JUNE 24, 2020 | VERSION 1.0

WHITE PAPER

ECMO (ExtraCorporeal Membrane Oxygenation) in Covid-19 Disease

Summary of Current Information from Fresenius Medical Care (EMEA Region†)

Jürgen O. Böhm, MD, Priv.-Doz. Dr. med.
Chief Medical and Chief Operating Officer, Xenios AG

Luca Corazza, M. Eng.
Team Lead Therapy Management, Business Development and Marketing, Xenios

ABSTRACT

- ECMO enables gas exchange and circulation, respectively, when standard treatment fails – thus providing clinicians time to treat patients; despite a currently unclear overall benefit ECMO numbers in COVID-19 are increasing rapidly in Europe and USA
- Mortality in ECMO cases reported from China was quite high (94%) and sounded unconvincing compared to other temporary reported experiences from Europe and USA; on the other side, mortality in patients requiring Invasive Mechanical Ventilation is high (ca. 50% and higher) and aligned with severe ARDS mortality rate
- COVID-19 patients have been described being hypercoagulable and with an unusual combination of severe hypoxemia and almost normal lung compliance. Existing therapeutic concepts (e.g. for ARDS) might have to be adapted for COVID-19 as per the above-mentioned peculiarities.
- The patho-physiology of COVID-19 is yet not fully understood. Thus, it is unclear what is caused directly by the virus SARS-CoV2, by the individual immune response or due to inappropriate treatment
- The value of ECMO in COVID-19 will become clear within the next few months, while more consistent data will have been collected and analyzed; in the meanwhile we need to be aware of that SARS-CoV2 will not disappear and the situation remains critical until we have a vaccine, have suitable medication, achieve "herd immunity" with time – if possible at all or we learn to live with SARS-CoV2.

FRESENIUS MEDICAL CARE
Global Medical Office

† Europe, Middle-East, Africa

INTRODUCTION

COVID-19 disease has today spread globally, infecting more than 9.1 million people, with a mortality rate around 5% (472k deaths counted)[1] and an unprecedented stress onto the national health systems, respectively. Despite SARS-CoV2 patho-mechanisms of action are not fully understood and the optimal therapy to heal the lungs is not established, there are already some important facts over pathophysiology and supportive therapies which is worth sharing and to be critically reviewed.

COVID-19 PATHO-PHYSIOLOGY

In a cohort of more than 1000 patients, Guan W et al. investigated the characteristics of COVID-19 patients both in non-severe and severe conditions. It is worth to note that severe COVID-19 patients exhibited signs of multi-organ failure, where Acute Respiratory Distress Syndrome (ARDS) played the predominant role (>15% of severe patients group), followed by Acute Kidney Injury (AKI).[2] None of the above mentioned was present significantly in the non-severe group.[2] Accordingly, the severe group received invasive mechanical ventilation (14.5%) plus also as a rescue support therapy, VV-ECMO (2.9%), while ECMO was practically never used in the non-severe group.[2] Death rate for severe cases only confirmed to be around 8%. Another report from China is based on data from the Chinese Center for Disease Control and Prevention from more than 72.000 cases. This study highlighted some characteristics of the COVID-19 disease with the patient groups between 30 and 80 years of age being the most affected. A small portion of patients (1%) has been asymptomatic, while only 62% of cases are confirmed through viral nucleic acid test result. The remaining 37% of cases are either clinically diagnosed or suspected cases. Among confirmed cases, the vast majority (~80%) is affected only in a mild form. Nevertheless, case-fatality rate in the critical cases from this group is pretty high with 49%.[3]

The lungs are the organs most affected by COVID-19 where the virus accesses host cells via the ACE2 receptor, which is most abundant in type II alveolar cells of the lungs. The virus uses a special surface glycoprotein called a "spike" (peplomer) to connect to the ACE2 receptor and to enter the host cell.[4] The virus also affects the gastrointestinal tract as the ACE2 receptor is abundantly expressed in the glandular cells of gastric, duodenal and rectal epithelium as well as endothelial cells and enterocytes of the small intestine.[5] It can affect people of various age, race and sex but seems to be more associated with male patients and in higher age.[5] The virus can cause myocardial injury and effects the vascular system for which the underlying mechanism is far from being fully understood, respectively.[6] Thus, elevated troponin levels (7-28%) were frequently observed in COVID-19 patients.[6] Rates of cardiovascular symptoms are high and cytokine release during COVID-19 is comparable to cancer patients on immune-modulating therapies. Such inflammatory reaction in conjunction with additional findings like elevated troponin levels combined with new-onset ventricular arrhythmias in the setting of COVID-19 should raise suspicious for myocardits.[6] Thrombotic events appear to be a common complication of this infectious disease with SARS-CoV2, but also a high incidence of thrombocytopenia (36%) and elevated D-dimer levels (46.4%) have been found in ICU patients and are even higher in the most critical cases.[7] More and more data support the idea that COVID-19 patients are exposed to a higher risk of developing coagulation disorders like Disseminated Intravascular Coagulopathy (DIC). These findings and especially the above-mentioned low platelet count may be factors related with a poor prognosis.[8] The International society of Thrombosis and Hemostasis did publish a first guideline document to deal with the complex coagulation disorders for COVID-19 patients; therefore low-molecular weight heparin is recommended to all the patients admitted to the hospital and ICU, who reveal a raise of D-dimers, a prolonged Prothrombin time, reduced platelet count (<100.000µl) or Fibrinogen levels (<2.0 g/l), respectively.[9] This might work as a protective measure to decrease clots and pro-thrombotic COVID-19 activity.[9]

A case series published early results from the Seattle region in USA and outlined that the most common reasons for admission to the ICU were hypoxemic respiratory failure, hypotension requiring vasopressor treatment, or both. Respectively 75% of patients required invasive mechanical ventilation and 71% required vasopressors.[10]

ARDS DEFINITION

Diagnostic criteria for ARDS have changed over time as the learning about the patho-physiology has led to a better comprehension. The international consensus criteria for adult ARDS published in 2012, known as the so called "Berlin definition,"[11] are characterized by the following:

- lung injury of acute onset, within 1 week of an apparent clinical insult and with progression of respiratory symptoms
- bilateral opacities on chest imaging (chest radiograph or CT) not explained by other lung pathology (e.g. effusion, lobar/lung collapse, or nodules)
- respiratory failure not explained by heart failure or volume overload
- decreased PaO_2/FiO_2 ratio (a decreased PaO_2/FiO_2 ratio indicates reduced arterial oxygenation from the available inhaled gas):
  - mild ARDS: 201 – 300 mmHg (≤ 39.9 kPa)
  - moderate ARDS: 101 – 200 mmHg (≤ 26.6 kPa)
  - severe ARDS: ≤ 100 mmHg (≤ 13.3 kPa)

The cardiac function, assessed through ECHO, is generally not affected. Mortality varies widely according to the disease severity, spanning from ca. 27% in mild ARDS to over ca. 40% in the most severe cases.[11]

Invasive Mechanical Ventilation represents still the current gold standard and thus a cornerstone in supporting ARDS-diseased lungs; despite its wide and long-lasting use it is not free from potentially fatal or at least morbid side effects. A landmark review article by Dreyfuss and Saumon from 1998 already showed the potential deleterious and destructive inherent effects of mechanical ventilation on lung tissue in animal lab studies.[12] An off-spring analysis of several CT-scans from ARDS patients' lungs led Gattinoni et al. to the development of the concept that such lungs can be considered functional as "baby lungs," because the remaining ventilated surface equals the lung size of a 5-6 years-old child. In consequence this leads to the hypothesis that the smaller the baby lung is, the more potentially unsafe mechanical ventilation can become.[13] The positive pressure applied during Invasive Mechanical Ventilation brings various side effects, which exacerbate when the therapy is delivered by means of intubation. Intubated patients regularly develop ventilation-associated pneumonia (VAP) as a function of intubation length and they are generally sedated[14] with all related side effects. Invasive Mechanical Ventilation may increase the alveolar/capillary permeability by overdistension of the lungs (volutrauma), it can exacerbate lung damage due to the recruitment/de-recruitment of collapsed alveoli (atelectrauma) and may cause subtle damages due to the activation

of inflammatory processes (biotrauma).[15] Deep sedation results in a consecutive muscles atrophy related to controlled Invasive Mechanical Ventilation.[16] This atrophy is not only related to the diaphragm but also to all other respiratory related muscles during the time Invasive mechanical Ventilation is performed.[16] In addition, various data have indicated a consistent and strong association between early deep sedation and poor long-term outcomes, including mortality, cognitive decline and psychological complications.[17] In summary, the patient undergoing Invasive Mechanical Ventilation is nearly always sedated, immobile and passive, leading to prolonged muscle weaknesses that might even favour re-hospitalizations.[18] However, the current standard therapeutic approach for patients with moderate-severe ARDS comprises the concept of volume restriction, pharmacotherapy inclusive sedation and neuromuscular blockade, lung protective ventilation, prone positioning and escalating to ECMO as a lifesaving support therapy only in case that Invasive Mechanical Ventilation fails.[11]

Based on recent reports about treatment of patients with COVID-19 related lung failure the question arose whether this disease which is fulfilling formally all criteria of ARDS can be regarded as a "common" ARDS or not. According to the emerging knowledge, COVID-19 patients seem to show some peculiarities when it comes to lung injury: the lung mechanics are often well-preserved regards compliance, but there seems to be no direct correlation with the observed severe COVID-19 hypoxemia.[19] Therefore Gattinoni L et al. proposed a classification of COVID-19 patients based on CT-scan examination: type 1 are patients with nearly normal lung function and isolated pneumonia, while type 2 (the most critical version), show as well decreased lung compliance (<40 ml/cmH_2O), a typical sign of severe ARDS cases.[19] It is then suggested, taking into account these differences, to apply different strategies regards respirator adjustments during Invasive Mechanical Ventilation accepting higher tidal volumes in type 1 patients not limited to 6 ml/kg but with PEEP levels kept lower compared to a more strict protective ventilation allowing higher PEEP in conjunction with lower tidal volumes and obligatory prone positioning in the type 2 COVID-19 patients with ARDS.[20]

ECMO FOR LUNG SUPPORT

ECMO (extracorporeal membrane oxygenation), also called ECLS (extracorporeal life support), in its actual application is an evolution of the heart-lung machines used in cardiac surgery and optimized for long-term treatment on ICU. Depending on its configuration, veno-venous or veno-arterial, it is used to support respiratory function, circulation, or both. This treatment provides a bridge, either to a healing of the natural organs or to long-term devices or transplantation. As Warren Zapol, one of the pioneers of respiratory ECMO, pointed out in an editorial in the *New England Journal of Medicine* in 1972, the goal of ECLS is to "buy time" while sustaining an adequate tissue perfusion. However, the first successful use of prolonged life support with a heart–lung machine was conducted by J. Donald Hill already in 1971. The patient was 24 years old and affected by posttraumatic ARDS being supported with ECMO during the acute phase of his disease for 3 days. The patient was eventually weaned from ECLS and did survive.[21] In 1979 nine medical centers joined efforts to start a large multicentric trial to test ECMO versus conventional therapies in acute respiratory failure. The results were disappointing, with just nearly 10 % survival in both groups and no significant difference between ECMO and conventional therapy.[22] ECMO "disgrace" lasted until the results of the CESAR trial have been published. This multicentric study compared once again conventional therapies to VV ECMO support in ARDS and demonstrated with help of a combined primary endpoint consisting of survival and disability at 6 months a significant advantage for the ECMO group[23] (63% in the ECMO group vs 47% in the control group). However, this trial was extensively discussed and also criticized for several design characteristics and thus results should be interpreted carefully. Another consolidation of trust into VV-ECMO therapy came from the H1N1 influenza management; Noah MA, Peek GJ and coworkers observed a significant lower hospital mortality rate among patients referred to an ECMO center to receive this form of support compared to the control group receiving no ECMO (23.7% vs 52.5%).[24]

Through the last 4 decades a lot has changed also from the technological point of view; todays ECMO equipment includes sophisticated, lightweight machine platforms with various safety-enhancing sensors (e.g. air detection, pressure measurement, etc.) and on the disposable side current gas exchangers are designed by far more compact with higher performance than the initial bubble oxygenator, and not to forget the avoidance of plasma leakage related to the advent of polymethylpenthene (PMP) membranes with a functional outer-skin enabling plasma tightness. In addition to that, the frequent use of centrifugal pumps and coated circuits results in less blood trauma, a lower inflammatory response and less coagulation activation which become all important factors for favorably supporting long-term therapy. For VV- and VA-ECMO clinically there are different indications; VV-ECMO has affirmed itself mainly in the severe hypoxic failure in ARDS patients as a rescue measure, finding additional indications as a bridge to lung transplant or in case of sudden respiratory and cardiac collapse or in case of CO_2 retention on mechanical ventilation.[25] VA-ECMO, on the other side, was initially used only as rescue therapy for post-cardiotomy cases with weaning failure; only recently VA-ECMO gained a place outside the operating theater to become an advanced treatment for cardiogenic shock.[26] Another emergency application where VA-ECMO gained a pivotal role as a unique option is that of refractory cardiac arrest; additional indications might be fulminant myocarditis, pulmonary embolism and bridge to transplant or to destination therapy (e.g. VAD, full artificial heart).[26] The development of miniaturized systems and more biocompatible circuits made it possible to bring ECMO everywhere in the hospital, to retrieve patients from hospitals without ECMO facilities or even out of the hospital. This was simply unimaginable just two decades ago. Back to VV-ECMO focus, towards the end of 2018 the results of the long-awaited multicentric EOLIA trial lead by Alain Combes were published. At day 60, in the ECMO group 35% of patients had died compared to 46% in the control group. The relative risk was 0.76, though statistically non-significant (p = 0.087).[27] This was probably related, at least to a certain extent, to the high number of cross-overs (28%) from the control group (mechanical ventilation only) to the VV-ECMO group as a rescue measure. An 11% difference in survival rate was considered by many eminent physicians a clear sign of a relevant clinical benefit for early ECMO compared to conventional care with late rescue ECMO in ARDS. Anyway, intense discussions are still ongoing on the EOLIA trial results; Goligher EC et al. tried to take the topic from a different perspective; running a post-hoc sophisticated Bayesian analysis. They tested various degree of optimistic and cautious assumptions over ECMO efficacy and the results was a posterior probability of mortality benefit (relative risk <1) ranged between 88% and 99%.[28] In consequence these findings led to the point best described by Abrams et al. that the questions is not anymore whether ECMO works or not, but rather when and how should it be used to maximize the benefits at a reasonable cost.[29]

Before COVID-19 the world already faced a similar but fortunately more localized smaller challenge: the Middle East Respiratory Syndrome (MERS) which is caused by another type of coronavirus (MERS-CoV) and is characterized by hypoxemic respiratory failure. Alsharnani MS et al. showed that ECMO used as a rescue therapy was associated with lower mortality in MERS patients with refractory hypoxemia compared to controls treated with Invasive Mechanical Ventilation only (64.7% vs 100%; p 0.020). This small study (17 patients) might be regarded as a basis rationale to support the use of ECMO as a rescue therapy in patients with severe MERS-CoV infection and similar diseases.[30]

ECMO AND COVID-19

So far, most countries are still trying to busy manage the enormous stress put on their Health Systems, respectively, especially from the point of available resources and how to use them most efficiently. Nevertheless, some general statements on the role of ECMO in COVID-19 have been made. ECMO requires, to be deployed correctly, an expert team and a well-established organization within the hospital;[31] therefor this is not a therapy to be rushed and started in a small unexperienced center. It is rather advised and safer to refer patients to high-volume (>30 ECMO runs per year) centers, even if each local entity should take its own decision in agreement with hospital and responsible government/regional organizations.[32] ELSO recommends following strictly EOLIA study criteria to enrol ECMO patients in severe hypoxic cases refractory to any other treatment and renal failure is not regarded as an exclusion criteria,[32] which is an important advice considering the propensity of type 2 COVID-19 patients to develop multi-organ failure. So far the number of VV-ECMO treatments globally has shown a clear raising trend, topping 943 before end of March in Europe only.[33] Most of these European cases are run by La-Pitié Salpétrière Hospital from Paris, which is among those centers having gained extensive experience in ECMO treatments. Currently available numbers of ECMO cases in severely diseased COVID-19 patients from the Euro ELSO COVID-19 Survey cannot be interpreted as 47% of the 943 cases included are still on the device while 23% deceased on ECMO and another 30% have been successfully weaned, thus keeping the chance to reveal better results compared to the cited results in MERS.[33] In China some preliminary data contrast largely with the above mentioned from the Euro ELSO website; Brandon MH wrote a letter to the Editor about the metanalysis conducted on Chinese COVID-19 studies providing ECMO results raising some doubts; out of the 234 ARDS identified cases, only 17 received VV-ECMO and mortality was high (94%) and did not reveal any advantage compared to standard therapy without ECMO. One possible explanation for this unconvincing result might be that ECMO treatment could have been initiated late in the course of the disease in terms of a rescue measure only and thus having started too late to provide any relevant impact on the course of the patients' disease. However, detailed data regards the individual patients' situation, the start of each ECMO and the disease course are unavailable.[34] In contrast positive findings about ECMO in COVID-19 came also from the first published and successful North American ECMO case, where a patient was treated for multi-organ failure, requiring approx. 8 days of ECMO therapy concomitant to a forceful pharmaceutical treatment of the underlying inflammatory component in COVID-19.[35]

CONCLUSIONS

The value of ECMO in COVID-19 will certainly become more precise within the next few months, especially as treatment numbers are further raising rapidly. There are positive findings suggesting patient benefit, but it is rather too early to draw final conclusions. ARDS in a certain percentage of severely-ill COVID-19 patients is equivalent to what we knew before and given treatment standards remain valid but we have to accept that there might be another group of severely diseased patients who require a modified more suitable therapeutic approach. However, we learned that some facets in COVID-19 are different and a comprehensive understanding of the COVID-19 inherent patho-physiology inclusive long-term outcome will probably take months and years; this might have an impact on treatment and mortality and potentially on our future way of living.

Meet Our Experts

JÜRGEN O. BÖHM, MD, PRIV.-DOZ. DR. MED.
Chief Medical and Chief Operating Officer, Xenios AG

Jürgen Böhm serves as Chief Medical and Chief Operating Officer at Xenios AG. Prior to the Fresenius Medical Care acquisition he covered various senior management positions within former companies Novalung GmbH and Medos Medizintechnik AG (today both incorporated within Xenios AG as legal entity). From background he is a board certified cardiac surgeon with 14 years of clinical practice. During another 14 years of activity in Medical Device Industry he spent about 8 years with Xenios providing expertise and leadership in expanding extracorporeal life support therapies beyond the well-known ECMO application.

LUCA CORAZZA, M. ENG.
Team Lead Therapy Management, Business Development and Marketing, Xenios

Luca Corazza is trained as a Biomedical Engineer. He joined Fresenius Medical Care in 2018 bringing solid expertise in various extracorporeal therapies markets. After a few months he started to support Xenios Heart&Lung business, providing marketing knowledge within competitor analysis and market potentials estimations.

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Fresenius Medical Care Deutschland GmbH
61346 Bad Homburg v. d. H., Germany
+49 (0)6172-609-0 | FreseniusMedicalCare.com

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Global Medical Office