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## The expanding role of extracorporeal membrane oxygenation (ecmo) in the covid-19 pandemic

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## EDITORIAL ARTICLE

## THE EXPANDING ROLE OF EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) IN THE COVID-19 PANDEMIC

Coronavirus disease (COVID-19) is an infectious disease caused by a newly discovered coronavirus which has been recognized as global threat with pandemic dimensions (COVID-19 ongoing pandemic) involving until the beginning of June 2020 nearly 6.5 million cases with more than 350,000 deaths worldwide.

Most patients with COVID-19 infection have an asymptomatic or mild respiratory disease, while a small percentage of patients require hospital admission and supportive care with special treatment. Patients presenting with severe acute respiratory distress syndrome (ARDS) are being admitted in ICU receiving advance organ supportive treatment including mechanical ventilation.

However, COVID-19 infection can induce acute respiratory distress syndrome (ARDS), which can progress to refractory respiratory failure. These most critical ill patients with COVID-19 ARDS can exhibit refractory hypoxemia and / or hypercapnia, despite optimal management strategy (including muscle relaxation, prone position, and pulmonary vasodilators) with subsequent remarkable high in-hospital mortality.

In this specific group of critical ill COVID-19 patients, where there is no further treatment option, extracorporeal membrane oxygenation (ECMO) has been considered to have an important role as a rescue therapy in their treatment strategy to increase survival.

Extra-corporeal membrane oxygenation (ECMO) is a form of extra-corporeal life support in which an artificial extra-corporeal circulation system pumps venous blood (ECMO pump) from patient's central vein (inflow cannula) through a metabolic gas exchange system (membrane oxygenator) and return it back to the patient via the return cannula (outflow cannula) restoring metabolic gas physiology (oxygen and carbon dioxide).

During the last decade there has been an exponential increase of ECMO use in clinical practice particularly in those patients with severe ARDS.

The first important randomized clinical study that investigated veno-venous ECMO (VV-ECMO) for ARDS was the United Kingdom (UK) "CESAR" trial in 2009,<sup>1</sup> during the H1N1 epidemics, which has shown a significant benefit in terms of survival. Since then, there has been a worldwide spread of ECMO use with the establishment of ECMO referral centers. In UK in particular, the NHS has approved and sponsored a national Network of 5 Severe Respiratory Failure Centers able to provide ECMO service throughout the UK.

In the same context, another recent multicenter randomized study published later in 2018, the "EOLIA" (ECMO to Rescue Lung Injury in Severe ARDS) trial,<sup>2</sup> aimed to investigate and confirm the ECMO benefits in severe ARDS patients. Although there were no significant differences in mortality (primary end point) between the ECMO treatment arm and the conventional control group, a significant treatment failure was observed in the control arm. This was explained mainly from the cross-over of patients from the control to the ECMO treatment arm demonstrating a significant survival increase.

The above studies and a followed meta-analysis<sup>3</sup> provide supportive evidence that ECMO has an important role and should be considered and used as a rescue therapy in the treatment strategy of ARDS patients when conventional treatment (including protective mechanical ventilation, muscle relaxants, prone position) fails.

At the initial stage of COVID-19 pandemic, there were a lot of concerns and conflicting opinions with regards to safety, feasibility and efficacy of ECMO use in ARDS and the first case reports on March from Wuhan, China and Italy were rather disappointing.

Despite the uncertainties of ECMO beneficial effects in SARS CoV-2 infection, the U.S. Food and Drug Administration (FDA), taking into account the increased COVID-19 ICU mortality and the previous aforementioned positive ECMO results in H1N1 ARDS patients, has issued guidance to provide a policy to help expand the availability of devices used in ECMO therapy. Similarly, the WHO interim guidelines recommended consideration of referring patients for ECMO referral centers with sufficient case volumes to ensure clinical expertise, if there is refractory hypoxemia despite optimal conventional treatment.<sup>4</sup>

The experienced and high volume ECMO referral centers have progressively shown that ECMO service was feasible and can be performed safely in selected COVID-19 ARDS patients with pre-specified criteria mainly based on "EOLIA" or "CE-SAR" inclusion criteria.

Since March, the Extracorporeal Life Support Organization (ELSO) has well organized, structured and promoted a live ECMO registry for all COVID-19 patients being supported with ECMO in order to provide continuous ongoing clinical information of ECMO results in these patients. Although this is an ongoing process and ECMO patients are still being supported, it becomes evident from the already ELSO registry that there was an expansion of ECMO use worldwide (United States, Europe, but also from Asia) in order to address public health emergency with encouraging results.

At the end of May, the ELSO registry for COVID-19<sup>5</sup> demonstrates that there have been registered more than 1000 patients on ECMO with an ECMO decannulation and ICU/hospital discharge rate of more than 50%. Patients are predominantly males, have a median age of 49 years old, remain on ECMO for a median of 11 days and have a prolonged hospital length of stay (23 days). Although these preliminary descriptive data are only indicative, the statistics are really impressive considering the high mortality rate that these patients with similar characteristics would present on conventional treatment.

While awaiting the ongoing accumulating evidence of ECMO use effects in SARS CoV-2 infection, we must highlight the necessary preparation and planning that health-care institution and providers should take over in order to establish an optimal ECMO service from restricted high volume ECMO referral centers for COVID-19 patients keeping up with the strict prophylactic infection measures. Planning actions include personnel high level training, strict adherence to ECMO protocols and algorithms, special equipment availability, multidisciplinary team approach with a coordinated local, regional, and / or national referral protocol in order to reduce ECMO related adverse events and harms and optimize efficacy.<sup>6</sup>

Despite early preventive measures are of paramount importance for COVID-19 pandemic control, it seems also that ECMO service provided from special well-organized ECMO referral centers has an important expanding role as a rescue treat-

ment strategy for COVID-19 ARDS patients refractory to conventional treatment. For the above reasons ECMO should be offered particularly in those patients of younger age with fewer comorbidities.

While aiming to provide constantly an optimal ECMO service for the eligible COVID-19 ARDS patients, we wish and look forward to get the accumulative evidence and more robust data results from this ongoing ECMO clinical indication, which will clarify its definite role in COVID-19 pandemic.

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