Extracorporeal Membrane Oxygenation in Patients With COVID-19

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Abstract: Coronavirus disease 2019 (COVID-19) is characterized by a clinical spectrum of diseases ranging from asymptomatic or mild cases to severe pneumonia with acute respiratory distress syndrome (ARDS) requiring mechanical ventilation. Extracorporeal membrane oxygenation (ECMO) has been used as rescue therapy in appropriate patients with COVID-19 complicated by ARDS refractory to mechanical ventilation. In this study, we review the indications, challenges, complications, and clinical outcomes of ECMO utilization in critically ill patients with COVID-19-related ARDS. Most of these patients required venovenous ECMO. Although the risk of mortality and complications is very high among patients with COVID-19 requiring ECMO, it is similar to that of non-COVID-19 patients with ARDS requiring ECMO. ECMO is a resource-intensive therapy, with an inherent risk of complications, which makes its availability limited and its use challenging in the midst of a pandemic. Well-maintained data registries, with timely reporting of outcomes and evidence-based clinical guidelines, are necessary for the careful allocation of resources and for the development of standardized utilization protocols.

Keywords: COVID-19, SARS-CoV-2, extracorporeal membrane oxygenation, acute respiratory, distress syndrome

(*Cardiology in Review* 2022;30: 129–133)

The outbreak and global spread of severe acute respiratory coronavirus 2 to pandemic proportions have taken a devastating toll on human lives. As of May 2021, coronavirus disease 2019 (COVID-19) has infected more than 167 million people, with a death toll of 3.46 million globally.[1] The clinical spectrum of COVID-19 ranges from asymptomatic cases, to mild pneumonia, to acute respiratory distress syndrome (ARDS) and multiorgan failure. The subset of patients with ARDS often requires mechanical ventilation and other modes of oxygenation, the most aggressive being extracorporeal membrane oxygenation (ECMO).

Based on studies before the COVID-19 era, venovenous ECMO (VV ECMO) has been shown to be superior to conventional ventilatory support in patients with severe refractory ARDS.[2–4] As a result, ECMO has been used as rescue therapy in appropriate patients with severe COVID-19 complicated by ARDS that is not responsive to mechanical ventilation and the World Health Organization has recommended referring such patients with refractory hypoxemia to a center with expertise in ECMO. However, allocating such a resource-intensive therapy—involving specialized hospital staff and facilities—in the midst of a pandemic deserves careful consideration. In this study, we review the indications, patient selection, cannulation strategies, management, complications, and outcomes of ECMO in patients with COVID-19-related ARDS (Table 1).

INDICATIONS

The Extracorporeal Life Support Organization coronavirus 2019 consensus guidelines emphasize that the decision to use ECMO in COVID-19 patients should be made meticulously on a "case-by-case" basis, coupled with regular reassessments of overall patient load, resource constraints, and local hospital policies.[28] Thus, patient selection for ECMO varies across institutions and countries.[11] For instance, according to a study conducted by Zayat et al, critically ill COVID-19 patients were considered for ECMO when all other options, such as invasive mechanical ventilation, prone positioning, neuromuscular blockade, and inhaled nitric oxide rescue therapy had failed.[17] A similar criterion was used by Jäckel et al in selecting those patients who failed to improve with lung-protective mechanical ventilation for ECMO. These authors defined lung-protective mechanical ventilation as positive end-expiratory pressure (PEEP) ≤15 cmH$_2$O, plateau pressure ≤30 cmH$_2$O, driving pressure ≤15 cmH$_2$O, and the fraction of inspired oxygen FiO$_2$ ≤50%.[10] Shih et al, on the contrary, used ECMO for inadequate oxygenation despite maximal ventilatory settings, defined as respiratory rate 30/min, inspiratory pressure 30 cmH$_2$O, and F$_i$O$_2$ ≥80% or PEEP ≥10 cmH$_2$O.[8] Yet another study (n = 302) used the EOLIA (ECMO to Rescue Lung Injury in Severe ARDS) trial criteria,[29] based on the American-European Consensus Conference definition of ARDS,[30] which includes optimal mechanical ventilation for <7 days (F$_i$O$_2$ >80%, tidal volume 6 mL/Kg predicted body weight and PEEP >10 cmH$_2$O), with at least one of the following: (1) PaO$_2$:FiO$_2$ ratio <50 mmHg for > 3 hours despite optimal ventilatory settings and use of adjunctive therapies (prone positioning, recruitment maneuvers, inhaled nitric oxide, high PEEP strategies, and neuromuscular blockade); (2) PaO$_2$:FiO$_2$ <80 mm Hg for >6 hours with adjunctive therapies; (3) arterial blood gas with pH < 7.25 with PaCO$_2$ >60 mm Hg for >6 hours.[31,32]

PATIENT SELECTION

In general, conditions with poor expected recovery, such as advanced shock, multiorgan failure, severe brain injury, and advanced malignancies, are unsuitable candidates for ECMO support.

Relative contraindications for venoarterial ECMO (VA ECMO) support include patients with unrepaired aortic aneurysm, severe aortic, or mitral regurgitation with poor left ventricular function, severe chronic pulmonary arterial hypertension, and severe peripheral arterial disease limiting cannulation.[8] Even though

Table 1. Baseline Demographics and Clinical Characteristics of COVID-19 Patients Requiring ECMO Support Reported by Various Studies

Author	Year	Total Patients (n)	Patients on ECMO n (%)	Country	Age, years	Males n (%)	Hyper-tension	Diabetes	Smokers	Cardio-vascular Diseases	CKD/ESRD	Mortality n (%)
Barbaro et al[5]	2020	1035	1035 (100)	United States	49 ± 11.8	764 (74)	NR	245 (24)	NR	24 (2)	21 (2)	380 (37)
Beyls et al[6]	2020	12	12 (100)	France	62 (56–66)	10 (83.3)	NR	NR	NR	NR	NR	2 (16.7)
Marullo et al[7]	2020	333	333 (100)	Italy	52 ± 11	264 (79.3)	NR	NR	NR	NR	NR	57 (17.1)
Shih et al[8]	2020	37	37 (100)	U.S.	51 (40–59)	27 (73)	25 (67.6)	19 (51.4)	1 (2.7)	NR	1 (2.7)	16 (43.2)
Falcoz et al[9]	2020	17	17 (100)	France	56 (30–76)	16 (94.1)	9 (52.9)	3 (17.6)	NR	NR	NR	6 (35.3)
Jäckel et al[10]	2020	15	15 (100)	Germany	60.8 (54–67)	11 (73.3)	5 (33.3)	2 (13.3)	3 (20)	0	0	8 (51.4)
Jacobs et al[11]	2020	32	32 (100)	U.S.	United States	22 (68.8)	NR	11 (34.4)	NR	4 (12.5)	NR	10 (31.25)
Jozwiak et al[12]	2020	92	11 (12)	France	50 (38–59)	7 (63.6)	2 (18)	2 (18)	2 (18)	NR	NR	6 (54.5)
Li et al[13]	2020	8	8 (100)	China	64.2 ± 16.4	6 (75)	4 (50)	1 (12.5)	NR	1 (12.5)	1 (12.5)	4 (50)
Mustafa et al[14]	2020	40	40 (100)	United States	48.4 ± 1.5	30 (75)	23 (58)	10 (25)	7 (18)	1 (3)	4 (10)	6 (15)
Sultan et al[15]	2020	10	10 (100)	United States	31–62	7 (70)	NR	NR	2 (20)	NR	NR	1 (10)
Takeda et al[16]	2020	26	26 (100)	Japan	71 (45–81)	NR	NR	NR	NR	NR	NR	NR
Zayat et al[17]	2020	17	17 (100)	Germany	57 (39–73)	11 (65)	6 (35)	6 (35)	4 (24)	12 (71)	4 (82)	8 (47)
Zeng et al[18]	2020	12	12 (100)	China	50.9 ± 13.5	11 (98.7)	1 (8.3)	1 (8.3)	NR	1 (8.3)	NR	5 (41.7)
Zhang et al[19]	2020	43	43 (100)	United Kingdom	46 (26–66)	33 (76.7)	10 (23.3)	8 (18.6)	NR	NR	NR	14 (32.6)
Raasveld et al[20]	2021	71	71 (100)	Netherlands	52 (47–57)	57 (80)	15 (21)	6 (8)	NR	21 (30)	3 (4)	26 (37)
Shaefi et al[21]	2021	5122	190 (3.7)	United States	49 (41–58)	137 (72.1)	NR	NR	NR	7 (3.7)	2 (1.1)	63 (33)
Kon et al[22]	2021	412	27 (6.5)	United States	40 (30.5–47)	23 (85)	5 (19)	4 (15)	NR	1 (4)	0	1 (3.7)
Lebreton et al[23]	2021	302	302 (100)	France	52 (45–58)	235 (78)	103 (34)	87 (29)	11 (4)	10 (3)	NR	164 (54.3)
Biancari et al[24]	2021	132	132 (100)	France and Germany	51.1 ± 9.7	109 (82.6)	38 (28.8)	29 (22)	23 (17.4)	5 (3.8)	15 (11.4)	70 (53)
Cousin et al[25]	2021	30	30 (100)	France	57 (47–62)	24 (80)	16 (53.3)	10 (33.3)	1 (3.3)	0	NR	16 (53.3)
Supady et al[26]	2021	133	127 (95.5)	United States and Germany	59 (53–66)	100 (79)	NR	NR	NR	3 (2)	11 (9)	58 (46)
Saeed et al[27]	2021	292	292 (100)	United States	49 (39–57)	211 (72)	119 (41)	90 (31)	NR	12 (4)	NR	122 (42)

The values are represented as mean ± SD, median (IQR) or no. (%).
CKD, chronic kidney disease; ESRD, end-stage renal disease; NR, not recorded.

advanced age is not an absolute contraindication, the data from multiple studies suggest that ECMO was not considered in patients >65–70 years.[8,19,23,25,32]

ECMO CANNULATION

VV-ECMO requires venous cannulation with one or two cannulae, which can be accomplished via the femoral, internal jugular, or subclavian veins. Jäckel et al used a dual-lumen cannula inserted in the right jugular vein or, alternatively, a bifemoral approach with two cannulae.[10] Many used an ultrasound-guided femoral-jugular cannulation approach, using a large (23–29 Fr) drainage cannula inserted in the femoral vein and an 18–23 Fr return cannula inserted in the internal jugular vein.[12,23,25] Zayat et al, on the other hand, preferred bicaval, single-site cannulation with a dual-lumen 27–31 Fr cannula under direct transesophageal echocardiographic assistance over a 2-site cannulation (femoral-jugular or femoral-femoral) with 19 to 25 Fr cannula.[17] However, the authors noted that the bicaval single-site cannulation occasionally was inadequate to provide adequate flow and gas exchange when compared with the 2-site cannulation.[17] The multicenter experience in the United States reported that almost half of the patients (47%) underwent dual cannulation involving femoral and jugular veins while 19% were cannulated using bilateral femoral veins and the rest were cannulated through a single site double-lumen approach through the internal jugular vein.[27]

In addition to hypoxia, COVID-19 can be complicated by myocarditis and thromboembolic events like pulmonary embolism causing hemodynamic instability, necessitating VA ECMO, which provides circulatory support in addition to oxygenation. The data on utility and outcomes of this modality are limited, as VA ECMO was used only in about 4–6% of COVID-19 patients.[11,17,20,23,27,32]

MANAGEMENT

Patients supported on ECMO frequently require concurrent interventions, varying from adequate oxygenation and airway management to neuromuscular blockade and anticoagulation for preventing thrombus formation.[20,22,32] Conventional low pressure, low volume, lung protection mechanical ventilation is recommended alongside ECMO support and recruitment maneuvers, including prone positioning, should be continued as much as possible for early recovery.[32–34] Tracheostomy is safe if indicated; however, awake ECMO with early extubation has been reported and may be preferable.[14] In most settings, COVID-19 patients supported on ECMO

were maintained on pump flows between 2 and 6 L/min, with a goal of keeping oxygen saturation above 90%.[8,10,15–17,23,32] According to Kon et al, keeping circuit flow >3 L/min is a good strategy that helps prevent clot formation within the oxygenator.[22]

Since thrombus formation within the ECMO system can pose a serious risk of thromboembolic events, it is imperative to use adequate anticoagulation in these patients. Most studies suggest rinsing the cannulas with unfractionated heparin before ECMO initiation, followed by an intravenous infusion at 20 units/kg/hr to maintain a target partial thromboplastin time of 55–70 seconds.[8,10,13,17,22,23] In few centers in the United States, argatroban (32%) and bivalirudin (10%) were used in selected cases.[27] However, in case of visible thrombus formation within the pump head, a circuit change is necessary.[10,19] COVID-19 coagulopathy in patients requiring ECMO can lead to both thrombotic and hemorrhagic complications, such as circuit clotting, pulmonary embolism, and intracranial hemorrhage.[32,35] However, the adjusted rates of ECMO-related thrombotic and bleeding events do not seem to differ from non-COVID-19 populations,[5] suggesting that the standard ECMO anticoagulation regimen should be used for COVID-19 patients requiring ECMO.[5,32]

COVID-19 patients on ECMO are at high risk of acute kidney injury (AKI) and may require renal replacement therapy (RRT). A meta-analysis of 41 studies (n = 10,282 patients) including patients on ECMO support found a pooled incidence of AKI to be 62.8% [95% confidence interval (CI), 52.1%–72.4%], with nearly 45% requiring RRT.[36] A similar rate of AKI was observed among critically ill COVID-19 patients who were supported with ECMO.[8,20,23,27] Barbaro et al reported a high incidence of pre-ECMO AKI among 1006 patients, with RRT required in 444 (44%).[5] Similarly, 46% of patients with COVID-19 on ECMO support required RRT in the pooled report from multiple centers across the United States.[27] Moreover, patients with COVID-19 on ECMO who require RRT have an 89% higher mortality than those not requiring RRT, likely due to underlying multi-organ failure rather than RRT itself.[37]

Possible scenarios for ECMO withdrawal should be anticipated early in the patient's course. The initial consenting process should include a discussion of the patient's wishes regarding what course to take in the event of futility—if it becomes clear that there will be no meaningful recovery—which should include the patient's views on transplantation. Based on such discussions, COVID-19 patients on ECMO with no signs of lung recovery despite available therapies and single organ failure should be evaluated for lung transplantation.[32,38,39] In the event of futility where transplantation is not an option, discussions should focus on whether to de-escalate to conventional mechanical ventilation or to withdraw life-sustaining support and initiate comfort care.

COMPLICATIONS

Unsurprisingly, ECMO is associated with complications varying from medical to mechanical complications, with the latter being less frequently observed,[8] and such complications can contribute to morbidity and mortality. The median duration of ECMO in COVID-19 patients was 9–16 days.[12,20–23] Although it would seem reasonable to presume that longer ECMO duration would increase the risk of complications, only a weak association [OR 1.074; 95% CI (1.005–1.148)] has been reported.[40] According to a meta-analysis, the overall complication rate associated with the use of ECMO, regardless of the indication, was 40.2 % (95% CI, 25.8–56.5).[41] However, the complication rate for COVID-19 patients on ECMO was found to be twofold higher, with 82–85% of patients suffering at least 1 complication.[12,20] Common complications include AKI (22–64%),[20,21,24] hemorrhagic events (28–54%),[8,20,21] bloodstream infections (11–32%),[8,20,24,27] bacterial pneumonia (19–32%),[8,20,21,27] and urinary tract infections (11%).[27] However, more serious complications, such as

ischemic or hemorrhagic stroke and limb ischemia, are less frequently observed.[5,25,27] Deep vein thrombosis was reported in at least 15% of patients in the United States.[27]

When compared with non-COVID-19 ARDS patients on ECMO, no significant differences were found in the rate of occurrence of AKI, secondary infections, thrombotic, or hemorrhagic complications.[5,20,32] In fact, 28-day mortality in COVID-19 patients (37%) and non-COVID-19 patients (27%) receiving ECMO were similar [HR, 1.01 (95% CI, 0.60–1.69)]. Similarly, another study comparing complications and outcomes in COVID-19 patients with that of influenza patients on ECMO for refractory ARDS found no significant differences between the groups.[25] These findings indicate that COVID-19 patients receiving ECMO may not have a higher predisposition to develop complications than other patients on ECMO for ARDS.

SURVIVAL

Although earlier data had suggested staggeringly high mortality rates in COVID-19 patients receiving ECMO,[42] more recent studies have reported promising outcomes.[5,11,14,21,27] Barbaro et al reported a cumulative in-hospital mortality of 37.4% at 90 days after ECMO initiation among their patient cohort (n = 1035).[5] They also observed that VA ECMO was associated with almost a twofold greater in-hospital mortality, with an adjusted HR of 1.89 (95% CI, 1.20–2.97), compared with VV ECMO. This could stem from the fact that patients requiring VA ECMO generally have hemodynamic instability and shock, complicated by multiorgan failure. Additionally, age >60 years, development of AKI, chronic respiratory insufficiency, immunocompromised status, or cardiac arrest before ECMO were all identified as independent predictors of in-hospital mortality. Similar results were shown by 2 other studies reporting a 35% mortality rate at 60-days of ECMO support.[9,21] Most recently, the data from 17 centers in the United States reported a cumulative 90-day mortality of 42% (95% CI, 36–47%) with increasing age, AKI, and cardiopulmonary arrest requiring resuscitation during admission previous to ECMO associated with significantly reduced survival.[27] Multiorgan failure (34%) was the leading cause of death, followed by cardiac failure (16%) and progressive respiratory failure (13%).[27] Conversely, other studies have observed relatively higher mortality rates (≥50%),[10,23–25] which could be attributed to a comparatively higher proportion of severely ill patients with pre-ECMO sequential organ failure assessment (SOFA) scores ranging from 10 to 12. This correlates with a recent report of significantly lower 30-day survival among COVID-19 patients on VV-ECMO with SOFA score ≥7.[26] Moreover, in the study by Cousin et al, the authors noted a higher proportion of patients with obesity (median body mass index of 33 kg/m^2), which previously has been correlated with nearly a twofold increased odds of mortality among COVID-19 patients.[43]

The duration of mechanical ventilation before ECMO is another well-recognized independent predictor of survival, with a duration >8 days having a fivefold risk of mortality [OR 5.53 (95% CI, 1.94–15.8)].[44] The median duration of mechanical ventilation in COVID-19 patients before ECMO reportedly ranges from 3 to 6 days,[6,10,17,29] with survivors having a significantly shorter duration of mechanical ventilation than nonsurvivors.[26] In sum, these observations indicate that the mortality associated with ECMO in COVID-19 is multifactorial and support early initiation of ECMO in these patients.

CONCLUSIONS

Patients with severe COVID-19-related ARDS have an extremely poor prognosis. VV-ECMO has been shown to improve outcomes in respiratory failure refractory to mechanical ventilation

and should be considered early in such cases as a bridge to recovery or organ transplantation. However, ECMO remains a resource-intensive therapy with a significant risk of complications, which makes its availability limited and its use challenging. In a pandemic, like COVID-19, these considerations become even more pronounced and underscore the need for data repositories that document the outcomes of widespread practices, which in turn can constitute the basis for evidence-based guidelines to inform the judicious allocation of resources and use of this therapy.

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