Shimane J. Med. Sci., Vol.37 pp.57-60, 2020

The History of Extracorporeal Membrane Oxygenation and Its Role in Coronavirus Disease 2019

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（Received April 25, 2020; Accepted April 27, 2020）

In 2019, the severe acute respiratory syndrome coronavirus 2 spread worldwide. Despite the early speculation of the virus not inducing critical illness, many young healthy patients became severely affected. An extracorporeal membrane oxygenation（ECMO）machine oxygenates blood directly. Thus, it is believed to compensate for the most severe form of respiratory failure in patients. However, the history of ECMO shows that the benefit of ECMO can not be exploited if the machine is used inappropriately. In this review, we will discuss the basics and history of ECMO and its role in coronavirus disease.

Key words: ECMO, COVID-19, ARDS

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Background

Recently, with the spread of the severe acute respiratory syndrome coronavirus 2（SARS-CoV-2）, the number of patients with severe respiratory failure is increasing worldwide［1］. Coronavirus disease（COVID-19）is a disease that develops from SARS-CoV-2. The most severe form of COVID-19 involves severe acute respiratory failure. For patients with the most severe respiratory failure, mechanical ventilation is insufficient to restore oxygenation, and extracorporeal membrane oxygenation（ECMO）is required as a last resort for oxygenation. In this review, we will introduce the basics and history of ECMO and discuss its role in COVID-19.

What is ECMO?

An ECMO machine is an extracorporeal machine to compensate for lung and/or heart function. It is composed of a centrifugal pump and artificial lungs. The centrifugal pump drains blood by generating negative pressure. The artificial lungs are composed of holofiber with a semi-permeable membrane, and blood flows through this fiber. Gas exchange occurs through the membrane. Usually, the drainage cannula is approximately 23–29 Fr, and the returning cannula is approximately 20–24 Fr.

Mode of ECMO

ECMO can be used for extracorporeal lungs or extracorporeal lungs and heart. When blood is drawn from a vein and returned to a vein, ECMO compensates only for lung function; thus, this is called veno-venous ECMO（V-V ECMO）or respiratory ECMO. When blood is drawn from a vein and returned to an artery, ECMO compensates for heart

and lung function; thus, this is called veno-arterial ECMO (V-A ECMO) or cardiac ECMO. Extracorporeal cardiopulmonary resuscitation (E-CPR) is one of the types of V-A ECMO, which is used to resuscitate patients who have experienced cardiopulmonary arrest. In V-V ECMO, the drainage cannula is usually inserted from the femoral vein to the right atrium and the returning cannula is inserted in the jugular vein. In V-A ECMO, the returning cannula is inserted in the femoral artery. V-V ECMO is usually selected for patients with severe COVID-19 respiratory failure.

History of ECMO

Pre-CESAR era

The first successful application of respiratory ECMO for adult patients with respiratory failure was reported in 1972 by Hill et al [2]. However, two randomized controlled trials failed to show the survival benefits of ECMO in adult patients with severe respiratory failure because of the development of many complications, such as bleeding, lung injury, and clot formation [3,4]. Therefore, ECMO is used only by a limited number of researchers in Europe and the US. On the other hand, Japan, Korea, and Taiwan initiated using this machine to resuscitate patients who had experienced cardiopulmonary arrest; i.e., E-CPR. This tendency urged Japanese companies to manufacture a new type of ECMO machine, quick priming, but with low flow and an artificial lung causing plasma leakage when used for long durations. This machine is suitable for E-CPR, but not for respiratory ECMO.

CESAR and H1N1

In 2008, a landmark trial called the CESAR trial was published [5]. This multicenter randomized controlled trial showed favorable outcomes of patients who received ECMO. However, the design of this trial involved comparing patients transferred to a specialized ECMO centers vs. local intensive care units. ECMO centers can treat patients using their algorithm such that not all patients receive ECMO. This result showed the benefit of centralizing patients to a specialized center and providing treatment using an algorithm including ECMO.

At the time of publication of the CESAR trial, the H1N1 influenza had spread widely, and there were many patients with severe respiratory failure. Countries that had implemented nationwide centralization of patients receiving ECMO to specialized hospitals, such as Karolinska University in Sweden, showed a greater than 90% survival-to-discharge rate [6,7]. On the other hand, Japan showed only a 35% survival-to-discharge rate [8]. This is attributed to the implementation of a non-centralized system, low expertise in respiratory ECMO management, and inappropriate machines used for respiratory ECMO. Since then, Japan has initiated an ECMO project and developed the ability of managing patients with ECMO. By 2016, the survival rate of patients with H1N1 influenza receiving ECMO reached the global average rate [9].

EOLIA

After the CESAR trial and H1N1 pandemic, many intensivists believed in the usefulness of ECMO for adult patients with respiratory failure. Therefore, a randomized controlled trial comparing patients receiving and not receiving ECMO and was performed in 2018; however, the result indicated that ECMO is not superior to non-ECMO treatment in terms of planned primary outcomes of survival benefit ($p=0.07$) [10]. This result is controversial because "rescue ECMO" was included in the non-ECMO group, which means that patients receiving ECMO could have been included in the non-ECMO group when patients met the preset criteria. This design was utilized because of the ethical point of view.

COVID-19 and ECMO

COVID-19 can cause severe respiratory failure, which has led to many deaths. Thus, ECMO is anticipated to become a last resort for the treatment of these patients [11, 12]. A preliminary report indicated that the mortality rate of patients receiving ECMO is 94.1% [13]. The original data of this report mainly originated from China in the early stage, and the quality of the management was not discussed in detail. In Japan, ECMO specialists established a telephone consultation system for the treatment of patients with severe COVID-19 on Feb 15, 2020 [14]. This system is operated by the Jap-

anese Society of Intensive Care Medicine, Japanese Association for Acute Medicine, Japanese Society of Respiratory Therapy Medicine, and PCPS/ECMO study group. From Feb 15 to Apr 15, 2020, 75 patients received ECMO and 36 patients completed ECMO treatment. Of these 36 patients, 25 (69%) of the patients were successfully weaned off ECMO, and 11 (31%) of the patients died [15]. Thirty-nine patients continued treatment. The first successful case report from Japan published by Yokohama and coauthors also recommend the centralization of patients receiving ECMO [16]. These results indicate that if patients' needs do not overwhelm medical resources, the benefit of ECMO treatment may be promising.

Conclusion

We have reviewed the basics and history of ECMO. Historical data suggest that ECMO may be a last resort for the treatment of severe respiratory failure; however, it may be a futile treatment if not managed appropriately. Teams in Japan have learned this fact from their experience with H1N1 influenza and developed a telephone consultation system for patients with COVID-19. Improved survival is anticipated for patients receiving ECMO in Japan.

REFERENCES

1) Bedford J, Enria D, Giesecke J, *et al*. COVID-19: towards controlling of a pandemic. *Lancet* 2020;395:1015-8. doi:10.1016/S0140-6736 (20) 30673-5.

2) Hill JD, O'Brien TG, Murray JJ, *et al*. Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock- lung syndrome). Use of the Bramson membrane lung. *N Engl J Med* 1972;286:629-34. doi:10.1056/NEJM197203232861204.

3) Zapol M, Snider M, Hill D, *et al*. Extraorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. *JAMA* 1979;242:2193-6. doi:10.1001/jama.242.20.2193.

4) Gattinoni L, Pesenti A, Mascheroni D, *et al*. Low-frequency positive-pressure ventilation with extracorporeal CO2 removal in severe acute respiratory failure. *JAMA* 1986;256:881-6.

5) Peek GJ, Mugford M, Tiruvoipati R, *et al*: Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomized controlled trial. *Lancet* 2009;374:1351-63. doi:10.1016/S0140-6736 (09) 61069-2.

6) Holzgraefe B, Broomé M, Kalzén H, Konrad D, Palmér K, Frenckner B. Extracorporeal membrane oxygenation for pandemic H1N1 2009 respiratory failure. *Minerva Anestesiol* 2010;76:1043-51.

7) Sukhal S, Sethi J, Ganesh M, Villablanca PA, Malhotra AK, Ramakrishna H. Extracorporeal membrane oxygenation in severe influenza infection with respiratory failure: A systematic review and meta-analysis. *Ann Card Anaesth* 2017;20:14-21. doi:10.4103/0971-9784.197820.

8) Takeda S, Kotani T, Nakagawa S, *et al*. Extracorporela membrane oxygenation for 2009 influenza A (H1N1) severe respiratory failure in Japan. *J Anesth* 2012;26:650-7. doi:10.1007/s00540-012-1402-x.

9) Ohshimo S, Shime N, Nakagawa S, Nishida O, Takeda S; Committee of the Japan ECMO project. Comparison of extracorporeal membrane oxygenation outcome for influenza-associated acute respiratory failure in Japan between 2009 and 2016. *J Intensive Care* 2018;6:38. doi:10.1186/s40560-018-0306-8.

10) Combes A, Hajage D, Capellier G, *et al*. Extracorporeal membrane oxygenation for Severe Acute Respiratory Distress Syndrome. *N Engl J Med* 2018;378:1965-75. doi:10.1056/NEJMoa1800385.

11) Ramanathan K, Antognini D, Combes A, *et al*. Planning and provision of ECMO services for severe ARDS during the COVID-19 pandemic and other outbreaks of emerging infectious diseases. *Lancet Respir Med* 2020;8:518-26. doi:10.1016/S2213-2600 (20) 30121-1.

12) MacLaren G, Fisher D, Brodie D. Preparing for the most critically Ill patients with COVID-19: The potential role of extracorporeal membrane oxygenation. *JAMA* 2020 Feb 19. doi:10.1001/jama.2020.2342. [online ahead of print]

13) Henry BM, Lippi G. Poor survival with extracorporeal membrane oxygenation in acute respira-

tory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19): Pooled analysis of early reports. *J Crit Care* 2020 Apr 1;58:27-8. doi:10.1016/j.jcrc.2020.03.011. [online ahead of print]

14) Japan ECMOnet for COVID-19. Japan ECMOnet for COVID-19: telephone consultations for cases with severe respiratory failure caused by COVID-19. *J Intensive Care* 2020;8:24. doi:10.1186/s40560-020-00440-9.

15) https://www.jsicm.org/news/upload/COVID-19-ECMOnet-report_20200412.pdf (accsessed Apr. 22, 2020).

16) Taniguchi H, Ogawa F, Honzawa H, *et al*. Veno-venous extracorporeal membrane oxygenation for severe pneumonia: COVID-19 case in Japan. *Acute Med Surg* 2020;7:e509. doi:10.1002/ams2.509.