, et al. Cerebral outcome in adult patients treated with extracorporeal membrane oxygenation. Ann Thorac Surg. 2006 Apr;81(4):1401–6.

13. Herridge MS, Moss M, Hough CL, Hopkins RO, Rice TW, Bienvenu OJ, et al. Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers. Intensive Care Med. 2016 May;42(5):725–38.

14. Wilcox ME, Jaramillo-Rocha V, Hodgson C, Taglione MS, Ferguson ND, Fan E. Long-Term Quality of Life After Extracorporeal Membrane Oxygenation in ARDS Survivors: Systematic Review and Meta-Analysis. Journal of Intensive Care Medicine. 2017 Oct 19;088506661773703.

15. Morris T. The Matter of the Heart: A History of the Heart in Eleven Operations. Random House; 2017. 574 p.

16. Weisse AB. Cardiac surgery: a century of progress. Tex Heart Inst J. 2011;38(5):486–90.

17. Bartlett RH. Extracorporeal life support: history and new directions. Semin Perinatol. 2005 Feb;29(1):2–7.

18. Hill JD, O'Brien TG, Murray JJ, Dontigny L, Bramson ML, Osborn JJ, et al. Prolonged Extracorporeal Oxygenation for Acute Post-Traumatic Respiratory Failure (Shock-Lung Syndrome): Use of the Bramson Membrane Lung. New England Journal of Medicine. 1972 Mar 23;286(12):629–34.

19. Bartlett RH. Extracorporeal life support for cardiopulmonary failure. Current Problems in Surgery. 1990 Oct;27(10):627–705.

20. Antoniali F. There is one more thing to be done: ECMO! Revista Brasileira de Cirurgia Cardiovascular. 2015 Jul-Aug;30(4):IV–VI.

21. Bartlett RH. Esperanza: The First Neonatal ECMO Patient. ASAIO Journal. 2017;63(6):832–43.

22. Bartlett RH, Gattinoni L. Current status of extracorporeal life support (ECMO) for cardiopulmonary failure. Minerva Anestesiol. 2010 Jul;76(7):534–40.

23. Bartlett RH. ECMO: The next ten years. The Egyptian Journal of Critical Care Medicine. 2016 Apr;4(1):7–10.

24. Moerer O, Vasques F, Duscio E, Cipulli F, Romitti F, Gattinoni L, et al. Extracorporeal Gas Exchange. Critical Care Clinics. 2018 Jul;34(3):413–22.

25. Gattinoni L. Ultra-protective ventilation and hypoxemia. Crit Care. 2016 May 12;20(1):130.

26. Millar JE, Fanning JP, McDonald CI, McAuley DF, Fraser JF. The inflammatory response to extracorporeal membrane oxygenation (ECMO): a review of the pathophysiology. Critical Care. 2016;20:387.

27. Burrell A, Müller T. Inflammation in venovenous extracorporeal membrane oxygenation: villain or innocent bystander? J Thorac Dis. 2018 Aug;10(8):E652–3.

28. Chen Q, Yu W, Shi J, Shen J, Hu Y, Gao T, et al. The effect of venovenous extra-corporeal membrane oxygenation (ECMO) therapy on immune inflammatory response of cerebral tissues in porcine model. J Cardiothorac Surg. 2013 Aug 29;8:186.

29. Zapol WM, Snider MT, Hill JD, Fallat RJ, Bartlett RH, Edmunds LH, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. JAMA. 1979 Nov 16;242(20):2193–6.

30. Brodie D. The Evolution of Extracorporeal Membrane Oxygenation for Adult Respiratory Failure. Ann Am Thorac Soc. 2018 Feb;15(Supplement_1):S57–60.

31. Noah MA, Peek GJ, Finney SJ, Griffiths MJ, Harrison DA, Grieve R, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). JAMA. 2011 Oct 19;306(15):1659–68.

32. Gattinoni L, Vasques F, Quintel M. Use of ECMO in ARDS: does the EOLIA trial really help? Critical Care. 2018;22:171.

33. Desai M, Dalton HJ. Half-empty or half-full?-interpretation of the EOLIA trial and thoughts for the future. J Thorac Dis. 2018 Sep;10(Suppl 26):S3248–51.

34. Umbrello M, Formenti P, Bolgiaghi L, Chiumello D. Current Concepts of ARDS: A Narrative Review. Int J Mol Sci. 2016 Dec 29;18(1).

35. Acute Respiratory Distress Syndrome: The Berlin Definition. JAMA. 2012 Jun 20;307(23):2526-33.

36. Bellani G, Laffey JG, Pham T, Fan E, Brochard L, Esteban A, et al. Epidemiology, Patterns of Care, and Mortality for Patients With Acute Respiratory Distress Syndrome in Intensive Care Units in 50 Countries. JAMA. 2016 Feb 23;315(8):788–800.

37. Gattinoni L, Tonetti T, Cressoni M, Cadringher P, Herrmann P, Moerer O, et al. Ventilator-related causes of lung injury: the mechanical power. Intensive Care Med. 2016 Oct;42(10):1567–75.

38. ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. N Engl J Med. 2000 May 4;342(18):1301–8.

39. Fan E, Brodie D, Slutsky AS. Acute Respiratory Distress Syndrome: Advances in Diagnosis and Treatment. JAMA. 2018 Feb 20;319(7):698.

40. Young D, Lamb SE, Shah S, MacKenzie I, Tunnicliffe W, Lall R, et al. High-Frequency Oscillation for Acute Respiratory Distress Syndrome. New England Journal of Medicine. 2013 Feb 28;368(9):806–13.

41. Ferguson ND, Cook DJ, Guyatt GH, Mehta S, Hand L, Austin P, et al. High-Frequency Oscillation in Early Acute Respiratory Distress Syndrome. New England Journal of Medicine. 2013 Feb 28;368(9):795–805.

42. Li X, Scales DC, Kavanagh BP. Unproven and Expensive before Proven and Cheap: Extracorporeal Membrane Oxygenation versus Prone Position in Acute Respiratory Distress Syndrome. Am J Respir Crit Care Med. 2018 Apr 15;197(8):991–3.

43. Green TP, Timmons OD, Fackler JC, Moler FW, Thompson AE, Sweeney MF. The impact of extracorporeal membrane oxygenation on survival in pediatric patients with acute respiratory failure. Pediatric Critical Care Study Group. Crit Care Med. 1996 Feb;24(2):323–9.

44. Maclaren G, Butt W, Best D, Donath S, Taylor A. Extracorporeal membrane oxygenation for refractory septic shock in children: one institution's experience. Pediatr Crit Care Med. 2007 Sep;8(5):447–51.

45. Abrams D, Brodie D. Novel Uses of Extracorporeal Membrane Oxygenation in Adults. Clin Chest Med. 2015 Sep;36(3):373–84.

46. Metelo-Coimbra C, Roncon-Albuquerque R. Artificial placenta: Recent advances and potential clinical applications: Recent Advances in the Artificial Placenta. Pediatric Pulmonology. 2016 Jun;51(6):643–9.

47. Extracorporeal Life Support Organization, Version 1.4. ELSO Guidelines for Cardiopulmonary Extracorporeal Life Support [Internet]. [cited 2018 Dec 9]. Ann Arbor, MI, USA; 2017 Jan. Available from: www.elso.org

48. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. Am Rev Respir Dis. 1988 Sep;138(3):720–3.

49. Fan E, Brodie D. Higher Volumes, Better Outcomes: The End or Just the Beginning of the Story for Extracorporeal Membrane Oxygenation? American Journal of Respiratory and Critical Care Medicine. 2015 Apr 15;191(8):864–6.

50. Lindén V, Palmér K, Reinhard J, Westman R, Ehrén H, Granholm T, et al. High survival in adult patients with acute respiratory distress syndrome treated by extracorporeal membrane oxygenation, minimal sedation, and pressure supported ventilation. Intensive Care Med. 2000 Nov;26(11):1630–7.

51. Holzgraefe B, Broomé M, Kalzén H, Konrad D, Palmér K, Frenckner B. Extracorporeal membrane oxygenation for pandemic H1N1 2009 respiratory failure. Minerva Anestesiol. 2010 Dec;76(12):1043–51.

52. Broman LM, Holzgraefe B, Palmér K, Frenckner B. The Stockholm experience: interhospital transports on extracorporeal membrane oxygenation. Crit Care. 2015 Jul 9;19:278.

53. Extracorporeal Life Support Organization Registry Report. ELSO Guidelines. General Guidelines for all ECLS Cases. [Internet]. [cited 2017 Apr 23]. Available from: https://www.elso.org/resources/guidelines.aspx

54. Holzgraefe B, Andersson C, Kalzén H, von Bahr V, Mosskin M, Larsson E-M, et al. Does permissive hypoxaemia during extracorporeal membrane oxygenation cause long-term neurological impairment?: A study in patients with H1N1-induced severe respiratory failure. European Journal of Anaesthesiology. 2017 Feb;34(2):98–103.

55. Iguchi A, Ridout DA, Galan S, Bodlani C, Squire K, O'Callaghan M, et al. Long-term survival outcomes and causes of late death in neonates, infants, and children treated with extracorporeal life support. Pediatr Crit Care Med. 2013 Jul;14(6):580–6.

56. Hsu C-P, Lee W-C, Wei H-M, Sung S-H, Huang C-Y, Shih C-C, et al. Extracorporeal membrane oxygenation use, expenditure, and outcomes in taiwan from 2000 to 2010. J Epidemiol. 2015 Apr 5;25(4):321–31.

57. Lee SH, Chung CH, Lee JW, Jung SH, Choo SJ. Factors predicting early- and long-term survival in patients undergoing extracorporeal membrane oxygenation (ECMO). J Card Surg. 2012 Mar;27(2):255–63.

58. Burrell AJC, Pellegrino VA, Wolfe R, Wong WK, Cooper DJ, Kaye DM, et al. Long-term survival of adults with cardiogenic shock after venoarterial extracorporeal membrane oxygenation. J Crit Care. 2015 Jun 3;30:949–956.

59. Wolters AE, Slooter AJC, van der Kooi AW, van Dijk D. Cognitive impairment after intensive care unit admission: a systematic review. Intensive Care Med. 2013 Mar;39(3):376–86.

60. Terrando N, Brzezinski M, Degos V, Eriksson LI, Kramer JH, Leung JM, et al. Perioperative cognitive decline in the aging population. Mayo Clin Proc. 2011 Sep;86(9):885–93.

61. Madderom MJ, Reuser JJCM, Utens EMWJ, van Rosmalen J, Raets M, Govaert P, et al. Neurodevelopmental, educational and behavioral outcome at 8 years after neonatal ECMO: a nationwide multicenter study. Intensive Care Med. 2013 Sep;39(9):1584–93.

62. Luyt C-E, Combes A, Becquemin M-H, Beigelman-Aubry C, Hatem S, Brun A-L, et al. Long-term outcomes of pandemic 2009 influenza A(H1N1)-associated severe ARDS. Chest. 2012 Sep;142(3):583–92.

63. Mikkelsen ME, Christie JD, Lanken PN, Biester RC, Thompson BT, Bellamy SL, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. Am J Respir Crit Care Med. 2012 Jun 15;185(12):1307–15.

64. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. Am J Respir Crit Care Med. 2005 Feb 15;171(4):340–7.

65. Rothenhäusler HB, Ehrentraut S, Stoll C, Schelling G, Kapfhammer HP. The relationship between cognitive performance and employment and health status in long-term survivors of the acute respiratory distress syndrome: results of an exploratory study. Gen Hosp Psychiatry. 2001 Apr;23(2):90–6.

66. Kapfhammer HP, Rothenhäusler HB, Krauseneck T, Stoll C, Schelling G. Posttraumatic stress disorder and health-related quality of life in long-term survivors of acute respiratory distress syndrome. Am J Psychiatry. 2004 Jan;161(1):45–52.

67. Herridge MS, Tansey CM, Matté A, Tomlinson G, Diaz-Granados N, Cooper A, et al. Functional disability 5 years after acute respiratory distress syndrome. N Engl J Med. 2011 Apr 7;364(14):1293–304.

68. Herridge MS. The Homogeneous and Robust Clinical Phenotype of Severe Lung Injury. Chest. 2012 Sep;142(3):553–6.

69. National Board of Health and Welfare, Stockholm, Sweden. Cause of Death Register [Internet]. [cited 2018 Dec 9]. Available from: http://www.socialstyrelsen.se/register/dodsorsaksregistret

70. Wechsler D. Wechsler Adult Intelligence Scale - Fourth Edition (WAIS-IV): administration and scoring manual. 4th edition. San Antonio, TX: Psychological Corporation; 2008.

71. Schmidt M, others. Rey auditory verbal learning test: a handbook [Internet]. Los Angeles, CA: Psychological Corporation; 1996 [cited 2017 Jan 5]. Available from: http://v-psyche.com/doc/Clinical%20Test/Rey%20Auditory%20Verbal%20Learning%20Test.docx

72. Meyers JE, Meyers JE. Rey complex figure test and recogntition trial (RCFT), professional manual. Odessa, TX: Psychological Assessment Resoruces; 1995.

73. Wechsler D. Wechsler memory scale - Third edition manual. 3th edition. San Antonio, TX: The Psychological Corporation; 1997.

74. Ivnik RJ, Smith GE, Lucas JA, Tangalos EG, Kokmen E, Petersen RC. Free and cued selective reminding test: MOANS norms. J Clin Exp Neuropsychol. 1997 Oct;19(5):676–91.

75. Delis DC, Kaplan E, Kramer JH. Delis-Kaplan executive function system. San Antonio, TX: Pearson; 2001.

76. Sullivan M, Karlsson J, Ware JE. SF-36 Hälsoenkät: Svensk Manual och Tolkningsguide (Swedish Manual and Interpretation Guide). Göteborg: Sahlgrenska University Hospital; 1994.

77. Ferrer M, Villasante C, Alonso J, Sobradillo V, Gabriel R, Vilagut G, et al. Interpretation of quality of life scores from the St George's Respiratory Questionnaire. European Respiratory Journal. 2002 Mar 1;19(3):405–13.

78. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983 Jun;67(6):361–70.

79. Brewin CR, Rose S, Andrews B, Green J, Tata P, McEvedy C, et al. Brief screening instrument for post-traumatic stress disorder. Br J Psychiatry. 2002 Aug 1;181(2):158.

80. Garland A, Olafson K, Ramsey CD, Yogendran M, Fransoo R. Distinct determinants of long-term and short-term survival in critical illness. Intensive Care Medicine. 2014 Aug;40(8):1097–105.

81. Enger TB, Philipp A, Lubnow M, Fischer M, Camboni D, Lunz D, et al. Long-Term Survival in Adult Patients With Severe Acute Lung Failure Receiving Veno-Venous Extracorporeal Membrane Oxygenation: Critical Care Medicine. 2017 Oct;45(10):1718–25.

82. Gayat E, Cariou A, Deye N, Vieillard-Baron A, Jaber S, Damoisel C, et al. Determinants of long-term outcome in ICU survivors: results from the FROG-ICU study. Critical Care. 2018 Jan 18;22(1):8.

83. Lorusso R, Gelsomino S, Parise O, Di Mauro M, Barili F, Geskes G, et al. Neurologic Injury in Adults Supported With Veno-Venous Extracorporeal Membrane Oxygenation for Respiratory Failure: Findings From the Extracorporeal Life Support Organization Database. Crit Care Med. 2017 May 22;

84. Lorusso R, Barili F, Mauro MD, Gelsomino S, Parise O, Rycus PT, et al. In-Hospital Neurologic Complications in Adult Patients Undergoing Venoarterial Extracorporeal Membrane Oxygenation: Results From the Extracorporeal Life Support Organization Registry. Crit Care Med. 2016 Oct;44(10):e964-972.

85. Lockie CJA, Gillon SA, Barrett NA, Taylor D, Mazumder A, Paramesh K, et al. Severe Respiratory Failure, Extracorporeal Membrane Oxygenation, and Intracranial Hemorrhage*: Critical Care Medicine. 2017 Oct;45(10):1642–9.

86. Arachchillage D, Passariello M, Laffan M, Aw T, Owen L, Banya W, et al. Intracranial Hemorrhage and Early Mortality in Patients Receiving Extracorporeal Membrane Oxygenation for Severe Respiratory Failure. Seminars in Thrombosis and Hemostasis. 2018 Apr;44(03):276–86.

87. Bartlett RH. Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome: EOLIA and Beyond. Critical Care Medicine. 2019 Jan;47(1):114–7.

88. Krey J. Kunskap om hur vi dör blir sämre (The knowledge about how we die is getting worse). Dagens Medicin. 2014;(13):1–3.