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Role of Extracorporeal Membrane Oxygenation (ECMO) in COVID 19: A Boom in Treatment

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ABSTRACT:
Maximum physicians endorsed the use of extracorporeal membrane oxygenation (ECMO) support for COVID-19-related acute hypoxaemic respiratory failure patients. Initial investigations of ECMO use in patients with COVID-19 described very high mortality and there have been no large, international cohort studies of ECMO for COVID-19 reported to date. Extracorporeal membrane oxygenation (ECMO) therapy has been around since the 1970s and has completely changed how critical physicians view supportive therapy patient's care. ECMO provides cardio-respiratory support when other treatment therapies fail. In ECMO, different arrangements of cannulae shunt blood to circulate through the machine, and hence oxygenated outside the body. Extracorporeal membrane oxygenation configurations can be simple like Veno-venous and Arteriovenous venous or complex like hybrid cannulation modes and Venopulmonary artery configurations. ECMO is a lifesaving therapy but it is not without complications, patients' selection should be careful and monitoring during the treatment is crucial. This review paper emphasizes on the detail study of ECMO therapy used in COVID-19 patients.
Keywords: Acute respiratory distress syndrome (ARDS), cardiogenic shock, extracorporeal membrane oxygenation (ECMO), hybrid, cannulation, membrane lung, veno-venous extracorporeal membrane oxygenation, veno-arterial extracorporeal membrane oxygenation, clinical outcomes.

Introduction:

Recently corona-virus disease 2019 (COVID-19) caused by severe acute respiratory syndrome corona-virus 2 (SARS-CoV-2) has involved whole world attention for its potentially fatal course and complex clinical manifestations. This virus primarily affects the cardio-respiratory system,

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which can lead to acute respiratory distresssyndrome (ARDS) and shock.[1]Although the studies are ongoing for finding a curative therapyalongside an effective vaccination, the mainstay of management issupportive care at current stage, with a focus on delivering oxygenearly in the disease course.[2]In March 2020, the World Health Organisation (WHO) released interim guidelines that advocate the use of extracorporeal membrane oxygenation (ECMO) to support the cardio-respiratory system in patients who fail maximal conventional therapies with ARDS.[3]Extracorporeal membrane oxygenation (ECMO) therapy has been in the clinical practice since the 1970s and has completely changed how critical care physicians view supportive therapy patients' care. ECMO provides temporary cardio-respiratory support to critically ill patients when maximal conventional support proved to be ineffective[4]. It works by bringing the blood to the inside of the machine where it will be near oxygen allowing gas exchange across a thin membrane (Figure 1)[5].

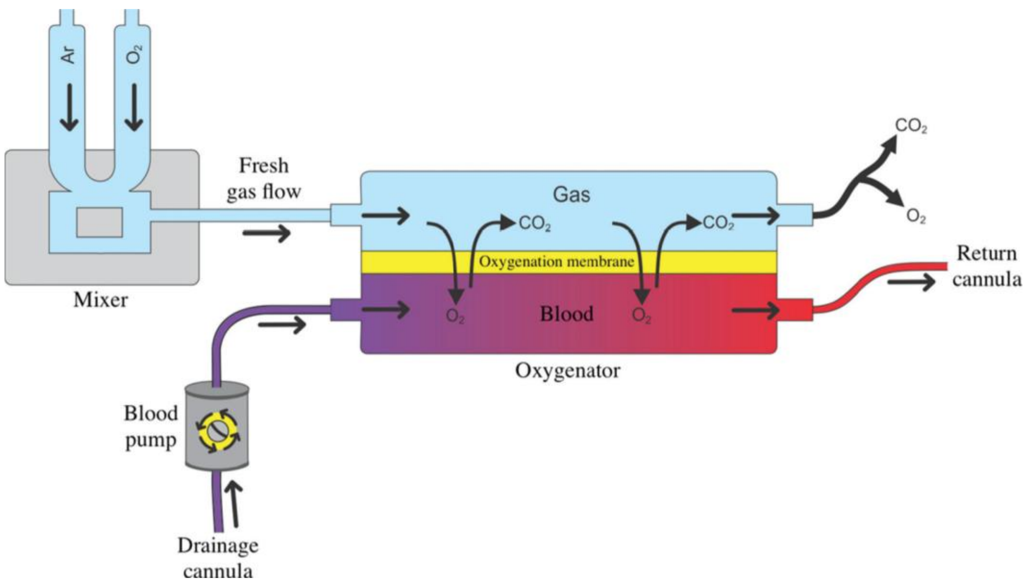

Figure 1.Oxygenator and oxygenation membrane.

The classical ECMO circuit consists of a blood pump, membrane oxygenator, drainage and return cannulae, flow and pressure sensors, heat exchanger for cooling or heating the blood, and arterial and venous access points for the collection of blood in the circuit (Figure 1)[4]. It is used for more than 50 years as salvage therapy for patients with severe cardio-pulmonary failure that is refractory to conventional treatment[6]. In 1972, reported the first successful use of long-term ECMO in an adult with the newly described acute respiratory distress syndrome (ARDS) was reported[7]. The focus of this paper is to provide a concise review of the best clinical practices for the utilization of ECMO in managing pulmonary and cardiovascular failures. Previous pandemics have proven the role of ECMO to support the recovery from severe respiratory and cardio-vascular compromise resulting from ARDS.[8,9] However, the role of ECMO in COVID-19 pandemic and its implications are yet to be understood, discussed and still the research is in progress for the successful treatment.

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Indications:
Four main categories of indications for the use of ECMO includes: hypoxemic respiratory failure, hypercapnic respiratory failure, cardiogenic shock and cardiac arrest.[10]

Contraindications:
No absolutecontraindication to the use of ECMO, but to reduce therisk and to increase the benefit of ECMO, each patient should have individualized ECMO support and riskassessment plans. Themain contraindications include uncontrolled activehemorrhage, incurable cancer, solid organ transplantor immune-suppression, irreversible central nervoussystem dysfunction, and irreversible or end-stage heartor respiratory failure in patients who are not listed astransplant candidates [10].

Hazards:
Although ECMO offers patients a chance of overcoming critical cardio-pulmonary illnesses and improves survival, it is not without significant hazards[4].

Modalities:
The ECMO circuit configurations include VV-ECMO (Figure 2) or as VA-ECMO (Figure 3). In both ECMO modalities, an access route is required for drainage, as well as an access route for the return of the blood to the patient (Figures 2 and 3). Usually, venous accesses are performed percutaneously and are ultrasound guided. The arterial accesses can be performed percutaneously or surgically.[11]

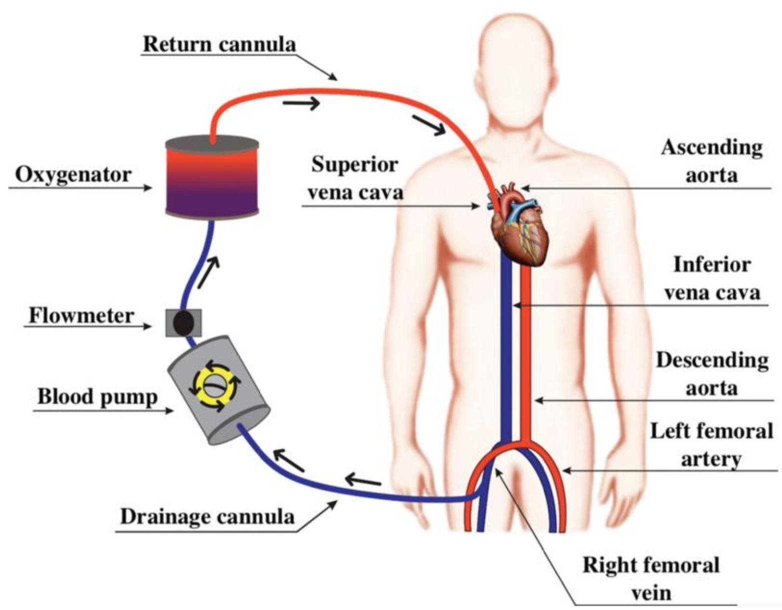

Figure 2.Diagram of a venovenous extracorporeal membrane oxygenation circuit.

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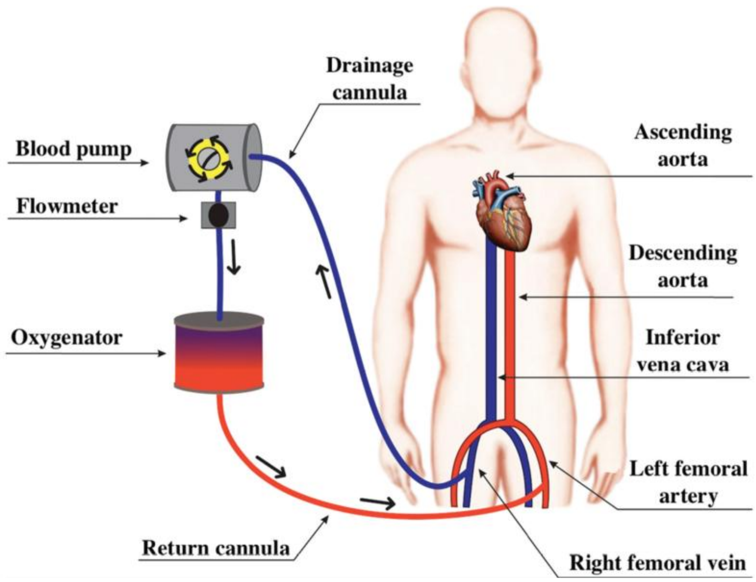

Figure 3.Diagram of a peripheral venoarterial extracorporeal membrane oxygenation circuit.

VV-ECMO:

The principle of VV-ECMO is that the membrane lung (oxygenator) is arranged sequentially with the normal lungs rather than in parallel like with cardiopulmonary bypass (Figure 2). Therefore, the lungs do not have to exert high effort to oxygenate the blood . Using a drainage cannula, blood is drained from the right atrium (RA) and after going through the membrane lung, the newly oxygenated blood is returned to the RA. Because of this, the newly oxygenated blood mixes with the native venous blood and helps provide enough systemic oxygen delivery to meet metabolism needs and preserve the airway even with at rest mechanical ventilation settings. With ventilator settings placed at lower tidal volume, there is less risk of barotrauma.[12]

VA-ECMO:

In this modality of extracorporeal membrane oxygenation the drainage cannula is inserted into venous access and the return cannula into arterial access, thus, a characteristic of VA-ECMO is the exclusion or bypassing of pulmonary circulation (Figure 3)[5].

Clinical Targets:

Utilizing this oxygenation circuit as a supportive therapy, physicians can provide treatment that is more effective for patients with respiratory, cardiac or cardio-pulmonary failure. This is because many of those patients are also on mechanical ventilators, which need to remain at low tidal volume and lower positive end expiratory pressure settings to prevent further destruction of an already damaged lung tissue. This is why ECMO therapy use has drastically increased [13].

Initial Setting:

Setting VV-ECMO:

An initial blood flow by the system of 50 ml/kg/minute of ideal body weight is suggested which is then fine-tuned to maintain the peripheral saturation of hemoglobin measured by pulse oximetry (SpO2) at a level of more than 80%. In addition to this initial value, a determinant

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factor for hypoxemia correction is the ratio between the system flow and native cardiac output, and system flow values of approximately 60% of cardiac output are required to ensure the desired systemic oxygenation of more than 80% is maintained.[11]

Setting VA-ECMO:

An initial blood flow by the system of 30 ml/kg/minute of ideal body weight is suggested and then is adjusted so that the central venous oxygen saturation is more than 70%. The fresh gas flow should be adjusted to maintain the blood pH at close to 7.40 and the partial pressure of carbon dioxide (PaCO2) at 40 mmHg and in a patient with PaCO2 more than 50 mmHg, the reduction must be slow and gradual, not exceeding reduction values greater than 10 mmHg per hour. In a patient with an indication for ECMO due to hypercapnia, it is suggested that initially the blood flow below (1 l/minute) and the fresh gas flow high (15 l/minute), with subsequent adjustment to maintain the blood pH at values at close to 7.40 and PaCO2 at values close to 40 mmHg[11].

Monitoring:

In addition to the routine intensive therapy care, monitoring, special aspects of ECMO parameters should be checked regularly and optimized.

Monitoring the patient

Regarding the patient-side, monitoring control of hemo-dynamics, gas exchange, anticoagulation status, leg perfusion, as well as neurological monitoring is of paramount importance.

Monitoring the device

In terms of device monitoring, pump flow per minute, fresh gas flow and inspiratory O2-fraction, have to be regularly recorded. A multi-professional and inter-disciplinary team of service providers and physicians well skilled in the use of the ECMO system is of extreme importance for the quality and patient-safe ECMO setting[14].

Patient Selection:

Patient selection in VV-ECMO:

The general indications for VV-ECMO ECMO are severe respiratory failure that is refractory to maximal efforts of conventional intensive care and estimated risk of mortality exceeding 80%. The underlying disease should be reversible or the patient should be a candidate for lung transplantation.

Patient selection in VA-ECMO:

VA-ECMO is a highly effective therapy for patients with cardiogenic shock and cardiac arrest. It is also favored as a bridge therapy as various studies have shown that VA-ECMO can have a beneficial effect as a bridge-to recovery therapy in patients with pulmonary hypertension and pulmonary embolism. VA-ECMO also has improved outcomes for post-cardiac surgery patients[15].

ECMO and ARDS:

The use of ECMO for hypoxemic respiratory failure increased very rapidly in the past decade, owing to its success in the H1N1 (Swine Flu) pandemic, CESAR trial and presently in COVID-19 pandemic. Although ECMO's specific role and optimal timing in ARDS and even its effect on the patho-physiology of ARDS have not been fully described, the recently published EOLIA

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trial suggests that ECMO's role in the treatment algorithm for ARDS and certainly severe ARDS should be expanded. The results of the studies suggest that in cases of ARDS, often the final common pathway for lung injuries that cause severe hypoxemia, ECMO should be instituted early, before ventilator-induced lung injury (VILI) occurs and possibly even before the onset of multiple organ dysfunction syndromes[6].

ECMO in Hypercapnic Respiratory Failure:
Hypercapnic respiratory failure (HRF) is defined as chronic respiratory failure characterized by the elevated levels of carbon dioxide in the blood. The main and frequent cause of HRF is chronic obstructive pulmonary disease or long-standing obesity hypoventilation syndrome. Treating this patient, with invasive mechanical ventilation, will lead to complications like dynamic hyperinflation and elevations of intrinsic positive end-expiratory pressure (PEEP); ventilator associated pneumonia and impairment of aerosolized medications delivery[16,17]. Because of these expected complications, ECMO therapy is an excellent supportive therapy for HRF. This has been confirmed with clinical trials, where ECMO therapy improved the prognosis of HRF patients[18].

ECMO in Cardiogenic Shock:
ECMO has been proven to have a good clinical outcome that is comparable to outcomes seen in patients of nonfulminant myocarditis. Cardiogenic shock secondary to acute myocardial infarction is also treated with VAECMO therapy. It offers an advantage over traditional medical therapy with inotropes and vasopressors, in that cardiac output increases without increasing the demand on the myocardial tissue. It also offers the benefit of rapid insertion, biventricular support, and lung rest in cases of simultaneous respiratory failure[15]. Early ECMO therapy initiation in patients with cardiogenic shock secondary to myocardial infarction has demonstrated improved 30-day outcomes in patients[20]. In a different study performed 2 years later, it was confirmed that patients benefited with improved 30-day outcomes and that their 1-year outcome was better with the ECMO therapy[21].

ECMO and Lung Transplantation:
Although there is not enough data to support its usage, there has been a recent increase in the utilization of ECMO as a bridge to lung transplantation. ECMO as a bridge to transplantation is not suited for all the patients. Careful selection of candidate patients is extremely important to optimize resource utilization and provide the best opportunity for transplantation[22].

Weaning:
The decision to remove ECMO support depends on the improvement of organ dysfunctions and resolution of the indication for using ECMO support for a particular patient[5].

Weaning from VV-ECMO:
Weaning from VV-ECMO, due to acute, hypoxemic or hypercapnic respiratory failure, can be initiated when the patient can satisfactorily maintain gas exchange with acceptable mechanical ventilation settings (peak pressure $\leq$ 30 cmH2O, PEEP $\leq$ 15 cmH2O, tidal volume $\leq$ 6 ml/ kg of predicted weight, RR $\leq$ 35 rpm and FiO2 $\leq$ 60%), in combination with improved radiographic parameters and pulmonary compliance[23]. Some institutions perform a spontaneous breathing test for weaning from VV-ECMO, which consists of interrupting the fresh gas flow from the system.

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During the spontaneous breathing test, it is essential that the respiratory and hemodynamic parameters, such as SpO2, RR, end-tidal carbon dioxide (EtCO2), heart rate, and mean arterial pressure, have rigorous monitoring. In patients who remain stable during the autonomy test for up to 6 hours, we perform an arterial blood gas analysis. If the pH and PaO2 are within the target range, we consider the removal of ECMO support.

Weaning from VA-ECMO:
Weaning from VA-ECMO depends on the improvement of cardiac function. Predictors that indicate cardiac function recovery include the maintenance of continuous arterial pulse pressure for at least 24 hours, echocardiography with evidence of recovery of systolic function (ejection fraction of the left ventricle ≥ 20%) and adequate arterial oxygenation. The most routine approach for VA-ECMO weaning consists of the gradual and progressive reduction of the pump flow until the contribution of the circuit to oxygenation and/or cardiac output of the patient is negligible, usually with pump flow values less than than 1 l/minute, Then clamping the arterial and venous circuits for 1 to 2 minutes. The hemodynamic parameters should have close monitoring, and the patient should remain stable during the spontaneous breathing test. An echocardiogram should be repeated after the ECMO circuit clamping. If the cardiac index is maintained at higher than 2.2 l/minute/ m2, with ventricular ejection fraction > 35% and the patient remains stable for at least 24 hours, VA-ECMO can be removed. If there is the impossibility of VAECMO removal, the use of a ventricular assist device, such as bridge-to transplantation should be considered.[24]Ideally, removal of the VA-ECMO cannula should be performed 30 to 60 minutes after discontinuation of heparin. The venous cannula can be removed at the bedside, and the arterial cannulae are usually removed in the operating room.[11]

Hybrid and Complex ECMO configurations:
In addition to the traditional VA and VV ECMO modes, other ECMO cannulation strategies and configurations are increasingly considered during the ECMO course[25]. Triple cannulation can be useful to improve venous drainage or combine both respiratory and circulatory support in the case of combined lung and heart dysfunction (Figure 4)[26]. Veno-Pulmonary artery cannulation is a novel modification of VV ECMO to provide respiratory support in case of right ventricular failure. For LV unloading, both surgical and percutaneous procedures are available. The combination of VA ECMO with intraaortic balloon pump (IABP), Impella, or Tandem-Heart may also be valuable therapies to enhance effective LV or right ventricular unloading (Figure 5)[27].

Complications:
Like any other therapy with vascular access device insertion, ECMO therapy can have complications. These include bleeding, deep venous thrombosis, possible stroke, and infection[28]. Other complications include intravascular catheter breaking with consequent trauma and lost or broken guidewire. With the increased training and use of ultrasound imaging guidance during insertion, these complications are gradually decreasing.[29]

Conclusions:
Literature discussed in this paper focuses on the various aspects of extracorporeal membrane oxygenation therapy used in COVID-19 pandemic. It elaborated details regarding the basic principle, mechanism, indication, contraindication, configurations, vascular access and

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complications. This review will allow the hardworking practicing physicians, pulmonologists and perfusionists to have a growing view and dealing with the present scenario of COVID-19 pandemic for life saving of patients with less complications and mortality rate.

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