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REVIEW ARTICLE

Basic Respiratory physiology in the use of ECMO in Critically-ill COVID-19 patients

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The use of ECMO may help sustain extracorporeal life support in cases where regular less-invasive modalities failed to adequately assist the body in maintaining basic life mechanisms. The authors synthesized information from articles found in trusted search engines using predetermined keywords. Typically, VV-ECMO is used in life-threatening respiratory failure. However, experts must consider relative contraindications, answering the question: 'Will the patient really benefit from this treatment, or will it only add emotional and economic burden, also exposing the patient to various risks of complications?'. The physiology of oxygenation within the lungs, tissues, and ECMO machine, is a modification of the basic principles of respiratory physiology. In typical VV-ECMO cannula insertion, drainage cannula is inserted via the right femoral vein percutaneously and is guided upwards through inferior vena cava with its tip 10 cm below cavoatrial junction while the reinjection cannula will be inserted through the intrajugular vein. This places the artificial lungs in series with the normal lungs rather than in a parallel form. The artificially-oxygenated blood was then returned and mixed with the native venous blood. It is important to measure maximum drainage flow to prevent shunting of the veins by setting the ECMO to the highest flow. Frequent complications during ECMO initiation due to critical COVID-19 manifestations include co-infection up to sepsis and coagulopathy up to complications following it. Therefore, it is always beneficial to acquire multidisciplinary judgement, particularly with hematologists, intensivists, and infectious disease specialists prior, during, and post-ECMO use.

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In accordance to how COVID-19 pandemic had swept across the world at an unprecedented rate, resiliency within the healthcare system in all parts of the world, with no exception to critical care, is being tested. During the early days of the pandemic, no prior extensive knowledge about how the virus operates poses as a major obstacle for critical care physicians to practice appropriate actions during critical care. And even on phases of continuation, the fact that SARS-CoV-2 mutates in order to survive, which suggests a possible outbreak such as those found in the alpha, beta, and delta variant, is unsettling. Aggravated by inequity of worldwide vaccine distribution, it is expected that more variants are coming, especially infecting those who are unvaccinated within the community. In the end, the herd immunity we all longed for does not mean total immunity. There will always be people within the community unvaccinated, both may be due to medical restrictions or due to unwillingness to be vaccinated. In both of these 'acute' and 'continuation' phase, our resiliency in knowledge and resourcefulness to continue providing critical care support through all means possible are being put to a test.

In various variants prior to omicron, SARS-CoV-2 was discovered to mainly affect the lower respiratory system, entering the body via hACE-2 (Human Angiotensin Converting Enzyme 2) receptors with prior cleaving by TMPRSS2 (Transmembrane Serine Protease 2), Cathepsin L, or furin.[1] However, new studies reported the possibility that latest SARS-CoV-2 variants predominantly affects the upper respiratory system via endocytosis, thus explaining an increase in incidence of upper over lower respiratory tract symptoms in COVID-19 patients.[2,3] Inoculation was then followed by host immune response, possibly started by the phagocytosis of apoptotic-infected-pneumocytes by antigen presenting cells (APCs) such as macrophages and dendritic cells.[1] As researched in prior coronaviruses, viral particles were then drained into the lymphatic system, sensitising B and T cells and activating adaptive immune response specific towards the pathogen.[4] By purpose, this response isn't fully pathological, unless there are presence of aberrates in multiple inflammatory and thrombotic proteins within the body. Studies had shown that severe COVID-19 infection induces an increase in pathogenic GM-CSF$^+$ Th1 cells, inflammatory CD14$^+$ and CD16$^+$ monocytes, and neutrophil-to-lymphocyte ratio, suggesting that dysregulation of immune response may be the culprit behind critical symptoms shown.[5]

With current knowledge about how different complications emerge according to respective phases within the clinical course, specific care must be directed to control the corresponding underlying cause, in hopes of halting progression of severity.[6] In cases where severe hyperinflammation reaches vital areas such as the heart, lungs, or the circulatory system as a whole, patients may manifest what was considered as 'severe complications', such as sepsis, acute respiratory distress syndrome (ARDS), systemic inflammatory response syndrome (SIRS), and multi-organ failure. Whilst not directly related to treating the underlying cause, the use of extracorporeal membrane oxygenation (ECMO) serves as a provider of temporary cardiopulmonary support for patients experiencing circulatory failure, with or without concomitant respiratory failure.[7] The use of ECMO may help sustain extracorporeal life support in cases where regular less-invasive modalities failed to adequately assist the body in maintaining basic life mechanisms, buying time and expanding the time window for a more extensive administration of treatment from critical care physicians. However, it must be noted that ECMO is a resource and labor-intensive therapy requiring interdisciplinary collaboration between trained healthcare professionals.[8]

MATERIALS AND METHODS

The authors reviewed articles using the keyword "Extracorporeal Membrane Oxygenation", "COVID-19", "Critical Care", "Complications", and "Respiratory Physiology" on reputable trusted search engines such as Google Scholar, PubMed, Cochrane, and Embase. Authors also cited information from ELSO (Extracorporeal Life Support Organisation).

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO)

Evolving progressively fast in the last decade, ECMO has been an invaluable state-of-the-art tool increasingly used by critical care physicians. There are two types of ECMO, all based on sites of insertion and are indicated in different cases; best results are obtained if usage is based on the right indication, right patient, and the right ECMO configuration.[9] In 2020 alone, international use of ECMO reached over 154 thousand runs, mostly run on adults (50%), followed by neonates (29%) and children (20%).[10] Survival rate post-ECLS (extracorporeal life support) reached 69% while survival until

discharge or transfer reached 54%.[10] ECMO works by draining blood from the vascular system, circulating it outside of the body – hence its name, 'extracorporeal' – towards a mechanical pump, then reinfusing it back into the circulation, forming a sealed closed circuit.[9] It works in a similar fashion as the haemodialysis machine, only performing a different function. The mechanical pump effectively works to fully saturate the haemoglobin with oxygen and removing CO_2 prior to reinfusion. Oxygenation, flow rate, and CO_2 elimination can be adjusted within the machine to achieve desired levels of perfusion.[11] The two types of ECMO well known are VV (veno-venous) and VA (veno-arterial) ECMO, used respectively to achieve a different type of extracorporeal life support. The main difference between the two is that VV-ECMO is used solely for lung support while VA ECMO may help support both the lungs and the heart.[12]

INDICATIONS AND CONTRAINDICATIONS

While ECMO by itself does not have an absolute indication, it is typically used in life-threatening conditions such as cardiac failure objectively shown by refractory low cardiac output (< 2L/min/m^2) and hypotension (SBP <90 mmHg), with or without respiratory failure (PaO_2 < 150 mmHg on FiO_2 > 90%).[13] However, in clinical setting, the definition of 'life-threatening condition' is a vague term indescribable by a single marker, which is why initiation of ECMO is best when determined by a group of interdisciplinary physicians whilst considering various biomarkers and clinical conditions case by case.[13] Here are a few indicators to keep in mind, possible to be used as an initiating mark, especially in COVID-19[14]:

- ARDS with or without respiratory acidosis
- COVID-19 induced viral fulminant myocarditis
- Intractable arrhythmias possibly due to respiratory acidosis

Not without risks, ECMO is contraindicated in a few patients, particularly in centres where resource constraints are apparent. With ECMO serving as the last gatekeeper between life and death, there are actually no consensus between experts about absolute contraindications of initiating ECMO except for the do-not-treat request made by patients. However, experts must consider the presence of cumulative relative contraindications, hence answering the question: 'Will the patient really benefit from this treatment, or will it only add emotional and economic burden, also exposing the patient to various risks of complications?'.(15) Each contraindications must be weighted accordingly based on its severity and possibility of recovery. Some experts define these contraindications into 'absolute' and 'relative' according to their implications towards the clinical outcome. For example, young patients with co-infection of endemic bacterial community-acquired pneumonia identified through cultured and tested for sensitivity and well-controlled by antibiotics differs to old patients with end-stage cancer.[15] It is recommended to refrain from ECMO treatment if there is an absolute contraindication or > 3 relative contraindications.[15] 'Absolute contraindications' are as follows:[15]

- Signed refusal / do-not-treat status
- Advanced stage of diseases with severely-reduced life expectancy
- Fatal brain injury / diseases with risks of brain stem-related deaths
- Irreversible destruction of vital organs without option of transplantation
- Relative contraindications are as follows:[15]
- Advanced age (usually > 70 years old, particularly with frailty)
- Severely immunocompromised
- Ventilator-Induced Lung Injury (VILI) for > 7 days
- Haematological malignancies
- Right heart failure (especially on VV-ECMO)
- Scorings: SAPS II > 60, SOFA > 12, PRESERVE ≥ 5, RESP ≤-2, PRESET ≥ 6

PHYSIOLOGY OF EXTRACORPOREAL LIFE SUPPORT

The physiology of oxygenation within the lungs, tissues, and ECMO machine, is a modification of the basic principles of respiratory physiology. Due to severe ARDS being the most prevalent indication to initiate ECMO in COVID-19 patients, we will discuss further about VV-ECMO, a type of configuration specific to support the lungs but not the heart. It is

(1.1) $$CaO_2 = (Hb\ x\ SO_2\ x\ 1.39) + (PaO_2\ x\ 0.003)$$

(1.2) $$CI = CO\ x\ BSA$$

(1.3) $$DO_2 = CI\ x\ CaO_2\ x\ 10$$

(2.1) $$CaO_2 = C_3 = \frac{C_{venous}\ x\ Q_{venous}}{T_f} + \frac{C_{ECMO}\ x\ Q_{ECMO}}{T_f}$$

(2.2) $$Q_B = Q_{ECMO}\left(\frac{C_{ECMO} - C_{venous}}{C_3 - C_{venous}}\right) = Q_{ECMO} + Q_{venous}$$

(2.3) $$DO_2 = (Q_B\ x\ BSA)\ x\ \frac{C_{ECMO}\ x\ Q_{ECMO}}{Q_B} + \frac{C_{venous}\ x\ Q_{venous}}{Q_B}\ x\ 10$$

CaO_2 Content of Oxygen in Blood

Hb Haemoglobin

SO_2 Saturation of Haemoglobin

PaO_2 Partial pressure of Oxygen in blood

CI Cardiac Index

BSA Body Surface area

DO_2 Delivery of Oxygen

Q_B Total Blood flow

C_{ECMO}, Q_{ECMO} Content of Oxygen, Flow in ECMO circuit

C_{venous}, Q_{venous} Content of Oxygen, Flow in venous part of native lung

Figure 1 *Calculating the oxygen delivery using ECMO in a VV-ECMO circuit*

useful to review a little bit about how oxygen is transported throughout the blood. Assuming that oxygen binding capacity is physiologic, we may calculate oxygen content through the following formula 1.1 (Figure 1)

Oxygen content (labeled as C) is a measure of volume of oxygen per a certain volume of blood, usually measured as mL(1)dL^{-1} It is a product of haemoglobin g^1dL^{-1} by SO_2 (%) and maximum oxygen carrying capacity per gram of haemoglobin in adults, usually defined as 1.39 mL^1g^{-1} in physiologic adults. In cases where oxygen carrying capacity is altered due to various factors (gas intoxication, age, etc.), this coefficient may be modified. The second bracket describes volume of oxygen carried by plasma. Due to its very small carrying capacity, this part of the formula is usually omitted during bedside calculations.

Therefore, oxygen delivery per minute (DO_2) measured in $mL^1min^{-1}m^{-2}$ is a product of cardiac index (CI) measured in $L^1min^{-1}m^{-2}$, arterial oxygen content (CaO_2) measured in mL^1dL^{-1} multiplied by 10 to synchronise the units measured. In regards to oxygen delivery and consumption (VO_2), homeostatic mechanisms played a huge role in keeping DO_2: VO_2 (measured in $mL^1min^{-1}m^{-2}$) to a physiologic ratio of 5:1. This condition is sustained as much as possible in extreme conditions such as ARDS, where a decrease in DO_2 occurred due to lung injury combined with an increase in VO_2 occurred due to stress experienced in the body. If this ratio is skewed to a value lower than 2:1, it can be stated that oxygen delivery is inadequate to supply oxygen consumption. Anaerobic metabolism and glycolysis will then be initiated, causing exhaustion and lactic acidosis. In cases where respiratory failure refractory to other forms of invasive ventilator therapies, the patient might be put under extracorporeal life support (ECLS).

Assuming that there is no lung function and no recirculation, total oxygen content (C_1) measured in mL^1dL^{-1} is the mean of both oxygen content times flow post-ECMO machine and native venous blood. Native venous blood is blood that didn't enter the ECMO, flowing through the veins as blood normally would. Total blood flow (Q_B) is a cumulative of ECMO (Q_{ECMO}) and native venous flow (Q_{venous}), also considered as the cardiac output (CO) in VV-ECMO

configuration. Combined, oxygen delivery could be calculated using formula 2.3 (Figure 1). However, the use of complex formulas as these aren't practical in bedside practice, therefore observation of difference between pre- and post-ECMO oxygenator CaO_2 may give a picture to how much DO_2 is given by the machine.

However, it must be noted that recirculation might occur when cardiac output is lower than ECMO flow. In cases where the COVID-19 patient also suffers from any decompensating heart disease, these equations must be altered to include the reduced heart flow.

CLINICAL SETTING: OPERATING VV-ECMO

To operate ECMO in a VV configuration, the operator must first evaluate presence of indications and contraindications within the patient. It is imperative that patients with heart failure be put into VA-ECMO and not VV-ECMO to prevent recirculation, thus partially or completely nullifying therapeutic effects of the machine. The patient must be put under sedation, is paralysed, and his/her definitive airway must be established. Central venous and arterial line must be inserted, allowing haemodynamic monitoring. The operator must plan the circuit based on an estimation of the patients' metabolic rate (3-4 $ml^1kg^{-1}min^{-1}$).

The operator will then insert two types of cannulas into the patients' vessels; one for draining deoxygenated blood and the other for reinjecting oxygenated blood. In double cannulation, drainage cannula is traditionally inserted via the right femoral vein percutaneously and is guided upwards through inferior vena cava (IVC) with its tip 10 cm below cavoatrial junction while the reinjection cannula will be inserted through the internal jugular vein. This places the artificial lungs in series with the normal lungs rather than in a parallel form. The artificially-oxygenated blood was then returned and mixed with the native venous blood. It is important to measure maximum drainage flow to prevent shunting of the veins by setting the ECMO to the highest flow.

Wean the ventilators and adjust sweep gas to keep $PaCO_2$ at 40 mmHg. After the patient stabilises (around 6-12 hours), perform follow-up analysis to calculate DO_2:VO_2 ratio via formula written above. If DO_2:VO_2 is above 3:1, then no changes are needed. If oxygen supply is inadequate and the patient is anaemic, perform transfusion to increase haemoglobin levels. However, if oxygen supply is inadequate and the patient isn't anaemic, change the drainage cannula to a larger size and increase flow. Alternatives include performing targeted temperature management (TTM) and adding another membrane lung.

In moments where SaO_2 began to increase spontaneously without modification in sweep oxygen nor blood flow, operators must be sensitive to lung recovery. An SaO_2 > 95% might indicate the return of native lung function, therefore attempt to wean and decannulate the patient is possible.

COMPLICATIONS

Not risk-free, physicians must also consider complications when initiating the use of ECMO. Meta-analyses recorded frequent complications during ECMO treatment in adults were sepsis (26%), acute renal failure (25%), and multiorgan failure (25%), followed by cannulation-related complications (7%), and central nervous system (CNS) complications (7%).[16]

In real-life clinical setting, co-infection is often considered an unavoidable risk though application of all means of aseptic procedures were tightly monitored. This is due to the location, which is the hospital, and due to the fact that blood is an aseptic matter. Even a single bacteria found during staining may indicate a positive bacteraemia. The hospital is usually a tight-packed building where people with different infections were jammed together into rooms (with no exception, the ICU). Reports showed that co-infections were mostly attributed to *Staphylococcus aureus* (46%).[17] Other reports stated that the most common co-infecting pathogens specific during ECMO usage due to COVID-19 are *Stenotrophomonas maltophilia* (28%), *Pseudomonas aeruginosa* (28%), and *Burkholderia cepacia* (19%).[18] Significant correlation was found between BMI, initial disease severity, and antibiotic treatment prior to admission. If undetected and not treated as early as possible, these co-infections may develop into sepsis and septic shock, therefore increasing ICU mortality.[17]

Coagulation abnormalities were often found due to the superimposed constant injection of heparin or other anticoagulants to prevent clotting over the existing COVID-19-associated coagulopathy.[19] As in haemodialysis, flowing blood through an external tube induces a prothrombic state, creating clots and therefore requiring infusion of anticoagulants. However, the body itself is naturally prone to bleeding due to excessive consumption of

coagulation factors especially in patients with long duration of hospitalisation prior to ECMO initiation.[19] Other complications include thrombosis on cannula, oxygenator, and acute pulmonary embolism.[20] Extracorporeal life support organisation (ELSO) in its COVID-19 interim guidelines recommended operators to follow existing anticoagulation guidelines.[21] It may also be helpful to rinse the cannulas with heparin prior to insertion.[20] Poor management of thrombosis may result in complications such as acute renal failure and other organ dysfunctions.

GLOSSARY

COVID-19	Coronavirus Disease 2019
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
ELSO	Extracorporeal Life Support Organisation
VV	Veno-Venous
VA	Veno-Arterial
SAPS	Simplified Acute Physiology Score
SOFA	Sequential (Sepsis-Related) Organ Failure Assessment
PRESERVE	Predicting Death for Severe ARDS on VV-ECMO
RESP	Respiratory ECMO Survival Prediction
PRESET	Prediction of Survival on ECMO
SO_2	Oxygen Saturation
PaO_2	Partial Pressure of Oxygen
DO_2	Oxygen Delivery
CaO_2	Arterial Oxygen Content
VO_2	Oxygen Consumption

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