Chapter

Development of a Membrane Oxygenator for Long-Term ECMO Support Using Fine Silicone Hollow Fiber

Ryo Yokoi, Masaki Anraku, Madoka Takai, Takashi Isoyama, Shintaro Hara, Kazuaki Sato and Fumikazu Watanabe

Abstract

A membrane oxygenator is an artificial organ that temporarily replaces the gas exchange functions of the lungs during medical procedures such as open-heart surgery or as respiratory support for patients with severe respiratory or cardiopulmonary failure. It can also serve as a bridge to lung transplantation. For long-term use of several months, the oxygenator must have durability and safety. Silicone rubber was focused on for its excellent gas permeability. A membrane oxygenator using fine silicone hollow fiber membranes was developed. This membrane has high permeability and no plasma leakage, making it potentially suitable for long-term lung support. An *in vitro* experiment with bovine blood evaluated the developed device. With a blood flow rate of 3 L/min, the oxygen transfer rate of the oxygenator with 2 m^2 membrane area was about 36% higher, and the carbon dioxide transfer rate about 28% higher, than the 1 m^2 membrane area oxygenator. However, the pressure drop increased with larger membrane area. The goal is to develop a silicone hollow fiber membrane oxygenator that can achieve low pressure drop and withstand long-term use.

Keywords: silicone, hollow fiber, membrane oxygenator, gas exchange, plasma leakage, extracorporeal membrane oxygenation (ECMO), long-term use, bridge to lung transplantation

1. Introduction

1.1 Membrane oxygenator

The oxygenator is an artificial organs that temporarily take over the blood oxygenation and carbon dioxide removal functions of the lungs. These oxygenators are already widely used in clinical settings, mainly used to substitute for lung function during open-heart

surgery. Recently, with improvements in the performance and management techniques of these oxygenators, the use of respiratory and circulatory assist methods involving oxygenators called extracorporeal membrane oxygenation (ECMO) has been increasing for patients with severe respiratory failure and those awaiting lung transplants [1–7].

Additionally, ECMO has been used to treat over 10,000 patients worldwide and over 1200 patients in Japan during the outbreak of corona virus disease-2019 (COVID-19) pandemic. ECMO was regarded as the "last stronghold" for critically ill COVID-19 patients and thus became widely known not only among healthcare professionals but throughout society [8–11].

Since ECMO treatment requires long-term use of an oxygenator, there is a strong need to develop oxygenators with stable gas exchange capabilities and high safety.

1.2 History of membrane oxygenator

The development of membrane oxygenators began in 1944 when Kolff and Berk showed that blood was oxygenated during hemodialysis using cellophane tubes in an artificial kidney [12, 13]. Membrane oxygenators enable gas exchange without direct contact between blood and gas like in biological lungs, by using a membrane. Hence, they were expected to serve as physiological oxygenators.

In 1969, the Lande-Edwards membrane oxygenator, which had stacked silicone flat membranes, was first put to practical use [14–16]. In 1971, Kolobow et al. commercialized a coil-type membrane oxygenator that had coiled a long bag made of silicone flat membranes into a coil shape [17–19]. This enabled extracorporeal circulation for

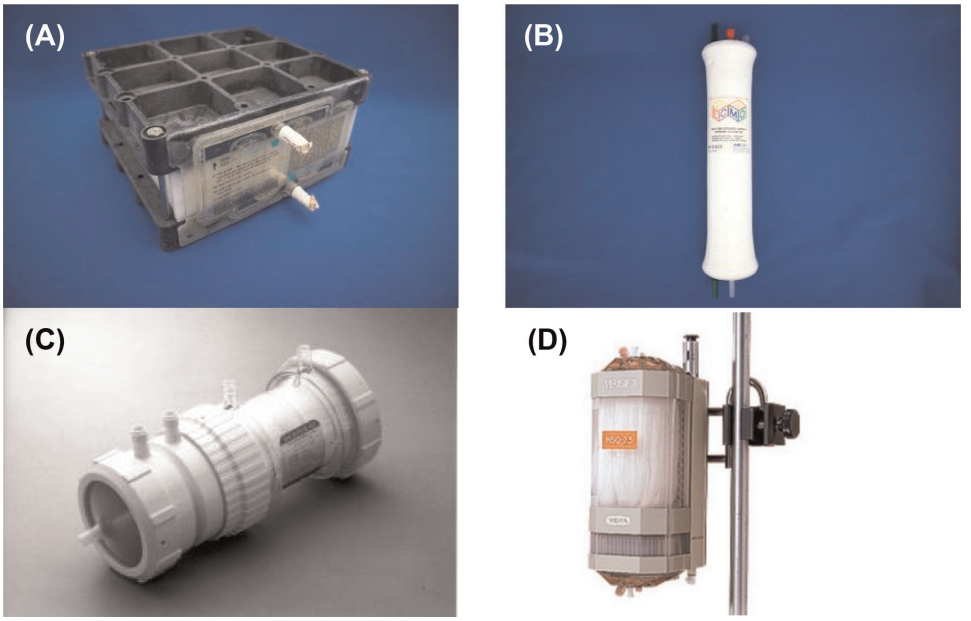

Figure 1.
Multilayer type membrane oxygenator, coil-type membrane oxygenator and capillary type membrane oxygenator. (A) Lande-Edwards disposable membrane oxygenator (Edwards laboratories, United States). (B) 0800 ECMO extended capacity membrane oxygenator (AVECOR cardiovascular Inc., United States). (C) CAPIOXII (TERUMO Corp., Japan). (D) Merasilox HSO-2.5 (SENKO MEDICAL INSTRUMENT Mfg. CO., LTD., Japan).

over 2 hours [20]. The development of membrane oxygenators progressed further. In 1982, Capiox II, the world's first product using porous hollow fibers, was commercialized by Terumo Corporation [21]. In 1984, Senko Medical Instrument Mfg. CO., LTD. released the world's first silicone hollow fiber membrane oxygenator [22].

Hollow fiber membrane oxygenators came into widespread use owing to the dramatic improvements in gas exchange performance and operability (**Figure 1**).

1.3 Type of gas exchange membrane

The gas exchange membrane used in oxygenators can be grouped into four principal types. These gas exchangers are structurally categorized as homogeneous membranes, microporous membranes, composite membranes, or asymmetric membranes (**Figure 2** and **Table 1**).

1.3.1 Homogeneous membrane

Homogeneous membranes are membranes that are nonporous and perform gas exchange through a gas dissolution and diffusion mechanism within the membrane.

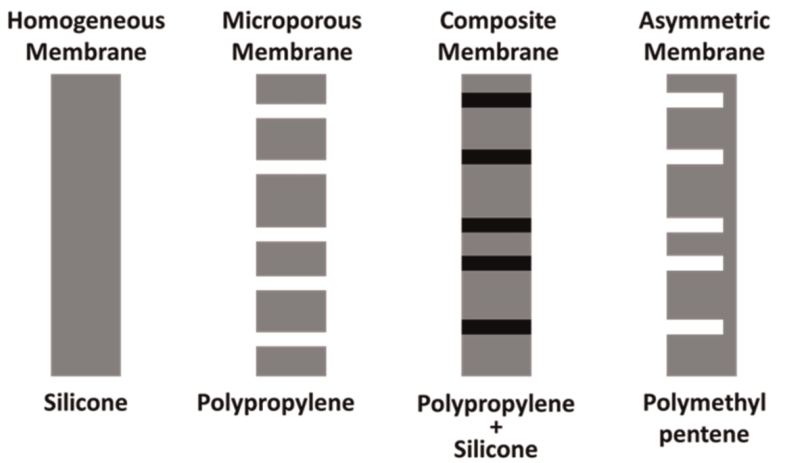

Figure 2.
Type of gas exchange membranes.

Membrane	Thickness (μm)	Gas permeability*	
		O_2	CO_2
Silicone	100	6	31
Polypropylene	25	40,000	34,000
Polypropylene + Silicone	25	3,100	15,500
Polymethylpentene	25	64	184

*$(\times 10^{-6} \mathrm{cm}^3(STP)/cm^2 \bullet sec \bullet cmHg)$.

Table 1.
Gas permeability of membrane for oxygenator.

Therefore, plasma leakage into the gas phase is prevented, allowing usage for long term circulation. Silicone, which exhibits remarkable gas permeability among general polymeric materials and is physiologically inert, thrombo-resistant, and biocompatible, is employed in these homogeneous membranes [23, 24]. However, silicone intrinsically demonstrates low mechanical strength, rendering membrane thickness reduction difficult, which leads to poor actual gas exchange performance [25–27]. To overcome this limitation, methods of enhancing membrane mechanical strength have been established, including filler incorporation and mesh reinforcement. Such innovations have enabled the development of practical thin homogeneous membrane oxygenators with superior gas exchange capacity [28, 29].

1.3.2 Microporous membrane

Microporous membranes contain numerous pores through which gases can diffuse to the blood side for gas exchange. The presence of pores allows some direct contact between blood and air, which enables more efficient gas transfer compared to homogeneous membranes. Studies have shown that microporous membranes facilitate superior gas exchange efficiency relative to non-porous membranes. And owing to the membrane pores hydrophobicity and blood contact angle and surface tension, plasma leakage is minimized. Thus, porous membranes provide adequate gas exchange for routine cardiopulmonary bypass operations [30–32]. The porosity, which represents the volume percentage of void spaces in the membrane, ranges from 30–50%. Manufacturing methods include stretching and wet spinning, using source materials such as polypropylene and polyethylene [33, 34].

However, long-term circulations exceeding 6 hours may compromise the membrane pore hydrophobicity, transitioning it to a hydrophilic state, and thereby eliciting plasma leakage and pore occlusion by protein adhesion, resulting in compromised gas exchange performance [35–37].

1.3.3 Composite membrane

The gas exchange membrane used in oxygenators is a composite membrane that combines a microporous membrane with excellent gas permeability and a silicone coating membrane with excellent blood compatibility [38–40]. This hollow fiber surface silicone coating technology was developed by SET Corporation in the United States. SET Corporation uses this technology in their intravenously implanted oxygenator (IVOX). Specifically, by continuously passing the porous polypropylene hollow fiber through a radicalized silicone monomer layer under high vacuum, a silicone thin film is formed on the surface of the hollow fiber. The silicone uses cyclosiloxane with a cyclic molecular structure. This radicalized silicone reacts and binds with the similarly radicalized polypropylene surface, which has been confirmed. As a result, a thin film is formed across the entire hollow fiber [41]. By coating the surface with a thin silicone film, affinity with blood components is enhanced, and adhesion of blood components to the membrane and occurrence of thrombosis can be suppressed. Thus, the composite membrane, which has both gas permeability and blood compatibility, is a useful material that can greatly improve the gas exchange efficiency and biocompatibility of membrane oxygenator [42, 43]. By optimizing the coating conditions and structure of the membrane, development of membrane oxygenator with even higher performance can be expected.

1.3.4 Asymmetric membrane

At the beginning of the 2000s, a new type of gas exchange membrane was developed to overcome the issues that could not be solved with the conventional microporous gas exchange membranes. It was an asymmetrical gas exchange membrane. In this asymmetric membrane, a dense layer is placed on the blood side to prevent plasma leakage, while a porous layer is provided on the gas side to allow smooth movement of gases. Polymethylpentene is one of the materials practically applied as an asymmetric gas exchange membrane for membrane oxygenator. The polymethylpentene asymmetric membrane has no plasma leakage and has durability to withstand use for 2–3 weeks [44–46].

The adoption of this asymmetric membrane has enabled the development of membrane oxygenator with unprecedented high gas exchange performance and blood compatibility.

1.4 Silicone membrane oxygenator

1.4.1 Gas transfer mechanisms in membrane oxygenator

Figure 3 shows the gas exchange mechanisms in membrane oxygenator. Gas exchange in membrane oxygenator is achieved by mass transfer between sweep gas and venous blood across a membrane. This mass transfer is driven by the partial pressure gradient of gases between the blood phase and gas phase. Oxygen gas moves from the gas phase with a higher oxygen concentration to the blood phase with a lower oxygen concentration. Carbon dioxide gas transfer occurs in the opposite direction to that of oxygen. When mass transfer occurs, transport barriers arise that inhibit the transfer. These barriers include gas phase boundary layer resistance, membrane resistance, and blood phase boundary layer resistance. In oxygenator gas exchange, the gas phase boundary layer resistance is negligible compared to other resistances. Also, the membrane resistance is proportional to membrane thickness, so it can be reduced by membrane thinning. However, microporous membranes allow gases that have entered pores to be in direct contact with blood for gas exchange, and thus their high gas permeability

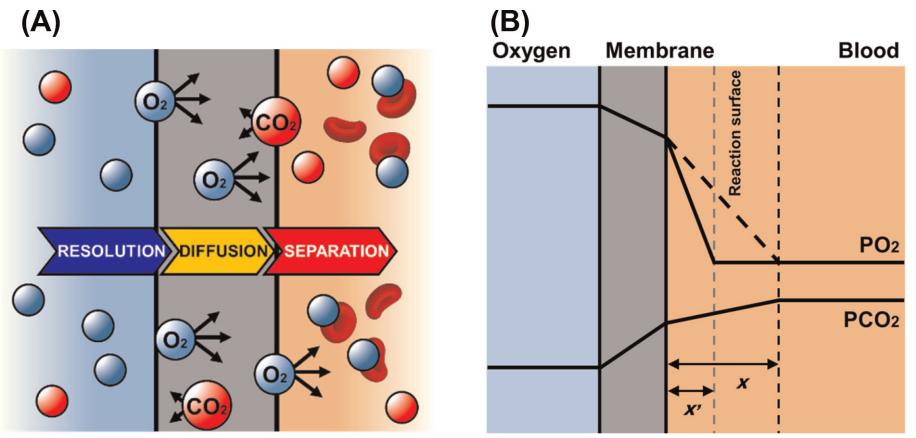

Figure 3.
Gas transfer mechanisms. (A) Scheme of gas exchange using homogeneous membrane. (B) Scheme of gas transfer. X': Blood oxygen saturated. X: Blood film layer.

makes membrane resistance negligible [47–49]. The gas exchange performance of an oxygenator depends on the blood phase boundary layer resistance regardless of the type of gas exchange membrane. This blood phase boundary layer resistance is affected by the flow pattern of blood. Therefore, blood phase boundary layer resistance can be reduced by inducing turbulent flow and mixing in the vicinity of the gas exchange membrane. Hence, hollow fiber membrane oxygenators with blood flowing outside the hollow fibers in a crossflow pattern have become mainstream.

1.4.2 Silicone rubber properties

The silicone that makes up silicone rubber has an inorganic siloxane bond (-Si—O-) as its main chain and an organic group as its side chain, making it a hybrid polymeric material of inorganic and organic substances. Compared to a C—C bond with a bonding energy of 356 kJ/mol, the Si—O bond has a higher bonding energy at 444 kJ/mol, indicating greater stability. Additionally, unlike a C—C bond, the Si—O bond exhibits about 50% ionic bond character, placing it between inorganic and organic substances. However, this relatively high degree of ionic nature also makes it comparatively vulnerable to attack from ionic compounds such as acids and bases. With its longer bond distance, lower electron density, and negligible bond rotation energy, rotation about the Si—O bond is facile. Moreover, the Si—O—Si bond angle can vary with very little energy input, conferring extremely high flexibility to the siloxane chains. Furthermore, with two of the silicon atom's four bonds occupied by oxygen atoms and the other two by methyl groups, the siloxane linkage presents a bulky, coil-like structure [50–52].

Based on these fundamental structural features, silicones possess excellent properties including heat resistance, water repellence, chemical resistance, gas permeability, and physiological inertness (**Figure 4**) [53].

1.4.3 Development of silicone membrane oxygenator by Fuji systems

In 1968, we started the development of artificial kidneys and oxygenators using silicone thin films with Dr. Nose from Cleveland Clinic. In 1971, we succeeded in developing an underwater gas exchanger (artificial gill) using silicone hollow fibers, which triggered our full-fledged basic research on membrane oxygenator [54–56]. In 1974, we kicked off joint research and development on membrane oxygenator using silicone rubber membranes with cleveland clinic. In 1975, we completed a membrane

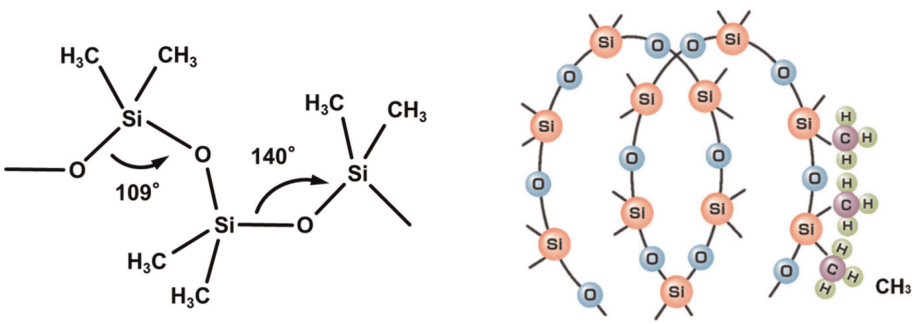

Figure 4.
Molecular structure of silicone. (A) Dimethyl silicone molecule. (B) Silicone helical structure.

oxygenator made of 100 μm thick ribbed silicone flat membrane wound into a coil shape. In 1976, we completed a hollow fiber bundle-type oxygenator using bundled 150 μm thick silicone hollow fibers.

After that, we worked with Dr. Nose and Professor Funakubo from Tokyo Denki University to advance research on improving the gas exchange performance of silicone hollow fiber membrane oxygenators by making the hollow fibers thinner, with smaller outer diameters, and devising the arrangement of the hollow fibers. As a result, we were able to reduce the priming volume and increase the membrane surface area, as well as improve the blood stirring effect [57–59]. In 1996, animal experiments confirmed 2 weeks of survival, representing major progress in performance [60].

On the other hand, silicone hollow fibers have a problem in that their mechanical strength is weak and it is difficult to cross-wind the hollow fibers. Therefore, we manufactured hollow fiber membranes in a plain weave structure, which improved the situation.

Currently, in order to improve manufacturability and uniformity of blood distribution, we are advancing research and development on a stacked hollow fiber membrane box-type membrane oxygenator with Dr. Anraku at Tokyo Metropolitan Institute for Geriatrics and Gerontology (**Figures 5** and **6**).

1.4.4 Surface modification of silicone membrane oxygenator

Silicone has a structure with ionic hydrophilic Si—O bonds oriented inward and the nonionic, hydrophobic organic groups oriented outward. Therefore, silicone hollow fiber membranes have high hydrophobicity, which makes it easy for air to be trapped in the hollow fiber membrane during priming of an oxygenator. This is the reason why the priming operation takes time. Additionally, it has been suggested that blood coagulation proteins adsorbing during blood contact can induce platelet aggregation and thrombus formation.

One method to address this issue is to substitute the methyl groups on the silicone surface with hydroxyl groups (-OH), which are hydrophilic, using oxygen plasma or excimer lamp treatment under vacuum [61, 62]. Research has also been conducted on surface treatments using a polymeric material called 2-methacryloyloxyethylphosphorylcholine (MPC), which suppresses blood coagulation protein adsorption and denaturation with the aim of achieving longer-term durability [63–65]. SEC coating has been commercialized as a surface modification of composite membranes for oxygenator [66].

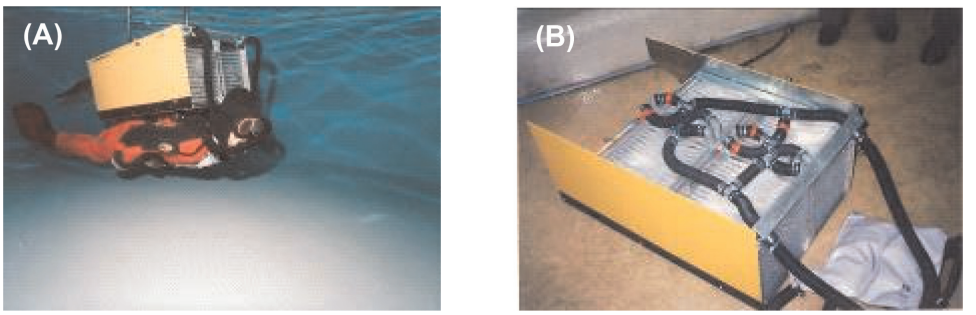

Figure 5.
Artificial gill. (A) SAGAMII. (B) Silicone hollow fiber for artificial gill.

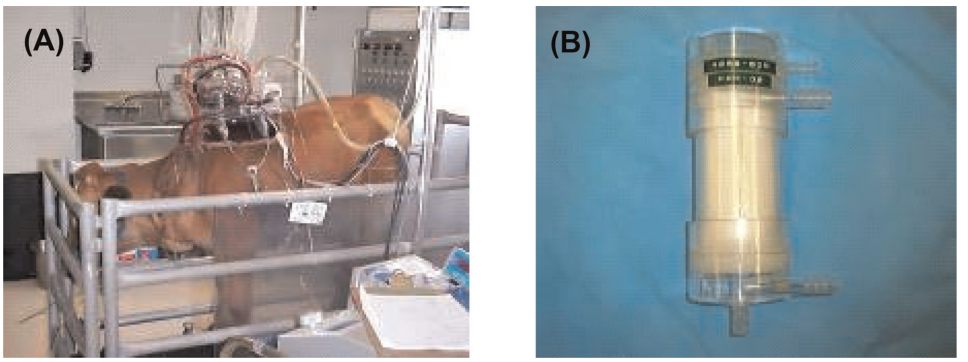

Figure 6.
The experimental animal for the prototype membrane oxygenator evaluation. (A) Ex vivo *for Baylor college of medicine. (B) Prototype silicone hollow fiber membrane oxygenator.*

2. Materials and methods

2.1 Silicone membrane oxygenator

Fine silicone hollow fiber membrane oxygenators were fabricated using this material, with a 400 μm outer diameter and a wall thickness of 50 μm. We developed a prototype membrane oxygenator consisting of these silicone hollow fibers inserted into a housing made of polycarbonate. The reed screen-shape silicone hollow fiber membranes are stacked for packing into the housing. With this structure, the short-cutting of blood flow paths can be prevented, and the distribution of blood can be homogenized. As a result, it is inferred that gas exchange performance is improved. Based on this idea, we fabricated this oxygenator in this study.

Regarding the specifications of the developed silicone hollow fiber membrane oxygenator, the membrane surface area was 1.0 m^2 for Prototype 1 and 2.0 m^2 for Prototype 2. The membrane unit of Prototype 2 was divided into three layers.

Additionally, the packing density of the silicone hollow fiber membranes in the housing, that is the volume percentage occupied by the hollow fiber membranes, was 43%. These prototype oxygenators are the blood flows outside the hollow fibers, while the gas flow is kept inside the fibers (**Figure 7**).

2.2 Test circuit

The gas exchange performance and pressure drop of the silicone hollow fiber membrane oxygenators were measured for performance evaluation. The evaluation experiment was conducted using bovine blood adjusted to standard venous blood properties in accordance with JIS T 3230:2008 (Blood temperature = 37°C, Hb = 12 $\pm$ 1 g/dL, BE = 0 $\pm$ 5 mmol, SAT% = 65 $\pm$ 5%, PCO2 = 45 $\pm$ 0.7 kPa). The adjusted bovine blood was pumped with a roller pump, passed through the prototype membrane oxygenator and collected in another blood reservoir.

The experimental blood circuit was arranged as shown in **Figure 8**. The circuit consisted of roller pump, flowmeter, pressure monitoring system, 3/8 inch inner diameter tubing, an electromagnetic blood flow meter, and the prototype membrane oxygenator. Blood was pumped with a roller pump, passed through the prototype

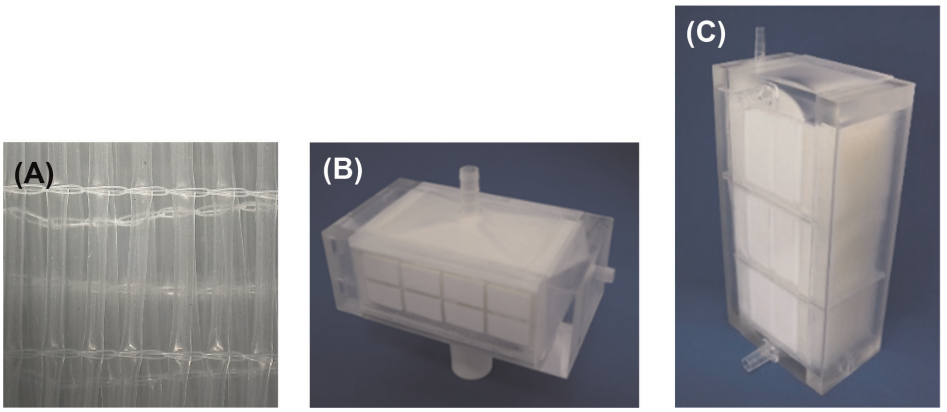

Figure 7.
Prototype fine silicone hollow fiber membrane oxygenator. (A) the reed screen shape silicone hollow fiber membranes. (B) Prototype 1 (1.0 m²). (C) Prototype 2 (2.0 m²).

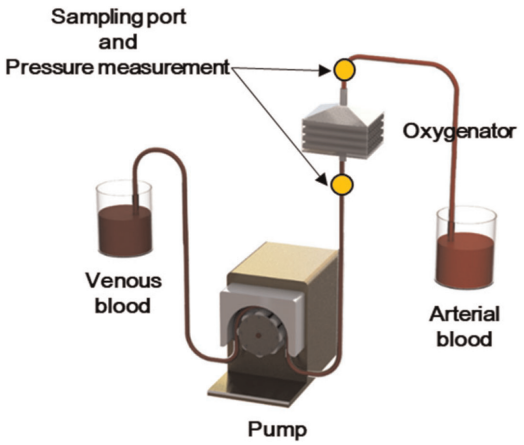

Figure 8.
A test circuit for gas transfer.

membrane oxygenator and collected in another blood reservoir. Blood flow rate was measured continuously by ultrasonic flowmeter (T400-Series, Transonic Systems Inc., NY, USA). And blood pressure was measured continuously by pressure monitoring system (UBS-100, UNIQUE MEDICAL Co., Ltd., Tokyo, Japan).

2.3 Gas exchange performance

The blood flow rate was set at 1, 2, and 3 L/min. The oxygenator was ventilated with oxygen gas at a flow rate adjusted in the range of according to blood flow rate (V:Q = 1:1, Q = Blood flow rate, V = Gas flow rate).

Blood was sampled at the inlet and outlet of the prototype membrane oxygenator for each blood flow rate, and immediately analyzed using a blood gas analyzer (Rapid Lab 348EX, Siemens Healthcare Diagnostics, Vienna, Austria) to determine the blood properties. Then, the blood properties of each sample were substituted into Eqs. (1), (2) and (3) to calculate the oxygen transfer rate and carbon dioxide transfer rate of the oxygenator.

$$O_2\ transfer\ rate\ (ml/min) = \left(\frac{SaO_2 - SvO_2}{100} \times 1.34 \times Hb + 0.00314 \times (PaO_2 - PvO_2)\right) \times \frac{Q}{100} \quad (1)$$

$$CO_2\ transfer\ (ml/min) = \left(2.226 \times \frac{TvCO_2 - TaCO_2}{100}\right) \times \frac{Q}{100} \quad (2)$$

$$TCO_2 = 0.03 \times PCO_2 + \left[HCO_3^-\right] \quad (3)$$

SaO_2 : *Oxygen saturation at the oxygenator outlet (%).*
SvO_2 : *Oxygen saturation at the oxygenator inlet (%).*
PaO_2 : *Oxygen partial pressure at the oxygenator inlet (mmHg).*
PvO_2 : *Oxygen partial pressure at the oxygenator outlet (mmHg).*
Hb : *Blood hemoglobin concentration (g/dL).*
Q : *Blood flow to the oxygenator (L/min).*
$TvCO_2$: *Total carbon dioxide content at the oxygenator inlet (mmol/L).*
$TaCO_2$: *Total carbon dioxide content at the oxygenator outlet (mmol/L).*
$\left[HCO_3^-\right]$: *mmol/L.*

2.4 Pressure drop

The blood inlet pressure and the outlet pressure of a prototype oxygenator were measured with the pressure monitoring system. Then, substituted the measured pressure values into Eq. (4) and calculated the pressure drop of the blood flow passing through the oxygenator.

$$Pressure\ drop\ (mmHg) = Pin - Pout \quad (4)$$

Pin : *Pressure at oxygenator inlet.*
$Pout$: *Pressure at oxygenator outlet.*

3. Results

3.1 Gas exchange performance

Figures 9 and **10** show the results of the gas exchange performance experiment. At a blood flow rate of 3 L/min, the oxygen transfer rate and carbon dioxide transfer rate of prototype 1 oxygenator were 164 and 107 ml/min, respectively. At the same blood flow rate of 3 L/min, prototype 2 oxygenator demonstrated higher gas transfer rates, with an oxygen transfer rate of 257 ml/min and a carbon dioxide transfer rate of 137 ml/min.

3.2 Pressure drop

Figure 11 shows the results of the pressure drop experiment. The pressure drops on the blood passage side across the membrane oxygenator were 15, 16, and 20 mmHg for prototype 1, and 48, 90, and 144 mmHg for prototype 2, at blood flow rates of 1, 2, and 3 L/min, respectively.

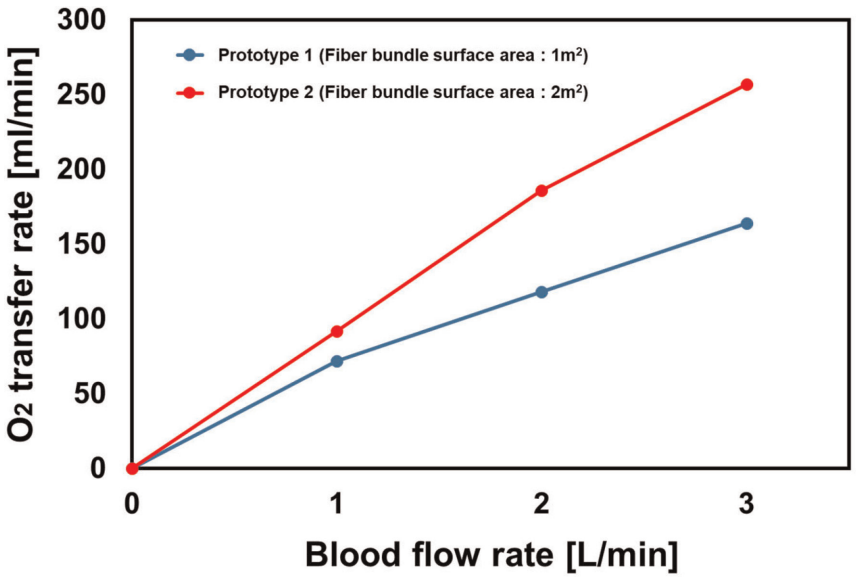

Figure 9.
O_2 transfer rate of the oxygenator.

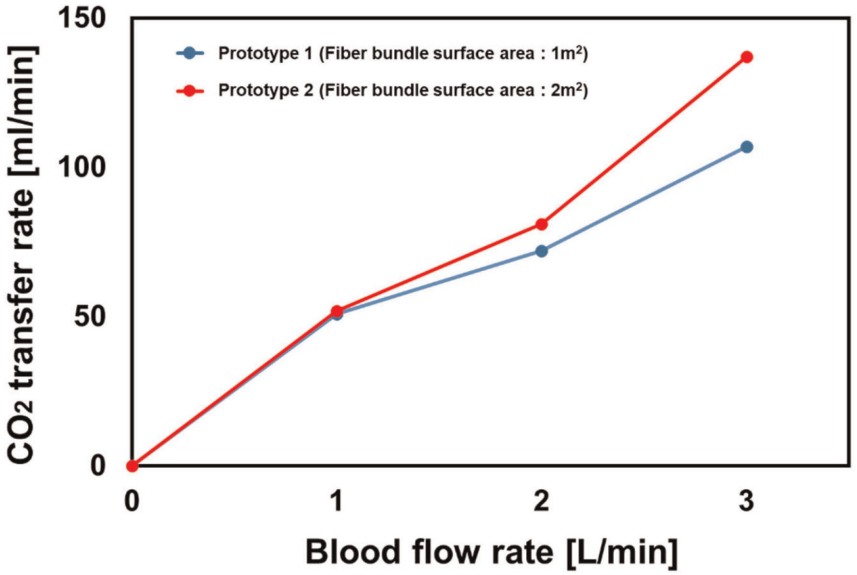

Figure 10.
CO_2 transfer rate of the oxygenator.

4. Discussion

In this study, two prototypes of oxygenators were the reed screen silicone hollow fiber membranes and evaluated for gas exchange performance and pressure drop *in vitro*. Prototype 2 had a shortened gas flow path length in the

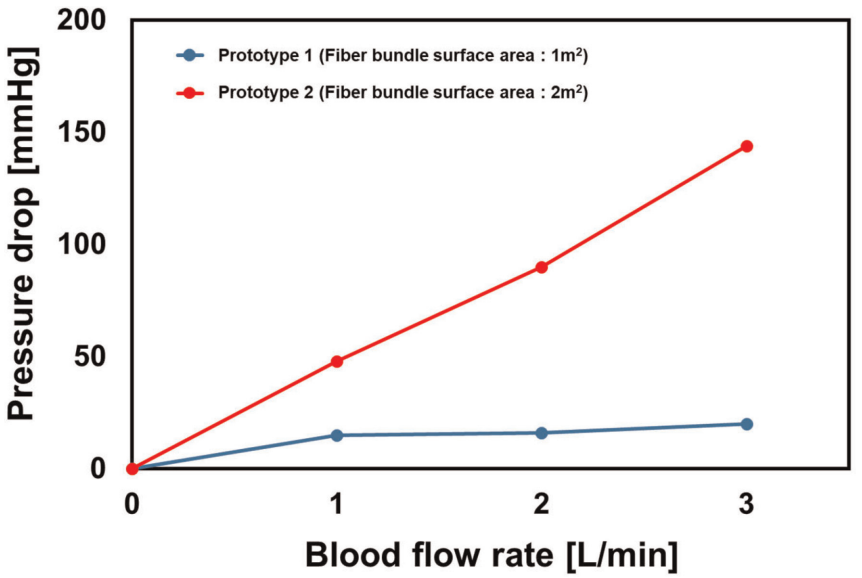

Figure 11.
Pressure drops on the blood side of the prototype oxygenator.

hollow fiber membrane part, three layers of hollow fiber membrane parts, and an extended blood flow path length to increase the contact area between blood and the hollow fiber membrane part compared to Prototype 1. As a result, Prototype 2 showed approximately 36% improvement in O_2 transfer rate and approximately 28% improvement in CO_2 transfer rate compared to Prototype 1 at a blood flow rate of 3 L/min. These results suggest that, in Prototype 1, blood was concentrated in the axial direction in the oxygenator and could not diffuse uniformly, resulting in the hollow fiber membranes not being sufficiently utilized. In contrast, it is considered that Prototype 2 had improved gas exchange performance due to its longer blood flow path length and larger membrane area. It is also estimated that extending the flow path length was effective based on the gas exchange mechanism in silicone, as a certain amount of time is required for gas exchange in blood. However, the pressure drop increased in Prototype 2 due to the extended flow path length, which could adversely affect the centrifugal pump for pumping blood and cause hemolysis. The increase in pressure drop is considered to be due to the increase in flow resistance from arranging hollow fiber membranes with the same packing density in series. Going forward, it will be necessary to optimize the design of membrane oxygenators to achieve both low-pressure drop and high gas exchange performance by focusing on three factors: blood flow path length, membrane packing density, and effective membrane area.

5. Conclusions

Current membrane oxygenator products have sufficient gas exchange performance and biocompatibility for standard open-heart surgery with the range of blood flow rates and short duration. However, with the COVID-19 pandemic starting late 2019, ECMO has gained considerable attention as treatment for acute respiratory

failure. In addition, the potential application of ECMO is expanding to bridge to transplantation (BTT) and bridge to recovery (BTR) for patients with severe respiratory failure. Therefore, the development of next-generation membrane oxygenators capable of long-term usage is urgently needed. Advancement in this oxygenator field depends heavily on engineering approaches including field of materials. At Fuji Systems, we have been conducting research and development of ECMO systems that can be used for long-term application of time by taking advantage of our silicone processing technology and silicone features that we have cultivated over the years.

In the future, it is expected that more patients with respiratory disease will benefit from the realization of innovative ECMO systems.

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