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REVIEW PAPER

Artificial Lung / ECMO

Evolutions of extracorporeal membrane oxygenator (ECMO): perspectives for advanced hollow fiber membrane

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Abstract

Hollow fiber membrane is incorporated into an extracorporeal membrane oxygenator (ECMO), and the function of the membrane determines the ECMO's functions, such as gas transfer rate, biocompatibility, and durability. In Japan, the membrane oxygenator to assist circulation and ventilation is approved for ECMO support. However, in all cases, the maximum use period has been only 6 h, and so-called 'off-label use' is common for ECMO support of severely ill COVID-19 patients. Under these circumstances, the HLS SET Advanced (Getinge Group Japan K.K.) was approved in 2020 for the first time in Japan as a membrane oxygenator with a two-week period of use. Following this membrane oxygenator, it is necessary to establish a domestic ECMO system that is approved for long-term use and suitable for supporting patients. Looking back on the evolution of ECMO so far, Japanese researchers and manufacturers have also contributed to the developments of ECMO globally. Currently, excellent membrane oxygenators and systems have been marketed by Japanese manufacturers and some of them are globally acclaimed, but in fact, most of the ECMO membranes are not made in Japan. Fortunately, Japan has led the world in the fields of membrane separation technology and hollow fiber membrane production. In the wake of this pandemic, from the perspective of medical and economic security, the practical use of purely domestic hollow fiber membranes and membrane oxygenators for long-term ECMO is imperative in anticipation of the next pandemic.

Keywords Long-term ECMO · Hollow fiber membrane · Silicone rubber · Polypropylene · Polymethylpentene

Introduction

Hollow fiber membrane is used for extracorporeal membrane oxygenator (ECMO) to support severe acute respiratory distress syndrome patients caused by 2019 novel coronavirus disease (COVID-19) [1–3]. The extracorporeal membrane oxygenator (ECMO) is the "last stronghold" for severely ill COVID-19 patients [1]. The survival rate for severely ill COVID-19 patients supported by ECMO in Japan is 67%, which is one of the highest in the world [2].

Perhaps the effect of ECMO support was recognized due to the impact of the COVID-19 pandemic, the HLS SET advanced system (Getinge Group Japan K.K.) was approved for the first time in Japan in 2020, as a membrane oxygenator with a two-week period of use [4]. Furthermore, in the revision of medical treatment scores in 2022, the item of V-V ECMO was newly established, and medical fees for treatment and management (K601-2, K916) related to ECMO for severe respiratory failure were added. It was stipulated that a clinical engineer should be stationed at all times [5]. In consequence, the level of the support system for patients with severe respiratory failure would be improved, and clinical engineers take on even more responsibilities.

This paper focuses on the evolutions of hollow fiber membrane used in ECMOs based on these expectations for ECMOs. It is significant that there are some choices of ECMO devices because some manufacturers have unique ECMO devices on the market in Japan and worldwide. However, in fact, most of the hollow fiber membranes built into ECMO are manufactured overseas, and there are serious concerns from the point of medical and economic security. There have been numerous studies conducted on ECMO, but our focus is on the materials and pore structures of hollow

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fiber membranes summarizing the evolution of ECMO as well as prospects of next-generation ECMO devices.

The world's first membrane oxygenators using silicone and polypropylene hollow fiber membranes

The first generation of gas exchange membranes that have been put into practical use as membrane oxygenators is homogeneous membrane (dense membrane, nonporous membrane) using silicone rubber. The second generation is microporous membrane using polymer materials such as polypropylene, and the third generation is composite membrane such as silicone-coated polypropylene or polymethylpentene membrane. At present, the mainstream is polypropylene and polymethylpentene membranes. Table 1 shows a summary for evolutions of extracorporeal membrane oxygenator.

In 1981, Yada et al. developed the world's first hollow fiber oxygenator using silicone rubber [6]. The inner diameter of the hollow fiber membrane was 200 μm, the wall thickness was 100 μm, and 12,000 hollow fibers were fixed to the housing with polyurethane at both ends so that the effective length was 160 mm, and the membrane area was 1.2 m^2. Compared to the conventional coil-type Kolobow lung [7], which used the flat silicone membrane, pressure drop was much smaller during long-term use, and problems, such as decreased gas exchange capacity and hemolysis, were reduced. At that time, hollow fiber membrane oxygenators had already been reported not using silicone rubber [8].

On the other hand, Motomura and Nose et al. developed an ECMO module (Fuji-Baylor College of Medicine (Fuji-B.C.M.)) using a silicone hollow fiber membrane with a wall thickness of 35 μm [9]. It was ultrathin hollow fiber, because the wall thickness of silicone hollow fiber membrane on the market at that time was 100 μm (with an inner diameter of 200 μm) (Silox, Senko Medical Instruments, Mfg., Co., Ltd, Tokyo, Japan). Although silicone membranes were said to have high gas permeability, there was a problem with strength that they had to be thickened in order to be produced in the manufacturing process. As the wall thickness increases, the gas permeability decreases and the device becomes larger. To eliminate these weaknesses of silicone membranes, a special silicone rubber compound and an innovative extruding method have been developed to achieve a rigid membrane structure for the Fuji-B.C.M. membrane.

However, ECMO using silicone hollow fiber membrane itself was withdrawn from the market, probably due to difficulty in achieving both functions and manufacturability. Silicone, as one of the membrane materials, is continued to be used in ECMOs. In 1985, Matsuda et al. reported a siliconized polypropylene membrane in which the pores of a porous polypropylene hollow fiber (Capiox® II) were wetted with silicon oil from the inner side of hollow fiber [10]. Nakanishi et al. bonded tetramethylcyclotetrasiloxane (1,3,5,7-tetramethylcyclotetrasiloxane: TMCTS, cyclic silicone cyclosiloxane (silicone)) that constituted a cyclic molecule to the outer surface of a porous polypropylene hollow fiber membrane by a radical reaction and developed a novel composite membrane. The thickness of the silicone layer was 0.1 μm [11–13]. Currently, the polypropylene membrane CELGARD® manufactured by 3 M™ (Membrana) is used.

Prior to these, Mori et al. developed a membrane oxygenator using a porous polypropylene hollow fiber membrane [14]. The inner diameter of the hollow fiber membrane was 200 μm, the wall thickness was 25 μm, the porosity was 50 vol%, and the pore radius was 650 Å. Due to high pressure drop and low durability in clinical use of the coil-type oxygenator using flat membrane, they prototyped a completely new membrane-type oxygenator equipped with this hollow fiber membrane.

Based on this ECMO prototype, Terumo launched the world's first oxygenator using porous polypropylene hollow fiber membrane (Capiox®II) in 1982 [15]. The design looked like a modern dialyzer, a heat exchanger and a gas exchanger (hollow fiber membrane) were separated at the center of the device. Terumo's porous polypropylene hollow fiber membrane oxygenator was called Capiox® Lung. Initially, the blood flow path was an intra-capillary perfusion type in which blood perfused inside the hollow fiber membrane, but in 1987, an extra-capillary perfusion type with low pressure drop in the blood flow path and high gas exchange performance was launched [16, 17]. At present, the extra-capillary perfusion hollow fiber membrane oxygenator is the mainstream worldwide. The world's first extra-capillary hollow fiber membrane oxygenator was Maxima® [18].

In the 1990s, extensive researches were conducted to improve long-term durability of polypropylene membranes. Hagiwara et al. reported in detail the development of a polypropylene membrane that achieved both gas exchange performance and plasma wetting resistance [19]. Polypropylene membranes are generally produced by the melt–extrusion–stretching method and by the thermally induced phase separation method (TIPS process).

In 1982, Masuda et al. succeeded in synthesizing three types of polymethylpentene polymers, 4-methyl-1-pentyne, 3-methyl-1-pentyne, and 4-methyl-2-pentyne, using the Transition Metal Catalysts method [20]. Furthermore, Morisato et al. prepared a flat membrane made from poly(4-methyl-2-pentyne) and measured the oxygen permeability coefficient, etc., and demonstrated the superiority of the gas-permeable membrane made from poly(4-methyl-2-pentyne) [21]. Investigations into the use of polymethylpentene as a hollow fiber membrane for a membrane oxygenator progressed, and in 1990, Tatsumi et al. developed the world's first extracapillary membrane oxygenator using hollow fiber membrane made from poly(4-methyl-1-pentyne) [22–24].

Table 1 Evolutions of extracorporeal membrane oxygenator (ECMO)

year	Author, manufacturer	Topics, specification of membrane	Remarks	refs
1963	Kolobow, et al	Silastic-coated Dacron membrane	Coil-type membrane oxygenator	[7]
1981 1984	Yada, et al Senko Medical Instruments, Mfg., Co.,Ltd, Tokyo, Japan	Silicone hollow fiber membrane oxygenator Inner diameter: 200 μm, wall thickness: 100 μm	The world's first membrane oxygenators using silicone hollow fiber membrane	[6]
1979 1982	Mori, et al Terumo Co. Ltd., Tokyo, Japan Mitsubishi Rayon Co. Ltd., Tokyo, Japan	Porous polypropylene hollow fiber membrane oxygenator Inner diameter: 200 μm, wall thickness: 25 μm, porosity: 50 vol%, pore radius: 650 Å	the world's first membrane oxygenators using polypropylene Hollow fiber membrane Capiox® lung	[14, 15]
1986	Johnson & Johnson	Maxima® Hollow Fiber Oxygenator	The world's first extra-capillary hollow fiber membrane oxygenator	[18]
1987	Nogawa Terumo Co. Ltd., Tokyo, Japan	Porous polypropylene hollow fiber membrane oxygenator Inner diameter: 200 μm, wall thickness: 50 μm, porosity: 35 vol%, pore radius: 1300 Å	Extra-capillary hollow fiber membrane oxygenator	[15–17]
1990	Tatsumi, et al Kurare Co. Ltd., Kurashiki, Japan	Menox® Inner diameter: 200 μm, wall thickness: 25 μm	The world's first membrane oxygenators using polymethylpentene hollow fiber membrane	[22–24]
1996	Nakanishi, et al Senko Medical Instruments, Mfg., Co., Ltd, Tokyo, Japan	Silicone-coated polypropylene hollow fiber membrane		[11–13]
1998	Maquet membrane: Membrana	QUADROX-D, polymethylpentene		
2003	Motomura, Nose Fuji-Baylor College of medicine (B.C.M)	Ultrathin silicone hollow fiber membrane Wall thickness: 35 μm, effective length: 150 mm, fiber density: 28%		[9]
2004	Eash, et al Celgard Inc., Charlotte, NC Membrana, Wuppertal, Germany Dainippon Ink and Chemicals, Inc., Japan Senko Medical Instrument Mfg., Tokyo, Japan	Polypropylene 240 μm, 30 μm PMP (Polymethylpentene) 200 μm, 90 μm Poly-4-methyl-1-pentene 165 μm, 30 μm TMCTS (1,3,5,7-tetramethylcyclotetrasiloxane) / Polypropylene (Celgard×30,240) 240 μm, 30 μm (inner diameter, wall thickness of hollow fiber membrane)		[30]
2005	Khoshbin, et al	Medos Hilite 7000LT, poly-methyl pentene, 1.9 m^2, priming volume 275 ml Medtronic 1–4500-2A, silicone membrane, 4.5 m^2, priming volume 665 ml		[26]
2016	Beely, et al Maquet GmbH, Rastatt, Germany	Quadrox HLS Advanced 5.0 MO, polymethylpentene		[28]
2020	Akiyama, Tatsumi, et al Nipro Co. Ltd., Tokyo, Japan	BIOCUBE 6000, polyolefin	Ultra-compact durable ECMO system	[38]
	Getinge Group Japan K.K	HLS SET Advanced, polymethylpentene	Approved for the first time in Japan, as a membrane oxygenator with a two-week period of use	[4]

The inner diameter of the hollow fiber membrane was 200 μm, the outer diameter was 250 μm (wall thickness was 25 μm), and the micropores were concealed from the blood contacting surface to prevent serum leakage, allowing continuous use for 2 weeks. This device was the prototype of the current Nipro BIOCUBE®. Anzai et al. coated the surface of the oxygenator CX-SX18R that comes in contact with blood with poly2methoxyethylacrylate (PMEA), and reported that the activated coagulation system, platelet system, and leukocyte system, which were indicators of biocompatibility were significantly suppressed [25]. Khoshbin et al. studied the performances of membrane oxygenator Medos 7000LT

(1.9 m^2, priming volume 275 ml) using PMP membrane and membrane oxygenator Medtronic 1–4500-2A (4.5 m^2, priming volume 665 ml) using silicone membrane [26].

Improved durability of ECMO

Dysfunctions of the membrane oxygenator are caused by excessive pressure drop due to blood coagulation/thrombus in the blood flow path [27, 28], plasma leakage [29–31], and the decrease in the gas exchange rate due to the decrease in the effective membrane area caused by the coagulation and plasma leakage. The plasma leakage is more likely to occur in ECMO support, which is used for longer periods than that of cardiovascular surgeries. For this reason, in Japan, in addition to the normal "extracorporeal circulation membrane oxygenator" for open heart surgery, the "assisting circulation/ventilation membrane oxygenator" for ECMO support is approved. Both are supposed to be used within 6 h. A requirement for the assisting circulation/ventilation membrane oxygenator is that "plasma leakage can be prevented by the effect of the properties of the silicone membrane or special polyolefin membrane." Plasma leakage is less likely to occur with silicone membranes or special polyolefin (polymethylpentene) membranes.

In the 2000s, there were many reports on the current status of plasma leakage and how to suppress them [29–31]. Lund et al. reported in detail that condensation already occurred in less than 0.5% of the membrane length on the oxygenator inlet side, so condensation occurred on the inner wall of the pores [29]. Eash et al. verified the long-term durability of the membrane oxygenators from the viewpoint of plasma wetting. They prototyped small devices using various hollow fiber membranes and calculated plasma leakage rates (fiber wetting studies) [30]. The DICII (poly-4-methyl-1-pentyne) and Senko's composite membrane had lower plasma leakage than the Membrana's poly(4-methyl-2-pentyne) membrane. Plasma leakage (or plasma wetting) begins at the pore entrance layer of the hydrophobic membrane, and plasma gradually permeates into the pores. It was reported that the different temperatures of the gas and blood caused water vapor to condense (condense) on the insides of the pores, leading to plasma leakage.

Our studies and future prospects of ECMO membrane

ECMO has played a crucial role in the COVID-19 pandemic since 2020. The extracorporeal membrane oxygenator (ECMO) is the “last stronghold” for severely ill COVID-19 patients [1]. There is, however, a concern that SARS-CoV-2 in plasma may permeate through the wall of hollow fiber membrane and diffuse as an aerosol from the gas outlet port during ECMO supports for severely ill patients with COVID-19 [3]. If the pore diameter of the hollow fiber membrane is 50 nm or more, there is a risk that SARS-CoV-2 with a diameter of 50–200 nm [32] will permeate through the wall of hollow fiber membrane. In addition, SARS-CoV-2-positive reactions have been detected from gas outlet ports of the membrane oxygenator even without visible plasma leakage [3].

However, the membrane and pore structures of recent ECMO membranes have not been clarified, and an evidence regarding the permeability of substances such as viruses in ECMO membranes was not clear. Therefore, we observed and analyzed the pore structure of typical ECMO membranes in Japan by previous approaches [33] using a scanning probe microscope (SPM) and a field emission electron microscope (FE-SEM) [34]. In addition, the SARS-CoV-2 permeability was calculated within the membrane using permeation theory in membrane engineering (steric exclusion model and diffusion hindrance model) [35]. We find there is a risk that SARS-CoV-2 permeates through the ECMO membrane and leaks out of the blood circulation circuit of the ECMO system [34].

In relation to these, there were concerns about the risk of SARS-CoV-2 leakage from Terumo's Capiox® membrane (“membrane oxygenator assisting circulation and ventilation”). Terumo has two types of Capiox® on the market, the "membrane oxygenator with extracorporeal circulation" and the "membrane oxygenator assisting circulation and ventilation" are approved. Therefore, we analyzed the pore structures of two types of Capiox® gas exchange membranes and verified the leakage risk of SARS-CoV-2 [36]. In addition to two-dimensional structure analysis, three-dimensional structure analysis using new techniques such as FIB-SEM tomography [37] is also recommended.

Because ECMO supports for critically ill patients with COVID-19 take several weeks [1–3], incidents occur and the membrane oxygenator or circuit must be replaced. The timing of replacement with an unused device is left to the discretion of the physician, which is not complied with regulation that the maximum usage period of the membrane oxygenator is 6 h. In Japan, the period of use for membrane oxygenators (devices, disposable oxygenators) has been 6 h, but in the EU, the HLS SET Advanced assisting circulation system is allowed to be used for up to 30 days (CE marking). In the United States, it was changed from 6 h to 15 days as a special case during the COVID-19 pandemic. Perhaps because of these achievements, the HLS SET Advanced (Getinge Group Japan K.K.) was approved in Japan in 2020, with a maximum use period of 14 days [4]. In addition, medical fee (K916) and management fee (K601-2, 30,150 points on the first day, 3000 points from the second day onwards) categories have been newly established for patients with acute respiratory failure or acute exacerbation of chronic respiratory failure who are treated with an extracorporeal

membrane oxygenator, who cannot be treated with a ventilator. As one of the facility standards for the management fee, one or more full-time clinical engineers must always be assigned within the hospital [5]. When we reconsider the history so far, these are significant advances and are expected to further improve the quality of ECMO support.

Akiyama et al. have already completed a preclinical biocompatibility study (in chronic animal experiments) of an ultra-compact durable ECMO system aiming for 2 weeks of use [38], and have already conducted clinical trials. Wan et al. coated a PP membrane with a PMP layer and then coated it with anticoagulants poly (sodium 4-styrenesulfonate) and cross-linked poly(vinyl alcohol), and proposed a composite membrane in order to enhance CO_2/O_2 selectivity and biocompatibility [39].

In Japan, domestic long-term ECMO with long-term durability must be put into practical use. Recently, no in-depth research has been conducted on hollow fiber membrane in Japan, but there are insights for a next-generation ECMO membrane in looking back on the history. Suitable long-term membrane oxygenator systems are still at an early stage of development [40]. At the same time, the question remains for the approval of HLS SET Advanced. Currently, there is a disparity between different usage periods, such as 6 hours and two weeks. The maximum length of usage should be changed to an appropriate period based on clear evidences.

Conclusion

Japanese manufacturers have launched distinctive membrane oxygenators and systems, and are contributing to the supports of severely ill patients with the new coronavirus infection even during the COVID-19 pandemic. Although some membrane oxygenators have been well received worldwide [41], most of the gas exchange membranes built into membrane oxygenators are not produced in Japan. Fortunately, Japan has led the world in the fields of membrane separation technology and membrane production, such as hemodialysis, lithium-ion battery separators, and seawater desalination. In the wake of COVID-19 pandemic, from the perspective of medical care and economic security, we should address the needs to manufacture domestic gas exchange membranes and membrane oxygenators for long-term ECMO in anticipation of the next pandemic.

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Data availability The data that support the findings of this study are available.

Declarations

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