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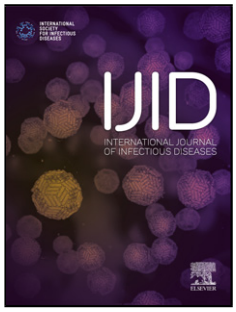

Extracorporeal membrane oxygenation (ECMO): does it have a role in the treatment of severe COVID-19?

Xiaoyang Hong, Jing Xiong, Zhichun Feng, Yuan Shi

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Title: Extracorporeal membrane oxygenation (ECMO): does it have a role in the treatment of severe COVID-19?

Running title: ECMO and COVID-19

Xiaoyang Hong, PhD, MD[1], Jing Xiong, MD[2,¶], Zhichun Feng, PhD, MD[1*] , Yuan Shi, PhD, MD[2*]

Affiliations

[1]Bayi Children's Hospital, The Seventh Medical Center, PLA General Hospital, Beijing, China

[2]Department of Neonatology, Ministry of Education Key Laboratory of Child Development and Disorders; National Clinical Research Center for Child Health and Disorders; China International Science and Technology Cooperation base of Child development and Critical Disorders; Children's Hospital of Chongqing Medical University; Chongqing Key Laboratory of Pediatrics, Chongqing, 400014, P.R China.

[¶]Dr Xiong contributed equally to this study.

*** Co-corresponding authors:**

Zhichun Feng, PhD, MD. Bayi Children' Hospital; The Seventh Medical Center of Chinese PLA General Hospital, Beijing, 100000, China. Email:

zhichunfeng81@163.com

Yuan Shi, PhD, MD. Department of Neonatology, Children's Hospital of Chongqing Medical University, Chongqing, 400014, China. Email:

shiyuan@hospital.cqmu.edu.cn

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Highlights

- ECMO has been used as a rescue therapy for severe respiratory failure and ARDS for years and ECMO should also be considered as a rescue therapy for COVID-19 with refractory hypoxemia despite lung-protective ventilation according to WHO.

- Although the clinical trials of ECMO for COVID-19 are lacking, its use in COVID-19 might also offer promise based on the previous experience.

- In the current situation of pandemic outbreak, many issues of ECMO use deserve our attention.

Abstract

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has emerged since December 2019 in Wuhan city, and has quickly spread throughout China and other countries. To date, no specific treatment has been proven to be effective for SARS-CoV-2 infection. According to World Health Organization (WHO), management of coronavirus disease 19 (COVID-19) has mainly focused on infection prevention, case detection and monitoring, and supportive care. Given to the previous experience, extracorporeal membrane oxygenation (ECMO) has been proven to be an effective therapy in the treatment of respiratory failure or acute respiratory distress syndrome (ARDS). On the basis of similar principle, ECMO may be also an effective therapy in the treatment of severe COVID-19. In this study, we described and discussed the clinical outcomes of ECMO for ARDS patients, ECMO use for severe COVID-19 in China, the indications of ECMO use, and some important issues associated with ECMO.

Keywords: acute respiratory distress syndrome; respiratory failure; extracorporeal membrane oxygenation; coronavirus disease 19

Since the end of 2019, an outbreak of pneumonia caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has occurred in China. In a recent report published in JAMA, 26.1% of 138 coronavirus disease 2019 (COVID-19) patients needed to be admitted to intensive care unit (ICU), of which 61.1% were suffering from acute respiratory distress syndrome (ARDS). The case fatality rate of COVID-19 has been reported about 4.3%[1]. Until now, no specific treatment has been recommended for COVID-19.

Historical perspective

Extracorporeal membrane oxygenation (ECMO), which can provide effective respiratory or cardiac support, has been regarded as a rescue therapy for severe ARDS. ECMO therapy during the influenza A (H1N1) pandemic in 2009 appeared to benefit, with ECMO-treated patients with H1N1-related ARDS achieving a mortality of 21%, which greatly increased interest in its use [2]. Another cohort study by using ECMO

database of patients with H1N1-related ARDS showed that hospital mortality rate was 23.7% for ECMO-referred patients vs 52.5% for non-ECMO-referred patients (RR, 0.45 [95% CI, 0.26-0.79]; P=0.006) when individual matching was used; 24.0% vs 46.7%, respectively (RR, 0.51 [95% CI, 0.31-0.81]; P=0.008) when propensity score matching was used; and 24.0% vs 50.7%, respectively (RR, 0.47 [95% CI, 0.31-0.72]; P=0.001) when GenMatch matching was used. These suggested that for patients with H1N1-related ARDS, ECMO-referred patients were associated with significantly lower hospital mortality compared with matched non-ECMO-referred patients [3]. A clinical trial, named as CESAR, was encouraging as well [4]. However, EOLIA Clinical Trial showed that 60-day mortality with very severe ARDS patients was not significantly lower, yet was largely reduced in the ECMO group compared with the conventional mechanical ventilation group (35% vs 46%; RR, 0.76 [95% CI, 0.55-1.04]; P = 0.09), but there was a 28% crossover to ECMO for failure of conventional mechanical ventilation, suggesting a lack of clinical equipoise [5]. Otherwise, a post hoc Bayesian analysis of EOLIA with various assumptions of prior belief and knowledge about ECMO efficacy in ARDS had shown the posterior probability of a mortality reduction with ECMO in the EOLIA trial [6]. In 2018, a retrospectively study on middle east respiratory syndrome (MERS) patients with refractory respiratory failure indicated that ECMO should be used as a rescue therapy, and ECMO group was associated with lower mortality in MERS patients with refractory hypoxemia compared with the conventional group (65 *vs* 100%, P = 0.02)[7]. (Table 1)

Application situation of ECMO for COVID-19 in China

According to the interim guidance formulated by the World Health Organization (WHO), ECMO should be considered as a rescue therapy for COVID-19 with refractory hypoxemia despite lung-protective ventilation [8]. However, there is little experience with using ECMO to support SARS-CoV-2-infected patients [1,9-12]. Most of studies didn't report the clinical outcomes of ECMO use except for two studies. In the retrospective study conducted by Yang et al., 52 critically ill adult patients were identified with SARS-CoV-2 pneumonia and were admitted to intensive care unit (ICU), among them, 31 patients had died at 28 days. 6 patients were received ECMO, and 5 of them died and 1 patient was still on ECMO at the endpoint [9]. Another retrospective study implemented by Guqin et al. included 221 patients with laboratory confirmed SARS-CoV-2 pneumonia, 48 of severe patients developed ARDS, and 10 of them received invasive mechanical ventilation (IMV) and ECMO support. 2 patients had clinical benefits and had been discharged and 3 of them were non-survivors. The rest 5 patients were still on ECMO at the endpoint [10] (Table 2). Given lacking of clinical trial of ECMO on COVID-19, we could not conclude whether SARS-CoV-2-infected patients have benefited from ECMO at this time. But our concern may be settled by the ongoing trials in China (ChiCTR2000030744 and ChiCTR2000029804).

Indications for the treatment of COVID-19 by ECMO

Based on the entry criteria of EOLIA, ECMO should be considered when meeting one of the following three criteria despite optimization of mechanical ventilation for

<7days ($FiO_2 \geqslant 0.80$, tidal volume of 6 ml/kg predicted body weight, PEEP$\geqslant$ 10cmH_2O) [13]: (1) PaO_2: FiO_2 < 50mmHg for > 3 hours; (2) PaO_2: FiO_2 < 80 mmHg for > 6 hours; (3) pH<7.25 with $PaCO_2 \geqslant$60mmHg for > 6 hours with a respiratory rate increased to 35 breaths per minute, adjusted for plateau pressure$\leqslant$32 cmH_2O. Alternatively, after lung protective ventilation (tidal volume 6ml/kg, PEEP$\geqslant$ 10cmH_2O) was adopted and combined with lung recruitment maneuver, prone position ventilation and high-frequency oscillation ventilation, patients are still under the condition of pure oxygen inhalation, in these situations, ECMO should be considered for ARDS as rescue therapy when meeting one of the following criteria: (1) PaO_2/FiO_2<100mmHg; (2) $P_{(A-a)}O_2$>600mmHg; (3) pH<7.2 and plateau pressure >30cmH_2O with respiratory rate more than 35 breaths per minute; (4) Age<65 years old; (5) Mechanical ventilation<7d; (6) Absence of contraindications [14]. Besides, for the patients with a harmful potential of ventilator-induced lung injury, lower ventilation and volumes and pressures may lead to hypercapnic acidosis, in this situation, extracorporeal carbon dioxide removal (ECCO2R) can be an important tool by providing direct removal of CO2 from blood [13].

What should we do next?

Indeed, many factors could affect the outcomes of ECMO treatment, including the duration of mechanical ventilation, the severity of underlying disease, the experience of trained medical staff, and ECMO equipment. Early evaluation, rapid assembly, and cannulation timely are important. Regardless of the efficacy of ECMO, under the special situation of the SARS-CoV-2 outbreak, we should also pay more attention to

the safety of medical staff since they get infected easily when manipulating ECMO. Some approaches, such as intubation, ventilator venting, and sputum suction pose a high risk of infection to medical staff. Therefore, all related staff should be supplied with sufficient protection and be restricted in the independent area. As the pandemic spread, a shortage of ECMO consoles may be another problem to be solved due to a surge of critically ill patients worldwide. Furthermore, trained staff and isolation rooms should be in full preparedness to meet the coming challenges.

Author contributions

XH conceptualized the study and revised the final manuscript. JX drafted the initial manuscript. ZF reviewed the manuscript for important intellectual content. YS conceptualized and designed the study and critically reviewed the manuscript for important intellectual content. All authors reviewed the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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Ethical Approval

Not applicable

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Table 1. Clinical studies of ECMO for respiratory failure

Application	Publication time	Study design	Outcomes of ECMO	Reference
Influenza A (H1N1) ARDS	2009	Observational study	A mortality rate of 21% in the ECMO-treated patients	[2]
ARDS (CESAR)	2009	Multicenter RCT	63% (57/90) of patients considered by ECMO survived to 6 months without disability compared with 47% (41/87) of those allocated to conventional management (RR, 0.69; 95% CI 0.05-0.97, p = 0.03)	[4]
Influenza A (H1N1) ARDS	2011	Cohort study	ECMO-referred patients was associated with lower mortality compared with match non-ECMO-referred patients	[3]
ARDS (EOLIA)	2018	Multicenter RCT	60-day mortality was not significantly lower with ECMO than with a strategy of conventional	[5]

			mechanical ventilation(35% vs 46%, p = 0.09)	
MERS	2018	Retrospective study	ECMO use was associated with lower mortality in MERS patients with refractory hypoxemia (65% vs 100%, P=0.02)	[7]

ARDS = acute respiratory distress syndrome; CI = confidence interval; ECMO = extracorporeal membrane oxygenation; MERS = middle east respiratory syndrome; RCT = randomized controlled trial; RR = relative risk.

Table 2. Current clinical uses of ECMO for COVID-19

Application	Study design	Cases on ECMO (total cases)	Outcomes of ECMO	Reference
Critically ill patients with SARS-CoV-2 pneumonia	Single center, retrospective, study	6 (52)	Five patients died while one patient was still on ECMO at the endpoint	[9]
Patients with ARDS caused by SARS-CoV-2	Single center, retrospective study	10 (221)	Two patients were discharged, three patients died, and five patients were still on ECMO at the endpoint	[10]
Critically ill patients with SARS-CoV-2 pneumonia	Single center, retrospective study	4 (138)	NA	[11]
Critically ill patients with SARS-CoV-2 pneumonia	Multicenter retrospective study	5 (1099)	NA	[12]
Critically ill patients	Single center	2 (41)	NA	[13]

with SARS-CoV-2 pneumonia	prospective study			

ARDS= acute respiratory distress syndrome; COVID-19= coronavirus disease 2019; ECMO= extracorporeal membrane oxygenation; NA= not available; SARS-CoV-2= severe acute respiratory syndrome coronavirus 2.