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The use of extracorporeal membrane oxygenation (ECMO) for critically-ill COVID-19 patient in clinical setting: A literature review

O uso de oxitenação de membrana extracorpórea (ECMO) para pacientes críticos com COVID-19: Uma revisão de literatura

El uso de oxitenación por membrana extracorpórea (ECMO) para paciente críticamente enfermo con COVID-19: Una revisión de la literatura

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Abstract
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. 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 include co-infection

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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.
Keywords: Extracorporeal membrane oxygenation; COVID-19; Critical care; Complications; Operation.

Resumo
O uso de ECMO pode ajudar a sustentar o suporte de vida extracorpóreo nos casos em que modalidades regulares menos invasivas não conseguiram ajudar adequadamente o corpo na manutenção dos mecanismos básicos de vida. Normalmente, a VV-ECMO é usada em insuficiência respiratória com risco de vida. Contudo, os especialistas devem considerar as contraindicações relativas, respondendo à pergunta: 'O paciente realmente se beneficiará com este tratamento, ou apenas acrescentará carga emocional e econômica, expondo também o paciente a vários riscos de complicações?'. A fisiologia da oxigenação nos pulmões, tecidos e máquina de ECMO é uma modificação dos princípios básicos da fisiologia respiratória. Na inserção típica da cânula VV-ECMO, a cânula de drenagem é inserida através da veia femoral direita por via percutânea e é guiada para cima através da veia cava inferior com sua ponta 10 cm abaixo da junção cavoatrial, enquanto a cânula de reinjeção será inserida através da veia intrajugular. Isto coloca os pulmões artificiais em série com os pulmões normais, em vez de em paralelo. O sangue oxigenado artificialmente foi então devolvido e misturado com o sangue venoso nativo. É importante medir o fluxo máximo de drenagem para evitar o desvio das veias, ajustando a ECMO para o fluxo mais alto. As complicações frequentes incluem coinfecção até sepse e coagulopatia até complicações posteriores. Portanto, é sempre benéfico adquirir julgamento multidisciplinar, particularmente com hematologistas, intensivistas e especialistas em doenças infecciosas antes, durante e pós-uso da ECMO.
Palavras-chave: Oxigenação por membrana extracorpórea; COVID-19; Cuidados intensivos; Complicações; Operação.

Resumen
El uso de ECMO puede ayudar a mantener el soporte vital extracorpóreo en los casos en que las modalidades regulares menos invasivas no lograron ayudar adecuadamente al cuerpo a mantener los mecanismos vitales básicos. Normalmente, VV-ECMO se utiliza en insuficiencia respiratoria potencialmente mortal. Sin embargo, los expertos deben considerar las contraindicaciones relativas, respondiendo a la pregunta: "¿El paciente realmente se beneficiará de este tratamiento, o sólo añadirá una carga emocional y económica, exponiendo además al paciente a diversos riesgos de complicaciones?". La fisiología de la oxigenación dentro de los pulmones, los tejidos y la máquina ECMO es una modificación de los principios básicos de la fisiología respiratoria. En la inserción típica de la cánula VV-ECMO, la cánula de drenaje se inserta a través de la vena femoral derecha de forma percutánea y se guía hacia arriba a través de la vena cava inferior con su punta 10 cm por debajo de la unión cavoauricular, mientras que la cánula de reinyección se insertará a través de la vena intrayugular. Esto coloca los pulmones artificiales en serie con los pulmones normales en lugar de en forma paralela. Luego se devolvió la sangre oxigenada artificialmente y se mezcló con la sangre venosa nativa. Es importante medir el flujo máximo de drenaje para evitar la derivación de las venas ajustando la ECMO al flujo más alto. Las complicaciones frecuentes incluyen coinfección hasta sepsis y coagulopatía hasta complicaciones posteriores. Por lo tanto, siempre es beneficioso adquirir un criterio multidisciplinario, en particular con hematólogos, intensivistas y especialistas en enfermedades infecciosas antes, durante y después del uso de ECMO.
Palabras clave: Oxigenación por membrana extracorpórea; COVID-19; Cuidados críticos; Complicaciones; Operación.

1. Introduction

The rate of how COVID-19 pandemic had swept across the world at an unprecedented rate had resiliency within the healthcare system in all parts of the world, with no exception to critical care, 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 (Suteja et al., 2020). Even on phases of continuation, the fact that SARS-CoV-2 mutates in order to survive, which suggests a possible outbreak such as those in 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 doesn't 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 provide critical care support through all means possible are being put into a test. This article aims to uncover the basic indication and workings of extracorporeal membrane oxygenation (ECMO) as a modality to treat critical COVID-19.

2. Methodology

This study is a narrative review of journal articles and guidelines which reports on SARS-CoV-2 and the use of ECMO to treat critically-ill COVID-19 patients. We searched PubMed and Google Scholar for articles containing the term "SARS-CoV-2", "COVID-19", "ECMO", and "Extracorporeal Membrane Oxygenation" on November 10th, 2022 and synthesized information with the aim to help readers in understanding the use of ECMO in critically-ill COVID-19 patients from a clinical (and not textbook) perspective.

3. Results and Discussion

3.1 SARS-CoV-2

In various variants prior to omicron, SARS-CoV-2 was discovered to mainly affect the lower respiratory system, entering the body via hACE-2 receptors with prior cleaving by TMPRSS2, Cathepsin L, or furin (Yuki et al., 2020). 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 (Glebov, 2020; Menni et al., 2022). 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 (DCs) (Yuki et al., 2020). As researched in prior coronaviruses, viral particles were then drained into the lymphatic system, sensitizing B and T cells and activating adaptive immune response specific towards the pathogen (Channappanavar et al., 2014). 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 (NLR), suggesting that dysregulation of immune response may be the culprit behind critical symptoms shown (Qin et al., 2020).

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 (Calabrese & Calabrese, 2020). 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 (MOF). 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 (Eckman et al., 2019). 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 (Fitzsimons & Crowley, 2022).

3.2 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 three 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 (Makdisi & Wang, 2015). In 2020 alone, international use of ECMO reached over 154 thousand runs, mostly run on adults (50%), followed by neonates (29%) and children (20%) (Extracorporeal Life Support Organization, 2022). Survival rate post-ECLS (extracorporeal life support) reached 69% while survival until discharge or transfer reached 54% (Extracorporeal Life Support Organization, 2022). 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 (Makdisi & Wang, 2015). It works in a similar fashion as the hemodialysis machine, only performing a different function. The mechanical pump effectively works to fully saturate the hemoglobin with oxygen and removing CO2 prior to reinfusion. Oxygenation, flow rate, and CO2 elimination can be adjusted within the machine to achieve desired levels of perfusion (Schmidt et al., 2013). 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.

3.3 Indications and Contraindications

While ECMO by itself doesn't have an absolute indication, it is typically used in life-threatening conditions such as cardiac failure objectively shown by refractory low cardiac output and hypotension, with or without respiratory failure (Gattinoni et al., 2019). 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 (Gattinoni et al., 2019). A few indicators too keep in mind, possible to be used as an initiating mark, especially in COVID-19 are as follows (Ranieri et al., 2012):

- Acute respiratory distress syndrome (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 centers 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-resuscitate (DNR) 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?' (Harnisch & Moerer, 2021). Each contraindication 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 (CAP) identified through cultured and tested for sensitivity and well-controlled by antibiotics differs to old patients with end-stage cancer (Harnisch & Moerer, 2021). It is recommended to refrain from ECMO treatment if an absolute contraindication or > 3 relative contraindications are present (Harnisch & Moerer, 2021). Absolute contraindications are as follows:(Harnisch & Moerer, 2021):

- Signed refusal
- 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:(Harnisch & Moerer, 2021)

- Advanced age (usually > 70 years old, particularly with frailty)
- Severely immunocompromised
- Ventilator-Induced Lung Injury (VILI) in > 7 days
- Hematologic malignancies
- Right heart failure (especially on VV-ECMO)
- Scorings: SAPS II > 60, SOFA > 12, PRESERVE ≥ 5, RESP ≤-2, PRESET ≥ 6.

3.4 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 paralyzed, and his/her definitive airway must be established. Central venous and arterial line must be inserted, allowing hemodynamic monitoring. The operator must plan the circuit based on an estimation of the patients' metabolic rate (3-4 $ml^{1}kg^{-1}min^{-1}$). 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 (CAJ) 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. Wean the ventilators and adjust sweep gas to keep $PaCO_2$ at 40 mmHg. After waiting for the patient to stabilize (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 anemic, perform transfusion to increase hemoglobin levels. However, if oxygen supply is inadequate and the patient isn't anemic, 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.

3.5 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%) (Kim et al., 2021). 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 bacteremia. 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%) (Rozencwajg et al., 2018). 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%) (Yang et al., 2021). Significant correlation was found between BMI, initial disease severity, and antibiotic treatment prior to admission. If undetected and untreated as early as possible, these co-infections may develop into sepsis and septic shock, therefore increasing ICU mortality (Rozencwajg et al., 2018).

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 (CAC) (Yusuff, Zochios, & Brodie, 2020). As in hemodialysis, 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 hospitalization prior to ECMO initiation (Yusuff et al., 2020) Other complications include thrombosis on cannula, oxygenator, and acute pulmonary embolism.(Beyls et al., 2020). Extracorporeal life support organization (ELSO) in its COVID-19 interim guidelines recommended operators to follow existing anticoagulation guidelines (Bhagyalakshmi & Melbourne, 2015). It may also be helpful to rinse the cannulas with heparin prior to insertion (Beyls et al., 2020). Poor management of thrombosis may result in complications such as acute renal failure and other organ dysfunctions.

4. Conclusion

Evolving progressively fast in the last decade, ECMO has been an invaluable state-of-the-art tool increasingly used by critical care physicians. While ECMO by itself doesn't have an absolute indication, it is typically used in life-threatening conditions, a vague term indescribable by a single marker. This makes initiation of ECMO best when determined by a group of interdisciplinary physicians whilst considering various biomarkers and clinical conditions, case by case.

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