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Review Article

Evaluating Extracorporeal Membrane Oxygenation and Ventilation Treatment of Patients with COVID-19: A Review

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Abstract

The prevalence of COVID-19 in the world is rapidly increasing. Although some patients show mild symptoms of the virus, some others need special care due to the exacerbation of the disease. Therefore, invasive treatments are needed to treat these patients. Data were collected from PubMed and Google scholars at various time points up to the 2020 academic year. The related keywords are listed as follows: "COVID-19", "Treatment", "Pathogenesis", and "Lung disorder". Studies have shown that although the use of ECMO and ventilation can provide oxygen to patients and improve their clinical status; these procedures can lead to the activation of inflammatory responses and the activation of the renin-angiotensin system. Inflammation and activation of the renin-angiotensin system are among the weak prognoses for COVID-19-infected patients. ECMO and ventilation treatment procedures are like double-edged swords, and monitoring patients during treatment is essential to prevent renin-angiotensin activation.

Keywords: Coronavirus disease; Extracorporeal membrane oxygenation; ECMO, Ventilation; Lung disorder; Renin-angiotensin system; COVID-19.

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Introduction

Coronavirus disease (COVID-19) is one of the pandemic infections affecting almost the whole world nowadays (1). The virus was first detected in Wuhan, China, in 2019. Although the disease is infecting many people around the world, there is no primary cure for it (2). On the other hand, some people with underlying diseases such as asthma, heart disease, and diabetes have been shown to have increased mortality rates (3, 4). Treatments commonly used to treat COVID-19-infected patients include antiviral drugs, corticosteroids, and supportive therapies (5). Extracorporeal membrane oxygenation (ECMO) and mechanical ventilation are also new therapies that are currently being used in many countries. These two methods increase the oxygen level of patients, as COVID-19 affects the lung and causes pulmonary dysfunction (6). Although these methods can improve the clinical status of patients to some extent, they are associated with some complications and abnormalities in lung function (7, 8). Here, we reviewed the impact of ECMO and mechanical ventilation on the clinical status of patients as well as the possible complications that these methods may have on the lungs of these patients.

Extracorporeal membrane oxygenation

ECMO is used to help patients with acute viral pneumonia associated with Covid-19 when blood oxygenation levels remain low even after ventilation. The WHO Temporary Guidelines for the Management of Covid-19 are general recommendations for the treatment of acute respiratory distress syndrome (ARDS) and in the form of venovenous (VV) ECMO for eligible

patients (9). However, its effectiveness is influenced by the experience and readiness of the intensive care unit. In some cases, patients with concomitant heart failure such as myocarditis, myocardial infarction, and cardiomyopathy may also need to use veno-arterial (VA) ECMO. Precautions on infection control are essential to prevent the further spread of the disease and to keep the medical team and other patients safe. Careful selection of the patient for ECMO is necessary because age and comorbidity change the outcome of the patient with Covid-19. However, several variables, including reversible lung disease, secondary lung infection, and antiviral drugs, and other disease-modifying factors, may affect ECMO results (10). ECMO is extracorporeal life support (ECLS) for people whose lives are at risk due to heart and lung failure (10). The mechanism of action of ECMO is to collect blood from the body, remove CO2, and supply oxygen to RBCs (11). Improvements have been reported in 57% of patients with respiratory failure and 41% of patients surviving with heart failure following ECMO use (12). Complications from ECMO are prevalent, the most common of which are bleeding due to systemic heparinization, platelet dysfunction, and hemodilution of blood clotting factors. Pulmonary hemorrhage is also common, and intracerebral hemorrhage is seen in 10-15% of patients. Hemolysis and systemic thromboembolism are among the rare complications of ECMO, and the rate of neurological complications is reported to vary between 3-47% (13). Also, septic complications are caused by repeated external manipulations of the ECMO circuit and may increase the risk of infection. ECMO may also alter serum concentrations of drugs due to increased distribution volume and decreased renal and hepatic function (14). There is also a possibility of secondary cardiac thrombosis following ECMO treatment (15). In general, although ECMO as a treatment option reduces mortality, almost all patients treated with it suffer from a systemic inflammatory response syndrome (SIRS) (16). When the patient's blood comes in contact with the surface of the circuit outside the body, a variety of coagulation and inflammatory cascades are activated. Platelets can mediate inflammation during ECMO use. The platelets adhere to the fibrinogen absorbed by the circuit, and platelet activation occurs mainly in response to thrombin production. Although the activation of the complement system, and the physical properties of the circuit also play a role. Platelets are also able to form leukocyte compounds, which cause platelet-leukocyte interactions to secrete cytokines and anti-inflammatory monocytes (17). Clinical and empirical evidence suggest that the SIRS mechanism of ECMO is an important event due to the activation of neutrophils and other leukocytes, caused by contact with the outer surface of the circuit, shear stress, the expression of inflammatory cytokines, coagulation, fibrinolytic pathways, and an increase in the concentration of bioactive lipids (18). This process is rapid, during which the activated neutrophils attach to the capillary/venular endothelium and are degranulated to produce cytokines and arachidonic acid metabolites (19). Endothelial dysfunction is associated with poor outcomes in patients, and even without direct contact with the circuit outside the body, it plays an essential role in the inflammatory response during ECMO (20). Changes in the expression of endothelial cell genes lead to the release of pro-inflammatory factors, increased migration of leukocytes, and the penetration of neutrophils, which will lead to lung damage (17). For example, studies have shown that the use of ECMO leads to the expression of genes in endothelial cells that increase their expression can stimulate the immune system due to chemotaxis of immune cells. For this purpose, pdx1 is one of the genes whose expression is increased in endothelial cells during ECMO treatment. pdx1 increases the expression of receptors associated with innate immune stimulatory factors. On the other hand, in addition to pdx1, ICAM, VCAM and VEGF have been shown to increase their expression in endothelial cells (21, 22). Monocytes are also active in response to ECMO, but their activation appears to be slower than that of neutrophils. However, a number of inflammatory cytokines are secreted if monocytes are properly stimulated (23). The rapid increase in plasma concentrations of TNF-α and IL-8 almost

immediately after the onset of ECMO indicates that these cytokines are an essential mediator in the development of ECMO-related inflammation (16). According to the study by Ruan and colleagues, IL-6 concentrations increased steadily during ECMO use and were inversely related to survival (24). This increased concentration in the lung was due to the onset of ECMO and was associated with parenchymal damage. However, those who survived ECMO were able to return the IL-6 concentration to normal (25). In general, according to different studies, the leading cause of death in ARDS patients is organ failure, sepsis, inflammatory cytokines (IL-6, IL-8, IL-10), and immune cells. IL-10 is a significant immune regulator in SIRS or infection caused by pathogens, the level of which in ARDS patients has been linked to disease severity during ECMO. An increase in IL-10 predicts unsuccessful ECMO and death (26). During ECMO, the number and function of lymphocytes decrease significantly. Therefore, the number of lymphocytes should be closely monitored in patients with Covid-19 undergoing ECMO treatment. Finally, it is essential to consider the number of lymphocytes and IL-6 during ECMO to monitor and predict the patient's condition.

Mechanical ventilation

Ventilation is one of the treatment methods that improve the clinical condition of patients to a large extent by exchanging gas and providing sufficient oxygen to patients (27). Since Covid-19 is increased in the lungs of patients and leads to respiratory disorders, ventilation is used to treat them(28). In about 6% of patients, the use of ventilation leads to some side effects. One of these complications is the occurrence of nosocomial infections in patients. Other side effects of the hemodynamic change include loss of balance between intracellular and extracellular fluids and impaired blood pressure (29). However, the activation of the renin-angiotensin system (RAS) and the onset of inflammation appear to be the most severe side effects that may occur in patients infected with Covid-19 after ventilation (30). RAS is one of the body's hormonal networks that play an essential role in regulating blood pressure, establishing homeostasis, and balancing fluid and electrolytes inside and outside the cell (31). This system consists of several components that act against each other. Angiotensin-converting enzyme-2 (ACE2) is one of these components. ACE2 is reported to be expressed on many cells, including the heart, lungs, and kidneys. ACE2 is also one of the main receptors of Covid-19 for entering the cell (32). Recent studies have shown that ACE2 expression increases during ventilation. It has also been shown that by activating the NF-kB pathway and the cells of the immune system, ACE2 produces inflammatory cytokines. It also causes endothelial (EC) dysfunction through the secretion of matrix metalloproteinase (MMPs) and produces reactive oxygen species (ROS) (33).Finally, it should be noted that the ACE2 expression in patients should be considered when using ventilators. This allows the use of the right strategies to reduce the expression of ACE2 and prevent inflammation

Anesthesia agents

The use of general anesthesia for patients admitted to the intensive care unit (ICU) who need ventilation devices is on the rise (34). Some patients infected with Covid-19 require invasive treatments such as intubation or ECMO due to their underlying disease as well as lung involvement (35). Currently, most studies have focused on how to sterilize anesthetics and prevent the transmission of infection. Also, there are some protocols designed to prevent anesthesiologists from getting infected with Covid-19 in the operating room (36). However, no study has been yet conducted on the side effects of the use of anesthetics, whether through inhalation or intravenously. Some anesthetics can cause bronchospasm while some lead to the activation of mast cells and their degranulation (37, 38). Degranulation of mast cells and basophils leads to an anaphylactic shock and shortness of breath. As shown in Table 1, the possible mechanisms of lung dysfunction caused by anesthetic agents are enumerated.

Finally, although anesthetic agents are used for ventilation, some act like double-edged swords and can kill patients by stimulating basophils and mast cells and creating bronchospasm and anaphylactic

shocks. Therefore, assessing patients' sensitivity to anesthesia before surgery can lead to the design of appropriate strategies to prevent these unwanted complications.

Table 1. Summary of potential anaphylactic reaction induction by anesthetic agents.

Type of agents	Human/Animal	Clinical finding	Ref.
Combination sugammadex with desflurane	Human	Interaction sugammadex with circulating rocuronium molecules cause progression of bronchospasm	(39)
Inhalation agents	Human	Use of inhalation anesthesia agents cause reduce risk of bronchospasm reaction	(40)
Combination of dexmedetomidine and midazolam	Human	use of a combination of dexmedetomidine and midazolam compare for dexmedetomidine alone cause reduce bronchospasm reaction	(41)
Ketamine	Human	Ketamine cause mast cell degranulation and anaphylactic reaction	(42)
Combination of sevoflurane and fentanyl	Human	cause increased histamine secretion by mast cell degranulation	(43)
Inhalational anesthesia with rocuronium-sugammadex	Human	Safe and reduce bronchospasm after surgery	(44)

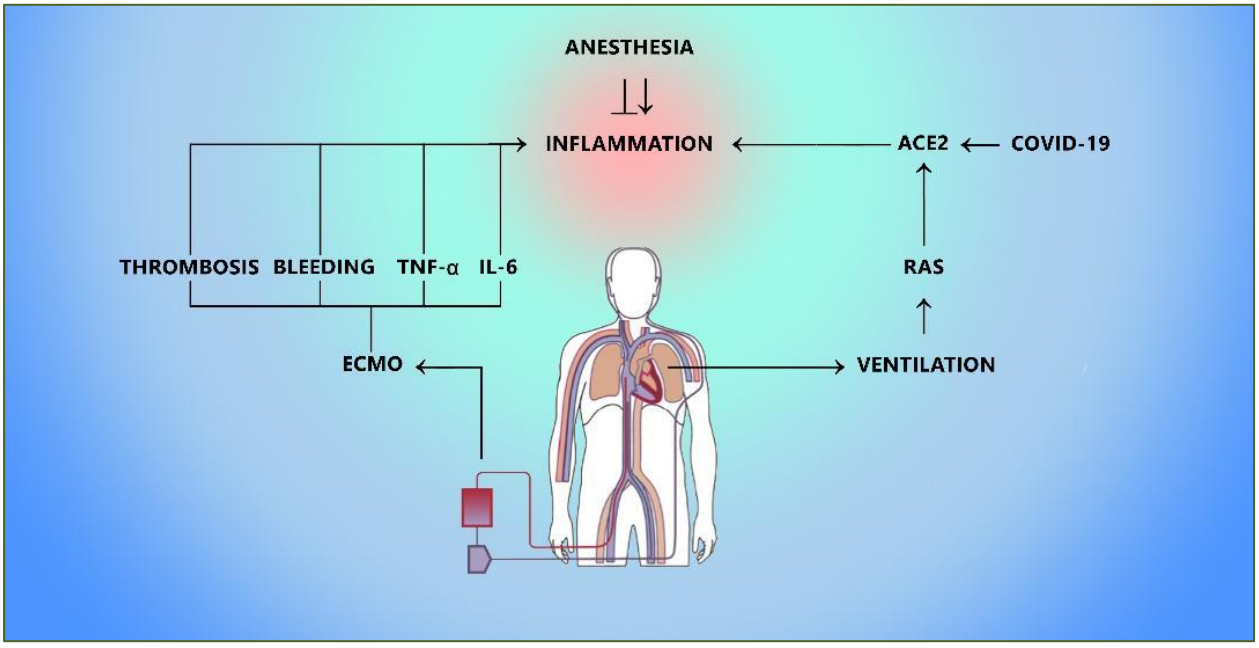

Figure 1. Evaluation of ECMO and Ventilation Therapies for COVID-19 Infected Patients: ECMO and ventilation are used for patients in acute conditions. ECMO leads to many complications, including bleeding, thrombosis, and inflammation due to stimulation of TNF-α and IL-6 production. Ventilation also activates the renin-angiotensin system, which eventually leads to the expression of ACE2. ACE2 is one of the main receptors for COVID-19, which causes the virus to enter the cell. Abbreviation: ACE2: Angiotensin-converting enzyme 2 gene; ECMO: Extracorporeal membrane oxygenation; TNF-α: Tumor necrosis factor-alpha; IL-6: Interleukin 6.

Conclusion

Although the number of patients recovering from COVID-19 is increasing every day, no treatment has so far been found for this disease. Adjuvant therapy for these patients includes ECMO and ventilation. Although ventilation increases the supply of adequate oxygen to patients, it not only

increases the expression of ACE2 in patients' lung cells but also causes inflammatory responses. ACE2 is one of the COVID-19 receptors for entering the cell. Therefore, when treating patients receiving ventilation, it is necessary to assess the level of ACE2 expression in patients' cells and increase their survival by preventing the progression of the disease.

Conflict of Interest

The authors declared that they have no conflict of interest.

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