**VILNIUS UNIVERSITY**
**MEDICAL FACULTY**

The Final thesis

# Extracorporeal Membrane Oxygenation for Cardiopulmonary Resuscitation

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# 1. Introduction

Extracorporeal membrane oxygenation (ECMO) has become an increasingly important intensive care treatment option for patients with refractory cardiac and pulmonary failure in recent years. Special focus has been placed on this therapy option in the last two years during the COVID-19 pandemic.

In addition, technical advances with improved biocompatibility permitting longer ECMO-heart or lung support have continuously increased the number of indications over the last decades.

The indications are numerous and include, among others, the bridging the heart and/ or lungs for recovery or transplant, support for resections in the area of the lung in unstable patients as well as the use in neonatology and infants with significantly impaired lung or heart function (1).

However, ECMO should not be understood as a disease-modifying, but rather as a supportive therapy, which is often used when other therapeutic options are limited.

ECMO patients therefore are high-risk patients with massive limited, life-threatening cardiopulmonary diseases and an increased risk of death.

In the following in this Master Thesis, I will focus on the extracorporeal membrane oxygenation from different points of view, and intend to evaluate clinical data with the question which predisposing clinical factors has influence on the outcome of patients suffering from COVID-19 associated refractory lung failure and the need for ECMO therapy during the pandemic period in Lithuania from 2020 up to 2022.

The history of extracorporeal membrane oxygenation is closely linked to the medical development of cardiac surgery. In the 1960s, complicated operations on the heart were characterized by a high mortality rate in the postoperative phase due to cardiac failure. Especially in neonatal and pediatric patients, complicated cases such as tetralogy of Fallot or transposition of the great arteries in open heart surgery had a mortality rate of over 50%.

Cardiac surgeons started to use heart-lung machines during those surgeries with the effect, that they lasted often longer than two hours, with long cross clamp time and in deep circulatory arrest, complications often arose afterwards.

The surgeon Robert Bartlett, at that time a resident in Boston, had the idea that these patients with cardiac or pulmonary failure could be kept on the heart-lung machine for a longer period, if there was the possibility to oxygenate the blood via a membrane outside the body and to restore adequate cardiac output. At this time, the first silicone rubber membrane oxygenators were just invented.

Bartlett and his colleagues experimented with the membrane oxygenator on animals and managed to keep a dog alive for four days via cardiac bypass (2) .

In 1971, Dr. Donald Hill was the first one, who saved a patient's life by the application of ECMO. The patient was a 24-year-old man who developed severe lung failure (ARDS) after a motorcycle accident with multiple trauma. Despite optimized ventilation therapy, the patient's pulmonary condition deteriorated and there was an agreement to use the new therapy of ECMO. The patient was on the ECMO for three days before the weaning of ECMO could initiated (3).

Bartlett and his team used ECMO mainly for patients who had undergone heart surgery - post cardiotomy. 1975 was the most important day in the history of ECMO. The Esperanza case is still known as the birth of ECMO. During birth, a newborn child aspirated large amounts of meconium, which led to a chemically induced pneumonia. Despite continuous mechanical ventilation, adequate oxygenation could not be achieved due to the fact that the meconium aspiration led to persistent pulmonary hypertension of the newborn (PPHN). When the situation already seemed hopeless, the thoracic surgeon Robert H. Bartlett decided to use ECMO as a rescue therapy. The therapy was successful and the newborn recovered completely without any neurological impairment (3,4).

Despite the successful therapy of ECMO in neonates following the “Esperanza Case”, early studies failed to demonstrate any advantage over conventional mechanical ventilation in adults, unfortunately the introduction of ECMO suffered a significant setback. However, ECMO is still used in pediatric and neonatal settings, as it could be proven that ECMO was a life-sustaining therapy with clear defined indications. This was

mainly due to the fact that neonates/children have a higher and faster pulmonary recovery rate than adult's due to their underlying pulmonary disease.

The use of ECMO in adults increased rapidly after the H1N1 pandemic 2009 and the CESAR publication (2009), which showed a significant reduction in the mortality rate and the number of subsequent severe disabilities after the use of ECMO in patients with massive lung failure compared to the use of conventional ventilation methods. Since then, the interest in the method has been growing and the indications of application have been steadily expanding (5) .

# 2. Mode of Action

Extracorporeal membrane oxygenation (ECMO) is a technique for the long-term treatment of patients by the use of a modified heart-lung machine. Oxygen-depleted blood is withdrawn from the patient, enriched with oxygen via an artificial oxygenator and then pumped back again into the patient (6,7). This procedure allows the patient's impaired vital functions to be maintained over a longer period of time. This allows either the underlying disease to be treated or bridging the time for a further planned therapy. The underlying disease must either be reversible or the intention of this therapy is to bridge the time for a scheduled organ transplantation in the future (8).

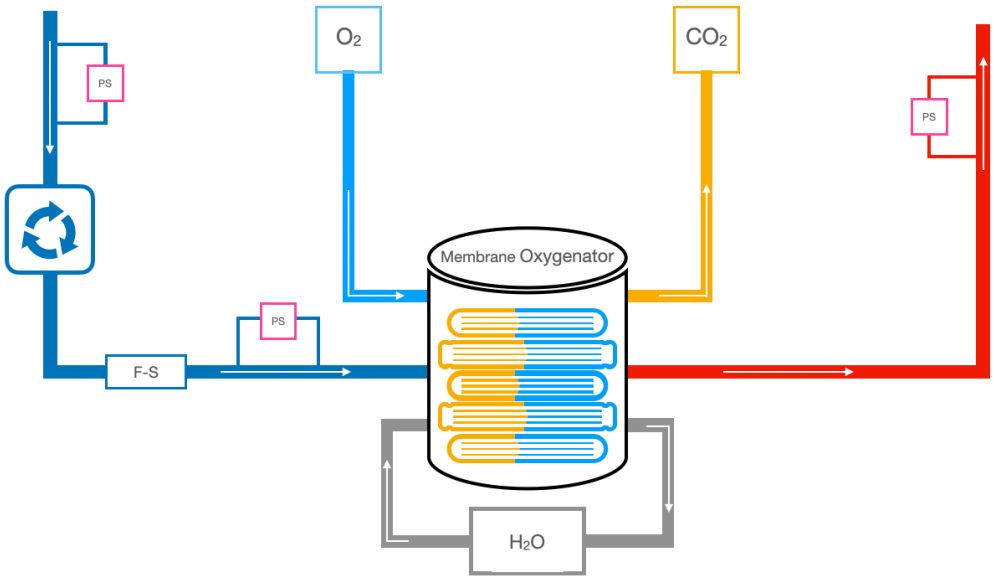
In principle, there are different mechanical pumps that can be used - rotary pumps and centrifugal pumps. As a result, for a long- term application, centrifugal pumps are mainly used nowadays (9).

Centrifugal pumps use centrifugal force to move the blood. The blood enters the pump via a suction tube, runs along the axis of rotation of a rotating pump wheel and is thereby forced spirally inside the pump to the outer section. The resulting pressure ensures that the blood passes out of the pump via the pressure tube. The outflow is controlled by a flow sensor, which is located directly behind the pump in order to be able to control the administered blood volume per minute (9). After the blood has passed through the pump, it will be pressed through the membrane oxygenator.

The membrane oxygenator is responsible for the gas exchange and takes over partial or full lung function depending from native lung function and blood flow through the oxygenator. It ensures that blood is enriched with oxygen (oxygenation) and carbon dioxide is removed (decarboxylation) from the blood. The membrane oxygenator consists of a semi-permeable membrane on which the gas exchange of the involved gases takes place via the partial pressure differences (10). Coatings are used to make the gas exchange as effective as possible and to keep complications to a minimum. Mostly, the membranes are coated with heparin or a bioline surface membrane to lower the risk of thrombosis (11).

For the drainage and the pumping of the blood in the body, cannulas will be placed in defined blood vessels. The vascular access of the cannulas depends on which type - VV or VA - ECMO will be necessary. To ensure optimal delivery, the size of the cannulae is chosen based on the estimated amount of support to be delivered (blood flow rate) and the size of the useable vessel (12).

As mentioned earlier, ECMO has a high risk of certain complications, such as infection, thrombosis or bleeding. The cannula system in particular is very susceptible to this, it is due to the fact that the cannulae are surrounded by a biocompatible lining, precisely to reduce the risk of cannula thrombosis. There are different techniques for the insertion of the cannulation. The Seldinger technique is the preferred technique for the transcutaneous insertion of the cannulas in ECMO therapy. It is well suited for catheterizing large blood vessels. First, the desired blood vessel is punctured with a puncture cannula using an ultrasound scan, then a wire is inserted through the puncture cannula. After dilatation of the vessel the chosen catheter can now be inserted via the wire, and once the catheter has been inserted, the wire will be removed (13).




*Scheme of Extracorporeal membrane oxygenation*

After the ECMO is connected to the patient, the blood flow is slowly increased until the pulmonary (oxygenation, decarboxylation) and hemodynamic parameters are sufficient.

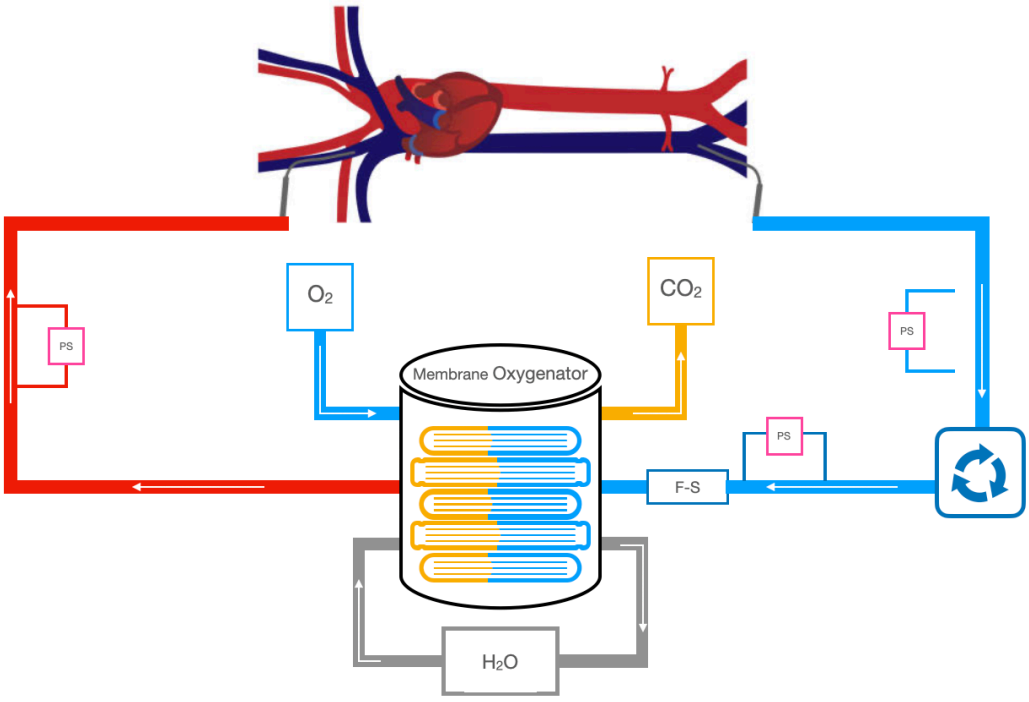
In summary, the basic physiological goals of ECMO therapy are to remove $CO_2$ and to oxygenate the blood, improve oxygen transport to the tissues and facilitate a normal physiological environment in the tissue area according to metabolic needs, so that there is the possibility for a lung recovery and / or adequate cardiac support.

# 3. Setup of ECMO and Different Therapeutic Options

It is possible to use ECMO via a veno-venous as well as a veno-arterial access. As the name suggests, in both cases blood is branched off from the venous system and fed into the extracorporeal circuit. In contrast to the veno-venous application method, the oxygenated blood of the VA-ECMO flows into the arterial branch of the systemic circulation supporting heart and lung function. In contrast in veno-venous ECMO (VV-ECMO) the heart is not relieved in its pumping function; the patient requires stable adequate hemodynamic conditions for the use of the VV-ECMO.

There are different options in the cannulation for VV-ECMO, in the femoro-jugular approach, the venous sampling cannula is placed transfemoral in the inferior vena cava. The return line is via the internal jugular vein and the superior vena cava directing the oxygenated blood into the right atrium. To place the cannula(s), a transcutaneous approach by percutaneous puncture is usually performed using the Seldinger technique. In the femoro-femoral approach, the sampling cannula is positioned in the distal inferior vena cava. The return line is via the contralateral femoral vein into the right atrium (14).

A possible alternative in VV-ECMO is the use of a double-lumen cannula (Avalon, Getinge), which is placed via the right internal jugular vein and drains the blood from the inferior and superior vena cava and restores it directly in the right atrium.



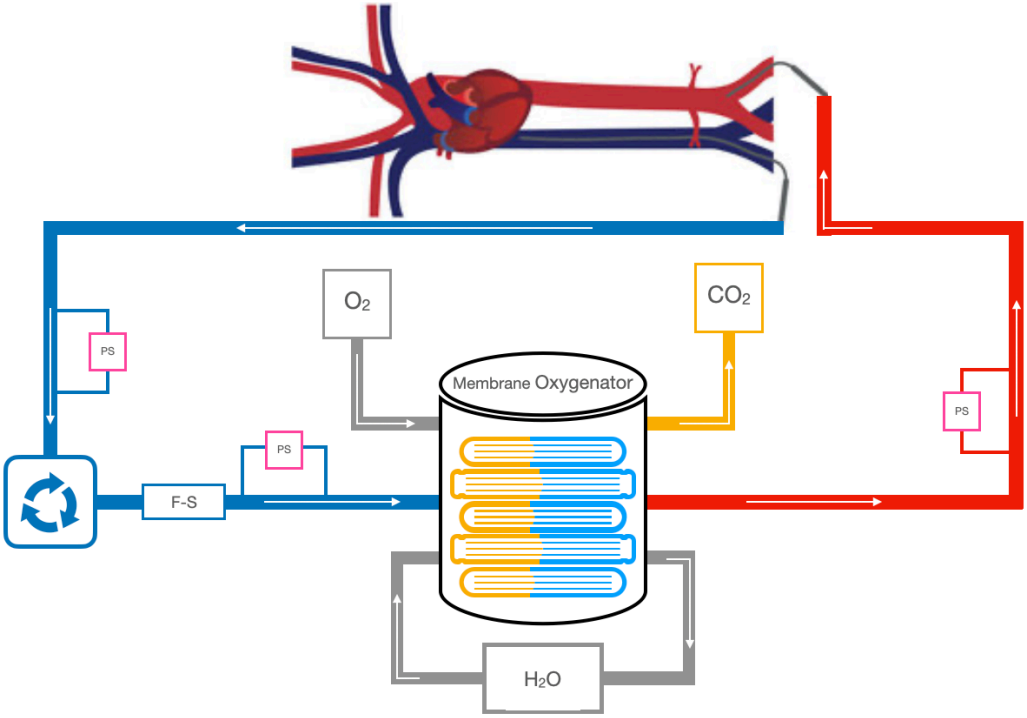

*VV-ECMO, femoro-jugular approach*

In addition to blood oxygenation, the veno-arterial approach also provides hemodynamic support; this type of ECMO is used in patients with insufficient cardiac output. The blood runs parallel to the heart and lung via the extracorporeal circuit and is then returned to the arterial system of the systemic circulation. For this purpose, the blood is diverted from the right atrium or from the vena cava and returned to the femoral artery via a peripheral cannulation. In neonates and small children up to two years oxygenated blood can also be returned via the carotid artery but this should be preferred in neonates, as the cerebral perfusion is still adequate instead of the closed carotid artery due to a perfect collateral perfusion in the circulus arteriosus cerebri (Willisi).

A central cannulation into the ascending aorta is also possible, but this method is usually used after a cardiotomy (post-cardiotomy), where the cannulae used for the cardiopulmonary bypass during the operation can be used to be connected to the ECMO system instead of the heart-lung machine.

The femoral approach in VA-ECMO is preferred in emergency situations or in the event of cardiogenic shock, as the insertion of the cannula is less invasive and faster to perform.

The amount of oxygen available to the blood via the ECMO system is directly proportional to the blood flow. The cardiac ejection plays an essential role here, as the system is connected in series with the heart. The veno-arterial approach, in which oxygenated blood is delivered directly into the arterial limb, offers a much more effective systemic oxygenation, as the oxygenated blood is mixed with the arterial blood and distal organs are perfused directly.




*VA-ECMO, femo-arterial approach*

VA-ECMO is usually the more complicated procedure compared to VV-ECMO. These complications can occur at different levels. A wide variety of complications depends on the cannulation. For example, incorrectly placed cannula can lead to vascular perforation with hemorrhages, cannula site bleedings, dissection of the arteries, ischemia distal to the

cannulation or the formation of pseudoaneurysm in the area of the implantation site. Also, to be compared with VA ECMO is the risk of cardiac thrombosis, which can occur with peripheral cannulation via the femoral vein and artery due to the retrograde blood flow into the ascending aorta. If adequate left ventricular ejection cannot be maintained, this will lead to stasis of blood flow in the left ventricle and has the risk of cardiac thrombus formation. Another problem that can occur with peripheral placement of the cannula into the femoral artery is, that the re-infused oxygenated blood primarily reaches the lower extremity and abdominal organs, which can lead to a minor perfusion of the coronaries or as a consequence to cerebral hypoxia. If the blood oxygenation is monitored at the lower extremity, such hypoxia may not be detected. Therefore, it is recommended to monitor oxygen saturation at the upper as well as the lower extremities. Of great advantage is the use of the near infrared spectroscopy (NIRS) as it can provide the monitoring of an adequate tissue oxygenation. If hypoxia in the upper extremities occurs, oxygenated blood can be additionally infused via the right atrium.

# 4. National Guideline for Application of ECMO

During ECMO, blood is drained from the vascular system and passed through an extracorporeal circuit using a mechanical pump and is then returned to the body's circulation. While the blood is outside the body, the hemoglobin is completely saturated with oxygen (oxygenation) and $CO_2$ is removed (decarboxylation). The extent of oxygenation is determined by the blood flow rate through the membrane as well as the elimination of $CO_2$, this being adjustable by the gas flow through the oxygenator (sweep gas flow). ECMO therapy is therefore a form of cardiopulmonary life support. The most important requirement for the indication of therapy with an ECMO system is the presence of a reversible underlying heart and/or lung disease.

Depending on which organ requires support, the indication for ECMO can be divided into three major sub-areas. It is used in patients who require support of cardiac function, pulmonary function or a combination of the two.

In general, it should be emphasized once again that ECMO is an intensive medical emergency measure that is only used when all other available therapy options have been exhausted and failed. It is not intended to cure a disease, but to bridge the time until an acute life-threatening condition has been prevented or another therapy is available. In general, the Extracorporeal Life Support Organization (ELSO) recommends the use of the technique in acute severe heart or lung failure with a high mortality risk despite optimal conventional therapy. If the estimated mortality risk is about 50%, ECMO should be considered, and if the mortality risk is about 80%, ECMO is indicated in most cases (15). One challenge is to estimate the mortality risk, which should be calculated as accurately as possible, depending on age and underlying organ failure.

The guidelines of the Extracorporeal Life Support Organisation (ELSO) list various scores that are used to assess a patient's chance of survival. The scores are assigned to specific populations, currently six different scores are used (PIPER, NEO-RESCUERS, RESP, SAVE, CDH PreECMO, CDH On-ECMO) (16).

It is also important to be clear that there are no absolute indications for ECMO therapy

and these are recommendations to better assess the therapy options. Furthermore, it is up to the multidisciplinary team to decide whether there is an indication for ECMO therapy or not.

Typical indications for cardiac support are a refractory cardiac output with a cardiac index below 2 l/min/$m^2$ BSA and a systolic blood pressure below 90 mmHg despite sufficient blood volume, high-dose drug therapy and the use of an intra-aortic balloon pump (17). Cardiac support by ECMO can only be provided by a venous-arterial application of ECMO, otherwise there is no relief of the heart and adequate perfusion.

The most common indication for VA-ECMO is therefore the cardiogenic shock, it is defined by various parameters: systemic systolic pressure is below 90 mmHg, the adult patient has a urine output of less than 30 ml/h, the lactate value is elevated above 2 mmol/l, the mixed venous saturation ($SVO_2$) is below 60% and the patient has an altered state for more than 6 hours (18). In addition, a prediction score is used to calculate the patient's chance of survival. If a patient has a refractory cardiogenic shock and the doctors are thinking about ECMO therapy, they use the “Survival After Veno-arterial ECMO” (SAVE) score. The "SAVE" score uses various parameters like previous heart disease, age and weight of the patient and whether the patient still has co-existing morbidities of other organ systems (liver, kidney, CNS, lung). The scoring system has a range from -15 to 15, the lower the score the lower the patient's chance of survival. However, the ELSO itself says that "It should not be considered a substitute for clinical assessment”(19).

Other indications include severe heart failure of various causes, such as acute coronary syndrome, severe cardiac arrhythmias unresponsive to other therapeutic agents, sepsis or drug overdose with impending heart failure, myocarditis, pulmonary embolism, isolated cardiac trauma and acute anaphylactic shock.

Following a cardiotomy, ECMO may be used if the discontinuation of cardiopulmonary bypass is complicated. After heart transplantation or heart and lung transplantation, such supportive therapy can be used effectively if there is primary dysfunction of the transplant.

Other cardiac indications include chronic cardiomyopathy as a bridging therapy until a long-term ventricular assist device is installed or until a decision can be made about its prognostic or therapeutic options.

In contrast to the cardiac fields of application, a veno-venous mode of application is also possible in addition to the veno-arterial mode of application when using ECMO for respiratory support, since the problem here is not a defective pump function but an insufficient gas exchange. With both procedures, time can be gained in the case of acute respiratory insufficiency and the cardiovascular system can be maintained until the condition has improved. In this case, ECMO takes over the function of oxygenating the blood and removing carbon dioxide until the lungs recover, or to bridge the time for a lung transplant in the case of end-stage lung disease.

Respiratory support can be used in acute progressive respiratory distress syndrome (ARDS) due to severe viral or bacterial pneumonia, it is also the most common indication for a VV-ECMO therapy.

In cases of airway obstruction, lung contusion or smoke inhalation, extracorporeal support can be used to protect the lungs. ECMO is also used in lung transplantation for primary transplant dysfunction after transplantation, as a bridging measure for a planned lung transplantation or as an intraoperative support (20).

As mentioned earlier, different prediction scores are used before starting an ECMO therapy. In the case of VA-ECMO after a refractory cardiogenic shock, the "SAVE" score is recommended. In the case of veno-venous-ECMO for respiratory failure, the "RESP" score is used. In this case, various patient parameters are also taken into consideration and calculated. It considers the patients age, if the patient is immunocompromised or had previous mechanical ventilation. Also of great importance is if the patient has other respiratory illnesses such as bacterial pneumonia or viral pneumonia as well as the involvement of other organ systems and laboratory values. The resulting scores give an indication of the patient`s chance of survival or mortality rate (21).

Conventional therapy for the treatment of acute lung failure has the disadvantage that the effectiveness of the therapy decreases with increasing lung damage. The essential condition for this is the maintenance of adequate gas exchange via the lungs, which becomes progressively more difficult as the disease progresses. In addition, the lungs are iatrogenic damaged by mechanical positive pressure ventilation, also called ventilator-

induced lung injury (VILI). ECMO, on the other side, can help to relief the lung by the reduction of the baro- and volutrauma.

Refractory ARDS is the main indication for lung replacement therapy. The disease is characterized by a pronounced disturbance of gas exchange. Acute respiratory failure is a potentially life-threatening disease in which massive hypoxia occurs due to various pulmonary or systemic factors through pulmonary inflammatory mechanisms. In many cases, it affects younger patients without significant pre-existing conditions due to severe trauma, pneumonia, aspiration of gastric contents or hemorrhagic shock. If the course of the disease is severe, this may mean that the resulting oxygen deficiency can no longer be managed with conservative therapeutic methods. In addition, invasive ventilation, which is necessary to maintain adequate oxygen levels, causes further damage to the lung tissue (22).

In 2018 the EOLIA study was published in the "New England Journal of Medicine". The study had the indication to estimate whether ECMO therapy for ARDS has a higher survival rate compared to conventional ventilation therapy. Patients with severe ARDS were divided into two groups. It was important that the patients had one of the three criteria for ARDS:

- The ratio of partial pressure of arterial oxygen ($PaO_2$) to the fraction of inspired oxygen ($FiO_2$) < 50mmHg for 3h or $PaO_2$:$FiO_2$ < 80 mmHg or arterial blood pH < 7.25 with partial pressure of arterial carbon dioxide of at least 60 mmHg > 6h.

The primary end point mortality was at day 60. After 60 days, 44 of 124 patients in the ECMO group had died and 57 of 125 patients in the control group who underwent conventional therapy. The complications that occurred during the study were not significantly different. The only two abnormalities were that there was more bleeding and severe thrombocytopenia in the ECMO group.

The researchers made the conclusion that the 60-day mortality rate was not significantly lower with ECMO. This was sobering as many had hoped that this would be the study that would support the positive effect of the ECMO therapy on the mortality in ARDS mortality. (24). However, cross-over to the ECMO group was possible for the patients in the control group with severe ARDS and refractory hypoxemia (28% of the patients).

Including these patients, outcome of the ECMO patients was significantly improved compared with the control group.

Most contraindications are relative and relate to a comparison of risk and potential benefits. There are actually no definitive absolute contraindications, as ECMO is an intensive care procedure that is the last possibility to maintain the patient's vital signs. With both procedures – VV- and VA-ECMO - there are isolated contraindications, but these depend on the situation.

With VA-ECMO, there are relative contraindications if the patient has other diseases that could compress the therapy of ECMO from the beginning (18).

However, in some situations, ECMO therapy can be expected to have a high mortality rate, so there are some relative complications that has to be focused on. One of the most important indication criteria for the use of ECMO is the existence of an exit strategy, i.e. its use as a bridging technique to be able to gain time for a subsequent therapy that is not possible in the acute state. If such a therapy is not in prospect, the use should be questioned.

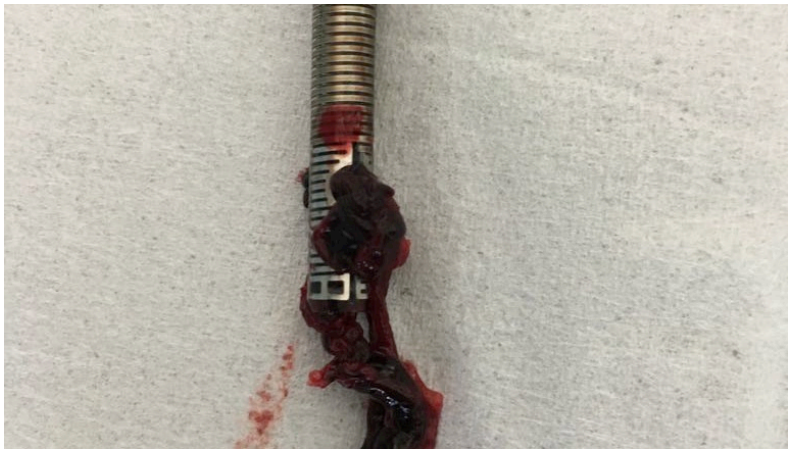
ECMO is a procedure with many complications and is associated with a high mortality rate (table 1). There are different reasons for these relative negative clinical results in the performance of ECMO. On one hand, patients who require ECMO are in a critical condition, whereby the underlying pathology offers a great potential for complications. Furthermore, all the necessary invasive steps for the application of ECMO are of course fraught with complications. Anticoagulation, with its increased likelihood of bleeding, is also a serious source of danger. It should be mentioned, however, that the handling of ECMO systems, which have been further developed over time, has become simpler and safer, so that in general the complication rate in this regard has been significantly reduced. Major bleeding due to new anticoagulation strategies has been significantly reduced as well. Today, it is possible to support patients for weeks or even months with this life-sustaining technique, but the probability of success is significantly lower the longer the patient is on ECMO therapy. For example, a 2016 study by the physician Karagiannidis found that mortality increases with ECMO therapy when it exceeds above day 18 (25).

Typically, the application of ECMO for respiratory support has fewer complications than

the application for cardiac relief. VA-ECMO has a higher complication rate than VV-ECMO and, with the exception of neurological complications, the application in adults are more complicating than the application in children (6).

The most common complication of ECMO use is hemorrhage, which can occur in 10-30% of cases, with a bleeding that lead to the need for surgical intervention. The incidence is higher in VA-ECMO than with VV-ECMO(1). The risk of bleeding is increased due to systemic drug anticoagulation of the blood and can be reduced by reduced heparin administration, administration of platelet concentrates and additional clotting factors.

Hemorrhages in the area of the lungs also occur frequently when ECMO is used. It is therefore important to check regularly for evidence of hemorrhage performing regular bronchoscopies to keep the airways clear. The risk of intracerebral hemorrhage or infarction in patients with ARDS is about 10-15%. In about 43% of all patients who die during ECMO therapy, death is due to intracerebral hemorrhage. Systemic thromboembolism can also occur during therapy due to the formation of thrombi in the extracorporeal circulation. The effects are more severe with VA-ECMO, as the thrombi are directly fed into the arterial circulation in this case (6).



Thrombosis of a cannula

Heparin infusion for correct adjustment of the activated coagulation time and permanent control of the coagulation parameters can reduce the occurrence of this complication.

However, heparin infusion can also lead to heparin-induced thrombocytopenia (HIT). If the condition of HIT has occurred, the heparin administration should be replaced by another anticoagulant (G IIb/IIIa-platelet inhibitor, low molecular weight heparin). Neurological complications are also not uncommon and range from epileptic seizures to intracranial hemorrhages and infarctions. Neonatal patients are particularly affected. The patient group with neurological complications has the highest mortality rate.

# 5. Clinical Data of ECMO in the COVID-19 Pandemic from 2020 up to 2022

As mentioned in the beginning of my Master thesis, I intend to analyze specific clinical data from Lithuania in the following chapter. The clinical data are from the Clinic of Emergency Medicine, Vilnius University Hospital (Vilniaus universiteto ligonine Santaros klinikos) and were collected between 2020 and 2022 in the COVID-19 Pandemic in Lithuania.

54 patients with severe COVID-19 infection were included in the time period between 2020 and 2022 and were treated with a VV-ECMO indicated by a deteriorated pulmonary function due to COVID-19.

The data includes several variables collected from the patients during their stay on the ICU of the hospital. Data includes information about the patient's age, weight and calculated body mass index. Furthermore, it was recorded whether the patients had pre-existing co-morbidities and certain risk factors, such as smoking and obesity, as well as chronic diseases, such as COPD, diabetes, diseases of the cardiovascular system, renal insufficiency or arterial hypertension.

In addition, we collected relevant clinical data of the disease progression as time of symptom onset, time of ICU admission, time of intubation, and time of connection to extracorporeal membrane oxygenation and as well as the calculated interval between the different phases of COVID-19.

Furthermore, the arterial blood gases and ventilatory parameters were recorded before ECMO therapy was started. Thus, the $PaO_2$, $PaCO_2$, pH and $FiO_2$ were measured before ECMO was applied, and whether the patient was given NMBA or received inhalative NO.

In addition, the complications that occurred during therapy in individual patients were listed. These were multi-organ failure, sepsis, renal failure, bleeding, cerebral stroke, as well as gastrointestinal complications and whether the patients had lung problems.

At the end, it is listed whether the patient survived with the therapy of extracorporeal membrane oxygenation and could be weaned from ECMO or died.

Comparing the data from Lithuania with the results in the multicentre study "In-hospital and 6-month outcomes in patients with COVID-19 supported with extracorporeal membrane oxygenation" published in 2022 in the Lancet (26), the results are quite similar (table 2).

The VV-ECMO treated patients in Lithuania with COVID-19 (n=54) were divided in the two groups by the clinical outcome. 17 patients survived (31,5%) and 37 patients (68,5%) did not survive after the treatment of COVID-19 with VV-ECMO.

Comparing the data from Vilnius Lithuania there is a moderate higher mortality and body mass index than in the multicenter study by Larusso et al. (26).

The definitive course and pathomechanism of the systemic disease COVID-19 is still not clear, but interestingly the duration between the onset of the symptoms and the need for intensive care therapy ranged from ten to fourteen days with no difference in the survivor (n=17) or non-survivor group (n=37).

Comparing the two groups (survivor and non-survivor) there were no predictive factors (age, BMI) for the clinical outcome (table 1) especially the calculated oxygenation index (OI), the time of ventilation or the pre-existing comorbidities.

Complications during VV-ECMO showed no difference between the two groups.

The only significant difference could be shown in the time between intubation and the initiation of VV-ECMO ($p<0,05$).

In the published data in Lancet in 2022 there was a definitive limit if the time between intubation and the initiation of VV-ECMO exceeded three days. This suggests that an early initiation of ECMO therapy may offer a higher chance of survival.

Further investigations are needed to find clear and definitive indicators for the timing of ECMO use in COVID-19 disease.

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# Appendix

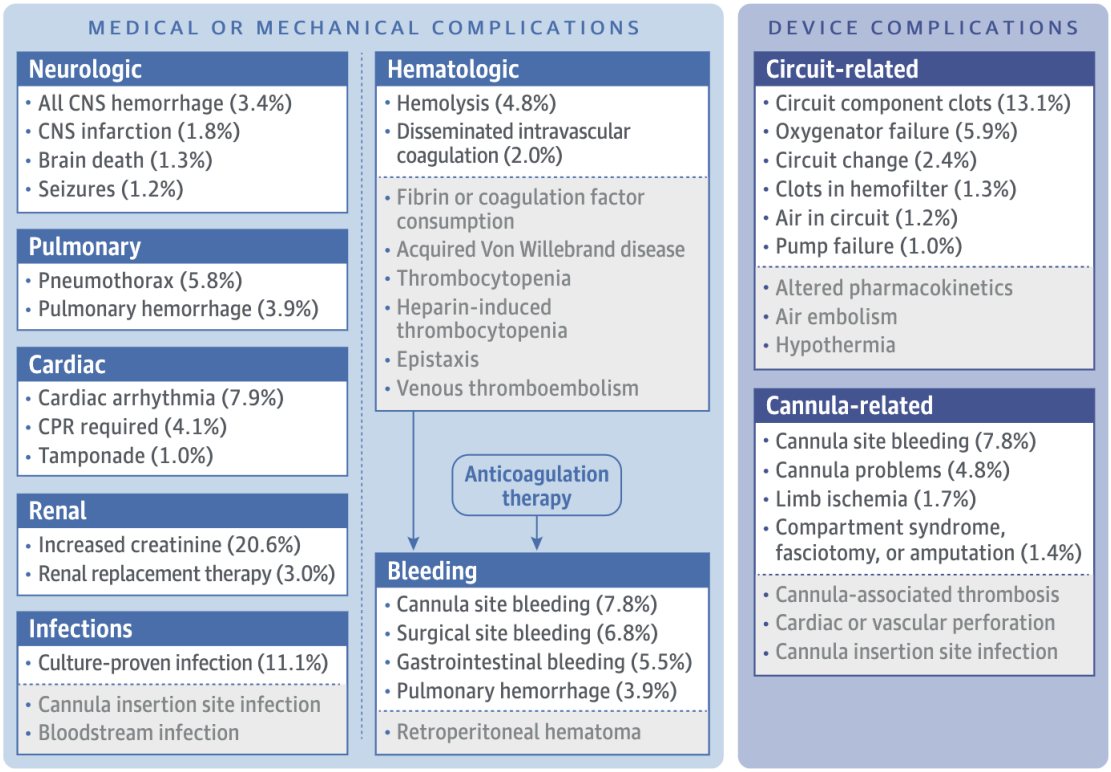



*Table 1, Possible Complications in the use of ECMO, Brodie et al. JAMA 2019*

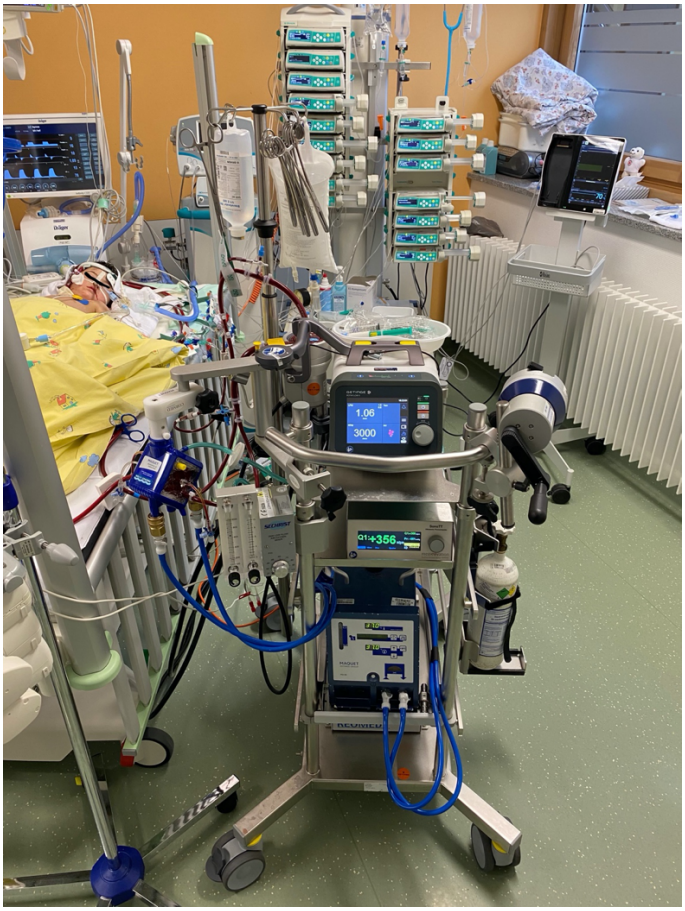
| | All patients (n=54) | In-hospital survivors (n=17) | In-hospital non-survivors (n=37) | P-Value |
|---|---|---|---|---|
| Any complications | 45 (83.3%) | 12 (70.6%) | 33 (89.2%) | |
| Multiorgan failure | 37 (68.5%) | 3 (17.7%) | 34 (91.9%) | |
| Sepsis | 50 (92.6%) | 13 (76.5%) | 37 (100%) | |
| Renal failure | 27 (50%) | 6 (33.3%) | 21 (56.8%) | |
| Major bleeding | 11 (20.4%) | 3 (17.7%) | 8 (21.6%) | |
| Neurological complications | | | | |
| Ischaemic Stroke | | - | - | |
| Haemorrhagic stroke | 1 (1.9%) | - | 1 (2.7%) | |
| Intracranial bleeding | 1 (1.9%) | - | 1 (2.7%) | |
| Seizures | | - | - | |
| Delirium | 6 (11.1%) | 6 (33.3%) | - | |
| Gastrointestinal complications | | | | |
| Bowel Ischaemia | 1 (1.9%) | 1 (5.9%) | - | |
| Gastrointestinal bleeding | 2 (3.7%) | 1 (5.9%) | 1 (2.7%) | |
| Ileus requiring medications | 2 (3.7%) | 1 (5.9%) | 1 (2.7%) | |
| Gastrointestinal Perforation | 2 (3.7%) | 1 (5.9%) | 1 (2.7%) | |
| Respiratory Complication | | | | |
| Pneumothorax or pneumomediastinum | 10 (18.5%) | 2 (11.8%) | 8 (21.6%) | |
| Lung bleeding | 1 (1.9%) | - | 1 (2.7%) | |
| Haemothorax | 7 (13%) | 1 (5.9%) | 6 (16.2%) | |
| Pulmonary superinfection | 19 (35.2%) | 4 (23.5%) | 15 (40.5%) | |
| Pulmonary abscess | 3 (5.6%) | 1 (5.9%) | 2 (5.4%) | |
| HAP or VAP | 38 (70.4%) | 8 (47.1%) | 30 (81.1%) | |
| Weaning of ECMO | 20 (37.1%) | 16 (94.1%) | 4 (10.8%) | |
| ICU length of stay, days | 24.5 (17.0-37.0) | 26.0 (18.0-55.0) | 24.0 (17.0-32.0) | |
| Hospital length of stay, days | 30.0 (20.0-48.0) | 41 (33.0-75.5) | 28 (19.0-28.0) | p = 0.008 |
| Time between onset of symptoms and ICU admission | 10.0 (8.0-14.0) | 10 (9.0-14.0) | 10 (8.0-14.0) | p = 0.786 |
| Time between ECMO and Intubation | 2.0 (1.0-3.0) | 1.0 (0-2.0) | 2 (1.0-3.0) | p = 0.045 |
| Time between ECMO and ICU | 3.0 (1.0-7.0) | 3.0 (1.0-5.0) | 3.0 (2.0-7.0) | p = 0.365 |
| Time between onset of symptoms and ECMO | 14.0 (11.0-19.0) | 13.0 (12.0-21.0) | 16.0 (11.0-18.0) | p = 0.830 |

*Table 2, Data of VV ECMO in Lithuania during COVID-19 Pandemic (Median (Q1-Q3), Incidence (%), Mann-Whitney U-test)*

| | All patients (n=54) | In-hospital survivors (n=17) | In-hospital non-survivors (n=37) | P-Value |
|---|---|---|---|---|
| Age | 50 (39-57) | 47 (34-55) | 51 (40-57) | p = 0.794 |
| Sex | | | | |
| BMI | 33.5 (27.7-40.8) | 37.1 (28.3-41.8) | 32.5 (27.7-38.5) | p = 0.411 |
| Pre-existing comorbidities | | | | |
| Diabetes | 4 (7.4%) | 3 (17.7%) | 1 (2.7%) | |
| Arterial hypertension | 21 (38.9%) | 7 (41.2%) | 14 (37.8%) | |
| Cardiovascular disease | 3 (5.6%) | 2 (11.8%) | 1 (2.7%) | |
| Renal failure | 1 (1.9%) | 1 (5.9%) | - | |
| COPD | 1 (1.9%) | 1 (5.9%) | - | |
| Obesity | 30 (55.6%) | 9 (52.9%) | 21 (56.8%) | |
| Smoking | 2 (3.7%) | 1 (5.9%) | 1 (2.7%) | |
| Pre-ECMO support | | | | |
| Prone Position | 44 (81.5%) | 12 (70.6%) | 32 (86.5%) | |
| Neuromuscular blockade | 52 (96.3%) | 16 (94.1%) | 36 (97.3%) | |
| Inhaled nitric oxide | | - | - | |
| Inotropes | 8 (14.8%) | 2 (11.8%) | 6 (16.2%) | |
| Vasopressor | 45 (83.3%) | 11 (64.7%) | 34 (91.9%) | |

| | All patients (n=54) | In-hospital survivors (n=17) | In-hospital non-survivors (n=37) | P-Value |
|---|---|---|---|---|
| Blood gases before ECMO | | | | |
| pH | 7.36 (7.28-7.46) | 7.33 (7.28-7.44) | 7.37 (7.28-7.46) | p = 0.819 |
| $PaO_2$, mmHg | 62.6 (52.4-74.8) | 62.7 (59.2-67.4) | 62.4 (50.4-75.2) | p = 0.737 |
| $PaCO_2$, mmHg | 50.8 (39.0-66.9) | 52.2 (38.1-69.5) | 49.4 (41.8-59.6) | p = 0.985 |
| $PaO_2/FiO_2$, ratio | 66.8 (55.7-83.5) | 67.4 (59.2-78.4) | 62.9 (55.4-83.6) | p = 0.993 |

*Table 2, Data of VV ECMO in Lithuania during COVID-19 Pandemic (Median (Q1-Q3), Incidence (%), Mann-Whitney U-test)*




*Example of a VV-ECMO, 10-month year old boy COVID-19, Pediatric Intensive Care Unit, Klinikum Kassel*