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Membrane Oxygenator for Extracorporeal Blood Oxygenation

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Highlights:

- ECMO could provide an alternative solution for treating patients with respiratory or cardiac failure.
- The pores in the membrane wall play a more significant role in determining the resistance to plasma leakage than the surface pores.
- PMP membrane oxygenators can be used for long-term operation.
- Surface modification can successfully improve membrane biocompatibility.

Abstract. Extracorporeal blood oxygenation has become an alternative to supply O_2 and remove CO_2 from the bloodstream, especially when mechanical ventilation provides insufficient oxygenation. The use of a membrane oxygenator offers the advantage of lower airway pressure than a mechanical ventilator to deliver oxygen to the patient's blood. However, research and development are still needed to find appropriate membrane materials, module configuration, and to optimize hydrodynamic conditions for achieving high efficient gas transfer and excellent biocompatibility of the membrane oxygenator. This review aims to provide a comprehensive description of the basic principle of the membrane oxygenator and its development. It also discusses the role and challenges in the use of membrane oxygenators for extracorporeal oxygenation on respiratory and cardiac failure patients.

Keywords: *blood oxygenation; COVID-19; gas transfer; membrane oxygenator; respiratory.*

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1 Introduction

Mechanical ventilation is widely used as a primary management tool for patients with respiratory failure to supply O_2 and remove CO_2 from the bloodstream. It is the medical term for artificial ventilation where mechanical means are used to assist or replace spontaneous breathing. The oxygen is forced into the lungs through a tube inserted into the trachea. The ventilator pumps oxygen and the lungs inflate to mimic the process of breathing. The essential goals of ventilatory support to achieve safe treatment are stabilizing hydrodynamic, patient-ventilator synchrony, preserving muscle strength, minimizing dynamic hyperinflation, and limiting tissue damage [1,2]. Lung injury can occur due to high airway pressure and oxygen concentration without excessive lung strain or damage due to restricted chest wall movement [1].

When mechanical ventilation is not sufficient to provide oxygenation, extracorporeal blood oxygenation is an alternative rescue therapy with beneficial results [3]. Extracorporeal membrane oxygenation (ECMO) uses a semipermeable membrane to facilitate the transfer of oxygen to the blood of the patient. In a membrane oxygenator, gas exchange between the blood and gas streams occurs with non-dispersive contact, preventing the entrainment of the blood to the gas stream [4]. Since the gas exchange occurs in non-dispersive contact, the blood and the gas streams can be controlled independently to prevent damage to blood constituents. In addition, the membrane has a high packing density [5-8], resulting in a compact membrane oxygenator. Compared to a mechanical ventilator, the ECMO system provides an adequate amount of oxygen (O_2) to the bloodstream without high pressure, which also simultaneously removes carbon dioxide (CO_2). There are two types of commercially available ECMO systems, namely venous-arterial (VA) ECMO systems and venous-venous (VV) ECMO systems. VA-ECMO is used for patients with various etiologies of cardiogenic shock and entails either central or peripheral cannulation [9]. Meanwhile, VV-ECMO is used mainly for patients with severe respiratory failure [10]. A part that plays a vital role in ECMO systems is the membrane oxygenator, which acts as an artificial lung for gas exchange to maintain physiologic O_2 and CO_2 levels in the blood [11]. The membrane oxygenator has to meet a number of criteria, including high gas transfer performance, high mechanical property, low plasma leakage, high anti-thrombogenic properties, low protein adsorption, and low platelet adhesion [12-14].

Membrane oxygenators are usually fabricated using polymeric materials, such as polysulfone [15], polyurethane [16], polypropylene [17], polyimide [18], and silicon [19-22]. Among these polymers, non-porous silicon-based hollow fiber is used in commercial ECMO systems due to its ability to avoid plasma leakage during the long time of extracorporeal circulation. Recently, a silicone hollow

fiber membrane with ultra-thin wall thickness has been developed, which exhibits high oxygen and carbon dioxide transfer rates [5]. During the ECMO treatment, clot formation on the membrane surface is the main challenge due to interaction of the vascular endothelium with plasma proteins and platelets. Surface modification of the membrane oxygenator with anticoagulants, such as heparin or hydrophilization of the membrane surface, has been proposed to reduce clot formation [16,17,23].

In the last 20 years, numerous scientific studies have focused on membrane oxygenator development and several applications have been published (Figure 1(a)). Most of these articles were published in medical and health or biomedical journals, followed by engineering and biochemistry journals. In 2009, the application of membrane oxygenators was further increased to treat severe acute respiratory distress syndrome (ARDS) patients during the influenza A (H1N1) and SARS (Severe Acute Respiratory Syndrome) pandemic. Since polymethylpentene (PMP) oxygenators were developed in the same year as bearingless centrifugal pumps and better cannula technology, the number of research articles on the application of membrane oxygenator in ECMO systems increased significantly [24]. Recently, Coronavirus Disease 2019 (COVID-19) has spread in more than 200 countries and infected more than 140 million people in the world, with more than 3,000,000 deaths [25].

COVID-19 is caused by a novel SARS-CoV-2 virus, which enters the human body through the respiratory tract, oral mucosa, and conjunctival epithelium [26,27]. Most COVID-19 patients suffer worsening breathing difficulties due to respiratory failure and acute respiratory distress syndrome (ARDS) [28,29]. Several research papers on the role of ECMO in COVID-19 patient treatment have been published. Based on the number of publications in the last 20 years, the study on ECMO applications for patients with respiratory or lung failure is higher than those for cardiac failure (Figure 1b).

Previously, several reviews have discussed the ECMO and its importance during the COVID-19 pandemic. Alentiev and co-workers [30] elaborated on the progress of ECMO technology by discussing membrane materials, methods for increasing compatibility, and rational approaches for designing the membrane contactor. Savarimuthu, *et al*. [31] emphasized that the use of an ECMO should be prioritized for critically ill patients that have been selected carefully due to the limited number of ECMO units.

They also provide the prospect of ECMO playing an important role in the near future for combatting COVID-19. This paper aims to provide a comprehensive review of a wide spectrum of membrane oxygenators and their application in extracorporeal blood oxygenation. This includes the fundamental background,

system and materials' development, and the crucial role of the membrane oxygenator in ECMO systems during the treatment of patients with respiratory and cardiac failure.

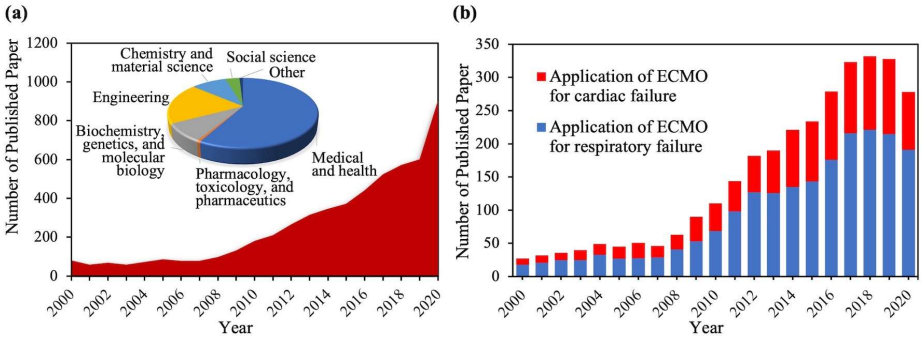

Figure 1 Number of publications per year: (a) related to membrane oxygenator or extracorporeal membrane oxygenation (ECMO), and (b) its applications. The number of publications was collected by using Elsevier's Scopus database with the query 'TITLE (membrane oxygenator or extracorporeal membrane oxygenation)'; attn: 6th Dec 2020.

2 Fundamental Background of Membrane Oxygenator

2.1 Blood Oxygenation in ECMO

An ECMO module has two compartments, which are separated by a semipermeable membrane. The patient's blood flows into the first compartment or the shell side of the module, while a rich-oxygen gas passes through the second or lumen side of a hollow fiber (HF) membrane. The membrane serves as a contactor and facilitates the gas exchange between the blood and the fresh gas, where both oxygen delivery to the blood and carbon dioxide removal from the blood occur [32,33]. The VV-ECMO process replaces the native lung function. Unlike a conventional bubble oxygenator, an ECMO system prevents direct contact between the blood and the fresh gas, allowing one to optimize both streams independently and minimizing blood trauma.

The gas transfer between the blood and the gas through the membrane is a crucial step in the oxygenation process. A natural lung membrane has a surface area of 150 m^2 [34] or 70 m^2 [35], is 1 to 3 μm thick, and has a surface/blood volume ratio of 300 cm^{-1}, leading to 3,000 mL/min oxygenation and carbon dioxide removal. In contrast, an ECMO membrane has a lower surface area (<4 m^2), a thicker membrane (10 to 30 μm), and a lower packing density (30 cm^{-1}) than a

natural lung. Consequently, an ECMO can only carry a maximum gas exchange of 250–200 mL/min [34].

Aside from the gas diffusion process, plasma leakage and activation of coagulation are significant concerns in ECMOs [34]. Constant contact of the blood with non-biological artificial material, i.e. the membrane oxygenator material may trigger coagulation activation, resulting in thrombosis, bleeding, and device problems during oxygenation [36].

ECMO generally uses two types of membranes, dense (or non-porous) and microporous membranes, as selective barrier. A solution-diffusion mechanism usually governs the gas transport in the dense membrane. The flux of gas through the membrane, J_i, is expressed by Fick's law [37]:

$$J_i = -D_i \frac{dCi}{dx} \tag{1}$$

where C_i is the concentration of species i in the membrane, D is the diffusion coefficient of species i in the membrane, and x is the gas flow direction across the membrane. According to Henry's law, the gas concentration in the membrane is proportional to pressure p and gas solubility S in the membrane ($C = S\,p$). This is based on the assumption that the gas solubility in the polymer is very low. The product of D x S is known as the gas permeability (P). By introducing P_i, Eq. (1) can be integrated and rewritten as [37]:

$$J_i = \frac{P_i}{l}(p_f - p_p) \tag{2}$$

where l is the membrane thickness, p_f and p_p are the pressure in the feed and permeate sides, respectively. According to this mechanism, selective transport occurs for gases with different permeability. For ECMOs, the membrane should allow high permeation of O_2 and CO_2 during the oxygenation while retaining other gasses like N_2 in the fresh gas.

The dense homogenous membrane exhibits high mass transfer resistance due to the small membrane pores. Therefore, a microporous hydrophobic membrane has been introduced [38]. The flux of the gas into the liquid stream, J, in microporous membranes is defined as [39]:

$$J = K\,\Delta C \tag{3}$$

where ΔC is the overall concentration difference across the membrane and K is the overall average mass-transfer coefficient. The mass-transfer coefficient can be determined experimentally by measuring the gas concentration in the liquid phase. The average mass-transfer coefficient is then expressed by [39]:

$$K = \frac{Q}{A} \ln\left(\frac{C - C*}{C_0 - C*}\right) \tag{4}$$

In Eq. (4), A is the membrane surface area, C is the gas concentration, C_0 is the initial gas concentration, C^* is the equilibrium gas concentration, and Q is the volumetric flow rate of the liquid. It should be noted that the main resistance to gas transfer in the blood oxygenation using microporous membranes is the liquid side concentration boundary layer. Hence, K, the overall average mass transfer coefficient can be represented by the liquid side mass-transfer coefficient. Here, the hydrodynamic condition is one of the main parameters that affect the efficiency of mass transfer.

2.2 Membranes and Module Design for ECMO

ECMO requires a hemocompatible membrane that can perform efficient gas exchange [40]. Various membrane types used in membrane oxygenators are illustrated in Figure 2(a). Non-porous membranes can be free from plasma leakage since they have very small pores, preventing the intrusion of blood cells [41], however, they are usually limited by low gas permeability [42]. This poses another challenge, because the larger membrane area must achieve sufficient gas transfer to the patient's blood. Therefore, the recent development of non-porous membranes for ECMO application is directed at obtaining highly permeable membranes (discussed in Section 3).

For ECMOs that use a microporous membrane, a hydrophobic membrane material is required to prevent liquid penetrating into membrane pores. This is because liquid penetration will wet the membrane, leading to a dramatic decrease in the gas exchange rate and increased mass-transfer resistance (see Figure 2(b)) [38]. As a result, the long-term blood oxygenation performance will be compromised. In addition to the membrane's hydrophobic/hydrophilic property, a recent study has revealed that liquid infiltration is related to the pore size in the membrane wall [38].

This study then suggests that the membrane pore size distribution and the presence of surfactants in the patient's blood determines the membrane's resistance to plasma leakage. Lastly, membrane leaking and plasma leakage could also occur because of the formation of a hydrophilic surface at the membrane pore openings by blood phospholipids [43]. The hydrophilic surface allows plasma to infiltrate the membrane pores, leading to further formation of a hydrophilic surface along the pore walls, which leads to membrane wetting [44,45]. Increasing the gas flow rate can be used as a countermeasure, but this risks introducing a gas embolism in the bloodstream [43].

Based on the module design, membrane oxygenators can be classified into three types, i.e. parallel-plate, spiral-wound (cylindrical), and HF membrane oxygenators. In the parallel-plate type, the flat-sheet membranes are separated by

screens. This is the simplest arrangement, but the diffusion is limited. In the spiral-wound type, the flat-sheet membranes are wrapped around a central cylinder [46,47], in which the blood flows parallel to the axis of the cylinder between the membrane folds, while oxygen flows through the cylinder. The latter type has the advantage of the best flow control [30], where the blood can flow inside the fiber or outside the fiber. In addition, there are several option for optimizing the flow direction and fiber arrangement.

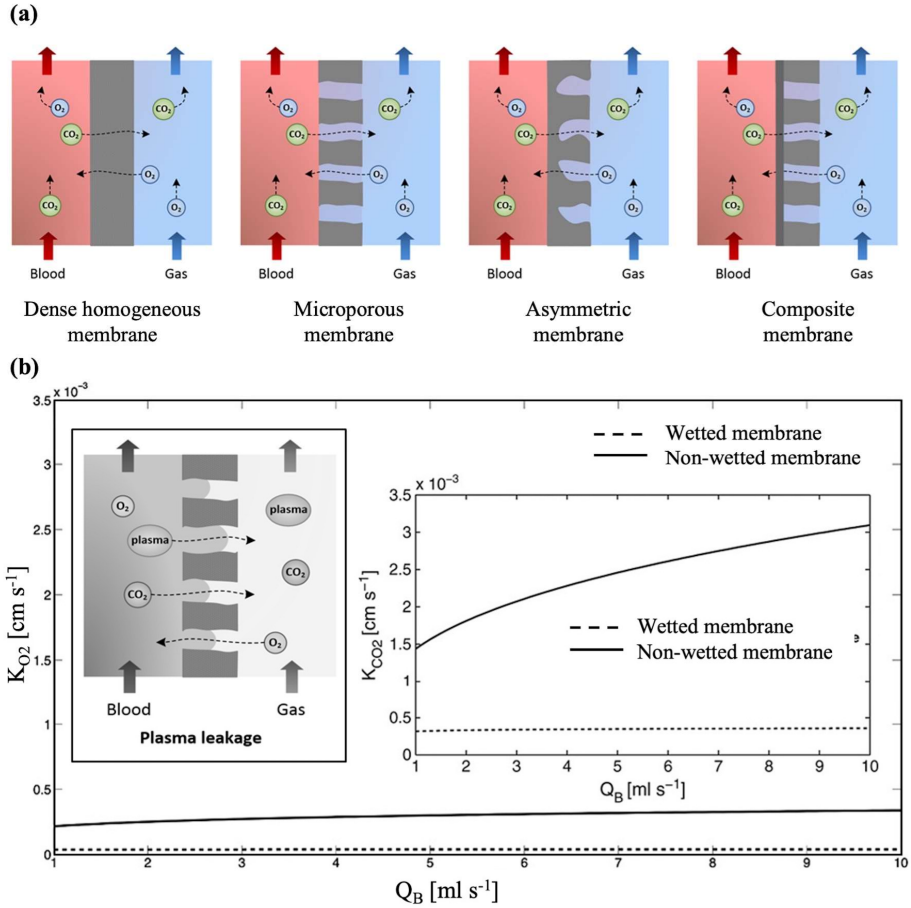

Figure 2 Membrane types and wetting in membrane oxygenator: (a) various membrane types used for membrane oxygenator, (b) wetting decreases the gas transfer rate significantly (reprinted with permission from [48], © 2012 John Wiley and Sons; the plasma leakage in the inserted figure is from this work).

In 2005, Wickramasinghe, *et al*. [39] reported the mass-transfer and friction-factor correlations to predict the gas transfer rate and pressure loss of blood in microporous HF and flat-sheet membrane oxygenators. By considering the average shear stress of the blood (5-20 Pa), the shear-thinning behavior of blood was taken into account using the Generalized Graetz, Reynolds, and Schmidt numbers. Meanwhile, a mass-transfer enhancement factor based on film theory was used to capture the role of the oxygen-hemoglobin reaction, which occurs in real conditions.

Both experimental and numerical simulations were carried out using blood analog fluids, i.e. Newtonian and non-Newtonian fluids and bovine blood. For the flat-sheet membrane module, the mass-transfer correlation is defined by the Graetz (*Gr*) and Sherwood (*Sh*) numbers (see Figure 3(a)):

$$Sh = \frac{K(4B)}{D} \tag{5}$$

$$Sh = 0.5\ Gr\ (0.5 < Gr < 10) \tag{6}$$

$$Sh = 3.0\ Gr^{0.33}\ (10 < Gr < 500) \tag{7}$$

where B is the average half-thickness of the rectangular channels, D is the diffusion coefficient of O_2, and Gr is a function of module geometry (thickness and length of the channel), the diffusion coefficient of the gas, and liquid velocity. For microporous HF membrane, the mass-transfer correlation is defined by dimensionless numbers (the Sherwood, Reynolds, and Schmidt numbers, see Figure 3(b)):

$$Sh = 0.8\ Re^{0.59} Sc^{0.33} \tag{8}$$

According to these equations, the efficiency of the oxygen transfer in an ECMO not only relies on the membrane's properties but also on the module design and the hydrodynamic conditions. The results show that the Sherwood number is significantly affected by the liquid flow rate.

The concentration of the liquid boundary layer limits the mass transfer, which applies to all fluid types used. This issue is typically addressed by placing a passive mixing unit in the ECMO module so that the liquid boundary layer can be disrupted. Increasing the liquid flow rate leads to improved oxygen transfer, but increases the risk of pressure loss. Furthermore, the oxygen transfer rate and the pressure loss appear to depend on the module design [49].

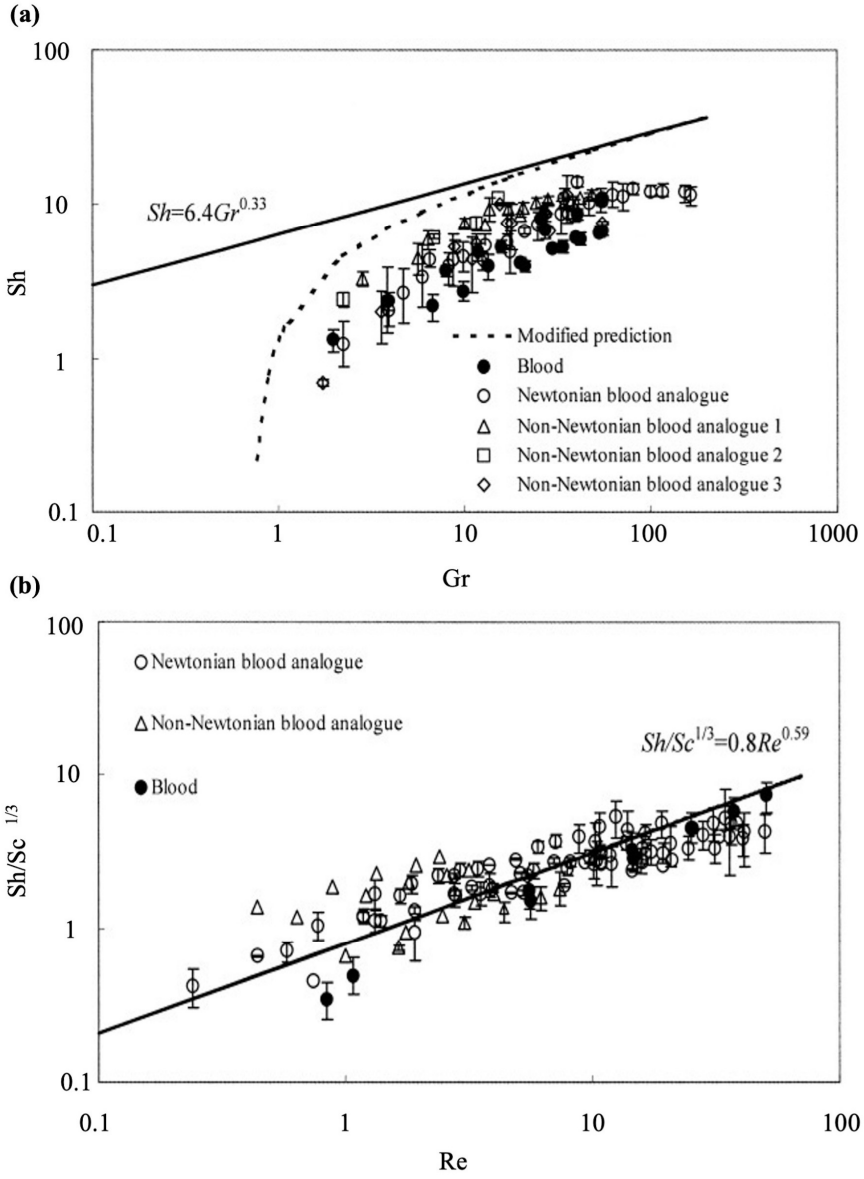

Figure 3 Membrane oxygenator modules: (a) Sh vs. Gr of flat sheet module, (b) $Sh/Sc^{1/3}$ vs. Re of hollow fiber module (reprinted with permission from [39], © 2005 John Wiley and Sons)

3 Recent Development of Membrane Oxygenators

The ECMO has been introduced in 1944 when Kolff & Berk [50,51] came up with the idea to add a protective membrane between the blood and the air in extracorporeal oxygenators to decrease the potential of blood trauma inherent in direct-contact oxygenators. The emphasis in early membrane oxygenator development was on finding suitable biomaterials. However, most biomaterials had low gas exchange performance and poor mechanical properties, thus limiting the development of membrane oxygenators [52].

In the 1950s, Clowes investigated polyethylene as the oxygenator membrane material [46,53]. The polyethylene membrane had good mechanical properties but relatively low permeability. In the recent development of membrane oxygenators for application in ECMOs, silicone, polypropylene (PP), and polymethylpentene (PMP) have been studied predominantly. Membrane oxygenators based on these materials are individually reviewed in this section.

3.1 Silicone-based Membrane Oxygenators

Silicone is an attractive material for medical devices such as membrane oxygenators because of its excellent biocompatibility [54]. In addition, since the silicone membrane is typically homogenous, plasma leakage can be avoided. However, it is necessary to minimize membrane resistance to enhance the gas transfer rate and, on the other hand, it is quite challenging to fabricate thin-walled silicone HFs because of the poor mechanical strength of conventional silicone.

Researchers from Baylor College of Medicine and Fuji Systems Corporation have developed a fine silicone HF membrane oxygenator for ECMOs. In 1996, as reported by Funakubo, *et al*. [55], a novel silicone material was developed using methylvinylsiloxane as the base polymer, vinyl resin, and hydrogen siloxane. The new silicone has sufficient mechanical strength with a wall thickness that is approximately half that of a conventional one. As a result, fibers with a surface area of 2 m^2 exhibited a high O_2 and CO_2 rate of 195 ml/min and 165 ml/min, respectively, at a blood flow rate of 3 L/min, which are values comparable to those of a microporous membrane oxygenator. Moreover, with a much smaller surface area, its performance was similar to that of the silicone sheet oxygenator [56].

A preclinical evaluation showed that the silicone HFs should be considered for one week of ECMO application [57]. A two-week long-term experiment showed that the silicone HFs exhibited excellent efficiency, with less blood trauma, but further improvement was required to prevent the occurrence of hemolysis [58]. In a more recent study, it was revealed that a silicone HF-type module had a higher gas transfer rate than a silicone coil-type module [59].

A different way to reduce the gas transfer resistance has been proposed by Kachab, *et al.* [60]. Mimicking the bee comb structure, they fabricated a hollow silicone sphere. In the presence of microspheres, gas can diffuse easily, resulting in a higher gas transfer rate. Other studies used a silicone micropore membrane as the support structure for a thin layer of gas-permeable polydimethylsiloxane (PDMS) [19,42]. The membrane had an oxygen transfer rate of 0.03 mL/min at a liquid flow rate of 10 mL/min with a membrane area of 6.5 x 10^{-4} m^2 [42]. Gas transfer performances of membrane oxygenators based on silicone material are summarized in Table 1.

3.2 Polypropylene-based Membrane Oxygenators

Polypropylene (PP) membrane oxygenators for ECMO systems have been reported since the 1980s [61,62]. The adoption of microporous PP was able to reduce coagulation issues associated with silicone [43]. In addition, PP membrane oxygenators offer high gas transfer rates, low priming volume, and low resistance.

Fried & Bell-Thomson [63] compared the performance of a PP oxygenator configured with a flat sheet and an HF (PPHF). They reported that the PPHF oxygenator showed a superior trade-off between factors such as diffusion distance, surface area, priming volume, and blood flow rate. Besides that, the flow configuration also affects the efficiency of the gas transfer. In an HF membrane oxygenator where the blood flows inside the fibers, it is possible to create laminar blood flow without diffusion limitations. However, blood flow inside the fibers can generate an increase in the hydrodynamic resistance of the channels, which could lead to an increase in the pressure differential in the oxygenator.

Meanwhile, in an HF arrangement where the blood flows on the outside and gas flows on the inside of the fibers, it is possible to control the packing of the fibers for the creation of small-thickness channels with a turbulent blood flow [30]. The turbulent blood flow leads to an intensification of the convective mass transfer, thus increasing the efficiency of the gas transfer. Another study revealed that based on theory for tube banks, different PP fiber arrangements (parallel or crossed) resulted in a different mass transfer performance [64].

Even though a PPHF membrane oxygenator is able to provide high gas transfer performance, it is not appropriate for use over prolonged periods because of the wetting phenomenon [43]. As can be seen in Table 1, PPHF membrane oxygenators have a very short operation life. To overcome this problem, efforts have been made to modify the structure of the PPHF membrane from microporous to non-microporous by silicone coating [62]. The study by Shimono,

et al. [65] reported that a silicone coated PPHF oxygenator is more durable and offers greater gas transfer capabilities than an uncoated PPHF oxygenator. The silicone layer could reduce the contact activation of the oxygenator due to its good biocompatibility and complete prevention of contact between blood and gas.

3.3 Polymethylpentene-based Membrane Oxygenator

In the early 2000s, a new generation of polymethylpentene (PMP) membrane oxygenators has been introduced to avoid complications linked to HF oxygenators, such as plasma leakage. Different from PPHFs, which are typically microporous, PMPHFs have an asymmetric pore structure with a dense outer skin that provides complete physical separation between the blood and the gas phases, thus avoiding plasma leakage [66,67]. In addition, the asymmetric structure of the PMPHF also allows for efficient gas exchange to take place for extended periods [68,69].

Table 1 Gas transfer performance of silicone-based, PP, and PMP membrane oxygenators.

Membrane	Membrane area (m^2)	Priming volume (L)	Blood flow rate (L/min)	O_2 transfer rate (L/min)	CO_2 transfer rate (L/min)	Operation life (day)	Ref.
Silicone-based (HF*)	2	0.230	3	0.195	0.165	-	[55]
Silicone-based (HF*)	1.1	0.228	2	0.1182 ± 0.005	0.066 ± 0.009	-	[56]
Silicone-based (HF*)	1.5	0.175	1[a]	0.07316 ± 0.001	0.033 ± 0.001	-	[57]
			1[b]	0.040	0.06	-	
Silicone-based (HF*)	1	0.200	1[a]	0.072 ± 0.001	0.0399 ± 0.003	-	[58]
			2[a]	0.128 ± 0.001	0.047 ± 0.005	-	
			1[c]	0.042 ± 0.004	0.041 ± 0.014	-	
Silicone-based (HSF*)	0.0197	0.00174	0.2	0.0126	0.010	-	[60]
PP (Terumo**)	2.5	0.25	0.5-7.0	0.05-0.55	0.02-0.60	0.25	[71]
PP (Medtronic**)	2.5	0.26	1.0-7.0	0.05-0.40	0.10-0.35	0.25	[72]
PP (Medtronic**)	2.5	0.27	1.0-7.0	-	-	0.25	[73]
PP (Eurosets**)	1.65	0.225	≤ 7.0	-	-	0.25	[74]
PP (MicroPort**)	2.0	0.16	≤ 6.0	-	-	0.25	[75]
PMP (Maquet**)	1.8	0.273	0.5-7.0	-	-	30	[76]
PMP (Sorin**)	1.2	0.15	≤ 5.0	0.08-0.35	0.05-0.20	5	[77]
PMP (Eurosets**)	1.35	0.19	0.3-4.0	-	-	14	[74,78]

[a] in vitro study; [b] one-week ex vivo experiment; [c] two-week ex vivo experiment.
*module type: HF – hollow fiber; HSF – hollow sphere fiber; ** manufacturer

Thiara, *et al.* [70] evaluated the performance of PP and PMP-based membrane oxygenators. The results showed that the lifespan of the oxygenators was significantly longer for PMP than for PP membrane oxygenators. In addition, plasma leakage was observed in the PP-based oxygenators but did not appear in PMP-based oxygenators. This is because PP fibers have a microporous structure, while PMP fibers are covered with a dense but very thin outer skin. Therefore, PMP membranes have a longer operating life than PP membranes. Furthermore, gas permeability for oxygen and carbon dioxide in PMP membranes is excellent, with the gas exchange capability remaining equivalent to that of microporous membranes [66].

In commercially available HF membrane oxygenators, PP microporous membranes are mainly used for short-term operation, while PMP non-porous membranes can be used for long-term operation. The main characteristics of commercial PP and PMP membrane oxygenators are presented in Table 1. It can be seen that PP membrane oxygenators are only able to survive up to 6 hours. Meanwhile, the operation life of PMP membrane oxygenators varies from 5 to 30 days.

3.4 Surface Modification of Membrane Oxygenator

To improve the biocompatibility of the membrane oxygenator, the existing membrane surface can be modified with biocompatible materials. One of the most widely used methods is the covalent binding of heparin molecules with the membrane surface [79]. It has been found that a heparin coating could decrease the activation of platelets and also possesses anti-inflammatory properties [17,30,80]. A heparin coating can also decrease thrombin generation by binding to circulating antithrombin [36].

Zheng, *et al*. [81] compared different materials, i.e. acrylic acid with heparin (AA-Hep), 2-methacryloyloxyethyl phosphorylcholine (MPC), and collagen, to study their biocompatibility. A series of low-temperature plasma treatments (LTPT) was used for grafting onto the polysulfone HF membrane. It was found that grafting with AA-Hep provided the best hemocompatibility, indicated by the lowest protein adsorption, which was consistent with the platelet adhesion evaluation that was done. Moreover, the AA-Hep-modified PSF could maintain a high gas transfer rate compared to the unmodified PSF. However, heparin exposure during long-term ECMO can lead to heparin-induced thrombocytopenia (HIT) [82,83]. Therefore, a biomimetic coating with alternative materials is encouraged.

A bioline coating has been used to imitate human endothelial tissue. This reagent plays an important role in decreasing the interaction of clotting factors with the plastic tubing, thus leading to less activation of the coagulation cascade. Daniel and co-workers [67] reported that a bioline coating on a PMP membrane oxygenator could reduce the heparin required by patients. Another option is a phosphorylcholine coating, as used by Agati, *et al*. [84], to improve the hemocompatibility of a PMP membrane oxygenator. It was observed that neither plasma leakage nor device failure occurred in the PMP oxygenators after 105 hours of operation. A great improvement in hemocompatibility with high stability was then successfully obtained by using poly(MPC-co-BMA-co-TSMA)(PMBT) coating [85]. The cross-linkable PMBT film formed on the membrane surface exhibits strong resistance to protein adsorption as well as platelet adhesion. As a result, no adhered thrombus was observed on the PMBT-coated membrane

surface, while a dense thrombus layer covered the bare membrane. MPC coating on the PMP membrane oxygenator also reduced the protein and platelet interaction on the membrane surface [86]. Studies on biocompatibility modification of membrane oxygenators are summarized in Table 2.

Table 2 Surface Modification of Membrane Oxygenators to Improve Their Biocompatibility

Membrane material	Modifying component	Modification method	Ref.
PSF	AA-heparin MPC Collagen	Low-temperature plasma treatment	[81]
PP	PEG	Graft polymerization	[87]
	Silicone	Coating	[65]
	Heparin	Coating	[17] [80]
	Carmeda	Coating	[70]
TPX	PMBT Poly(MeOEGMA) Poly(HEMA) Poly(HPMA) Poly(PCMA) Poly(SBMA) Poly(CBMAA)	Dip-coating Single electron transfer-living radical polymerization	[88]
PMP	MPC Heparin	Plasma-induced grafting	[86]
	Phosphorylcholine	Coating	[84] [89]

TPX – poly(4-methyl-1-pentene); PMP – polymethyl pentene; PEG – polyethylene glycol; MPC – 2-methacryloyloxyethyl phosphorylcholine; PMBT – poly(MPC-co-BMA-co-TSMA);

4 ECMO Applications

Registration of the use of ECMOs across the world is organized by an international non-profit consortium called the Extracorporeal Life Support Organization (ELSO). Members of this consortium are known as ECMO centers. A steady increase in the establishment of ELSO-registered ECMO centers began about a decade ago, dominated by the North American region. To date, ECMO centers have spread in five regions, i.e. North America (2 countries), Latin America (26 countries), Asia Pacific (11 countries), South and West Asia, and Africa (12 countries).

ECMO systems have been applied for treating patients with respiratory or cardiac failure. The use of ECMOs for both conditions is discussed below. Besides that,

the role of ECMOs in treating COVID-19 patients is discussed separately in the last part of this section.

4.1 ECMO for Respiratory Failure

Respiratory failure occurs when the respiratory system fails to perform the gas exchange functions, i.e. oxygenation, carbon dioxide removal, or both. This then results in hypoaxemia (the arterial oxygen tension is less than 8.0 kPa) with or without hypercapnia (arterial carbon dioxide tension is more than or equal to 6.5 kPa) [90]. Patients with respiratory failure often require respiratory support, especially when simple measures such as supplemental oxygen therapy, secretion control, and antibiotic therapy are unsatisfactory. Mechanical ventilation can be used as respiratory support. However, the use of mechanical ventilation can cause lung injury, which is ascribed to excessive energy delivered to the lung, resulting from excessive pressure, volume, or respiratory rate [91]. An ECMO is then considered as an attractive alternative way of treating patients with severe respiratory failure, in which the gas exchange functions of the lung are expected to be taken over by the ECMO so that the lung can rest. Besides that, high airway pressure on the patient's respiratory organs is no longer necessary, preventing lung injury.

Patients with respiratory failure who need an ECMO are generally indicated by a reversible pulmonary disease [92]. Acute respiratory distress syndrome (ARDS) is a respiratory indication for ECMO treatment, which is also the most widely studied. Early trials have demonstrated that ECMOs do not provide greater survival in ARDS patients compared to conventional mechanical ventilation [93,94]. A study conducted by Suchyta, *et al.* [95] then found increased survival of ARDS patients meeting the blood-gas criteria of ECMOs, which could be due to different patient selection, advances in medical technology, and hospital-specific reasons. A study conducted by Liao, *et al.* [96] revealed the efficacy of 7 days of ECMO supplementation for the treatment of ARDS patients caused by scrub typhus. Also ECMO was compared with conventional treatment for patients (180 in total) with severe adult respiratory failure (CESAR), showing that 63% of patients who received ECMO treatment could survive for 6 months without disability, in contrast to only 47% for the conventional treatment [97]. The success of ECMO in suppressing the mortality rate has also been shown when this system was used for treating patients with ARDS during the influenza A (H1N1) pandemic in 2009, the avian influenza A (H7N9) pandemic, and for the middle east respiratory syndrome (MERS) [98,99]. However, there are multiple risk factors in ARDS. Thus, appropriate selection of ARDS patients to be treated using an ECMO is an important factor for success. To address this issue, an algorithm to guide which ARDS patients should be treated with an ECMO has been suggested by Bullen, *et al.* [100].

4.2 ECMO for Cardiac Failure

There are wide indications for ECMO treatment for patients with cardiac failure, which have been comprehensively reviewed by Bermudez, *et al.* [101]. For treating patients with cardiac indications, venoarterial ECMO (VA-ECMO), which provides not only respiratory support but also hemodynamic support, is recommended to use rather than venovenous ECMO (VV-ECMO), which provides no direct hemodynamic support [102]. In addition to providing circulatory support, VA-ECMO may provide a bridge to recovery or may be used as a bridge to a more durable mechanical solution [103]. However, careful consideration of patient selection, the cannulation strategy, and other cardinal considerations should be taken when implementing VA-ECMO.

A medical record review of patients treated with VA-ECMO for cardiac support showed a high proportion of survivors, where out of 22 patients, 16 patients (72%) survived to hospital discharge [104]. Moreover, 15 discharged patients were in good neurological condition. Another medical report by Luo and co-workers [105] showed that of the 45 patients supported with ECMO during cardiac failure, 27 could be successfully weaned. A recent study on VA-ECMO for post-cardiotomy cardiogenic shock revealed a significant difference in nadir lactate levels between survivors and non-survivors, which could be helpful in predicting early survival [106]. Despite the proven efficacy, it should be noted that ECMO is suggested to be employed as soon as possible before any organ failure develops in cardiac failure patients [105]. For example, a high mortality rate was reported when patients were treated with a combination of continuous renal replacement therapies (CRRT) and ECMO [107]. In such cases, the acute renal failure suffered by the patients may deteriorate the health condition of the patient before their condition could be improved through ECMO intervention.

4.3 ECMO for COVID-19

Based on the successful experiences on respiratory failure treatment, ECMO has been considered as a potential therapy for COVID-19 patients. For centers capable of providing ECMO, the World Health Organization recommends the treatment of ARDS using ECMO [108]. However, there is also a concern related to the limited usefulness of and the lack of evidence for supporting critically ill patients suffering from ARDS due to COVID-19 [109]. Initial experiences in Japan and South Korea with ECMO in more than 50 COVID-19 cases had survivors, though many were still receiving treatment at the time of study.

Several studies have recently been performed to study the use of ECMO as therapy for patients with ARDS induced by COVID-19. The results varied among the reported cases. Yang, *et al*. [110] reported six severely ill patients in Wuhan, China who were treated with ECMO. At the endpoint of the study period of 28

days, five patients had died, while one patient was still on ECMO. Zhang, *et al*. [111] conducted a single-center, retrospective case series investigation of 221 hospitalized patients in Wuhan, China, with confirmed COVID-19, from January 2nd to February 10th, 2020. Out of 55 patients in severe condition, ECMO was utilized for ten patients with refractory hypoxemia. At the time of data collection, two patients exhibited clinical benefits and were subsequently discharged, five patients were still under ECMO support, and the other three were non-survivors. Other studies also mention ECMO cases; unfortunately, the outcomes were not available [112-114]. A weaning rate of 50% was reported by Haye, *et al*. [115], who studied the impact of a mobile ECMO team during the first three weeks of the COVID-19 outbreak in France.

A more comprehensive investigation based on pool analysis of 331 COVID-19 cases supported with ECMO showed a mortality rate of 46% (95%CI = 34-59%) [116], which was smaller compared to the mortality rate of severely ill COVID-19 patients who received conventional treatment, around 59-71% [110-117]. Based on the abovementioned results, it should be stressed that the efficacy of ECMO treatment in COVID-19-induced ADRS conditions is not yet clear. This is because several challenging factors affect the success of ECMO. One of the important requirements is more data on the death mechanism and disease, from which the appropriateness of the use of ECMO to treat COVID-19 patients is determined [108].

However, more promising results are being reported by researchers. Wang *et al.* [118] reported a COVID-19 patient with cytokine storm who fully recovered using ECMO support after four times negative results of nucleic acid testing and was then discharged on day 38. Ikuyama, *et al*. [119] reported the successful recovery of a 76-year-old female patient in Matsumoto, Japan from acute COVID-19 pneumonia via ECMO treatment. While the use of lopinavir-ritonavir and premivir treatment did not show significant benefits, the application of ECMO from symptom onset day (SOD) 19 to 31 led to complete recovery. A similar successful recovery case was also found in a 45-year old male patient in Tokyo, Japan [120]. It was suggested that risk factors, e.g. old age and other comorbidities (hypertension, diabetes, and asthma) may correspond to the mortality after ECMO treatment rather than ECMO itself [119]. Another report indicates that early ECMO treatment could have more considerable benefits than that applied after conventional therapies [121]. Since ECMO usage can also inflict adverse side effects on patients, judicious selection of patients who urgently need ECMO support is necessary to optimize the treatment of COVID-19 patients with ECMO [99].

5 Conclusions and Future Outlook

ECMO treatment has great potential to provide sufficient oxygenation for respiratory failure patients with decreasing pulmonary function, which conventional ventilation can no longer manage. As the key to ECMO, the membrane oxygenator must be biocompatible and able to perform efficient gas exchange. Research and development have been devoted to finding appropriate membrane materials, module types, and flow configurations to achieve these goals. Silicones have been long used as membrane material because of their blood compatibility and ability to avoid plasma leakage, but they have poor gas permeability. Hence, microporous PP membrane oxygenators have then been developed. However, the wetting phenomena hinder their use for prolonged periods; thus, a modification such as silicone coating is required. In a recent development, PMP membrane oxygenators have been fabricated for long-term usage. Membrane oxygenators have dramatically evolved, from plate-type and spiral-wound-type to HF module with different fiber arrangements and flow directions. In addition, surface modification using biocompatible materials has also been attempted. It is imperative to consider the mean pore size of the membrane oxygenator rather than the maximal pore size since the pores in the membrane wall play a more significant role in determining the resistance to plasma leakage than the surface pores. Two membranes may have the same maximal pore size, but their mean pore differs significantly, leading to a severe problem during the ECMO treatment. However, to be applied successfully, an adequate preclinical evaluation is needed, including determining surface-active species in the patient's blood, e.g. phospholipid, alcohol, and drug molecules. These strategies should be able to minimize the health risk during the ECMO treatment. Unfortunately, not all existing studies have addressed them.

ECMO could provide an alternative solution for treating patients with respiratory or cardiac failure. Reported studies have shown that there were improved outcomes when using ECMO compared to conventional treatments. However, careful consideration should be taken, especially with regard to patient selection. ECMO has also been considered to use as therapy for patients with respiratory failure induced by COVID-19. Although the effect of ECMO on severely ill COVID-19 patients has not yet been established, more cases are continuously being reported in which the ECMO treatment exhibited a positive impact on the recovery of COVID-19 patients. In this regard, the presence of comorbidities should also be taken into account, since they play a significant role in determining the mortality rate of COVID-19 patients. After all, COVID-19 is a challenging novel disease, where all treatments including ECMO must be performed with vital precautions. An effective organization comprising a synergy of the aspects of personnel, equipment, facilities, and systems will improve the efficacy of ECMO deployment.

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