

Extracorporeal membrane oxygenation and COVID-19: The causes of failure

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Abstract

Introduction: Venovenous extracorporeal membrane oxygenation (VV-ECMO) is a therapeutic strategy for the coronavirus disease 2019 (COVID-19) induced acute respiratory distress syndrome (ARDS). There are inconclusive data in this regard and causes of VV-ECMO failure are not yet understood well.

Case Series: Here, seven patients with COVID-19-induced ARDS who underwent VV-ECMO introduced and causes of VV-ECMO failure discussed. Medical records of seven COVID-19 patients treated with VV-ECMO were retrospectively evaluated to determine the clinical outcomes of VV-ECMO. Oxygenator failure occurred in four patients whom needed to oxygenator replacement. Successful VV-ECMO decannulation was done in three patients, however finally one patient survived.

Conclusions: Hypercoagulability state and oxygenator failure were the most main etiologies for VV-ECMO failure in our study. All patients with COVID-19 undergoing VV-ECMO should be monitored for such problems and highly specialized healthcare team should monitor the patients during VV-ECMO.

KEYWORDS

acute respiratory distress syndrome, extracorporeal membrane oxygenation, hypercoagulability, SARS coronavirus, SARS-CoV infection

1 | INTRODUCTION

The pandemic caused by the severe acute respiratory syndrome coronavirus 2 is a healthcare concern causing extensive mortality worldwide.^{1,2} Venovenous extracorporeal membrane oxygenation

(VV-ECMO) support may be used as a therapeutic strategy for the management of patients with coronavirus disease 2019 (COVID-19) and acute respiratory distress syndrome (ARDS).³ There are inconclusive data regarding the use of VV-ECMO during the outbreaks of COVID-19. VV-ECMO was used to treat ARDS caused by 2009 influenza A (H1N1)

and Middle East respiratory syndrome coronavirus-related ARDS.⁴ Since the efficacy and safety of VV-ECMO in patients with COVID-19-induced ARDS are still unclear, here we report seven patients with COVID-19-induced ARDS who underwent VV-ECMO.

2 | CASE SERIES

2.1 | ECMO center protocol

This is a single-center study, based on a retrospective cohort analysis of cases treated at the Dr. Masih Daneshvari Hospital, Tehran, Iran, which is the main referral center for patients with COVID-19 in Iran. This study was approved by the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.NRITLD.REC.1399.010). The operation team had experience with more than 150 VV-ECMO procedures during the last 10 years, and had successful experience with about 20 cases of H1N1. This center is the main referral center for ECMO in Iran, however there are some other centers in Iran, which have good clinical experience in this regard (eg, Rajaie Heart Center). Medical records of seven patients with COVID-19 treated between 1st March and 30th March 2020 were retrospectively evaluated to determine the clinical outcomes of VV-ECMO in such cases. The patients' demographic characteristics, VV-ECMO settings, treatment modalities, clinical response, and complications during VV-ECMO were retrieved. Descriptive statistics were performed to summarize the patients' characteristics.

The VV-ECMO procedure was the same for all patients. In all patients with refractory hypoxemia not responding to noninvasive ventilation, endotracheal intubation was performed, using low tidal volume, with a maximum plateau airway pressure of 30 cm H₂O. When necessary, the respiratory rate was increased to a maximum of 30 breath/min, which was the mainstay of lung protective ventilation. Patients with a PaO₂/FiO₂ ratio inferior to 80 for 6 hours, or a PaO₂/FiO₂ ratio inferior to 50 for 3 hours, were candidate for VV-ECMO, regardless of having high positive end-expiratory pressure and neuromuscular blockage. Trans-thoracic echocardiography was performed, and if left ventricular ejection fraction was less than 50%, VA-ECMO would be applied.

The console of the VV-ECMO was centrifugal pump system (Liva Nova Deutschland GmbH, München, Germany). The oxygenator was EOS hollow fiber oxygenator intended for long duration procedures (Liva Nova, Mirandola, Modena, Italy). The drainage femoral cannula was RAP FV two stage 23 out of 25 (Liva Nova), which was inserted by close Seldinger's maneuver in the left or right femoral vein. The return cannula was a 23-F Easy Flow DUO arterial femoral cannula (Liva Nova), inserted by close Seldinger's maneuver in the right internal jugular vein. The position of the cannula was verified by chest x-ray, as well as by evaluating the efficacy of the system, by increasing the arterial oxygen saturation and partial pressure of arterial oxygen. The bolus dose of heparin (50 units/kg) was injected before cannulation. ECMO was initiated if activated clotting time (ACT) was in the range of 150 to 180 seconds. The heparin infusion would be continued at dose of 10 to 20 units/kg to maintain aPTT between 50 to 70 seconds. The rate of infusion was adjusted according to aPTT result, which was checked every 6 hours.

During the index period, patients with severe ARDS were referred to our institution. We evaluated seven COVID-19 cases that underwent VV-ECMO because of severe ARDS. The median age of patients at the time of hospitalization was 45 years (range, 26-71 years). One patient was female and the rest were male. All patients complained of high-grade fever, cough, and dyspnea at admission time. The median time from symptom onset to hospitalization was 7 days (range, 5-12 days). All patients had at least one underlying disease.

A combination of hydroxychloroquine and lopinavir/ritonavir were administered to all patients according to Iranian national guideline.⁵ During the implantation of VV-ECMO, all patients had severe hypoxemia (peripheral oxygen saturation between 30%-60%). Only 1 patient was discharged with a stable condition. Clotting formation in the oxygenator was seen in four patients, in first 5-day of VV-ECMO. Patients' details are summarized in Table 1 and the chest X-ray findings of patients at first day of VV-ECMO starting is shown in Figure 1.

2.2 | Case 1

A 26-year-old male nurse with severe COVID-19 pneumonia was referred to the hospital. He complained of fever, cough, and dyspnea from 12 days before admission. For 3 days, he was intubated for invasive mechanical ventilation due to severe ARDS. His medical history showed a diagnosis of influenza H1N1 3 months before. He developed a worsening hypoxemia refractory to conventional ventilation. Chest x-ray showed a severe bilateral infiltration in both upper and lower lobes; therefore, he was treated with VV-ECMO. The patient died after 3 days because of sudden hypoxia due to oxygenator failure of the VV-ECMO, causing clotting and subsequent cardiac arrest.

2.3 | Case 2

A 71-year-old man diagnosed with severe COVID-19 pneumonia was referred to the hospital. He complained of fever, cough, dyspnea, myalgia, and diarrhea from 7 days before. At admission, patient had severe hypoxemia and he was intubated for invasive mechanical ventilation due to ARDS. Chest x-ray showed a severe bilateral infiltration in both upper and lower lobes. After 2 days of invasive mechanical ventilation, hypoxemia persisted. The patient became oliguric (urine output less than 20 mL/h) and developed hemodynamic instability. Serum creatinine increased to 2.8 mg/dL. He was treated with VV-ECMO and continuous renal replacement therapy. Then, oxygen saturation increased to 90%, whereas creatinine decreased to 2.6 mg/dL. However, after 7 days, the serum creatinine increased again from 2.6 mg/dL to 3.7 mg/dL, serum lactate dehydrogenase (LDH) increased to 3171 U/L, hemoglobin decreased to 7.6 mg/dL, and platelet decreased to 8700/L. The patient died due to multisystem organ failure.

TABLE 1 Characteristics of patients with severe ARDS caused by COVID-19, treated with venovenous extracorporeal membrane oxygenation (VV-ECMO)

	P1	P2	P3	P4	P5	P6	P7
Demographics							
Age, y	26	71	56	37	37	51	45
Sex	Male	Male	Female	Male	Male	Male	Male
Symptoms	Fever	Fever	Fever	Fever	Fever	Fever	Fever
	Cough	Cough	Cough	Cough	Cough	Cough	Cough
	Dyspnea	Dyspnea	Dyspnea	Dyspnea	Dyspnea	Dyspnea	Dyspnea
		Myalgia	Myalgia		Myalgia	Myalgia	Myalgia
	Diarrhea	Diarrhea					
Symptoms onset, d	12	7	9	5	11	6	5
Underlying diseases diagnosed before COVID-19	Influenza (H1N1)	HTN	HTN	DM	Dyslipidemia	HTN	None
	3 mo before	DM	DM		HTN		
		BPH	IHD				
Weight, Kg	74	73	75	68	85	71	66
Pre-ECMO clinical status							
ICU length of stay pre-ECMO, d	0	5	3	2	4	5	0
Vasopressors required	Yes	Yes	Yes	No	No	No	No
Duration of VV-ECMO, d	3	7	8	4	7	7	9
Laboratory results							
Creatinine, mg/dL (admission time/pre-ECMO/last time)	1.4-2.9-2.7	0.9-2.8-3.7	1.0-0.9-0.6	3.6-4.6-3	1.1-0.8-0.4	0.9-0.8-2.1	1.1-1.1
Bilirubin, μ mol/L at admission time/pre-ECMO/last time	1-13.1-13.9	1-1.3-11.30	0.4-0.1-31.10	0.6-0.5-4.10	0.8-1-8.5	0.6-2.6-2.7	1-1.5-1.3
Hemoglobin, g/L at admission time/pre-ECMO/last time	8.1-7.2-9.4	10.4-9.6-7.6	13.1-11.4-10.4	13.2-13.1-9	15.0-12.0-	13.0-12.0-9.2	11.1-10.7-10.3
WBC, $\times 10^9$ /L at admission time/pre-ECMO/last time	15.0-33.1-34.8	5.1-15.1-20.3	5.5-6.9-10.6	7.8-9.2-5.9	4.3-10.7-16.5	8.0-8.9-6.9	14.1-12.56-13.8
Platelet, 10^9 /L at admission time/pre-ECMO/last time	197-682-755	204-255-87	340-247-101	237-299-226	85-169-135	249-209-176	122-124-50
CPK, U/L at admission time/pre-ECMO/last time	224-510-1668	8940-10370-5262	425-622-627	684-3363-8999	1054-213-248	92-81-311	321-198-155
AST, U/L at admission time/pre-ECMO/last time	95-8112-7262	30-124-11	29-40-178	79-67-240	55-56-90	46-41-78	35-29-30
ALT, U/L at admission time/pre-ECMO/last time	67-4113-3546	13-28-22	10-9-68	64-55-100	38-33-52	32-31-37	40-32-31
ALP, U/L at admission time/pre-ECMO/last time	141-332-349	122-144-200	188-53-479	185-229-260	91-103-110	152-185-162	303-271-274
LDH, U/L at admission time/pre-ECMO/last time	959-19311-18841	1480-3571-2696	570-1053-2687	821-1139-4344	1025-1639-1465	898-1009-833	1702-1834-1589
Blood group	AB+	A+	B+	A+	O+	A+	O+
Oxygenator failure	No	No	Yes	No	Yes	Yes	Yes
Outcomes							
Successful VV-ECMO Decannulation	No	No	Yes	No	No	Yes	Yes
Survival to hospital discharge	No	No	No	No	No	No	Yes

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; CPK, creatine phosphokinase; DM, diabetes mellitus; HTN, hypertension; ICU, intensive care unit; IHD, ischemic heart disease; LDH, lactate dehydrogenase; P, patient; WBC, white blood cell.

2.4 | Case 3

A 56-year-old woman with severe COVID-19 pneumonia was referred to the hospital. She complained of fever, cough, dyspnea, myalgia, and diarrhea from 3 days before admission. Dyspnea persisted for the next 2 days and chest x-ray revealed progressive infiltration. Because of severe persistent hypoxemia, the patient was

intubated for invasive mechanical ventilation; however, due to progressive hypoxemia, the VV-ECMO was applied 2 days later, and oxygen saturation increased to 96%. In the 5th day of VV-ECMO, she showed gradual hypoxia and elevated d-dimer, and the oxygenator was changed in the 6th day. Hypoxia was reversed and the patient's condition improved. After 8 days, she was weaned of VV-ECMO successfully. However, 24 hours after the removal of VV-ECMO, she

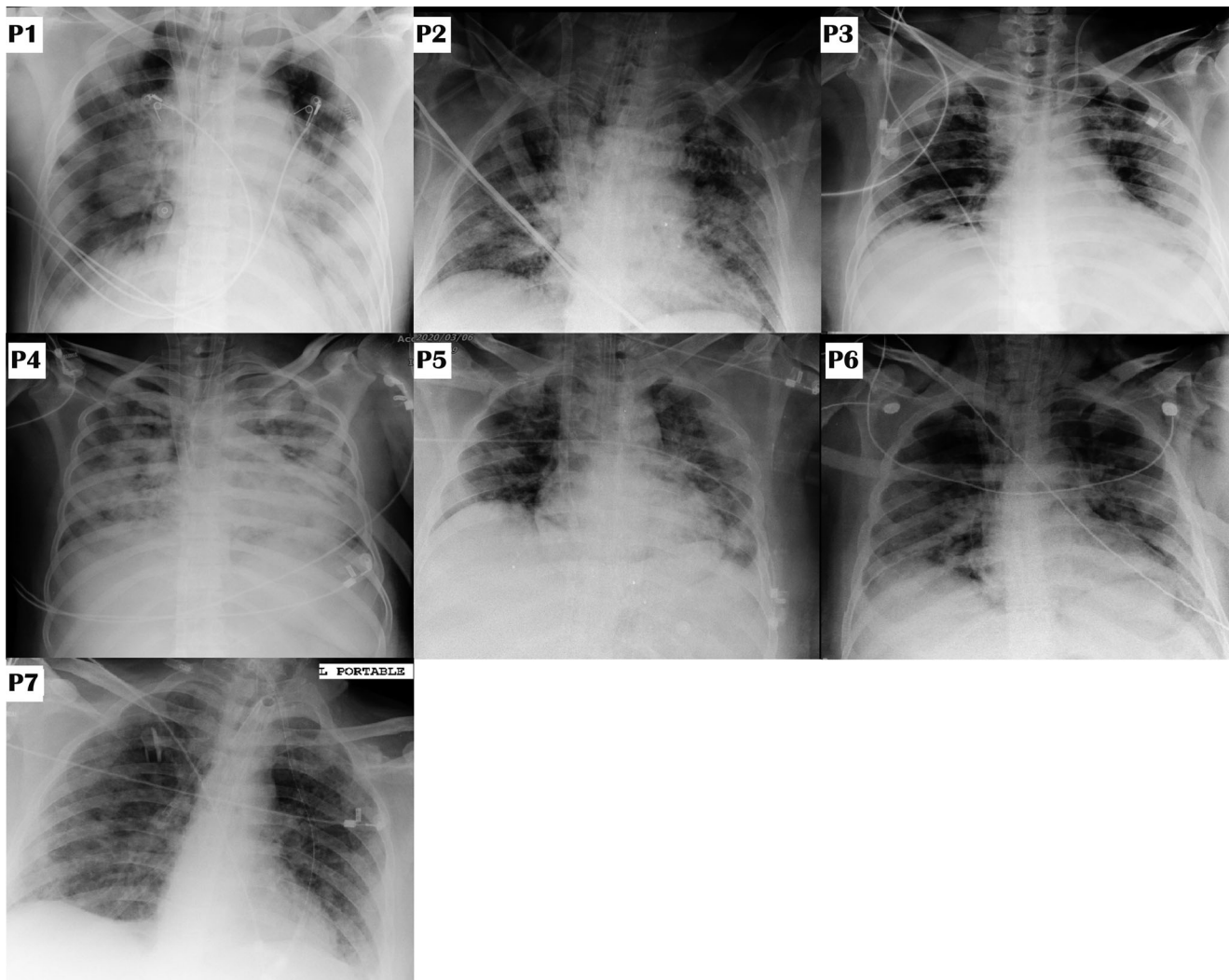


FIGURE 1 The chest X-ray imaging of patients at first day of venovenous extracorporeal membrane oxygenation starting

suddenly developed subcutaneous emphysema and tension pneumothorax. A chest tube was inserted in each thoracic cavity; the patient developed renal failure and despite all efforts she died 48 hours later.

2.5 | Case 4

A 37-year-old man diagnosed with severe COVID-19 pneumonia was referred to the hospital. He complained of fever, cough, and dyspnea from 5 days before admission. He was intubated for invasive mechanical ventilation due to severe hypoxemia. However, hypoxemia persisted and he was treated with VV-ECMO. Chest x-ray showed a severe bilateral infiltration in both upper and lower lobes. After VV-ECMO was initiated, oxygen saturation increased to 92%. After 3 days, creatine phosphokinase (CPK) and LDH increased from 3,363 U/L to 8,999 U/L and 821 U/L to 4344 U/L, respectively. Liver enzymes also increased significantly on the 3rd day of VV-ECMO. He died 24 hours later, due to multisystem organ failure.

2.6 | Case 5

A 37-year-old man diagnosed with severe COVID-19 pneumonia was referred to the hospital. He complained of fever, cough, dyspnea, and myalgia from 11 days before admission. He was intubated due to severe ARDS. Chest X-ray showed a severe bilateral infiltration in both upper and lower lobes. Invasive mechanical ventilation failed to improve hypoxemia and patient was treated with VV-ECMO. Oxygen saturation increased to 90%. On the third day, the VV-ECMO oxygenator was clotted and changed immediately. After 7 days, the patient's clinical condition deteriorated and he died due to multisystem organ failure.

2.7 | Case 6

A 45-year-old physician diagnosed with severe COVID-19 pneumonia was referred to the hospital. He complained of fever, cough, dyspnea, and myalgia from 6 days before admission. He was

intubated due to severe ARDS. Chest x-ray showed a severe bilateral infiltration in both upper and lower lobes. The hypoxemia and lung infiltration progressed during hospitalization; therefore, the patient was treated with VV-ECMO. Oxygen saturation increased to 95%. On the 4th day of VV-ECMO, the oxygenator was changed due to decreased oxygenation and hypercarbia. After 7 days, the patient's clinical condition improved and no metabolic disturbances occurred. He was decannulated from extracorporeal support, although he developed convulsions after decannulation of VV-ECMO. Convulsions were not controlled by pharmacological interventions and extensive cerebrovascular accident happened and finally the patient died despite all efforts.

2.8 | Case 7

A 45-year-old man, diagnosed with severe COVID-19 pneumonia was referred to the hospital. He complained of fever, cough, dyspnea, and myalgia from 3 days before admission. After 2 days of hospitalization, hypoxemia occurred, and oxygen saturation decreased to 60%. Chest x-ray showed a severe bilateral infiltration in both upper and lower lobes. Hence, the patient was intubated for invasive mechanical ventilation due to severe hypoxemia. However, hypoxemia persisted and he was treated with VV-ECMO. Following VV-ECMO, oxygen saturation increased to 95%. On the 5th day of VV-ECMO, oxygen saturation decreased and partial pressure of carbon dioxide increased. The oxygenator was changed immediately and the aPTT was maintained in therapeutic range. The patient tolerated 9 days of VV-ECMO, and no significant complications occurred. The tracheotomy was performed and patient was transferred to ward under acceptable medical conditions. The management of this patient was improved in comparison with previous cases due to achievement of more experiences. Coagulopathies and oxygenator failure did not occur and finally the patient was discharged after 5 days.

3 | DISCUSSION

In some patients with ARDS, positive pressure ventilation may worsen the clinical condition and even multisystem organ failure may occur. VV-ECMO will benefit a selected patient population, such as those with severe ARDS. VV-ECMO is a highly specialized and very expensive form of advance life support and there are some guidelines, such as EMPROVE protocol, with proven outcomes in this regard.⁶ The treatment of severe ARDS due to COVID-19 with VV-ECMO remains a challenge and controversial.^{3,7} Since some studies showed a higher mortality rate, compared with patients receiving only conventional respiratory care (100% vs 65%, respectively).^{1,8}

The most important finding in these cases was the hypercoagulability state, with high rate of oxygenator failure, and the necessity to change it, which occurred at least twice than in other studies.⁹ On the other hand, all patients were treated with

continuous intravenous heparin to maintaining the aPTT between 70 and 90 seconds. Also, according to the results, our protocol changed and we suggest that for anticoagulation management of patients with COVID-19 under ECMO, aPTT should not be used. Instead of aPTT, ACT should be monitored and kept between 220 and 250 seconds. We examined this protocol in two patients with satisfactory results. Oxygenator dysfunction leading to oxygenator replacement was seen in 10% to 30% of VV-ECMO patients. Nevertheless, such rate was unusual, particularly among those without hepatic failure.¹⁰ The fourth patient developed hepatic failure, probably due to a hypercoagulability state. The persistent hypoxemia in most patients might lead to rapid clinical deterioration, multi system organ failure and death. Another main issue was the late diagnosis of oxygenator failure, due to excess work load of nurses.

Most of our cases had non-O blood group, and the only survived case had O blood group. It has been demonstrated that non-O blood group has a higher risk of thromboembolic events,¹¹ which can be an investigation subject for future studies and for risk stratification of COVID-19 cases. Moreover, it has been shown that in Chinese patients with COVID-19, abnormal coagulation parameters were associated with poor prognosis, and anticoagulation in patients decreased the mortality of COVID-19 patients with coagulopathy.¹² On the basis of our study, and considering the evidence from Chinese patients, we think that the hypercoagulability state might be a phenomenon among severe cases of COVID-19 that requires to be carefully monitored.

Previous studies showed that the mortality rate related to VV-ECMO could be reduced if VV-ECMO is introduced within the first 7 days of mechanical ventilation.¹³ In our cases, the high rate of mortality may be explained by the delayed implantation of VV-ECMO in patients under critical conditions. Future investigations should consider that since VV-ECMO is unlikely to improve patients' overall outcomes, if potentially fatal complications cannot be prevented.

Hypercoagulability state and oxygenator failure were the most important etiologies for VV-ECMO failure in COVID-19 patients with severe ARDS in our study. All patients with COVID-19 undergoing VV-ECMO should be monitored for such a phenomenon and managed meticulously to improve their survival. Moreover, the implementation of highly specialized healthcare team, state-of-the-art medical devices, and diagnostic laboratories are deemed indicated for enhancing care delivery.

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CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

All authors collected the clinical data, drafted and revised the manuscript.

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