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ASPECTS OF CIRCULATORY FAILURE IN RESPIRATORY EXTRACORPOREAL MEMBRANE OXYGENATION

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Cover illustration: Stockert/Shiley CAPS™ roller pump with neonatal ECMO configuration

Aspects of circulatory failure in respiratory extracorporeal membrane oxygenation

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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The thesis will be defended in public at Ulf von Euler auditorium, Karolinska University Hospital Solna, Thursday 12th of January 2023 at 09.00 a.m.

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“There is a theory which states that if ever anyone discovers exactly what the Universe is for and why it is here, it will instantly disappear and be replaced by something even more bizarre and inexplicable.

There is another theory which states that this has already happened.”

- Douglas Adams, The Restaurant at the End of the Universe

POPULAR SCIENCE SUMMARY OF THE THESIS

Patients in intensive care are treated with supportive and curative care. Usually, the treatment consists of supporting life by assisting the native organs while the patient is recuperating. This life support can be of any assisting medical device, medication, or intervention such as continuous renal replacement therapy (CRRT), inotropic treatment, ventilatory support etc. These mentioned critical care treatments can been seen in any conventional intensive care unit. However, when conventional supportive techniques are inadequate, and the patient deteriorates despite all conventional assets are employed one needs to go from just supportive to a pure overtake of the patient's organs. An example already mentioned is CRRT but when the ventilatory system is failing there is basically only one technique that can overtake the ventilatory function namely extracorporeal membrane oxygenation (ECMO). Concerning cardiac function there are a variety of techniques that can takeover in part or fully such as Impella™, Tandemheart™, Heartmate™, Berlinheart™ etc. However, there is just one technique that can both takeover cardiac function as well respiratory function videlicet, venoarterial (VA) ECMO. ECMO was from the beginning intended for support of respiratory failure. However, studies performed in the seventies showed a remarkable lethality among adult patients treated with VA ECMO for respiratory failure. These results more or less froze all ECMO activity among respiratory adult patients for several decades.

With the H1N1 pandemic as well as the presentation of a large multicentre randomized trial in 2009 interest in ECMO for adult patients re-awoke since both the pandemic and the trial demonstrated positive results. However, the trial only had venovenous (VV) ECMO patients enrolled. The reason for preferring VV ECMO is that the technique is less invasive than VA ECMO and that it offers a very good support for patients with single organ respiratory failure without a circulatory component. Hence, this set the standard for how to treat adults with respiratory failure, i.e. with VV ECMO. Nevertheless, since the respiratory system is an intrinsic part of the cardiocirculatory system and these systems exist in conjunction with each other, a respiratory failure may also inflict impairment on the circulation. Because of this, it is important to understand that when both cardiocirculatory and respiratory support is needed the choice of appropriate mode needs to take into account the circulatory failure thus using VA support.

This thesis first study targeted adult patients with septic shock, with the intention of describing how these patients faired from ECMO treatment. In total thirty-seven patients were included. Hospital survival was 78%. The study also showed that patients with a plain distributive shock, i.e. not from a failing heart, had a markedly improved survival not demonstrated in other previous studies. Furthermore, the study showed that patients initiated with VV ECMO had a less favourable outcome in terms of hospital survival.

Since the first study showed very poor results among patients on VV ECMO converted to VA ECMO we went on examining the outcome in patients on VV ECMO that were converted to VA ECMO. In this second study we enrolled forty-six patients. The results demonstrated a poor outcome in patients on VV ECMO that were forced to be converted to VA ECMO due to circulatory failure with a mortality rate of 62%. These results corroborated the fact that patients with circulatory failure should not be put on VV ECMO but rather on VA ECMO from the initiation of ECMO treatment.

In the third study we wanted to look deeper into the difficulties that the respiratory patients on VA ECMO may succumb to, namely differential hypoxemia (DH). This problem arises solely in patients on VA ECMO with extensive pulmonary compromise. The cause is quite simple to understand. We normally have a serial circulation with blood being pumped from the left heart out to the body and then returned with lower oxygen content. This this blood is then pumped via the right ventricle through the lungs for oxygenation and out again to the body from the left ventricle. However, if the lung function is compromised there will be no oxygenation taking place in the lungs and the blood will be pumped out to the body with a low oxygen content. When VA ECMO is connected to the patient it will drain the deoxygenated blood from the right atrium and reinfuse it in the lower part of the aortae. Thus, the circulation becomes parallel. To be able to oxygenate the blood properly we looked at the drainage position of the cannula on whether we attained a better saturation in the upper body if we drained the most desaturated blood, i.e., from the upper body. Our results showed a marked improvement on the oxygen saturation and that the patients could be more awake after repositioning of the cannula to drain from the upper part of the body.

The fourth and last study investigated if computed tomography (CT), and pulmonary blood flow could help guiding the clinician in taking informed decision regarding patient outcome on prolonged ECMO, i.e., ECMO treatment for more than 28 days. We found that CT could not discriminate between patients that had a poor prognosis and those with a favourable prognosis. However, patients with a poor prognosis had a diminishing pulmonary blood flow already at 25% of the treatment time suggesting that pulmonary blood flow could be used to identify patients with poor prognosis on prolonged ECMO.

In summary the thesis demonstrates that septic shock patients should be treated with VA ECMO and that the survival vastly exceeds the survival with conventional care. Furthermore, that such patients, i.e., patients with circulatory failure originating from the lungs should be put on VA ECMO. And moreover, that the main drainage point in patients on VA ECMO with respiratory failure should be from the upper part of the body. Finally, that patients on prolonged ECMO should be assessed in regard of the pulmonary blood flow for a better assessment of the prognosis.

ABSTRACT

Extracorporeal Membrane Oxygenation (ECMO) was developed in the seventies for the intended use of supporting respiratory failure. Today ECMO has become a well-established treatment for patients with both respiratory and circulatory failure where conventional intensive care is inadequate. The conventional way of treating adults with respiratory failure has been venovenous ECMO (VV ECMO) and for cardiogenic failure venoarterial (VA ECMO). However, since the respiratory system is an intrinsic part of the cardiocirculatory system and these systems exist in conjunction with each other, a respiratory failure may also inflict impairment on the circulation. Furthermore, a distributive shock differs from a cardiogenic shock. Therefore, it also remains to be clarified if, and to what extent vasoplegic (distributive) circulatory failure in conjunction with respiratory failure benefits from ECMO support, and which mode (VV or VA) should be preferred. Furthermore, if VA ECMO is instituted in a patient with a respiratory failure there are several issues that needs to be addressed that differ from the VA patient with single organ cardiogenic failure.

AIMS

The first aim of this thesis was to describe if ECMO and more specifically VA ECMO has a positive effect on survival in adult patients with septic shock (Study 1). In Study 2 we investigated the incidence, indication and outcome in patients who were converted from VV to VA ECMO to clarify whether conversion has an impact on mortality. Furthermore, since patients on peripheral VA ECMO will have parallel circulations with ensuing differential hypoxemia (DH), we went on with investigating patients with signs of DH. Thus, in Study 3 we investigated the impact on oxygen saturation in the upper body by change of drainage position from the inferior vena cava (IVC) to the superior vena cava (SVC). Since septic shock on ECMO can lead to prolonged ECMO with significant lung parenchymal damage we continued in study 4 to investigate if pulmonary blood flow (PBF) measured with echocardiography may assist in assessment of the extent of pulmonary damage, and if echocardiography and CT findings were associated with patient outcome.

METHODS

All studies are retrospective, originating from a high-volume ECMO centre. Patients who were not treated at our unit during the whole ECMO run, and patients with ongoing cardiopulmonary resuscitation (CPR) at the time of ECMO initiation were excluded in all studies. In Study 1 all patients treated for septic shock between 2012 and 2017 with an age >18 years, fulfilling septic shock criteria according to Sepsis-3, and a vasoactive- inotropic support equivalent to a Vasoactive inotropic score (VIS) >50 to reach a mean arterial pressure >65 mmHg despite adequate fluid resuscitation, were included. In Study 2 all patients >18 years old who were commenced on VV ECMO between 2005 and 2018 were included. Patients who were converted to VA ECMO within the first six hours after ECMO treatment was commenced were excluded. In Study 3 all patients from the age of 15 years between 2009 and 2020 identified with differential hypoxemia were included. Patients were included if there had been a state of fulminant differential hypoxemia (FDH) leading to a repositioning or change of the drainage cannula. FDH was defined as a higher saturation in the lower part of the body compared to the upper part of the body or a saturation of the upper body below or equal to 60%. In Study 4, all patients from the age of 15 between 2011 and 2017 were screened. Patients with septic shock (according to Sepsis 2) originating from pneumonia and treated for >28 days were eligible for inclusion.

RESULTS

In Study 1, thirty-seven patients were included. Twenty-seven patients were submitted to VA and 10 patients to VV ECMO. Hospital survival was 90% in septic shock with left ventricular failure, and 65% in patients with distributive vasoplegic shock. In Study 2, 219 VV ECMO patients were evaluated, 21% (n=46) were converted to VA ECMO. The two main reasons for conversion were right ventricular failure (RVF) or cardiogenic shock. In the converted patients, there was a significant increase in Sequential Organ Failure Assessment (SOFA) scores between admission 12 (IQR 9-13) and conversion 15 (IQR 13-17), p<0.001. The converted patients had a higher mortality rate compared to the non-converted patients (62 vs. 16%, p<0.001). These patients also scored lower at admission on the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction (RESP) score (2 (0–4) versus −2.5 (−4–1), p<0.001). Mortality among RVF patients was 67% compared to 50% in converted patients with circulatory shock. In Study 3, 472 patients were screened and seven were identified with FDH. The mean peripheral capillary saturation increased from 54(±6.6) to 86(±6.6) %, (p=<0.001) after repositioning of the cannula from the IVC to the SVC. Pre-oxygenator saturation increased from 62(±8.9) % to 74(±3.7) %, (p=0.016) after repositioning. In Study 4, CT failed to indicate any differences in viable lung parenchyma between survivors and non-survivors at any time over the course of ECMO treatment. A mixed effects model with time, survivors and non-survivors and the interaction between time and the two groups as independent variables, showed that the interaction was significant (p=0.004) with different coefficient slopes between the two groups regarding PBF.

CONCLUSIONS

Study 1 supported the use of VA ECMO for distributive septic shock. Study 2 indicated that VA ECMO should be considered as the first mode of choice in patients with respiratory failure combined with a compromised circulation. Study 3 elucidated DH in a clinical patient setting which has never been presented previously, showing that moving the drainage zone into the upper part of the body had a marked positive effect on upper body saturation. Finally in Study 4 we presented results demonstrating that CT was supported as a prognostic tool in prolonged respiratory ECMO. However, we found that PBF may possibly assist in the prediction of pulmonary recovery.

LIST OF SCIENTIFIC PAPERS

I. L Falk, J Hultman, LM Broman, Extracorporeal Membrane Oxygenation for Septic Shock, Critical care medicine. 2019;47(8):1097-105

II. L Falk, A Fletcher-Sandersjöö, J Hultman, LM Broman, Conversion from Venovenous to Venoarterial Extracorporeal Membrane Oxygenation in Adults, Membranes. 2021;11(3).

III. L Falk, J Hultman, LM Broman, Differential hypoxemia and the clinical significance of venous drainage position during extracorporeal membrane oxygenation, Perfusion 2022 May 11;2676591221090667

IV. L Falk, MK Lidegran, S Diaz Ruiz, J Hultman, LM Broman, Severe lung dysfunction and pulmonary blood flow during extracorporeal membrane oxygenation, Submitted

Scientific papers not included in the thesis

L Falk, M Sallisalmi, JA Lindholm, M Lindfors, B Frenckner, M Broomé, LM Broman, Differential hypoxemia during venoarterial extracorporeal membrane oxygenation, Perfusion. 2019;34(1_suppl):22-9.

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LIST OF ABBREVIATIONS

ARDS	Acute Respiratory Distress Syndrome
APACHE	Acute Physiology and Chronic Health Evaluation
CO	Cardiac Output
CT	Computed Tomography
CPR	Cardiopulmonary Resuscitation
DH	Differential Hypoxemia
ECMO	Extracorporeal Membrane Oxygenation
ECPR	Extracorporeal Cardiopulmonary Resuscitation
FDH	Fulminant Differential Hypoxemia
ICU	Intensive Care Unit
IVC	Inferior Vena Cava
IQR	Interquartile Range
LVF	Left Ventricular Failure
MAP	Mean Arterial Pressure
MPA	Main Pulmonary Artery
P1	Pre-pump pressure, pressure 1
PBF	Pulmonary Blood Flow
PMP	Polymethylpenten
PP	Polypropylene
PVR	Pulmonary Vascular Resistance
PVRi	Pulmonary Vascular Resistance index
r	Radius
RA	Right Atrium
RASS	Richmond Agitation Sedation Scale
RESP	Respiratory Extracorporeal membrane oxygenation Survival Prediction
RVF	Right Ventricular Failure
SAPS-2	Simplified Acute Physiology Score (version 2)
SAPS-3	Simplified Acute Physiology Score (version 3)
SLC	Single-lumen cannula

SOFA	Sequential Organ Failure Assessment
$SpreO_2$	Pre-oxygenator saturation
SVC	Superior Vena Cava
VA	Venoarterial
VIS	Vasoactive Inotropic Score
VTI	Velocity Time Integral
VV	Veno Venous

INTRODUCTION

Over the last decade extracorporeal membrane oxygenation (ECMO) has become a standard treatment in critical care (1). This has not always been the case. When ECMO was first introduced in the 1970's the outcome was poor in the adult population whilst several studies showed promising results in the paediatric and especially the neonatal group (2, 3). However, during the last 15 years several publications with promising results in adults have been published (4, 5). With the H1N1 pandemic in 2009 the evidence grew concerning the benefit of ECMO for the most severe adult influenzae patients. Today ECMO has proven itself as a reliable technology in cardiogenic, and respiratory failure (4, 6-9).

1.1 SWEDISH ECMO HISTORY

For 18 hours, Kenneth "Palle" Palmér had tried to keep a new-born with GBS sepsis alive. That same morning in 1984, at St: Göran's hospital, the child died.

On the same day in the afternoon, Björn Frenckner held the plenary meeting for physicians and surgeons, where he recounted a new treatment method to assist the lungs and heart of children born with diaphragmatic hernia or those with meconium aspiration called ECMO. Those who listened to the lecture were anything but enthusiastic about the method. Björn's idea to start the treatment at St: Göran received a lukewarm reception from the audience. On the way back to his office, Björn and Palle bumped into each other. Up on seeing Björn's sad expression Palle asked why he looked so gloomy. Björn recounted his morning in the plenary meeting and how ECMO had the potential to save children with respiratory and circulatory failure, Palle's interest was immediately sparked.

Together they came to start an ECMO operation on a very small scale. They experimented with old oxygenators and did a number of experiments on dogs.

In the fall of 1985, Palle and Björn - with their own funds - made a joint trip to Washington to study how ECMO treatment was carried out. They managed to see a total of four patients during their time in the USA.

Back home, they decided to submit an ethical application to take a closer look at children with respiratory failure treated with ECMO. During the first months at home, they tried to find patients suitable for ECMO but had to settle for training on sheep.

In March 1986, a child was born with a right-sided diaphragmatic hernia. The child was quickly transported to St: Göran for surgery and intensive care. The child underwent emergency surgery and was then admitted to BIVA. Three days later, Palle is running a sheep on ECMO in the basement when he was called and asked to bring the ECMO-machine up for the child with the diaphragmatic hernia since he had deteriorated and was on the verge of dying. Palle euthanised the sheep and primed the ECMO-machine with a new ECMO system and ran up to the PICU where Björn was waiting to start canulation. The child then got bradycardic and eventually went into cardiac arrest. At the time, the routine was not to cannulate during CPR. However, they still decided to go ahead with the cannulation. Pretty soon after ECMO was started, the heart started beating again. The child was on ECMO for eight days and it is said that for several days after hay could be found around the patient that had been dragged up from the animal lab. All in all, the first ECMO procedure in Sweden went well and the patient is still alive today. Although St:Göran was ahead for its time, a hospital in Paris became the first in Europe to put a patient on ECMO just a week before Björn and Palle.

After the first treatment, 2 – 3 children were treated per year and in 1998 the ECMO centre was formed as its own unit under the children's anaesthesia clinic.

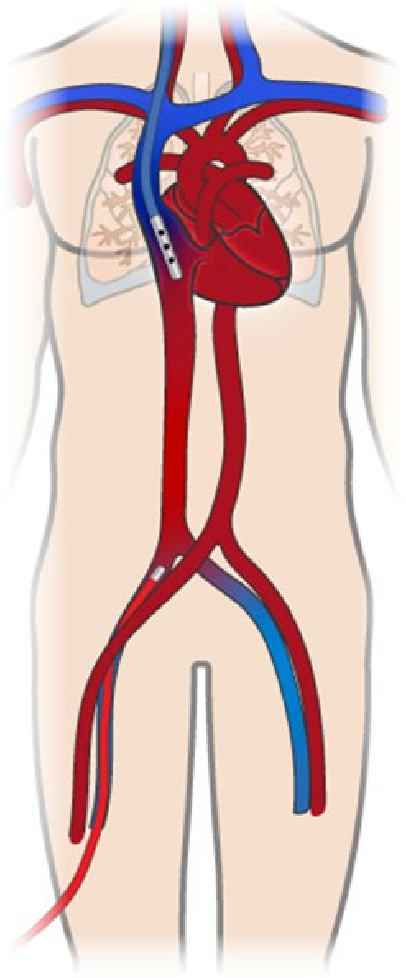

Figure 1a. Venovenous extracorporeal membrane oxygenation. Drainage cannula in right atrium and return cannula at the junction the femoral vein and abdominal aortae.

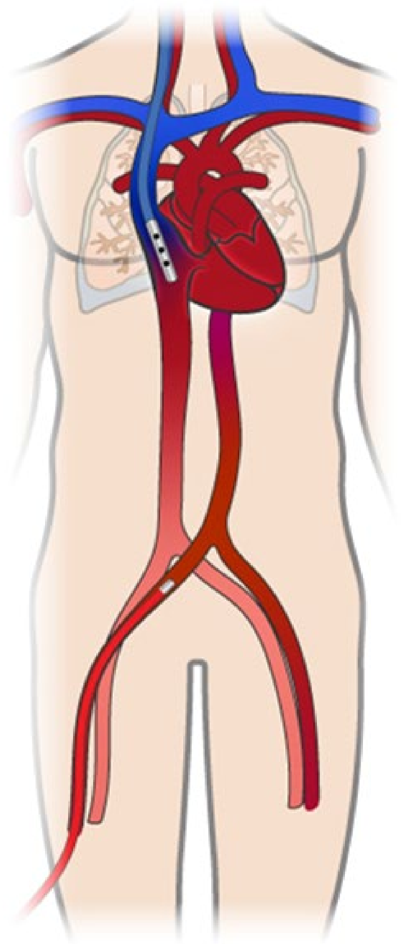

Figure 1b. Venoarterial extracorporeal membrane oxygenation. Drainage cannula in right atrium and return cannula in the femoral artery.

1.2 FUNDAMENTAL CONCEPTS OF ECMO

The basic working principle for ECMO is relatively easy to comprehend (10). Desaturated blood is drained from the right atrium or major central veins and then pumped through a membrane lung or, from here on, *oxygenator* where blood is oxygenated and cleared from carbon dioxide, and then returned to the body. If the blood is returned to the venous side, venovenous (VV) ECMO is offered which supports gas exchange, i.e., lung function (Figure 1a.). For cardiorespiratory support the oxygenated blood is returned to the arterial side, i.e., venoarterial (VA) ECMO support is provided (figure 1b.). However, to understand the pitfalls and dilemmas which may arise during an ECMO treatment it is important for the practitioner to have thorough knowledge of both the physiology of the patient as well as the physics regarding ECMO. The artificial circuit composed of drainage and return cannulas, tubing, connectors, the blood pump, and oxygenator will have to work together and interact with the physiology of the body (Figure 2). As is often the case, the theory is easy enough to explain but harder to apply in real life.

The circulation is a serially coupled system between the right heart, the pulmonary circulation, the left heart, and the systemic circulation. This serial circulation is not influenced by connection of VV ECMO since the blood is both drained and returned on the venous side. The patient's heart is the motor for perfusion of the whole body. When applying VA ECMO, however, the circulation becomes dual with two parallel circulating systems perfusing the body (11, 12). This is further complicated by drainage and return cannula positioning which impact how oxygen will be distributed in the patient during ECMO support. Patient oxygen profile is dependent on where deoxygenated blood is drained, and where the oxygenated blood is returned. Balancing these will be decisive for how the patient will fair while on VA ECMO.

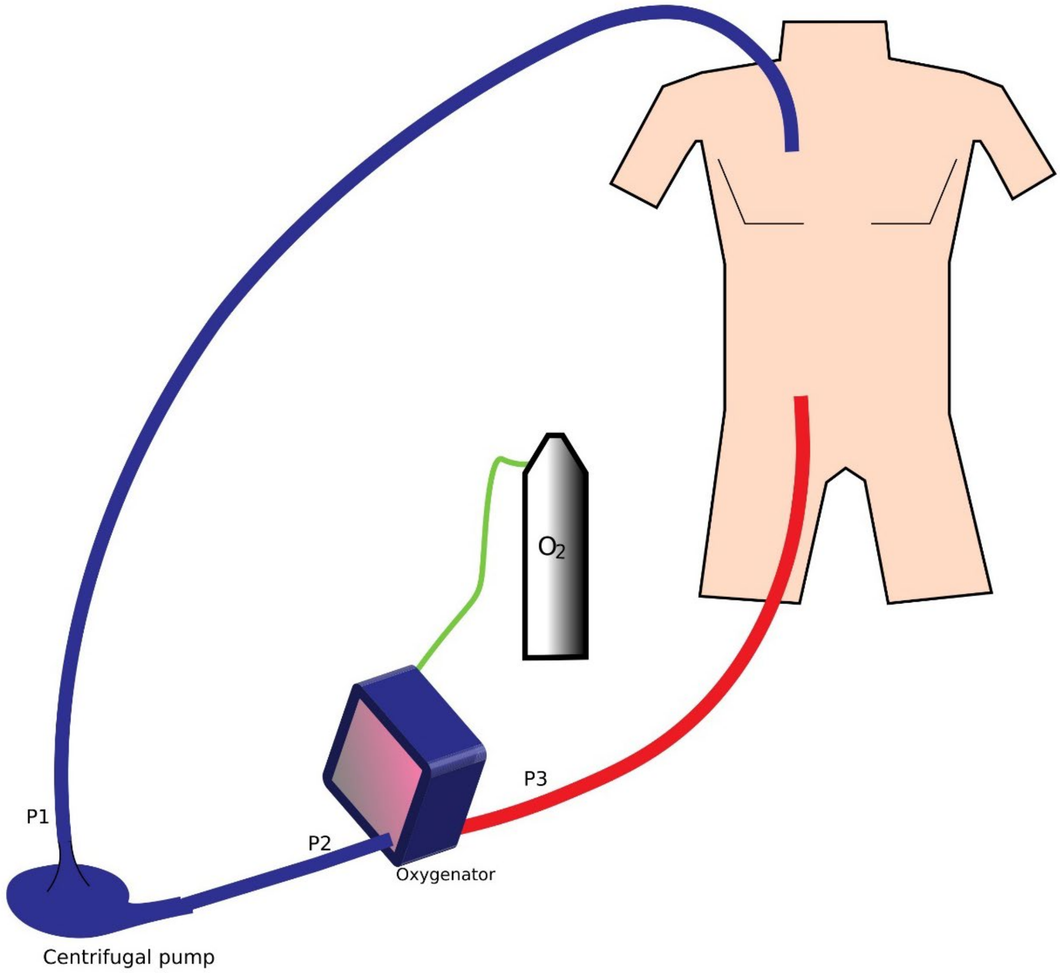

Figure 2. ECMO circuit with drainage tubing in blue, draining to the centrifugal pump which pumps the blood through the oxygenator where oxygenation and carbon dioxide removal takes place. The oxygenated blood is then returned to the patient via the return tubing represented by the red line in the figure. Pressure 1 monitoring just before the pump, pressure 2 between the pump and the oxygenator, pressure 3 directly after the oxygenator.

Abbreviation: P, pressure monitoring.

2 BACKGROUND

With ECMO treatment a secondary circulatory circuit is introduced that works in conjunction with the native circulation. The aim is to alleviate the native system both by perfusing the body as in VA ECMO as well as oxygenating the blood (13). With VV ECMO this is readily accomplished since oxygenated blood is delivered to the body in a “correct” physiologic manner by the left ventricle. However, ever since ECMO was introduced as a treatment for respiratory failure, situations have developed where VV ECMO alone cannot support the failing respiration adequately (14, 15). An example of such a case is the new-born with sepsis caused by group B Streptococcus, or congenital diaphragmatic hernia. Both these conditions are of respiratory nature but are considered to have such implications for the circulation that VA ECMO should be considered as first choice of support (16) .

VA ECMO should also be considered in adults since the respiratory and circulatory systems are inherently related and as such inseparable. Since the circulatory and respiratory systems interact it is also sensible that the support can be of either VA or VV ECMO mode. As the respiratory system is cojoined with the circulatory system one should always take into consideration if a patient in need of ECMO can be supported solely with VV support. If there is a risk of or established cardiocirculatory failure, then VA ECMO would be the choice. Circulatory failure is not always present at time of cannulation but may develop over time. Thus, it is a necessary to recognize the development of a circulatory compromise and consider conversion from VV to VA ECMO when needed.

The main underlying cause for developing cardiocirculatory failure during VV support of a cardiac origin is from a pulmonary damage with secondary right ventricular failure (RVF). In fact, the damage to the lungs may be extensive, leading to a total cessation of pulmonary blood flow. Circulatory failure may also develop as a result of a secondary infection causing sepsis and circulatory instability. This may lead to distributive shock which is better supported with VA ECMO than with VV support. VA support may provide perfusion and oxygen delivery even though vascular tone is reduced.

There are several reasons why the pulmonary blood flow may diminish during critical illness. In ECMO patients the most common acute reason is a loss of alveolar ventilation leading to hypoxic vasoconstriction and shunt from the under-ventilated alveoli to parts of the lung with alveolar ventilation (17). Von Euler and Liljestrand were the first to show that the oxygen content influenced the pulmonary vascular tone (18), and later Duke and Killick showed that the effect of hypoxia lay in the alveoli (19). The question of where the effect of low oxygen content is sensed is of importance when performing VV ECMO. If the vasoconstriction is mediated via the oxygen tension in the blood VV ECMO should be able to reduce pulmonary resistance of closed off parts of the pulmonary vascular bed since VV ECMO delivers oxygen into the right ventricle. However, clinically this has not been the case and a recent study in pigs failed to show that VV ECMO had an alleviating effect on pulmonary vasoconstriction caused by hypoxia (20).

VA ECMO in the respiratory patient poses challenges since a by-pass situation has been created with a poor gas exchange in the lungs. Since the ECMO circuit contributes with the major part of oxygen delivery and the lung's gas exchange is impaired, the saturation will differ between the two perfused areas, typically the upper and lower body in a femoro-femoral configuration. This phenomenon is called differential oxygenation or differential hypoxemia (DH) (21, 22) . The condition was partly described by Corso and colleagues in 1974 in a femoral-femoral venoarterial cannulation, where the lower part of the body was perfused and oxygenated by the extracorporeal circuit and the upper part perfused with blood from the left ventricle (23). The condition has since been elaborated upon by several authors (11, 12, 24-28).

Although the condition is well known the understanding of its clinical importance may be disputable. DH will always arise in patients on VA ECMO. This is because the body will receive perfusion via both from the ECMO circuit and the left ventricle. These two systems will deliver blood of different oxygen saturations depending on the oxygenator and lung function, respectively. However, DH will become problematic first when the perfusion of oxygen to the upper circuit (propelled by native cardiac output, CO) falls short of that perfused area's oxygen demand. This will lead to an oxygen deprivation and end-organ hypoxia /anoxia (11). In this case the condition is labelled as fulminant differential hypoxemia (FDH), typically arising in a situation where cardiac function has recovered in conjunction with a severely limited gas exchange in the native lungs.

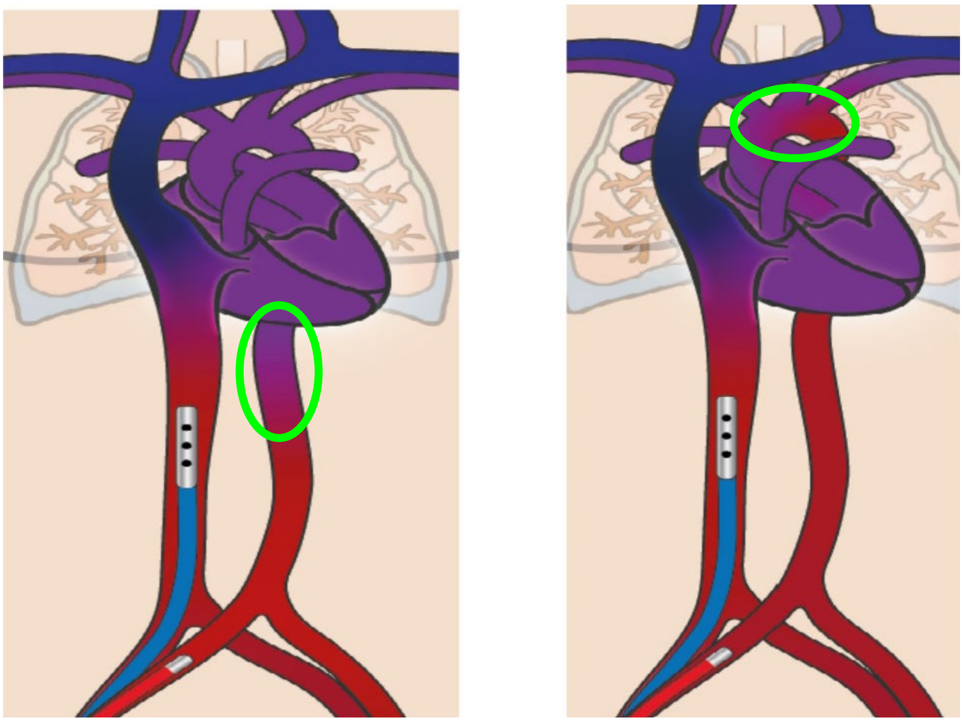

Figure 3. Differential oxygenation/hypoxemia in venoarterial extracorporeal membrane oxygenation. The configuration is femoro-femoral, i.e., drainage from the inferior vecna cava and return in an iliac artery. Water shedding zone marked with green circle. The zone will be dependent on the amount of ECMO flow and cardiac function.

The oxygenated blood from the ECMO will be reinfused in the femoral artery. This blood will reach different levels of the aortae depending on the amount of ECMO flow and the flow from the left heart. This area is called water shedding zone where the oxygenated blood from the ECMO circuit meets deoxygenated blood from the heart (Figure 3). The blood from the ECMO circuit will be perfused through the lower part of the body where some oxygen uptake will take place before the blood reaches the right atrium (RA). At this point, the still relatively well oxygenated blood, will be mixed with blood from the upper part of the body.

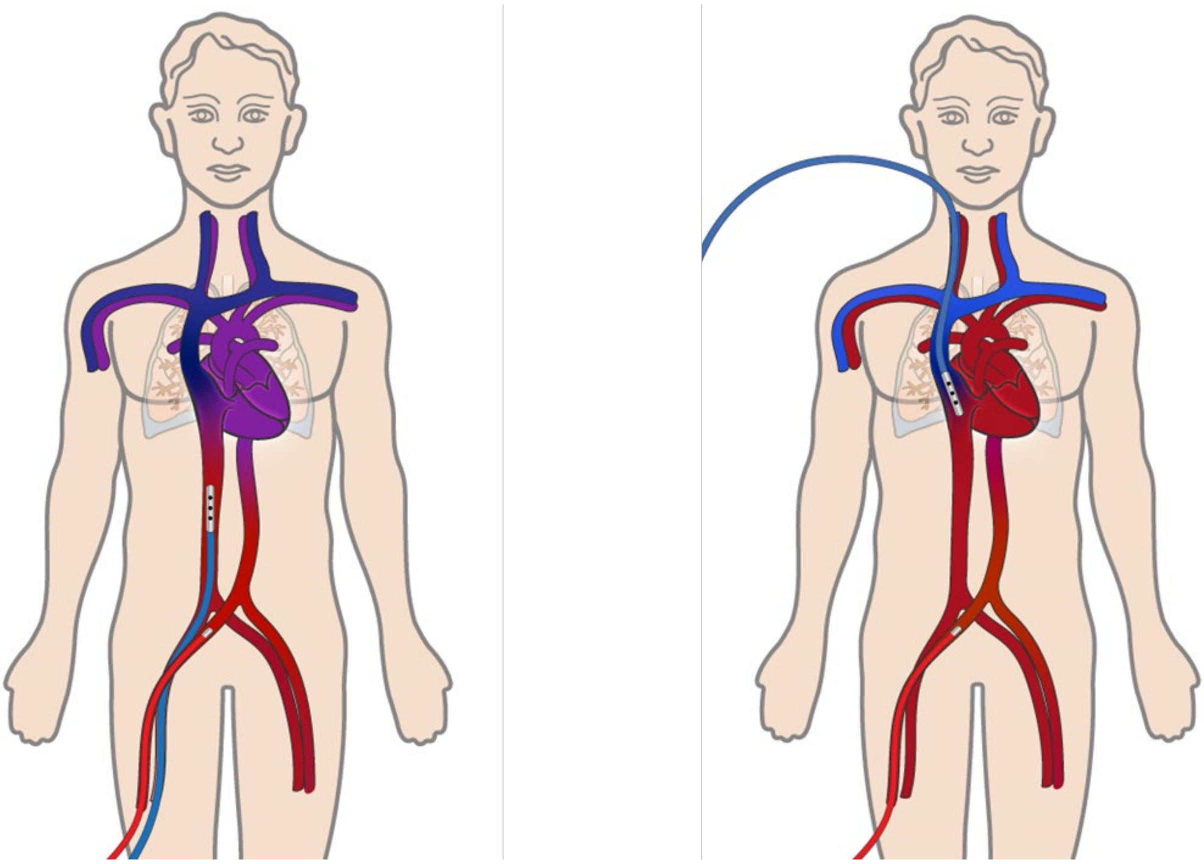

Figure 4. Differential Hypoxemia. On the left-hand panel an example of improper venous drainage mainly from the lower body, with significant negative impact on upper body saturation. On the right-hand panel, the cannula has been repositioned to drain mainly from the upper body resulting in improvement of upper body oxygenation.

A key issue with DH is the positioning of the drainage cannula. If the cannula is positioned in the lower part of the RA or in the inferior vena cava (IVC) well oxygenated blood will be drained from the lower part of the body (the arterial side of the vascular bed contributing to IVC flow, is fed with hyper-oxygenated ECMO blood). If the cannula tip is positioned high in the upper part of the RA or at the junction of the superior vena cava (SVC), and the design of the cannula is of single stage/lighthouse tip, it will drain blood from the upper part of the body which typically has a lower oxygen saturation (tissues fed with native CO and part ECMO blood). However, if the cannula design is of multistage design there will be a risk imbalanced drainage from the most proximal holes which will be positioned inside the vena cava thereby leading to uneven venous drainage (26). Thus, drainage of the venous blood with the lowest saturation will optimize performance of the oxygenator (Figure 4.). In the case of femoral return VA ECMO the best drainage will be from the SVC (11, 24). The SVC is supplying the right atrium with 35% of the combined venous return which is readily drained (29). Therefore, since the ECMO drainage is constant the main factor influencing the oxygen delivery will be the saturation of the blood returned by the ECMO circuit.

Equation 1.

$$D_{ECMO}O_2 = Q_{EC} \times (1.39 \times Hb \times SpostO_2 + (0.003 \times PpostO_2))$$

$D_{ECMO}O_2$: oxygen delivery (mL/min), Q_{EC}: ECMO flow (L/min), Hb: haemoglobin (g/L), $SpostO_2$: post oxygenator oxygen saturation (%), $PpostO_2$: post oxygenator oxygen partial pressure (mmHg)

If we consider a patient with totally consolidated lungs (i.e. without gas exchange), the lungs will only function as a transition vessel for the blood from the right to the left heart. Therefore, the saturation of the blood that reaches the left ventricle will also be the blood and saturation that will reach the upper part of the body, including the coronary arteries and the and brain. The blood delivered to the upper part of the body will be of rather low oxygen content leading to a further reduction of saturation after oxygen extraction by tissue before returning to the RA. Thus, the venous saturation from the upper body will be extremely low compared to the IVC blood saturation delivered from the lower body.

Besides the direct effect of hypoxia, ECMO patients may suffer from direct destruction of the lung parenchyma. This is for example seen in patients with Staphylococcus aureus pneumonia with toxin producing strains (Panton-Valentine leucocidin) (30). Necrotizing pneumonia can also be seen in cases of COVID-19 (31). Since the damage is directed towards the parenchyma it causes the functional residual capacity to decrease. The damage may lead to emphysematous scarring which increases alveolar dead space, but also a reduction of perfusion of the under-ventilated areas resulting in increased pulmonary resistance (32).

2.1 ECMO CIRCUIT COMPONENTS

The ECMO circuit starts at the tip of the drainage cannula, also referred to as the venous cannula, and ends at the tip of the return cannula. Nowadays, the circuit is coated with a lining for biocompatibility to reduce activation of coagulation and inflammation preventing the blood from clotting while in contact with the artificial surface of the tubing. Furthermore, ECMO patients are generally systemically anticoagulated to prevent clotting. The blood is commonly pumped by a centrifugal- or roller-pump which is perfusing the oxygenator. With a centrifugal pump the flow needs to be measured with a flow sensor since the pump is non-occlusive (picture 1). With a roller pump the flow is known since the pump is occlusive and therefore moves a set amount of blood through the raceway dependent on tubing size and the number of revolutions (picture 2).

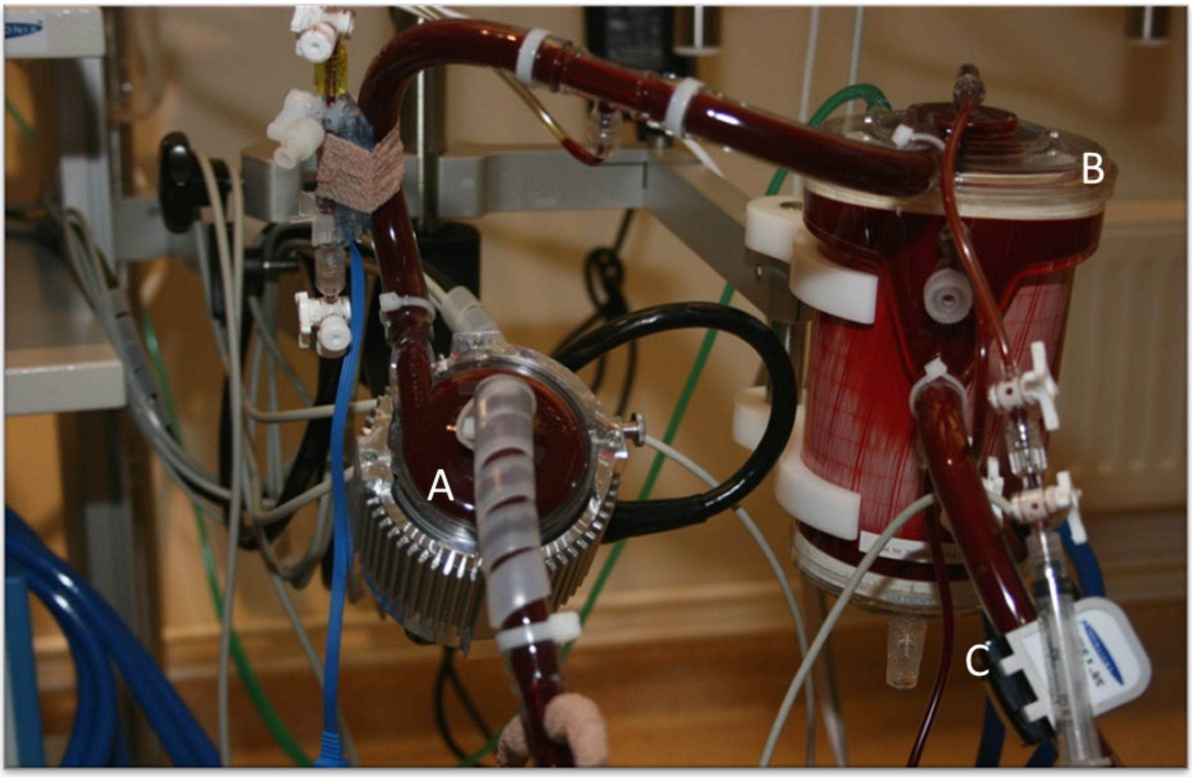

Image 1. Displaying: A: centrifugal blood pump, B: oxygenator, C: flow sensor.

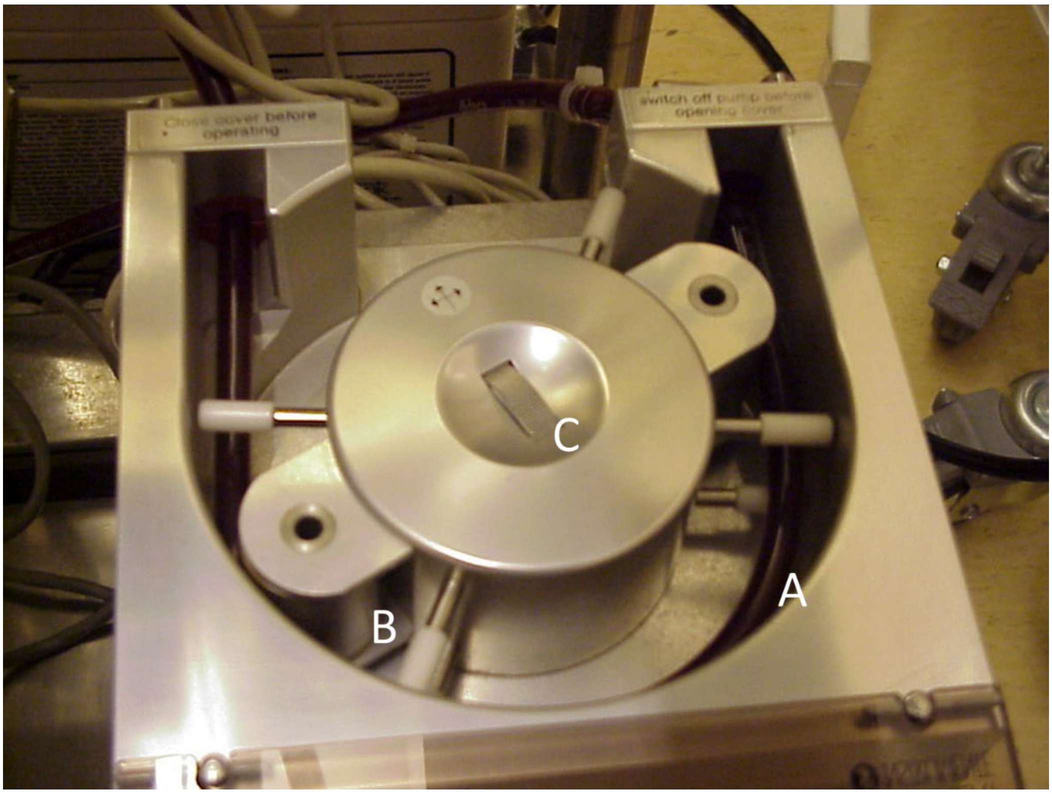
Close cover before operating
switch off pump before opening cover
C
A
B

Image 2. Roller pump with race-way tubing (A), roller head (B), occlusion setting knob (C).

2.1.1 Drainage

As previously stated, the deoxygenated blood is drained from the right atrium by the drainage cannula. Drainage is achieved by two principles.

1) Passive drainage of the blood by a siphoning effect to the pump. The efficiency of the drainage is determined by the height between the drainage cannula in the patient and the inlet of the pump (or bladder using roller pump). This difference in height will be the hydrostatic preload by which the pump can achieve a pump head, driving the blood forward in the circuit. Siphoning of drainage to a bladder (silicone reservoir) before the pump is standard in roller pumps to protect both blood/blood components and the venous vessels from low negative pressure including pressure spikes due to the risk of extremely negative pressures on the suction side.

2) A negative pressure created by the blood pump (diagonal, centrifugal, or roller). The centrifugal and diagonal pumps work by both principles of drainage: siphoning and applying a negative pressure thereby suctioning blood to the circuit. Roller pumps are considered occlusive while the centrifugal and

diagonal pumps are non-occlusive allowing recirculation inside the pump volute as well as back flow. Centrifugal pumps are the most commonly used blood pumps today in all age groups.

2.1.2 Centrifugal pump

The centrifugal pump works by accelerating blood over vanes (Figure 5). The major determinants of the efficiency of the centrifugal pumps are the preload exerted on the inlet of the pump, the afterload the pump needs to drive the fluid forward, the diameter of the pump (diffuser) and finally, the number of revolutions per minute. By altering any of these variables the efficiency of the pump will change.

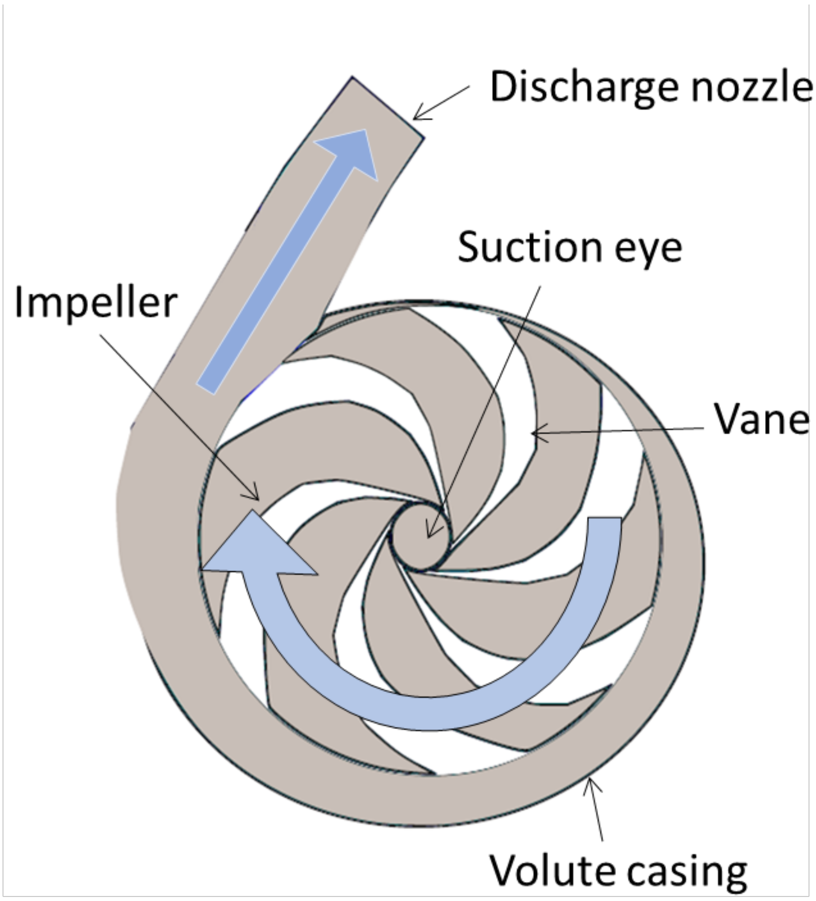

Figure 5. Schematic of a centrifugal pump. Blood enters the suction eye and is accelerated over the vanes, thus creating a negative pressure at the centre of the suction eye. As the blood is accelerated it builds up kinetic energy. This kinetic energy is converted to pressure energy when the blood flow hits the resistance in the volute casing as well as the resistance in the discharge nozzle.

2.1.3 **Oxygenator and gas transport**

The oxygenator is built up by a hydrophobic membrane, usually polymethylpentene (PMP) or polypropylene (PP). In older oxygenators the membrane was constituted of silicon. Both PP and silicon membranes are prone to leak plasma into the gas phase of the oxygenator.

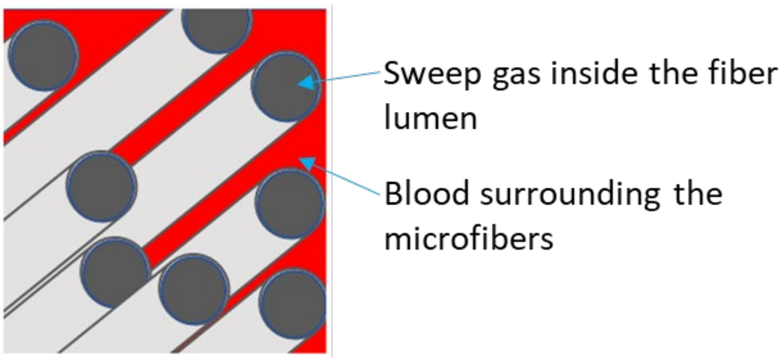
Sweep gas inside the fiber lumen
Blood surrounding the microfibers

Figure 6, Illustration of cross section of a microporous membrane of the oxygenator used for extracorporeal membrane oxygenation.

The hollow fibres contain the gas phase (sweep gas) inside the hollow fibre lumen. The fibres are surrounded by the blood phase (figure 6). The sweep gas flows in *opposite* direction to the blood flow. Between these two compartments mass transfer takes place where oxygen diffuses to the blood phase with its lower partial pressure of oxygen. Carbon dioxide moves in the opposite direction. The average distance between the erythrocyte and the fibre wall is around 200 µm whilst the distance in the native lung is negatable (33, 34). Thus, the distance between the fibre wall and the erythrocyte (plasma phase) will play a major role in determining oxygenation exchange. Besides the actual distance between erythrocytes and fibres there is also an obstacle of fluid flowing laminarly. In laminar flow, denser particles, typically the erythrocytes in blood, will become centralised in the stream and thus the distance between the erythrocyte and the respiratory membrane will increase with the length of the laminar flow (figure 7). To overcome this phenomenon, secondary flows are introduced which will cut into the primary flow and thus whisk around the erythrocytes, i.e., create a turbulent flow. The downside of turbulent flow is increased flow resistance which requires a higher pressure-gradient to achieve the same flow as in laminar flow. This results in increased shear stress forces on the blood components. (Shear stress in is the force acting on the erythrocyte when pushed over another boundary layer, i.e., surface).

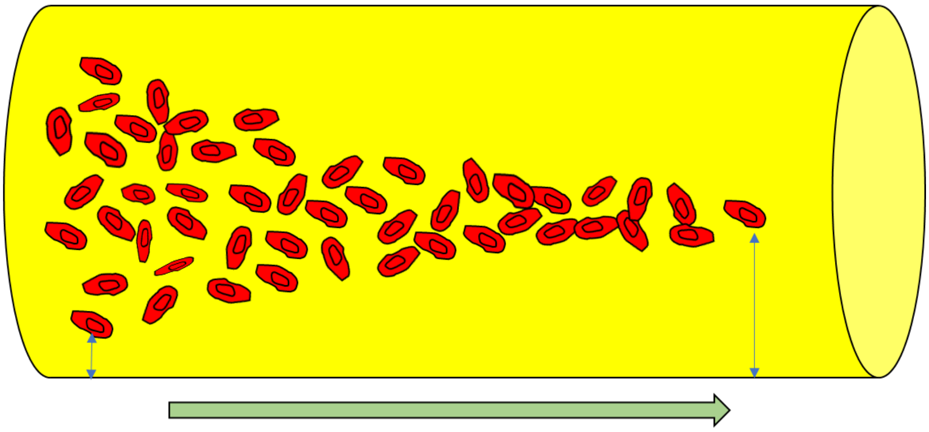

Figure 7. Schematic illustration of erythrocytes moving in a laminar flow with blue arrows indicating increasing distance between the erythrocytes and the tubing wall along the length of the laminar flow. Green arrow indicating the flow direction.

Since the purpose of the oxygenator is to achieve mass transfer of oxygen and carbon dioxide between the blood and gaseous compartments the principle of diffusion applies. Thus, the surface area together with the differences of partial pressures between the phases will determine the speed of mass transfer. Another important aspect of diffusion is time. Therefore, to achieve mass transfer the blood flow through the oxygenator cannot be too high. If the blood flow is too high the gases will not have time to equilibrate diffusion and the diffusion rate will be reduced. The performance of a manufactured oxygenator is denoted as its *rated flow*. This is defined as the maximum flow rate at which the oxygenator can increase the oxygen saturation from 75% to 95% at a haemoglobin concentration of 120 g/L and temperature of 37°C. Increasing the blood flow beyond this limit will reduce the oxygenator's performance regarding oxygen transfer (10). Rated flow is typically 7 L/min for an oxygenator intended for use in adults. The corresponding rated flows for paediatric and neonatal oxygenators are 2.4 L/min and 800 mL/min, respectively.

2.1.4 Cannulas

The ECMO circuit can be regarded as one long tube. Hence, Poiseuille's law is applicable. Poiseuille's law states that the flow is dependent on four variables: the difference of pressure between inlet and outlet, the radius of the tube, the viscosity of the fluid, and length of the tube. The radius (*r*) will play the most important role since *r* is calculated by the fourth power (Equation 1). Thus, a reduction of the radius by half (all other variables static) will lead to a loss of the flow by 16.

Equation 2.

$$Flow\ rate\ = \frac{\Delta P\pi r^4}{8\eta L}$$

Where ΔP is the inlet pressure minus the outlet pressure, η the viscosity and *L* is the length of the tube. Since the radius is the most important variable this is also the main factor to consider when designing an ECMO circuit. The narrowest segment of the circuit determines the maximum feasible blood flow (35). This will effectively be the narrowest part of the cannulas. More specific, the venous cannula will be the point where the blood flow is decided since this part of the system is dependent on negative pressure to be able to achieve drainage.

2.2 VENOARTERIAL ECMO

When applying VA ECMO, the heart is by-passed and the ECMO circuit will contribute with a variable degree of total cardiac output. In adults the drainage cannula is generally placed in the right atrium or IVC, and the returning cannula in a femoral artery.

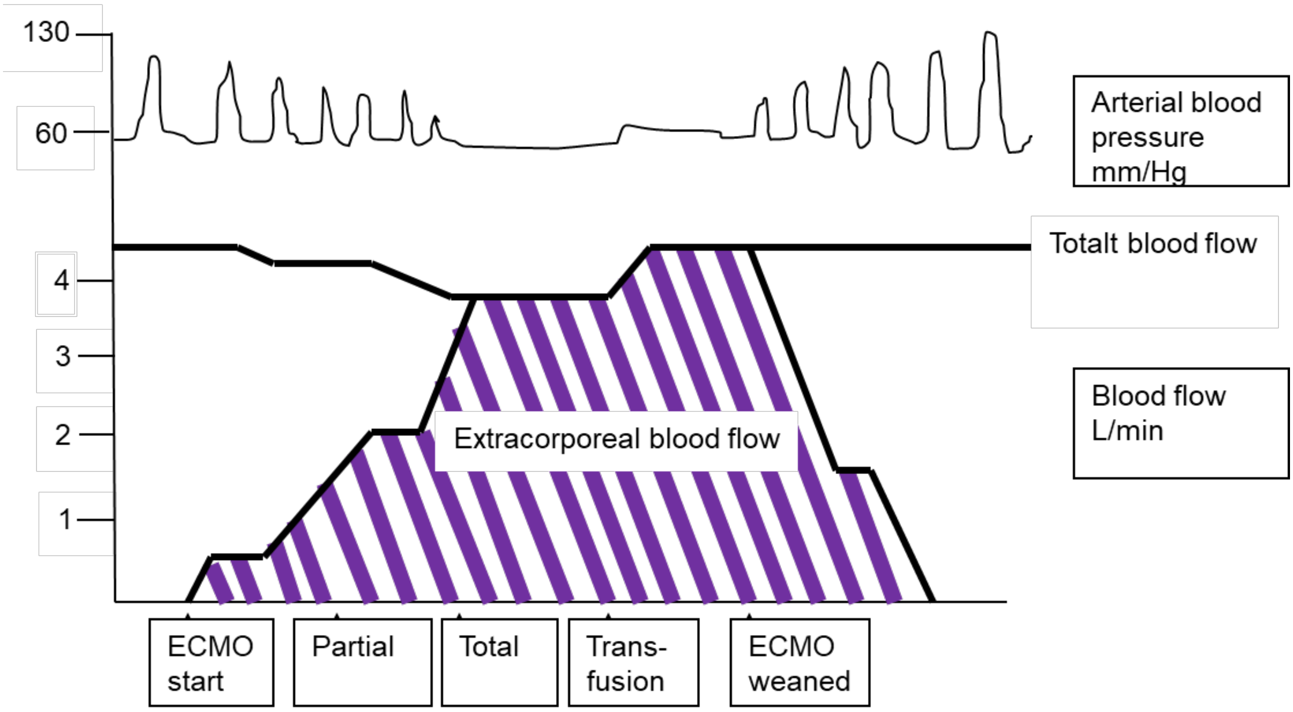

Figure 8. The bottom curve indicating the amount of ECMO support in litres per square meter and minute. The upper curve indicating the change in mean arterial pressure dependent on the amount of ECMO support.

Since the pump provides a non-pulsatile flow, the arterial pressure curve may be attenuated and even gradually disappear during total bypass (figure 8). This is not readily achieved or a treatment goal with VA ECMO since loss of pulse pressure may indicate blood flow stagnation of the pulmonary circulation or cardiac ventricles. At least a limited flow of blood has to pass through the lungs and the left heart. In some cases, left ventricular unloading may be necessary, although only rarely in cases of respiratory VA ECMO. Typically, during support about 80% of cardiac output is pumped extracorporeally and pulse pressure may be between 10 to 15 mmHg. However, there are occasions where the pulse pressure fades and disappears and the heart may cease contracting and enter a so-called *cardiac stun*. This can be a result of increased left ventricular afterload created by the retrograde ECMO flow injected into the aorta resulting in the inability of the aortic valve to open. Eventually this will lead to a dilated left ventricle unless it can be unloaded. There are different methods to unload the left ventricle. The obvious way to attain unloading is to restore pulse pressure. If this cannot be achieved by inotropy/afterload reduction, or increased filling pressure, a left atrial or ventricular catheter can be placed which drains blood from the left side to the drainage side of the ECMO circuit. Intermittent reduction of the ECMO pump flow at intervals of a few minutes, can also allow lung blood flow and the left ventricle to empty. The left ventricle may furthermore be unloaded by performing a septostomy and thereby relive pressure from the left to the right side of the heart. Septostomy has reportedly shown a larger benefit in children than in adults. In the last years the use of transvalvular mechanical assist devices (Impella^{TM}, Abiomed, Danvers, MA, USA), during ECMO (ECMO + Impella = ECPELLA/ECMELLA) has become more readily available and may provide effective unloading in older adolescents and adults (36, 37). If the left ventricular function is markedly reduced, the diastolic intracavitary pressure will incrementally rise reducing myocardial perfusion gradient augmented by the coronary vessels subsequently shut off by the ballooning ventricular wall causing the coronaries to collapse (38).

During VA ECMO, most of the coronary blood flow will be of blood ejected by the left ventricle. This blood has a lower oxygen content than normally because it has been “shunted” through the sick lungs where a limited oxygen exchange has taken place. In addition, there is an increased left ventricular afterload due to the applied ECMO support (circuit pumping blood towards the aortic valve) (39). The right side of the heart will have a reduced wall stress because venous blood is drained thus reducing preload.

2.3 VENOVENOUS ECMO

During treatment with VV ECMO in adults the desaturated blood is drained from the right atrium, SVC, or IVC, (same as in VA). In contrast to VA, however, the oxygenated blood is returned to the central venous compartment or right atrium (6).

This can be achieved either by a dual-lumen cannula with both drainage and return luminae in the same device, or with two separate single-lumen cannulas (SLC) (picture 3). With a SLC approach the drainage cannula is usually the same device with same placement as in VA ECMO. The return cannula is placed in a femoral or (right) jugular vein. The dual-lumen cannulas available today are designed for a jugular approach with the tip places in the upper IVC.

Since both drainage and return of ECMO blood takes place in the same vascular compartment the challenge of recirculation is always present. Depending on ECMO flow, cannula design, cannula placement, cannula positions in regard to each other in a SLC approach, patient cardiac output, volume status, etc., recirculation may range from 0 to >50%. Recirculation fraction typically ranges between 5 – 30 % and increases with increased flow (40).

The main advantage with VV ECMO is that normal circulatory physiology is maintained. Oxygenated blood is, more or less, returned before the heart and then pumped through the pulmonary circulation and ejected by the left ventricle. Thus, the coronaries will be perfused by a higher saturated blood compared to VA ECMO support. The oxygenation of the brain will also be closer to a physiologic oxygenation compared to a VA ECMO setup.

VV ECMO is considered a less invasive method preferably chosen in the patient without circulatory failure (41, 42).

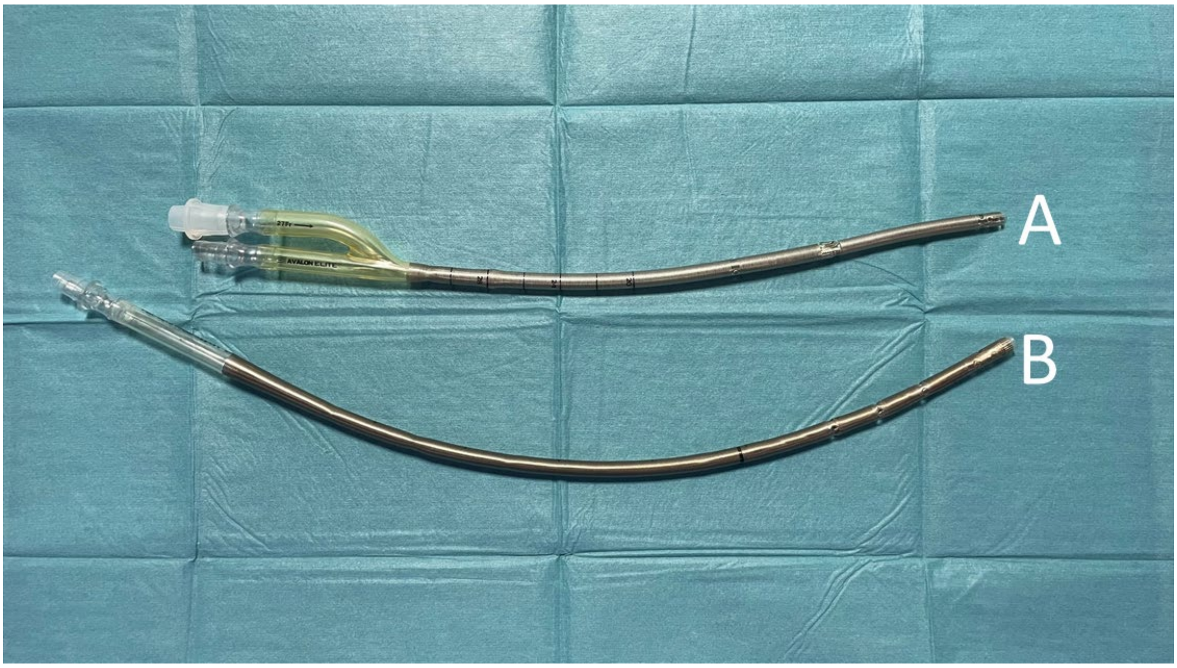

Image 3. A: double lumen cannula (Avalon Elite™ 27 F, 30 cm, Maquet /Getinge, Rastatt, Germany), B: single lumen multistage cannula (Biomedicus™ 25 F, 38 cm, Medtronic, Tolochenaz, Switzerland)

3 RESEARCH AIMS

The aims of this thesis were to:

- describe if ECMO and more specifically VA ECMO has a positive effect on survival in adult patients with septic shock.

- delineate and clarify whether conversion from VV ECMO to VA ECMO has an impact on mortality

- describe the impact on oxygen saturation in the upper body by change of drainage position from the IVC to the SVC in differential hypoxemia.

- investigate if PBF measured with echocardiography may assist in assessment of extent of pulmonary damage, and if echocardiography and CT findings are associated with patient outcome.

4 MATERIALS AND METHODS

All studies were based on retrospective data. In the first study *Extracorporeal Membrane Oxygenation for Septic Shock,* we obtained data from our local databases (PasIva™; Otimo Data AB, Kalmar, Sweden; TakeCare™, Acceptus AB, Stockholm, Sweden) and from patient charts. Patients were eligible for inclusion if admitted to our unit between January 2012 and December 2017. Criteria used for inclusion were age over 18 years; septic shock (International Classification of Diseases, 10th Edition [ICD-10]: R65.1, R57.2). Patients accepted for ECMO also needed to fulfil the “Sepsis-3” definition (43); presence of cardiocirculatory failure requiring a support equivalent to a Vasoactive Inotropic Score (VIS) (44) greater than 50 to achieve a mean arterial pressure (MAP) over 65 mm Hg; and signs of organ hypoperfusion. Patients who only had part of their ECMO treatment at our unit were excluded as well as patients receiving extracorporeal cardiopulmonary resuscitation (ECPR).

In the second study, *Conversion from Venovenous to Venoarterial Extracorporeal Membrane Oxygenation in Adults.* we performed a retrospective data collection of patients over 18 years of age who were treated at our unit between January 2005 and December 2018 where the initial ECMO mode was VV ECMO. Patients who were converted to VA ECMO after 6 hours were further analysed and included in the study. The cut off time for inclusion was used as a mean to sort out patients with the wrong mode at the onset of the ECMO treatment. In this setting the *wrong mode* was used to sort out patients who were in obvious need of circulatory support but had been put on VV ECMO. As in the previous study, exclusion was made if the patient was partially treated at a different hospital or had been subjected to ECPR.

Data was collected concerning sex, age, ECMO mode, Simplified Acute Physiology Score (SAPS-3) (45, 46), and Respiratory Extracorporeal membrane oxygenation Survival Prediction (RESP) score (47). In the converted patients the following data was also collected: body weight (at admission), ventilator settings, arterial blood gas data, blood pressure, number of vasoactive drugs, VIS (at admission, after 12 h and before conversion to VA). Sequential Organ Failure Assessment (SOFA) score (48) at initiation of ECMO and at the time of conversion to VA ECMO was calculated and included. The SOFA score was used to quantify organ failure severity and the evolvement of severity of disease over time. Survival After Venoarterial ECMO (SAVE) (49) score was calculated at time of conversion. Echocardiography was used to identify RVF and cardiac function. Circulatory shock was defined as a circulatory failure with a norepinephrine demand greater than 0.1 µg/kg per minute unresponsive to volume substitution with a mean arterial target blood pressure of ≥65 mmHg and circulatory failure was defined has a norepinephrine demand of >0.1 µg /kg/min to reach a MAP of ≥65 mmHg. Left ventricular failure (LVF) was defined as a reduced ejection fraction (<40%), as well as an increased plasma lactate. RVF was defined as end-diastolic dilatation of the right ventricle, or a tricuspid annular plane systolic excursion of less than 16 mm.

In study 3, *Differential Hypoxemia and the clinical significance of venous drainage position during Extracorporeal Membrane Oxygenation*, data was retrospectively collected for patients over 15 years of age treated at Karolinska University Hospital between 2009 and 2020 with signs of differential hypoxemia (DH). Patients were included into the study if DH had evolved to a state of fulminant differential hypoxemia (FDH) leading to change of drainage cannula or repositioning thereof. Peripheral oxygen saturation before and after repositioning of the drainage cannula was recorded together with pre-oxygenator saturation (SpreO2). ECMO configuration, drainage cannula design, size, and position together with method for determining cannula position were also recorded.

In Study 4 (manuscript: *Severe lung dysfunction and pulmonary blood flow during Extracorporeal Membrane Oxygenation*), patients from the age of 15 years treated on VV or VA ECMO between 2011 and 2017 at our centre were included. The criteria for inclusion were septic shock due to bacterial pneumonia, and prolonged ECMO care (>28 days). Exclusion criteria were part of ECMO treatment conducted at another centre, and/or ECPR. Treatment time on ECMO was divided into five time points: T0 at ECMO start, T25 at 25% of ECMO treatment time, T50 at 50%, T75 at 75%, T100 and at the time of weaning from ECMO. These time points were used to describe the trajectory of disease during the ECMO treatment and compared between survivors and non-survivors. Data concerning ECMO settings, echocardiographic findings, enhanced CT findings and tidal volumes were retrieved for the different time points. If data was not accessible at the end of ECMO, the last sample before was recorded. For all other sampling points, data/examinations were included if performed within ±5 days from the calculated time point. Assessment and evaluation of the CT examinations were independently performed by three separate radiologists. Viable lung parenchyma was defined as aerated parts of the lungs or condensed but perfused parenchyma, measuring >40 Hounsfield Units on contrast enhanced CT scans. The estimation of viable lung parenchyma was correlated to the total lung capacity bilaterally and presented in percent of total estimated lung parenchyma. Echocardiography exams were obtained from hospital charts where velocity time integral (VTI) over the proximal part of the main pulmonary artery (MPA) was measured. Pulmonary blood flow (PBF) was calculated according to equation 3 (50).

Equation 3.

$$PBF = \left(\frac{MPA_{diameter^2} \times \pi}{4}\right) VTI_{\ MPA} \times \ Heart\ Rate$$

Abbreviations: PBF: pulmonary blood flow, MPA: main pulmonary artery, VTI: velocity time integral.

4.1 STATISTICS

Data was tested for normal distribution using Shapiro-Wilk test except in study 3 where Kolmogorov–Smirnov test was used. Two-sided paired or un-paired T-test, or ANOVA followed by Tukey's post-hoc test when appropriate were used for comparison of normally distributed data. Mann-Whitney U test, Wilcoxon signed rank test, or Kruskal-Wallis' test was used for comparison of non-parametric data. Fisher's exact test or Chi^2 test was used for comparison of categorical variables. A p-value <0.05 was considered significant in all studies. For the purpose of this thesis and to complete the results in Study 4 a mixed effects model was used to analyse repeated measurements made over time.

4.2 ETHICAL CONSIDERATIONS

Ethical approval was sought at the Stockholm Regional Ethical Board or National Ethical Authority. These bodies also approved the respective ethical application. Due to the retrospective nature of all studies informed consent was waived. The data obtained was coded and can therefore not be traced back to individual patients. Only the primary investigator has the key to unlock the coded data.

Ethical approvals:

Extracorporeal Membrane Oxygenation for Septic Shock (Dnr: 2017/1671-32).

Conversion from Venovenous to Venoarterial Extracorporeal Membrane Oxygenation in Adults (Dnr: 2013/1561-31/3)

Differential Hypoxemia and the clinical significance of venous drainage position during Extracorporeal Membrane Oxygenation (EPM Dnr: 2021–04235).

Severe lung dysfunction and pulmonary blood flow during Extracorporeal Membrane Oxygenation, (manuscript) (Dnr: 2017/626-31/1)

5 RESULTS

5.1 STUDY 1

In Study 1, *Extracorporeal Membrane Oxygenation for Septic Shock*, we demonstrated that there was a benefit of using ECMO support in patients with septic shock (Table 1). Furthermore, our results not only showed an improvement for patients with LVF but also for patients with distributive shock. Thirty-seven patients were identified between 2012 and 2017 with septic shock according to Sepsis-3 (43) with a need of vasoactive drugs (VIS>50) to reach a MAP of 65 mmHg. Survival for septic shock with left ventricular failure was 90%. Furthermore, this figure improved to 94% if the patient was treated with VA ECMO from the onset of ECMO treatment. However, the study also showed a 65% survival in patients with distributive shock. Even though survival was lower in the distributive group, the calculated estimated survival rate according to SAPS-3 was 18% with continued conventional treatment.

Outcome	***Survival (%)***		
	ECMO	**Hospital**	**Long-term**
All (n=37)	81.1	78.4	59.5
LVF (n=20)	90.0	90.0	75.0
VV (n=2)	*50.0*	*50.0*	*50.0*
VA (n=18)	*94.4*	*94.4*	*83.3*
non-LVF (n=17)	64.7	64.7	47.1
VV (n=8)	*62.5*	*62.5*	*37.5*
VA (n=9)	*66.7*	*66.7*	*55.6*
LVF vs. non-LVF	NS	0.044	0.081

Table 1. Outcome in Study 1.In total 10 patients were treated with VV ECMO whereof 6 were converted to VA ECMO during the course of ECMO treatment. Non-LVF patients represents patients with distributive shock.

Abbreviations: ECMO=Extracorporeal membrane oxygenation, LVF=left ventricular failure, VV=venovenous ECMO, VA=venoarterial ECMO

5.2 STUDY 2

In the paper *Conversion from Venovenous to Venoarterial Extracorporeal Membrane Oxygenation in Adults* we performed a retrospective study investigating the incidence, indication, and outcome in patients who were converted from VV to VA ECMO. Between 2005 and 2018 we identified 219 VV ECMO patients whereof 46 were converted. The findings of this study demonstrated a relatively high mortality rate in the converted group compared to the non-converted group (62% vs. 16%, $p < 0.001$) (Table 2). The incidence of

RVF was higher among patients who were converted compared to patients who were not converted (72% vs 10%, p<0,0001). There was no difference regarding mortality among patients converted for circulatory shock or RVF (50% vs 67%, p=0.48). However, there was a significant increase in length of stay in the ICU for patients with RVF compared to circulatory shock patients (29.6 (17.3–42.1) vs. 10.4 (5.9–29.1) days (p = 0.048)) (Table 3). There was also a marked difference in RESP score between patients who were converted and not converted (−2.5 (−4–1) vs. 2 (0–4), respectively, p<0.0001). This difference was also present when comparing outcome among the converted patients where survivors had a mean RESP score 0 (−2.3–1) of and non-survivors −4 (−5.8–−0.3), p=0.012.

	Non-converted	**Converted**	*p-value*
Number, n	167 (missing n=6)	46	
Male sex, %	66	65	*1.0*
Age, years	49 (34.5-59)	50 (33-60)	*0.74*
SAPS-3	74 (67-81)	72 (67-80)	*0.87*
RESP*	2 (0-4)	-2.5 (-4-1)	*<0.0001*
Tidal volume**	288 (150-400)	200 (55-388)#	*0.11*
RVF, %	10	72	*<0.0001*
Circ. failure, %	51	86	*<0.0001*
Circ. Shock, %	49	44	*0.62*
Days on ECMO, n	6.6 (3-12)	22 (12-40)	*<0.0001*
Mortality rate, %	16	61	*<0.0001*

Table 2 Converted and non-converted patients

Baseline and outcome data for non-converted venovenous, and venovenous patients converted to venoarterial extracorporeal membrane oxygenation.

*) RESP score at decision for ECMO; **) Tidal volume for the non-converted group based on the lowest tidal volume registered during ECMO treatment. In the converted group the tidal volume was based on the lowest volume within 12 hours prior to the decision for conversion. #) missing or incomplete medical charts, n=6

Abbreviations: Circ., circulatory; ECMO, extracorporeal membrane oxygenation; RESP, Respiratory Extracorporeal membrane oxygenation Survival Prediction score; RVD, right ventricular dysfunction; RVF, right ventricular failure; SAPS-3, Simplified Acute Physiology Score

	Circulatory shock (n=12)	*p-value (Circ shock vs. RVF all)*	**RVF all (n=30)**
pre-ECMO data in patients who later were converted to VA ECMO			
Age, years, (range)	44.9±19.5 (19 – 74)	*0.66*	47.5±16.2 (19-78)
pO2, kPa	7.1(6.3-7.8)	*0.71*	7.0(6.2-8.5)
SaO2, %	80(70-84)	*0.14*	84(75-88)
FiO2, %	100(100-100)	*0.77*	100(100-100)
PIP, cmH2O	35±4.6	*0.76*	35±9.1
PEEP, cmH2O	15±4	*0.32*	14±4.4
Vt, mL	491±194	*0.60*	461±145
MAP, mmHg	61(58-74)	***0.006***	78(69-86)
Lactate, mmol/L	4.4(2.4-6.6)	***0.002***	2.1(1.2-2.4)
VIS	36(9-60)	***0.04***	9.7(3-33)
SOFAin	13(12-14.5)#	***<0.0001***	11(8.3-12)†
SAPS-3	76.3±15.0	*0.53*	73.7±10.8
RESP score	-2(-6 - 3.3)	*0.61*	-3(-4 - 0.8)
Data at time of conversion to VA ECMO			
Time to conversion, days, (range)	2.1(1.3-4.1) (1 - 18.9)	***<0.001***	11.1(5.4-15) (1 - 40.9)
Time from recognition of RVF or circulatory shock to conversion, days, (range)	0(0-0.5) (0 - 2)	*0.12*	0.9(0-1) (0 - 8)
SaO2 ; SpO2, %	85(76-90)	*0.11*	77(70-85)
FiO2, %	60(60-72)	*0.17*	50(50-62)
PIP, cmH2O	25±4.9	*0.47*	24±4.7
PEEP, cmH2O	8.6±4.3	***0.005***	5.1±2.8
Vt, mL	216±142	*0.37*	166±152
MAP, mmHg	67(64-72)	*0.87*	66(60-73)
ECMO blood flow, L/min	4.5(4-5.1)	*0.73*	4.5(4.2-5.1)
p-Lactate, mmol/L	3.8(2.2-7.0)	***<0.0001***	1.4(1.1-1.8)
VIS	29(23-52)	***0.006***	12(6-26)
SOFAconv	16(14.8-18)#	*0.07*	14(12.3-16.8)†
SOFAdelta	2.5(1-4.3)	*0.61*	3(1-5.8)
SAVE score at conversion	-9.5(-10.5 - -4.8)	*0.86*	-8(-10 - -6)
Days on ECMO, n	10.4(5.9-29.1)	***0.048***	29.6(17.3-42.1)
Mortality rate, %	50	*0.48*	67

Table 3. Circulatory shock and right ventricular failure. Data for the groups converted from venovenous to venoarterial extracorporeal membrane oxygenation due to circulatory shock or right ventricular failure (RVF). The right part of the table presents the subgroups of RVF with circulatory shock, or RVF with no circulatory shock. Normal distributed data is presented as mean±SD, and non-parametric data as median (IQR). Differences for variable trajectories within same group: *) p=0.052; **) p<0.01; #) p=0.014; †) p<0.0001; ǂ) p=0.028; $) p<0.0001

Abbreviations: ECMO, extracorporeal membrane oxygenation; FiO2, fraction inspired oxygen; MAP, mean arterial blood pressure; PEEP, positive end-expiratory pressure; PIP, peak inspiratory pressure; RESP, Respiratory Extracorporeal membrane oxygenation Survival Prediction score; RVF, right ventricular failure; SAVE, Survival After Venoarterial ECMO score; SOFA, Sequential Organ Failure Assessment score; SOFAconv, SOFA score before conversion; SOFAdelta, (= SOFAconv - SOFAin); SOFAin, SOFA score before ECMO; VIS, vasoactive inotropic score; Vt, tidal volume; w, with; w/o, without

5.3 STUDY 3

In Study 3, *Severe lung dysfunction and pulmonary blood flow during Extracorporeal Membrane Oxygenation,* we investigated if change of drainage position from the lower part of the body to the upper part of the body could impact DH in terms of oxygen saturation in the upper body. Seven patients were identified to have fulminant DH. Before cannula repositioning the mean peripheral saturation in the right earlobe or right hand was 54% (±6.6) which increased to 86% (±6.6) after adjustment, ($p<0.001$). At the same time pre-oxygenator saturation (SpreO2) increased from 62% (±8.9) to 74% (±3.7, $p<0.016$). Lactate had a descending trend from time of repositioning to 24 hours after from 6.5 (±6.7) to 2.8 (±2.8) mmol/L, ($p=0.08$). Patients' sedation could be reduced, and RASS increased from -5 (±0.45) to -3 (±0.8, $p<0.01$) 24 hours after repositioning (Figure 9). Furthermore, the pump speed (revolutions per minute) could be reduced ($p=0.056$) while maintaining the same flow ($p=1.0$) (Table 4). This was accomplished with a pre-pump pressure (P1) increase from a mean of -66 (± 35) to -31 (± 36) mmHg, ($p=0.037$) indicating improved drainage and less shear stress exerted on the blood. Besides improvement in SpreO2, patient saturation and lactate also showed improvements on individual level.

	Drainage cannula before intervention						**Drainage cannula after intervention**					
Patient No.	**Cannulation site**	**Tip position**	**Type of cannula**	**ECMO flow (L/min)**	**Pump speed (min^{-1})**	**Pre-pump pressure, P1 (mmHg)**	**Cannulation site**	**Tip position**	**Type of cannula**	**ECMO flow (L/min)**	**Pump speed (min^{-1})**	**Pre-pump pressure, P1 (mmHg)**
1	V fem dx	IVC	Multistage	5	4500	-70	V jug int dx	upper RA	Single-stage	4.6	4100	-10
2†	V fem sin	jnct. RA/IVC	Multistage	4.9	4500	-85	V jug int dx	upper RA	Single-stage	4.9	4000	14
3	V jug int dx	IVC	Single-stage	5.2	4500	-40	V jug int dx	upper RA	Single-stage	5.2	4500	-40
4	V fem sin	IVC	Multistage	3.5	missing data	-100	V jug int dx	upper RA	Single-stage	3.5	missing data	-70
5†	V fem dx	IVC	Single-stage	6	3900	-120	V jug int dx	upper RA	Multistage	6.3	3900	-90
6	V fem dx	IVC	Multistage	4.4	4200	-36	V jug int dx	upper RA	Multistage	4.45	3900	-35
7	V fem sin	IVC	Single-stage	4.2	4300	-14	V jug int dx	upper RA	Single-stage	4.3	4200	11
Average:				4.9 (4.2; 5.2)	4300 (±220)	-66(±35)				4.6 (4.3; 5.2)	4100 (±210)	-31(±37)
p-value before vs. after intervention:										1.0	0.056	0.037

Table 4. Comparing parameters before and after reposition of cannula drainage point.

Abbreviations: V, vein; IVC, inferior vena cava; jnct., junction; RA, right atrium; ECMO, extracorporeal membrane oxygenation; Pressure P1, pre-pump pressure.

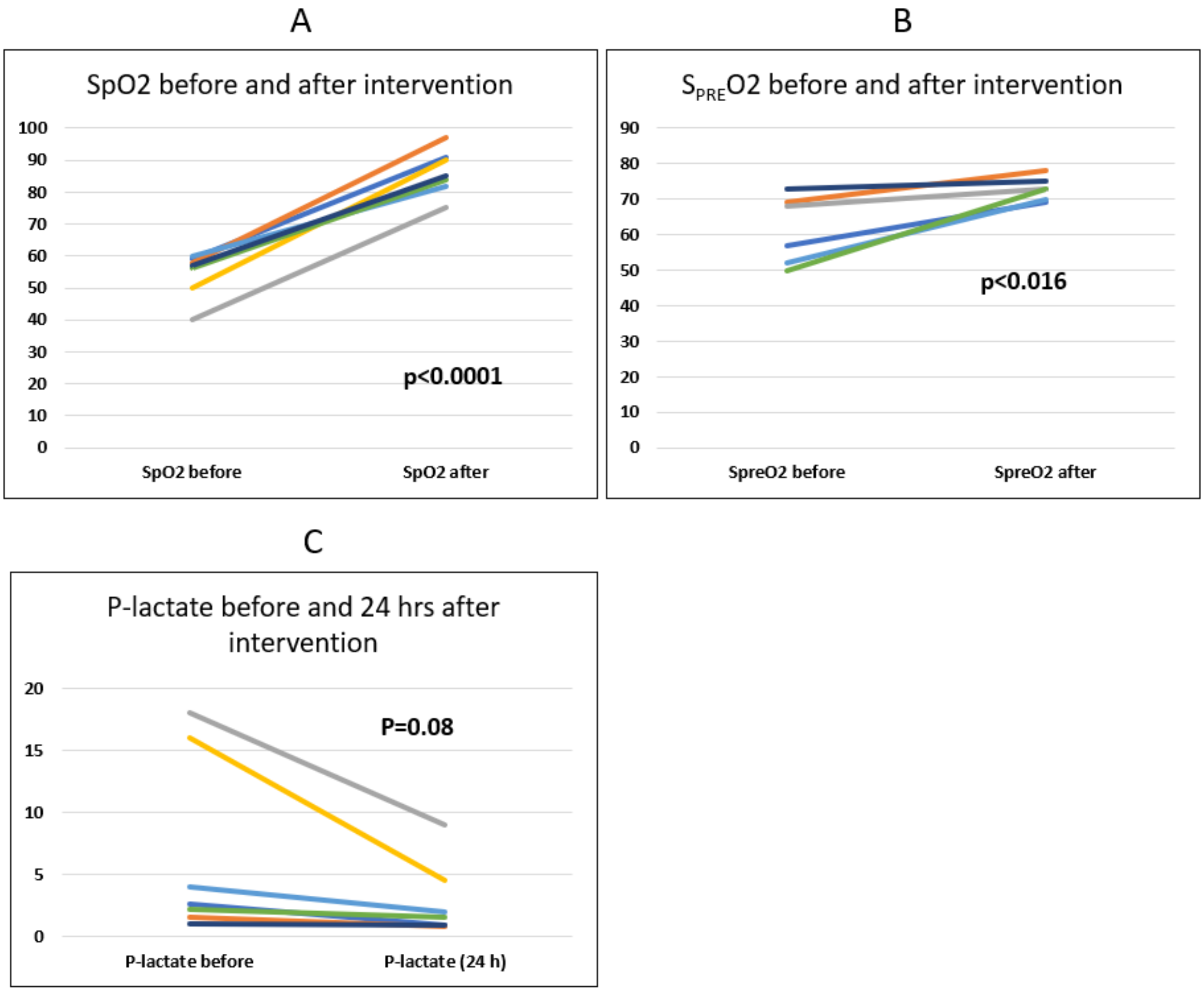

Figure 9. Individual outcome for all patients before and after intervention. In figure 5B the yellow line is absent due to missing data.

5.4 STUDY 4

In the fourth, in manuscript, *Severe lung dysfunction and pulmonary blood flow during Extracorporeal Membrane Oxygenation* we investigated if there was an association between measured pulmonary blood flow with echocardiography, pulmonary viability evaluated with enhanced CT, and mortality on ECMO. Nine patients requiring prolonged ECMO support with septic shock originating from bacterial pneumonia were included in the study.

There were discrepancies between the clinical picture, i.e., tidal volumes and CT exams regarding respiratory function (Table 5 and 6) where tidal volumes were significantly lower among the non-survivors whilst the CT scans did not show any significant difference in estimated viable lung parenchyma. PBF measured by echocardiography showed a trend of improvement between T0 and T100 for the survivors (p=0.08). This trend of improvement was not observed for the non-survivors (p=0.31). Furthermore, there was a significant difference in the coefficient of slope regarding PBF between survivors and deceased (p=0.004) indicating that the survivors had higher pulmonary blood flows over the course of treatment (Figure 10). Furthermore, a mixed effects model showed significant difference between survivors and non-survivors regarding tidal volumes (p=0.047) and SOFA score (p=0.03) indicating a more severe state of disease for the non-survivors over time (Figure 11 and 12). While there was an improvement among the survivors regarding awareness measured with Richmond Agitation Sedation Scale (RASS) between T0 and T100, this effect was not observed among the non-survivors (p= 0.00 vs. p=0.13) (Table 6). Right ventricular pressure did not differ over the course of treatment or between T0 and T100 between survivors and non-survivors (Table 5 and 6).

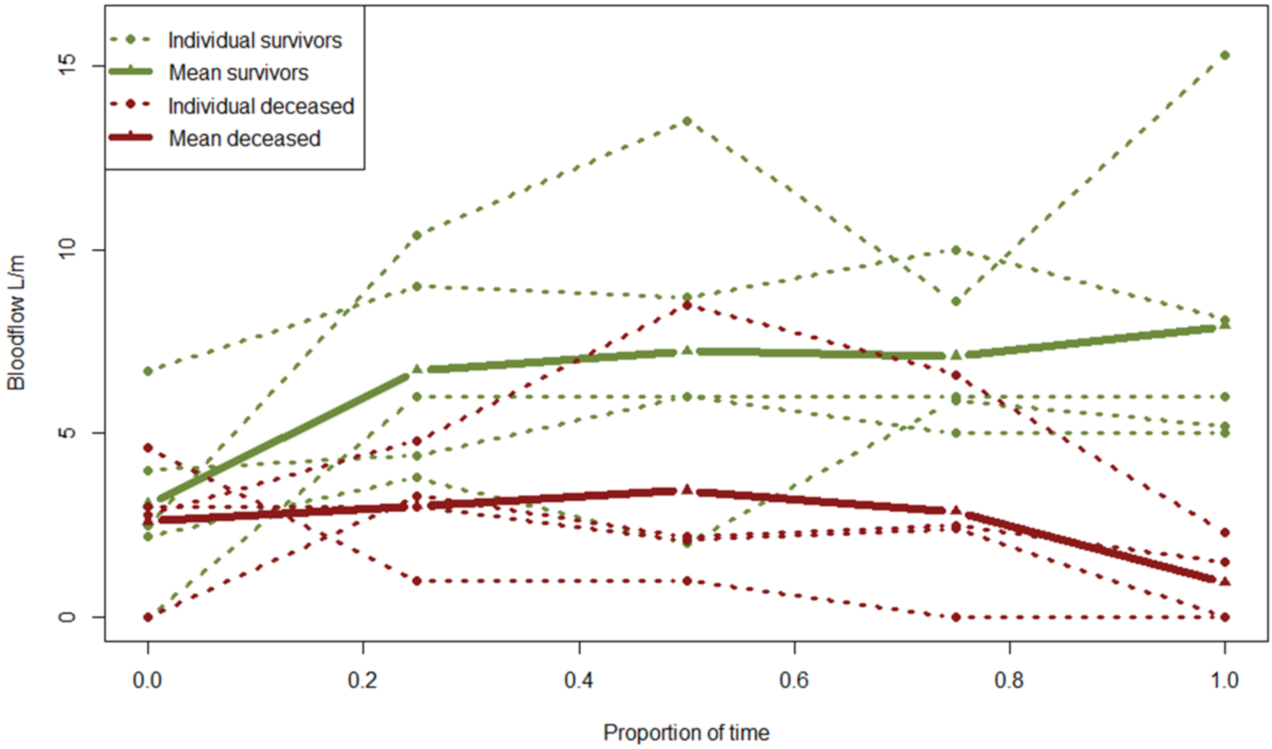

Figure 10. Pulmonary blood flow over time for the individual patients (dotted lines) and aggregated for the respective group (bold lines). Red colour marks non-survivors, and green colour survivors.

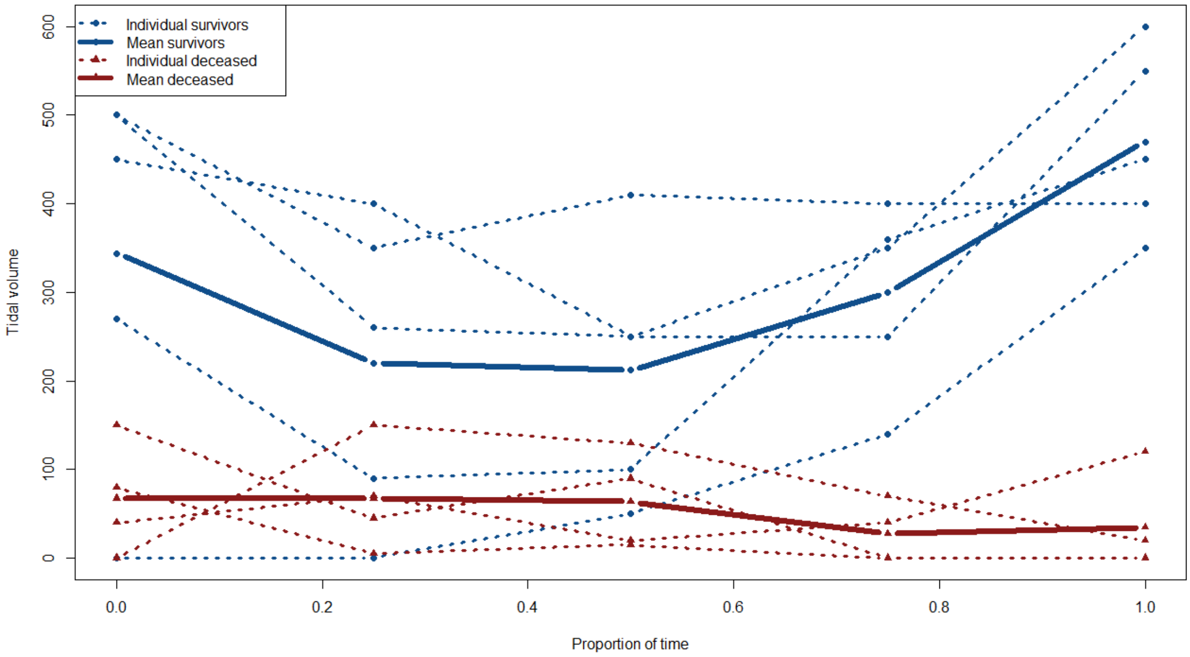

Figure 11. Comparison of tidal volume over time for the individual patients. Red dotted lines indicate non-survivors and blue filled lines survivors and aggregated for the respective group (bold lines).

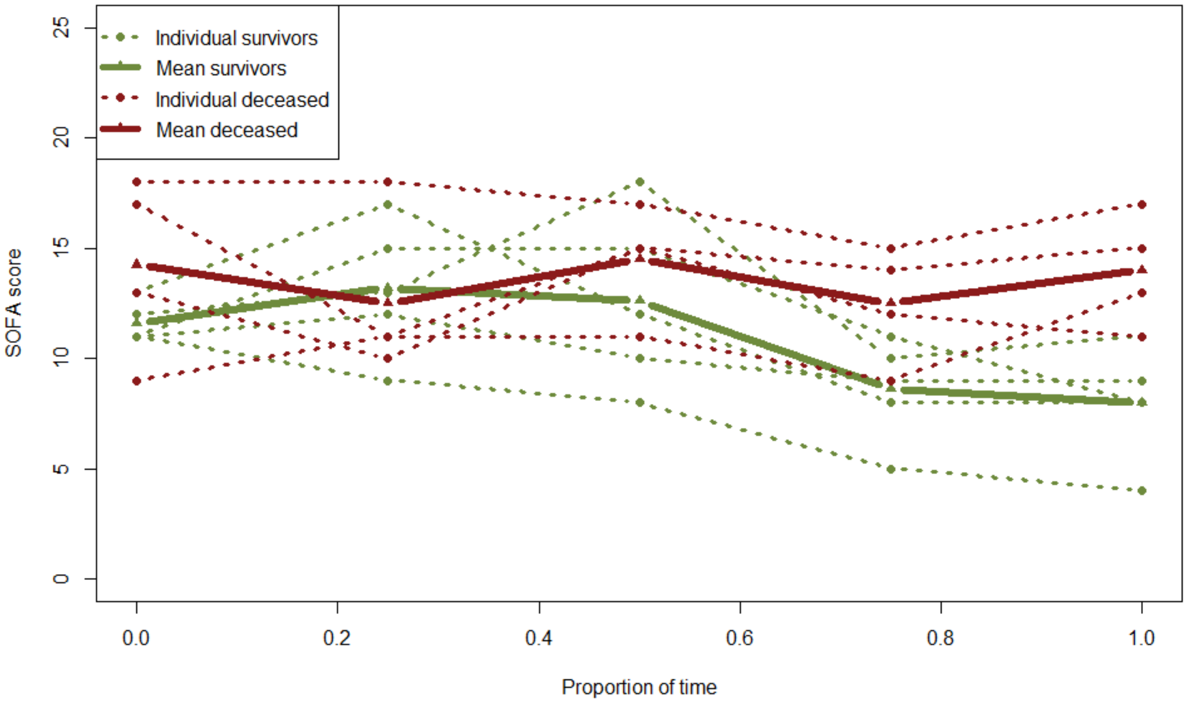

Figure 12. Comparison of SOFA over time for the individual patients (dotted lines) and aggregated for the respective group (bold lines). Red colour marks non-survivors, and green colour survivors.

Five patients survived (56%) to hospital discharge and were still alive at 5-year follow up. Four patients went through lung transplantation. Two survived the transplantation and were still alive at 5-year follow-up. Two patients succumbed in the immediate aftermath to transplantation surgery from uncontrolled bleedings. When examining the perioperative reports, these two patients exhibited a generalized bleeding at the sites of anastomosis between the recipient and the new organ. The survivors from lung transplantation had maintained tidal volumes and PBF in contrast to the transplanted who did not survive.

Variable	**P-value interaction time and survivors vs. non-survivors (mixed-effects model)**
RAAS	0.56
Tidal volume (ml)	**0.047**
Viable lung parenchyma (%)	0.85
Extracorporeal blood flow (L/min)	0.65
Right ventricular pressure (mmHg)	0.10
Blood flow main pulmonary artery (L/min)	**0.00**
SOFA	**0.03**
VIS	0.45

Table 5. Mixed effects model comparing survivors and non-survivors over time.

Abbreviations: RAAS: Richmond Agitation Sedation Scale, SOFA: Sequential Organ Failure Assessment, VIS: Vasoactive Inotropic Score

	P-value T0 v. T100 (paired t test)	
Variable	**Survivors (n=5)**	**Non-survivors (n=4)**
RAAS	**0.00**	0.13
Tidal volume (ml)	0.16	0.57
Viable lung parenchyma (%)	0.69	*
Extracorporeal blood flow (L/min)	0.86	**0.02**
Right ventricular pressure (mmHg)	0.55	0.48
Blood flow main pulmonary artery (L/min)	0.08	0.31
SOFA	**0.03**	0.87
VIS	**0.04**	0.13

Table 6. Comparison within survivors and deceased, respectively, between T0 and T100. * Insufficient data

Abbreviations: RAAS: Richmond Agitation Sedation Scale, SOFA: Sequential Organ Failure Assessment, VIS: Vasoactive Inotropic Score

6 DISCUSSION

After 2009 and the H1N1 pandemic the adult ECMO world has surged and the number of ECMO centres have more than doubled. This increase has been furthered by the Covid-19 pandemic (51). As with any new technology there are always new indications, and the frontier of treatment always moves forward. In the four works that this thesis is appertaining to, we set out to delineate some fundamental aspects of respiratory failure supported with ECMO.

6.1 PULMONARY INFECTION AND SEPTIC SHOCK

Since ECMO and especially VV ECMO was introduced as a means to support the respiratory compromised patient (52), it is evident that patients with pulmonary infections may be candidates for ECMO treatment. The standard ECMO treatment for these patients is VV ECMO since it is the respiratory system that is compromised (41). However, when the pulmonary infection turns into sepsis and the patient becomes circulatory affected, VV ECMO may not offer enough cardio-pulmonary support. We therefore investigated septic shock patients on ECMO. Other studies had been performed on these patients but demonstrated either poor outcome, or a benefit in patients with a direct cardiac compromise (53-57).

Two subsets of subjects were identified among the 37 included patients: septic shock with LVF i.e., septic cardiomyopathy, and patients with distributive shock. Patients with LVF exhibited a higher survival rate compared to the patients with distributive shock. Hence there were two reasons for these patients to develop circulatory failure. Either cardiac depression, or vasoplegia with capillary leakage causing displacement of intravascular volume exacerbating hypovolemia. Brechot et al. stipulated that ECMO would be ineffective in patients with vasoplegia (53). However, our results indicated that ECMO may have secondary beneficial effects presumably by improving tissue oxygenation and thereby improving the milieu intérieur. We, therefore, postulated that VA ECMO in distributive septic shock could support the failing circulation by limiting the negative impact of poor systemic oxygenation and an unfavourable metabolic situation in the extracellular space. Seventeen patients were found with distributive shock. Hospital survival for the LVF patients was 90.0% and the corresponding hospital survival for the distributive shock patients was 64.7% ($p=0.044$). We also found that commencement on VV ECMO was associated with a higher risk for in-hospital death, 50% versus 11% for the VA group ($p=0.011$). We therefore stipulated that VA ECMO should be considered, not only for patients with myocardial dysfunction, but also for distributive septic shock patients. Furthermore, we found that the majority of patients commenced on VV ECMO later were converted to VA ECMO during the course of treatment, and that the hospital mortality among the converted patients was 100%.

6.2 CONVERSION OF THE RESPIRATORY COMPROMISED PATIENT WITH EVOLVED CIRCULATORY FAILURE

The first work of this thesis presented questions whether conversion from VV to VA ECMO should be performed and if performed what the outcome might be. In the second study we found that out of 213 patients VV ECMO patients, 21% required conversion to VA ECMO. This number was higher than reported from the ELSO Registry (58). The converted patients had an increased in-hospital mortality compared to the non-converted, 61% versus 16%, (p=<0.0001). The converted patients also had a higher mortality compared to regular VA ECMO patients (61% vs. 36%). This could signify that there were patients where circulatory failure was present but not fully appraised among the VV ECMO patients. Thus, there seems to be patients in the VV group that may benefit from VA ECMO from the time of initiation of ECMO treatment.

There were two main indications for conversion, circulatory shock and RVF. In the subgroup of RVF patients who developed circulatory shock there was a marked difference in admission RESP score compared to the VV cohort that were not converted. Since the confidence intervals for the RESP scores -3 and 1, respectively, did not overlap this may indicate that patients with RVF who develop circulatory failure were in a worse state already at admission. A negative score indicates a mortality risk >50%; a positive RESP score indicates a chance of survival > 50%. The more positive the score, the higher the chance for favourable outcome, and vice versa. (https://www.respscore.com/).

During VV ECMO the patient is dependent on a preserved cardiac function for perfusion and oxygen delivery to the tissues (12). Therefore, patients with respiratory failure together with circulatory failure or shock on VV ECMO run a risk of deterioration in tissue perfusion and thus increased risk of failing organs. Hence, there may be an indication for conversion to VA ECMO if perfusion and oxygen delivery cannot be sustained with VV support together with intensified vasoactive-inotropic support. The results from this study indicate the need for a thorough evaluation of the patient's need of organ support at the onset of ECMO treatment, and furthermore not to choose VV but VA ECMO if the patient is in need of circulatory support. Erroneous primary or delayed correct mode may be deleterious. Moreover, VV patients converted to VA seems to have a higher risk of death compared to patients commenced on VA ECMO directly at the initiation of ECMO. These findings corroborates the results from the previous study in septic shock patients where the omission of VA mode for the circulatory compromised patient carried deleterious consequences. Hence, VV ECMO is not and should not be synonymous with ECMO for all cases in respiratory failure. Instead, the mode of choice should reflect the patient's need for support based on best clinical assessment considering respiratory, circulatory, and general organ status as well as the underlying disease. In most cases this evaluation may be uncomplicated and apparent. However, some cases will be more difficult to assess.

The results from this study also highlight the importance of routine and consecutive evaluation of patients on VV ECMO to identify patients in need of circulatory support.

Echocardiography is an important tool for repeated assessment and evaluation of the patient's cardiac function. Trend of daily SOFA scores may indicate a deterioration in organ function. Trends of biochemistry and physiology together with bedside observation and clinical course are also essentials in selecting the right care within the right time frames over the course of ECMO treatment. Further studies are needed to validate the use of risk scores in this setting. The RESP score was used as a means of retrospectively evaluate the condition of the patient at decision for ECMO. Patients who later failed VV support had a more negative RESP score compared to those who were not converted. However, the RESP, SAVE, SAPS, and Acute Physiology and Chronic Health Evaluation (APACHE (59)) scores, are not designed or evaluated for continuous use, neither have any risk stratification score proven valid in ECMO populations (60). Furthermore, there are great uncertainties regarding the SOFA score's ability to estimate mortality risk at admission to ECMO as well as its use to objectively follow organ failure trajectories on daily basis for prognostication.

Our results indicate that patients who required conversion may have been identified earlier using routine echocardiography but also lower RESP scores at start with a progressive deterioration in daily SOFA scores. Patients without circulatory failure should by default be treated with VV ECMO. However, in patients with signs of RVF and, or circulatory shock VA ECMO should be considered as the preferred ECMO mode.

6.3 THE RESPIRATORY PATIENT ON VA ECMO

The respiratory ECMO patient supported with VA ECMO, typically in a femoro-femoral configuration, is at high risk of development of DH (61). However, all patients on VA ECMO have some degree of DH due to the introduced parallel extracorporeally driven blood stream. This is usually not a problem in patients with a cardiac aetiology with a relatively spared lung function. However, with significant pulmonary compromise, DH may become a clinical problem. This will occur when the heart recovers and natively driven blood flow is not contributing with sufficient oxygen delivery (11).

In a patient with totally consolidated lungs there is no gas exchange taking place in the lungs. Consequently, the lungs will only function as a transition vessel for the blood between the right and left heart. Albeit this vessels capacity to allow a flow between the right and left side of the heart will be dependent on the vascular resistance of the lungs (62, 63). In a totally consolidated lung for example, there will be no oxygen in the alveoli leading to hypoxic vasoconstriction and risk of secondary right ventricular failure (64). Therefore, in femoral return VA ECMO with partially recovered cardiac function the upper body will be perfused with blood of similar oxygen saturation as the mixed venous saturation (SvO2). However, even if peripheral saturation levels equivalent to mixed venous saturation measured with regular pulse oximetry will raise concerns, it should be noted, that an arterial saturation of 80% corresponds to an altitude of 4500 m, or 57 kPa (65). At this altitude populated areas and cities are found. Therefore, a cerebral arterial saturation of 80% should *per se* not be considered a clinical problem during VA ECMO provided a normal acid-base balance and haemoglobin level. When oxygen is extracted from 80% saturation (in the upper body), oxygen saturation will be lower in the SVC than in the IVC perfused with hyper-oxygenated extracorporeal blood (femoral return and normal oxygen consumption). That inevitably leads us to the question of where to place the drainage cannula.

Normally the saturation is similar in the SVC and IVC in intensive care patients (66). During VA support the saturation in SVC and IVC will differ depending on the position of the return cannula(s), extracorporeal blood flow, residual lung function, and cardiac output (CO) (11).

To alleviate the problem with DH as shown in Study 3, the drainage was adjusted to, or focused to capture the venous blood returning from the upper part of the body. By this approach (SVC drainage), the leverage for oxygen transfer per volume unit of extracorporeal blood pumped increases when delivering the least saturated blood to the oxygenator. The hyper-oxygenated blood returned to the patient via a femoral artery, will perfuse the lower body and visceral organs. This blood will mix in the water-shedding zone with oxygen-poor blood entering via in the descending aorta. In the IVC however, the blood will still have a relatively high oxygen saturation. To maintain a stable CO the volume drained extra-corporally from the SVC will have to be replaced by IVC blood according to the Frank-Starling law. This blood of high oxygen content will enter the right ventricle and subsequently be ejected by the left ventricle to the upper part of the body. This will lead to a better peripheral saturation in the upper areas.

In Study 3 we also demonstrated that the drainage point had a significant impact on the effectiveness of the ECMO flow with improved drainage from the SVC compared to the IVC, a clinical observation also shared by others (67). Drainage cannula size is identified as the most flow limiting part of the ECMO circuit. Furthermore, it is important to position the cannula in a vessel compliant enough to allow for a suffice drainage to accomplish both a steady flow, but also to provide marginal for fluid removal without chattering of the drainage cannula (due to intravascular hypovolemia). In VV ECMO, SVC drainage seems superior in this respect compared to IVC drainage (67, 68).

6.4 PATIENTS WITH RESPIRATORY FAILURE ON PROLONGED ECMO

As ECMO technology has evolved treatment time has increased (69). Especially patients with respiratory failure on ECMO have longer mean treatment times compared to patients with isolated cardiac failure (70). Regarding respiratory failure, ECMO has also been used as a bridge to lung transplantation for several decades (71). However, respiratory failure is a condition which encompass a large variety of patients with different underlying diseases. Thus, it can be debated if all these underlying diagnoses are suitable for ECMO treatment and especially prolonged ECMO treatment. The most common diagnosis for respiratory ECMO is pneumonia (70). Usually, these patients can be weaned within a week, but a number of patients end up with longer ECMO treatment times (72). Among these, there are cases with extensive pulmonary destruction where recovery is impossible (73), whereof in selected cases lung transplantation may be considered (41). However, very little is known about the prognosis of patients with pneumonia which fails to recover during ECMO support.

In Study 4, *Severe lung dysfunction and pulmonary blood flow during Extracorporeal Membrane Oxygenation*, we tried to clarify whether CT and echocardiography exams can help in determining the prognosis of patients with septic shock based on pulmonary infection. We found that CT was of poor help to identify which patient was prone to succumb, and whom had a higher chance to survive. However, VTI measured with echocardiography to calculate PBF did contribute to assess patient outcome. The results showed that PBF was low and remained low over time in non-survivors whereas this variable was higher and tended to increase over time in survivors. Furthermore, there was no progression or alteration in tidal volumes within the respective groups. Hence, among survivors, tidal volumes were preserved over the course of ECMO treatment, contrary to the non-survivors where there the tidal volumes remained low.

The inability of CT examinations to determine the extent of pulmonary damage may be due to difficulties to visualize and discriminate viable parenchyma from damaged zones. In these ECMO patients, extensive consolidations, inflammation, and extravascular fluid together with other findings such as ground glass and emphysematous changes will make it difficult to discriminate between viable and non-viable parenchyma (74-76). These changes may lead to overestimation of the consolidated areas. At the same time, these consolidations may compress emphysematous parts and leading to a further underestimation of these areas.

There are several studies that highlight the importance of PVR in ARDS patients. The Fluid and Catheter Treatment Trial reported an association between pulmonary vascular dysfunction in terms of baseline indexed pulmonary vascular resistance index (PVRi) and 60-day mortality in patients with ARDS , where PVRi was significantly higher in non-survivors (77). In another prospective trial on 226 patients with moderate to severe ARDS, right ventricular dysfunction was found in 22% of patients and identified as an independent predictor of 28-day mortality as well (78).

With extended ECMO run times in patients without recovery there will be ethical questions on whether to discontinue ECMO treatment (79), or assess patient eligibility for lung transplantation. In this study four patients were offered lung transplantation whereof two died. To reduce suffering and improve outcome in patients accepted for lung transplantation, other treatment alternatives during the progress of disease may be considered. One management alternative described is pneumectomy at an early stage to minimize inflammation and surrounding tissue damage, and thereafter perform lung transplantation when inflammation has subsided (80, 81). Furthermore, there are emerging evidence that lung transplantation can be performed with acceptable results in ARDS patients (82-85). Moreover, there are also results that stress the importance that ECMO patients are transplanted within the first two weeks of their ECMO treatment (86). Thus, it is important not to delay lung transplantation in an ECMO patient accepted for transplantation, but rather perform it as soon as possible to increase the chance of survival.

Although our results are based on retrospective data, they show an association between survival and maintained pulmonary blood flow in septic shock patients on prolonged ECMO treatment. Furthermore, these observations can also help in improving the care of ECMO patients requiring lung transplantation. If a transplantation is required to be able to wean from ECMO, it may be advantageous if this decision is made during the initial part of the ECMO treatment. Consequently, in patients with preserved tidal volumes and PBF it could be stipulated that lung transplantation may have a positive outcome for the patient, since the patient can benefit from an early informed decision. On the other hand, the results also indicate that a diminished PBF forebodes an unfavourable outcome among these patients. This information may help in assessing the prognosis not only for the patient with native lungs, but as well as for the lung transplanted patients lungs.

6.5 LIMITATIONS

Research on ECMO patients can be challenging, and especially if your question is very specific. ECMO patients are scarce compared to other patient groups, and the specific subgroup of interest can be difficult to find and enrol. All studies in this thesis are retrospective. This retrospectivity will inherently lead to shortfalls since data is un-controlled and the enrolment has taken place over several years. Another limitation is that the studies are based on data from one high-volume ECMO centre with more than three decades of experience which put in to question the generalizability of results.

Study 1 spanned over a 5- year period and included 37 septic shock patients. This relatively short time means that the changes in technique and routine during the inclusion time will be negligible therefore strengthening the results of this study. In Study 2, which included patients over 14 years, however, the likelihood for alterations in patient management are higher, although we could not identify any significant changes in treatment protocols, etc. There may however be changes in the general care which also could influence the results. In this study we focused on conversion from VV to VA ECMO and over the time-period the number of conversions tended to decrease over the last years. This finding might be from coincidence or could signify that there was a true increase in awareness that VV ECMO on patients with signs of circulatory impairment or RVF could lead to a worse outcome influencing daily patient management.

In Study 1 we pointed out the limiting factor of mixed populations of both VV and VA patients with septic shock making it more difficult to interpretate the results. However, the mix made it possible for us to reflect and draw important conclusions regarding septic shock and outcome on VV ECMO, as it also led to the initiation of Study 2.

In Studies 3 and 4 the included patients were even fewer compared to the earlier works due to the very narrow research questions. This also reflects the problem of scarcity of the conditions addressed namely differential hypoxemia and the pathophysiology during prolonged ECMO. The first of these, Study 3, had an inclusion time ranging over 12 years.

However, since the research aim was on “integrative physiology” any changes in treatment protocol during the time span of inclusion should not have any effect on the results.

In Study 4 there were several challenges to structure the retrospective data in a way that it could be systemized, analysed, and compared. The division of treatment times can be debated since the different time slots represent a fraction of total treatment time of each individual and unique patient. Treatment times varied substantially between patients. However, to have distinct comparable times and to find a suitable number of patients within the inclusion criteria would have meant that a prospective trial would have had troubles in reaching a result during a representative time-period and the number of patients included would have had to be substantial. Furthermore, Study 4 has limitation regarding the CT evaluations since these were made on a subjective scoring. This shortcoming was addressed by having three independently working radiologist who performed the scoring process thereby decreasing the risk of interrater bias.

7 CONCLUSIONS

- VA ECMO may be indicated for septic cardiomyopathy as well as distributive septic shock.
- In ECMO patients with respiratory failure VV ECMO should not be the default modality if there are signs of circulatory impairment.
- Moving the venous drainage zone into the upper part of the body in patients exhibiting FDH experience a marked positive effect on upper body saturation as well as improved flow dynamics.
- Pulmonary blood flow meassured with echocardiography may predict pulmonary recovery at early to later stages of ECMO treatment.

8 POINTS OF PERSPECTIVE

Patients with a failing respiratory system on conventional critical care may be considered for ECMO. The main criteria to be considered before acceptance for ECMO is the imminent risk of death if continued on conventional respiratory support (87). Moreover, there are several factors that have negative prognostic impact such as underlying disease, multiple organ failure, age, time on ventilator, etc. (47, 49). All of these must be considered when assessing the patient eligibility for ECMO treatment. First and foremost, it is important to evaluate if the patient has the prerequisites for a reasonable chance to survive the ECMO treatment itself. In some patients the treatment might in fact pose a greater risk than continuing with conventional intensive care (87).

When all considerations have been made and the patient has been accepted for ECMO, a final clinical bedside evaluation of the patient's cardiocirculatory status should be performed. Often enough, physicians make the mistake to consider the acute primary disease as the indication for which mode of ECMO to choose. Therefore, patients with pneumonia or ARDS may by default be selected for VV ECMO. Regrettably, this can have deleterious consequences. If the patient with ARDS is offered VV ECMO without a thorough evaluation of the right ventricle as well as the rest of the circulation, the patient stands the risk of developing an acute cardiac failure with the need of acute conversion to VA ECMO. As described in Study 2 on conversion from VV to VA ECMO, the risk of death is much higher if the patient is commenced on VV ECMO if the there are signs of circulatory failure or RVF. This was also a finding in our study on septic shock (Study 1) where patients commenced on VV ECMO had a higher risk of death compared to those who were offered VA ECMO from start. It is however important to bear in mind that a stable patient on VV ECMO may progress to become circulatory compromised, i.e., RVF, and require conversion to VA ECMO. This is the typical pattern in cases of RVF which underlines the need for daily echocardiograms. In our analysis, patient assessment benefitted from daily SOFA scoring as a means of evaluating the progress of disease.

This thesis also raises the question on whether CT scans are of value to assess and prognosticate pulmonary recovery in ARDS patients with severe pneumonia. Study 4 indicated that we are prone to overestimate the fraction of viable parenchyma in prolonged ECMO using CT scans. Thus, we recently started a retrospective analysis of high number thoracic CT scans on ECMO patients with ARDS to determine if and with what certainty CT scans may predict patient outcome.

ECMO is as previously described, a relatively newly accepted treatment among adults. Just 15 years ago the technology was considered experimental and still is in parts of the world. In the meantime, the paediatric ECMO world has been thriving for more than 30 years. Paediatric ECMO centres often have experiences yet to be learned and adopted by adult ECMO providers. The relatively low number of adult cases before the H1N1 pandemic in 2009 can be illustrated by the fact that ECMO Centre Karolinska in 2008 performed almost

20% of all adult respiratory ECMO runs in the world (42). Hitherto, the department had performed 10% of all reported cases ever. In our experience paediatric centres have a different approach to patients in need of ECMO support. It could be speculated that adult ECMO centres typically choose ECMO mode based on which organ is failing, while paediatric centres tend to evaluate what kind of support will benefit the patient the most regardless of the underlying disease. You could call it a “physiological approach”. The backside of adult medical intensive care units developing “respiratory” ECMO programs is that many of these centres do not have the knowledge, experience, and resources to offer the complete care of ECMO support including arterial cannulation. Centres who decide mode based on “respiratory” or “circulatory” diagnosis run a higher risk selecting a mode which may not benefit the patient the most. This cannot, be avoided in all situations, but if the mainstay is to choose a VV configuration for respiratory failure the provider needs to be able to initiate VA ECMO as well. Resource and knowledge for provision of seamless transition between VV and VA ECMO, and *vice versa* based on patient’s need and not the underlying disease is recommended for best quality of care.

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