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Extracorporeal Membrane Oxygenation for Critically Ill Patients with COVID-19–related Acute Respiratory Distress Syndrome: Worth the Effort?



To the Editor:

According to Chinese and Italian reports, 15–42% of patients with coronavirus disease (COVID-19) develop acute respiratory distress syndrome (ARDS), with a 60% mortality rate (1–3). Venovenous extracorporeal membrane oxygenation (VV-ECMO) is therefore considered a rescue therapy to be used in the most severe ARDS, as recommended by the World Health Organization's interim guidelines for the management of patients with COVID-19 (4). However, without a significant impact on mortality, the benefit of ECMO in ARDS remains controversial (5). Generally, only few data on the use of ECMO in the present pandemic are available (1, 2) with a short follow-up (6, 7). However, accurately selecting patients with COVID-19–related ARDS, who may be good candidates for ECMO support, is important during a pandemic characterized by limited medical resources.

Methods

We prospectively included all patients referred to the five ICUs of the Strasbourg University Hospital, between March 3 and April 1, 2020, for severe ARDS due to COVID-19 (confirmed by RT-PCR test), and that had been supported by ECMO after failure of optimal medical treatment, including neuromuscular blocking agents, protective ventilation, and high positive end-expiratory pressure (PEEP). According to EOLIA (ECMO to Rescue Lung Injury in Severe ARDS) criteria (5), patients were eligible for ECMO if they developed a refractory ARDS defined by a $Pa_{O_2}/Fi_{O_2} < 80$ mm Hg or a $pH < 7.25$ with a $Pa_{CO_2} > 60$ mm Hg for more than 6 hours with a $Fi_{O_2} > 80\%$, despite low-pressure ventilation strategies and no participation of fluid overload. The contraindications for ECMO implantation were an age older than 70 years and severe comorbidities, including severe chronic respiratory failure, severe cardiac failure, and Child Pugh C cirrhosis. Invasive

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Table 1. Clinical Presentation and Clinical Outcomes of ECMO Patient Population (*N* = 17)

Characteristics	Patients (<i>N</i> = 17)
Age, yr	56 (30–76)
Sex, M	16 (94.1)
Obesity	10 (58.8)
Hypertension	9 (52.9)
Diabetes	3 (17.6)
Antiviral treatment	
Lopinavir-ritonavir	9 (52.9)
Hydroxychloroquine	8 (47.1)
Corticosteroid	8 (47.1)
Days of ventilation before ECMO implantation	4 (1–17)
SOFA score at implantation	8 (3–15)
Respiratory parameters and adjunctive therapeutics at ECMO implantation	
Neuromuscular blockade	17 (100)
Prone positioning session before implantation	16 (94.1)
Inhaled nitric oxide	5 (29.4)
$F_{I_{O_2}}$, %	100 (50–100)
$P_{a_{O_2}}/F_{I_{O_2}}$ ratio, mm Hg	71 (52–134)
Sa_{O_2} , %	90 (79–99)
V_T , ml/kg of predicted body weight	5.9 (3.5–7.1)
Respiratory rate, breaths/min	31 (20–35)
PEEP, cm of water	14 (11–16)
Plateau pressure, cm of water	29 (20–37)
Driving pressure, cm of water	15 (7–23)
Compliance, ml/cm of water	26 (17–55)
Oxygenation index, cm of water/mm Hg	29 (14–39)
Respiratory parameters under ECMO	
Sa_{O_2} , %	97 (92–100)
V_T , ml/kg of predicted body weight	3.9 (1.7–6.1)
Respiratory rate, breaths/min	20 (10–26)
PEEP, cm of water	12 (8–16)
Plateau pressure, cm of water	26 (20–39)
Driving pressure, cm of water	14 (8–23)
Prone positioning session during ECMO	0
Anticoagulation with unfractionated heparin	17 (100)
Respiratory parameters at ECMO weaning	
$P_{a_{O_2}}/F_{I_{O_2}}$ ratio, mm Hg	177 (53–281)
PEEP, cm of water	10 (5–15)
Plateau pressure, cm of water	26 (12–31)
Driving pressure, cm of water	15.5 (4–24)
Compliance, ml/cm of water	29.5 (11–61)
Oxygenation index, cm of water/mm Hg	10 (5–25)
Evolution at follow-up	
Mortality at day 60	6 (35.3)
ICU discharge at day 60	10 (58.8)
Adverse effect under ECMO	
Hemorrhagic shock	1 (5.9)
Bleeding leading to transfusion	6 (35.3)
Transfusion of packed red blood cells, units	4 (0–26)

(Continued)

Table 1. (Continued)

Characteristics	Patients (<i>N</i> = 17)
Thrombopenia leading to transfusion	1 (5.9)
Cardiac tamponade	1 (5.9)
Stroke	1 (5.9)
Thrombophlebitis or pulmonary embolism	3 (17.6)
Oxygenator thrombosis	2 (11.8)
Ventilator-associated pneumonia treated with antibiotics	10 (58.8)
Renal replacement therapy	12 (70)
Gas embolism	0

Definition of abbreviations: ECMO = extracorporeal membrane oxygenation; PEEP = positive end-expiratory pressure; SOFA = Sequential Organ Failure Assessment.

Data are reported as either median (range) or *n* (%). Percentages may not total 100 because of rounding. Obesity is defined by a body mass index (weight divided by the square of the height) ≥ 30 kg/m². Organ failure was assessed with the SOFA on a scale from 0 to 24, with higher scores indicating more severe organ failure. The driving pressure is the difference between plateau pressure and PEEP. The compliance is the V_T divided by the driving pressure. The oxygenation index is mean airway pressure $\times F_{I_{O_2}} \times 100/P_{a_{O_2}}$. Hemorrhagic shock was defined as hemorrhage leading to more than five units of packed red cells during 1 day and associated with hypotension.

mechanical ventilation for more than 7 days was a relative contraindication.

This study was approved by the institutional ethics committee of the Strasbourg University Hospital (ClinicalTrials ID: NCT04343404). Informed consent was waived as part of a public health outbreak investigation. SAS version 9.4 (SAS Institute) was used for all statistical analyses. Continuous variables are presented as median and ranges and were compared using nonparametric signed rank tests.

Results

Seventeen patients (4.5% of all those with ARDS admitted to our hospital's ICUs during the study period, *n* = 377) were supported by ECMO. The clinical presentation, ICU therapies, and outcomes are shown in Table 1. At the time of ECMO implantation, median $P_{a_{O_2}}/F_{I_{O_2}}$ was 71 (52–134) mm Hg and Sequential Organ Failure Assessment score was 8 (3–15). Sixteen patients had been prone positioned before ECMO implantation.

Sixteen patients were supported with VV-ECMO (12 Avalon cannula and 4 jugulofemoral cannulations). One was supported with venoarterial femorofemoral ECMO because of respiratory failure complicated by cardiogenic shock due to pulmonary embolism. All patients were eligible for ECMO because of a $P_{a_{O_2}}/F_{I_{O_2}} < 80$ mm Hg (*n* = 16) or blood pH of < 7.25 with a $P_{a_{CO_2}}$ of at least 60 mm Hg for more than 6 hours (*n* = 1). The median blood flow was 4 (0–6) L/min. In accordance with the French Society of Hematology's recommendations for patients with COVID-19, all patients were treated with therapeutic dosing of unfractionated heparin (anti-Xa 0.5–0.7 UI/ml) (8).

After ECMO implantation, the median V_T was significantly decreased from 5.9 to 3.9 ml/kg ($P < 0.01$) and PEEP from 14 to 12 cm of water ($P < 0.02$) with a lower plateau pressure:

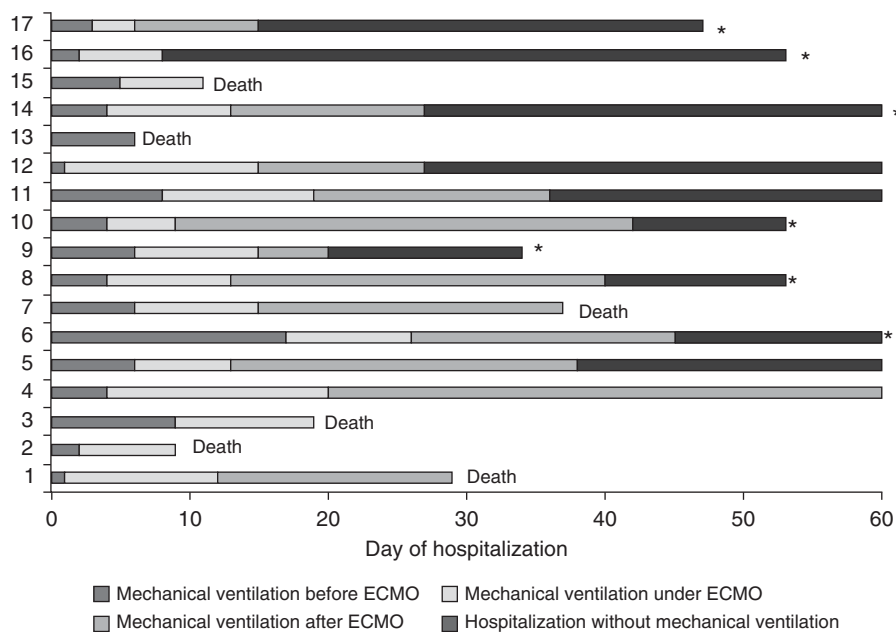


Figure 1. Outcomes for individual patients included in the case series. After 60 days of follow-up, six patients (35.3%) had died. All survivors except one had been weaned from mechanical ventilation and discharged from the ICU. Three (17.6%) patients were still hospitalized, and seven patients were discharged from the hospital (*). ECMO = extracorporeal membrane oxygenation.

26 (12–31) versus 29 (20–37) cm H₂O ($P < 0.05$). The median duration under ECMO was 9 (0–16) days. After weaning ECMO, the median oxygenation index decreased compared with the day of ECMO implantation (10 [5–25] vs. 29 [14–39] cm H₂O/mm Hg; $P = 0.01$), indicating better oxygenation. Compliance also increased from 26 (17–55) to 29.5 (11–61) ml/cm H₂O ($P = 0.05$).

Under ECMO, six patients had bleeding complications requiring transfusion. Most of the complications (in 5/6 patients, 83.3%) were due to bleeding at site of cannula insertion, and one was the result of a gastrointestinal bleeding. Despite therapeutic dosing of unfractionated heparin, we observed three oxygenator thromboses in two patients, and four patients developed thrombotic or ischemic complications under ECMO (Table 1).

At day 60, six patients (35.3%) had died and only one (5.9%) patient was still in the ICU receiving mechanical ventilation. All 10 (58.8%) patients discharged from the ICU were weaned from mechanical ventilation, and among them, 7 (41.1%) patients were discharged from the hospital (Figure 1).

Discussion

VV-ECMO facilitated protective ventilation with decreased plateau pressure, respiratory rate, and V_T in patients with COVID-19 with refractory ARDS. Compared with the EOLIA study, only a single patient was cannulated for indication related to pressure and the ECMO duration was shorter overall, which might be linked to the specificity of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-induced lung damages (9). To date, according to our usual strategy, no prone positioning procedure was realized under ECMO, the pandemic-induced work overload being also a limitation.

ECMO support is associated with an increased risk of both thrombotic and hemorrhagic complications. Considering the high risk of thrombotic complications in patients with severe COVID-19, we chose higher anticoagulation targets for all of our patients than usual, even if most of them were under VV-ECMO. Indeed, a high proportion of patients with COVID-19 developed life-threatening thrombotic complications. In an autopsy series (9), most of the patients were diagnosed with deep vein thrombosis or pulmonary embolisms. Furthermore, we have recently demonstrated that despite anticoagulation, patients with ARDS related to COVID-19 developed more thrombotic complications, secondary to the major systemic inflammatory response along with endothelial dysfunction (10). Furthermore, although 35.3% of the patients required blood transfusion, only one (5.8%) has developed hemorrhagic shock. Considering the high risk of thrombotic events in patients with COVID-19, we suggest that a therapeutic anticoagulation may be considered. Otherwise, despite higher targets of anticoagulation, we failed to prevent oxygenator thrombosis, requiring an urgent switch of the circuit. Indeed, only 7% of the circuits were changed in the EOLIA study because of clotting, compared with 12% in our cohort. Thus, the thrombotic complications seem to be more life-threatening than the hemorrhagic ones.

Considering the high frequency of severe adverse events, ECMO should probably remain a rescue therapy and therefore be undertaken only in ECMO-expert centers with adequate resources. In our cohort, one patient did indeed die during cannulation secondary to a cardiac tamponade.

The main strength of our study is to prospectively describe the clinical course of patients with COVID-19 who required ECMO, particularly as only few data are available. Our results are however limited by their single-center character.

In conclusion, although VV-ECMO is burdened with a high rate of life-threatening complications, it might be considered as a

rescue therapy in refractory COVID-19 ARDS. In addition, an adequate higher level of therapeutic anticoagulation than usual should probably be considered. ■

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Sonographic B-Lines, Fluid Resuscitation, and Hypoxemia in Malawian Patients with Suspected Sepsis



To the Editor:

The optimal approach to fluid resuscitation for patients with sepsis is uncertain. Data from sub-Saharan Africa have indicated

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