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Early Initiation of Venovenous Extracorporeal Membrane Oxygenation for Critically Ill COVID-19 Patients

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Abstract: The optimal timing for initiating extracorporeal membrane oxygenation (ECMO) after starting mechanical ventilation has yet to be clarified. We report herein the cases of two patients with coronavirus disease 2019 (COVID-19) acute respiratory distress syndrome (ARDS) who were successfully managed with an early ECMO induction strategy. Case 1 involved a 64-year-old man admitted in respiratory distress with polymerase chain reaction–confirmed COVID-19. On day 5 at hospital, he was intubated, but oxygenation remained unimproved despite mechanical ventilation treatment with high positive end-expiratory pressure (PEEP) (PaO_2/FiO_2 [P/F] ratio, 127; Respiratory ECMO Survival Prediction [RESP] score, 4). ECMO was initiated 4 hours after intubation, and stopped on day 16 at hospital. The patient was discharged from hospital on day 36. Case 2 involved a 49-year-old man who had been admitted 8 days prior. He was intubated on hospital on day 2. High PEEP mechanical ventilation did not improve oxygenation (P/F ratio, 93; RESP score, 7). ECMO was stopped on hospital on day 7 and he was discharged from hospital on day 21. The strategy of early initiation of ECMO in these two cases may have minimized the risk of ventilation-related lung injury and contributed to the achievement of favorable outcomes. **Keywords:** COVID-19, extracorporeal membrane oxygenation, early initiation, indication, acute respiratory distress syndrome. *J Extra Corpor Technol. 2022;54:79–82*

Patients with coronavirus disease 2019 (COVID-19) often present with acute respiratory distress syndrome (ARDS) and require mechanical ventilation. Some severely ill patients need the support of extracorporeal membrane oxygenation (ECMO). Relative indications for initiating ECMO have been suggested as a PaO_2/FiO_2 (P/F) ratio <150 under mechanical ventilation with a positive end-expiratory pressure (PEEP) ≥10 cmH_2O with additional treatments such as placement in a prone position, nitric oxide inhalation, and recruitment maneuvers, while a P/F ratio <60 has been determined as an absolute indication for ECMO (1).

The optimal timing of ECMO initiation following the start of mechanical ventilation has not yet been established. The Extracorporeal Life Support Organization recommends initiation of venovenous ECMO for patients with H1N1 influenza-induced ARDS within 6 days of intubation (2). Combes et al. reported that patients who received ECMO under conditions of P/F ratio <50 for >3 hours, P/F ratio <80 for >6 hours, or arterial blood pH <7.25 with partial pressure of CO2 < 60 mmHg for >6 hours displayed favorable prognosis (3). Although some reports have suggested that early induction of ECMO in patients with severe ARDS provides better outcomes compared to conventional ventilatory management (4–9), some patients reportedly display favorable prognosis without ECMO (10). Thus, arguments remain regarding the most appropriate timing for introducing ECMO to ARDS patients with COVID-19.

Herein, we report two cases of COVID-19 ARDS that were successfully managed with early initiation of ECMO.

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DESCRIPTION

Case 1

A 64-year-old man with a history of smoking (Brinkman index, 800–1,200) and a past medical history of atrial fibrillation and hypertension was admitted to our hospital because of mild respiratory distress with polymerase chain reaction–confirmed COVID-19.

On examination, body temperature, heart rate, blood pressure, respiratory rate, and oxygen saturation were 38.5°C, 84 beats/min, 140/86 mm Hg, 16 breaths/min, and 95% on room air, respectively. On day 5 at hospital, the patient showed severe hypoxia (PaO_2, 65.3 mm Hg with O_2 at 10 L/min via mask) and was intubated. Although mechanical ventilation support with high PEEP (pressure-controlled synchronized intermittent mandatory ventilation with pressure support ventilation mode; FiO_2, 0.6; respiratory rate, 15 breaths/min; PEEP, 15 cmH_2O; and driving pressure, 6 cm H_2O) was needed to maintain oxygen saturation, oxygenation showed no improvement. Arterial blood gas analysis showed the following results: PaO_2, 76.3 mm Hg with FiO_2 0.6; PEEP, 15 cmH_2O (P/F ratio, 127; Respiratory ECMO Survival Prediction [RESP] score, 4). Computed tomography (CT) of the chest showed bilateral diffuse high-density shadows with consolidation (Figure 1). We decided to initiate ECMO 4 hours after starting mechanical ventilation with high PEEP. Venovenous ECMO was administered through the right femoral vein for blood drainage with an HLS® 29-Fr, 55-cm long, BIOLINE-coated cannula (Getinge, Rastatt, Germany), and through the right internal jugular vein for blood infusion with a 25-Fr, 38-cm long BIOLINE-coated cannula, both inserted under fluoroscopic guidance. ECMO was managed using a UNIMO-assisted circulation unit (Senko Medical Instrument Mfg. Co., Tokyo, Japan). Heparin and nafamostat mesylate (6'-amidino-2-naphthyl-p-guanidinobenzoate dimethanesulfonate; 20–50 mg/h) were continuously infused to achieve an activated clotting time between 160 and 200 seconds and an activated partial thromboplastin time between 40 and 60 seconds.

The patient was stabilized by ECMO intervention with adjunctive mechanical ventilation using a lung-protective strategy (FiO_2, 0.4; respiratory rate, <12 breaths/min; PEEP, 15 cmH_2O to achieve $PaO_2 > 80$ mmHg with low tidal volumes; positive inspiration pressure <20 cmH_2O). A prone position was also implemented safely from day 8 to day 11 after introducing ECMO. PaO_2 and lung compliance gradually improved within 72 hours of prone ventilation, with PaO_2 increasing from 76 mm Hg to 129 mm Hg. Pump flow was decreased in steps to 2 L/min at sweep FiO_2 100%, then sweep FiO_2 was decreased to maintain $SaO_2 > 95\%$. As a trial for ECMO weaning, we clamped the O_2 sweep, and oxygenation was maintained well for a night (i.e., >16 hours) under lung-rest mechanical ventilation support. We finally discontinued ECMO on day 16 (12 days of ECMO; Table 1), and the patient was extubated on day 18. Mechanical ventilation settings after ECMO support were pressure-controlled ventilation (PCV) mode FiO_2, 0.4; respiratory rate, 14 breaths/

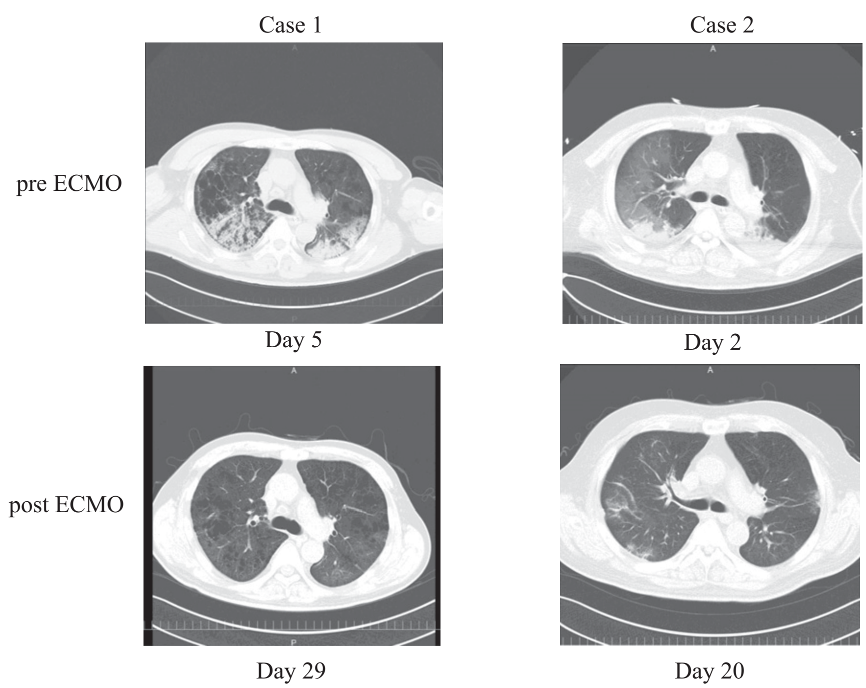

Figure 1. Chest CT images of COVID-19 patients.

Table 1. Patient characteristics.

	Case 1	Case 2
Age (years)	64	49
Sex	Male	Male
BW/height (kg/cm)	73/172	95/175
Pre-ECMO		
PEEP (cmH_2O)	15	14
P/F ratio	127	93
RESP SCORE	4	7
MV duration (hour)	4	3
ECMO		
Flow (L/min)	5.4	5.0
ECMO duration (days)	12	6
Cannulation size		
Drainage/Infusion (Fr)	29/25	29/25
Complications	No	No
Position	Prone	Semi prone
Total MV duration (days)	14	8
Medication		
Favipiravir (days)	14	15
Dexamethasone (days)	13	14
Remdesivir (days)	6	10
Nafamostat mesylate (days)	10	11

BW, body weight; ECMO, extracorporeal membrane oxygenation; PEEP, positive end-expiratory pressure; P/F, PaO_2/FiO_2; RESP, Respiratory ECMO Survival Prediction; MV, mechanical ventilation.

min; PEEP, 10 cmH_2O; and driving pressure, 3 cmH_2O. The patient was discharged from hospital on day 36.

Case 2

A 49-year-old man with a history of systemic lupus erythematosus, antiphospholipid syndrome, lupus nephritis type 4, deep venous thrombosis, and obesity (body mass index, 31 kg/m^2) was admitted to our hospital 8 days after developing cough and tested positive for severe acute respiratory syndrome coronavirus 2. On day 2 at hospital, respiratory status deteriorated and he was intubated. Arterial blood gas analysis 2 hours after intubation showed: pH, 7.214; PaO_2, 74.6 mm Hg; and $PaCO_2$, 48.0 mm Hg (PCV mode, FiO_2 0.8; respiratory rate, 12 breaths/min; PEEP, 14 cmH_2O; driving pressure, 10 cmH_2O; RESP score, 7). We decided to initiate venovenous ECMO in combination with the continuous renal replacement therapy for lupus nephritis. The ECMO system, cannulation site, cannulation size, and management of anticoagulation were similar to those in Case 1. The procedure was safely completed, and no complications were encountered. PaO_2 and lung compliance gradually improved within 48 hours after starting ECMO: PaO_2 increased from 74.6 to 141 mm Hg with PEEP of 14 cmH_2O. On day 7 at hospital, no decrease in oxygen saturation was seen when the flow rate of ECMO and sweep FiO_2 were reduced. Pump flow was decreased in steps to 2 L/min at sweep FiO_2 100%, then sweep FiO_2 was decreased to maintain $SaO_2 > 95\%$. Once SaO_2 remained stable under these settings, on venovenous ECMO, trial-off was performed using sweep FiO_2 21% on ventilator rest settings for 27 hours. Mechanical ventilation settings after ECMO support were pressure support ventilation, FiO_2 0.4; PEEP, 10 cmH_2O; and pressure support, 5 cmH_2O. Venovenous ECMO treatment was stopped on day 7 (ECMO duration: 6 days), and the patient was extubated on day 9 and discharged from hospital on day 21.

COMMENT

Both these cases of severe ARDS in patients with COVID-19 who received early initiation of ECMO after intubation showed favorable outcomes.

Yang et al. reported that ECMO should be implemented as soon as possible for P/F ratio <80 mm Hg under lung-protective mechanical ventilation strategies and prone positioning (11). Conversely, Uemura et al. insisted that indications and methods for initiating ECMO support in critically ill patients with COVID-19 pneumonia should be considered with care in the pandemic phase of COVID-19 from the perspective of appropriate resource utilization (12). Although the optimal timing of ECMO initiation is still disputed, our two cases in which ECMO was initiated a few hours after intubation had good prognosis, indicating early initiation of ECMO as a potential reason for the good outcomes. We consider that early ECMO induction enables the minimization of the risk of ventilation-related lung injury and could shorten the duration of mechanical ventilation (13–15). ECMO treatment achieves ultraprotective ventilation preventing the mechanical damage to the lung parenchyma seen with artificial ventilation. In this context, early initiation of ECMO may be more effective in severe ARDS patients than in less severe patients because the lung tissues in severe cases have already damaged in the early phase of ARDS (16). However, indications for early ECMO remain uncertain. Recent papers from the International ECMO registry have reported the current mortality rate of patients receiving ECMO is approximately 40%, and predictive factors for unfavorable outcomes include commodities such as chronic respiratory disease, cancer, and acute kidney injuries (17, 18). Improving the prognosis of COVID-19-related ARDS in patients with these conditions might thus be possible if ECMO can be initiated within a few hours of intubation. Taken together, patients showing severe respiratory failure because of COVID-19 with a past medical history of cancer or acute kidney injury could be indicated for early initiation of ECMO treatment.

To strengthen the benefits of early ECMO, we also applied an ECMO weaning strategy. Grant suggested daily follow-up chest radiographs to ensure that any “white out” is resolving and the lungs are aerating appropriately (19). However, in our Case 2, despite minimal improvements on chest X-ray, oxygen saturation was maintained in an ECMO weaning trial on day 7 with ECMO management. This may be effective to lower the sweep FiO_2 for assessing the respiratory state on a daily basis even when normalization of chest radiographs has not been confirmed.

In conclusion, ECMO was initiated a few hours after intubation. Early decisions and early initiation of ECMO indicated the possibility of success. We suggest lowering the sweep FiO_2 and assessing respiratory function daily while improving lung compliance and assessing normalization of chest radiographs.

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