Original Article

Development of a New Hollow Fiber Silicone Membrane Oxygenator for ECMO: The Recent Progress

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Throughout the last 50 years, many improvements have been made for a more effective oxygenator. A large plate type membrane oxygenator, used by Clowes, and a coil type, used by Kolff, has evolved into the small hollow fiber oxygenator. The complex bubble oxygenator, or rotating disk oxygenator, has become a small disposable bubble oxygenator. The currently available oxygenators are extremely small, efficient, and can be used for extended periods of time. However, there are some problems with extracorporeal membrane oxygenation (ECMO). Currently in the United States, there are no clinically applicable hollow fiber ECMO oxygenators available, in spite of the extended ECMO application. Therefore, the development of a small, yet efficient, silicone hollow fiber membrane oxygenator for long-term ECMO usage was attempted. Based on the results of many experimental models, preclinical oxygenator models for long-term ECMO were developed in our laboratory using an ultra-thin silicone rubber hollow fiber membrane. (Ann Thorac Cardiovasc Surg 2002; 8: 268–74)

Key words: extracorporeal membrane oxygenation, membrane oxygenator, hollow fiber, silicone rubber

Introduction

During the last 50 years, the pump oxygenator has become one of the most useful artificial organs. Without the availability of a good pump oxygenator, open-heart surgery could not be achieved. Also, throughout these last 50 years, many improvements have been made for a more effective oxygenator. Considering the initial oxygenator, the currently available oxygenators are extremely small, efficient, and can be used for extended periods of time. However, there are problems to use them for extracorporeal membrane oxygenation (ECMO).[1] In this paper, the present status of ECMO and the developmental achievement of our group will be mentioned.

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Present Status of ECMO

In 1972, Hill reported the first successful treatment of adult respiratory distress with ECMO.[2] Reports of several other successful cases soon followed. In 1975 after three years of success, the first neonatal ECMO survival case at the University of California was described by Bartlett.[3] He also reported 45 newborn cases with 23 survivors at the University of Michigan in 1982.[4] The application of ECMO has been extended with improved outcome.[5]

Extracorporeal life support (ECLS) refers to prolonged extracorporeal circulation for cardiac or pulmonary support. The registry of ECLS cases was begun in 1984 and includes almost all of the cases treated throughout the world since 1975. The first report of the registry by Toomasian et al.[6] was published in 1988. In 1989, the active centers using ECLS formed the Extracorporeal Life Support Organization (ELSO). From 1999, the ELSO registry,[7] reported 15,636 neonatal cases with 76% survival, 3,372 pediatric cases with 47% survival, 742 adult cases with 43% survival,

and 1,642 pediatric cardiac cases with 39% survival. In neonatal and pediatric cases, ECMO treatment is applied for congenital heart anomalies and its' induced lung dysfunction, primary pulmonary hypertension, congenital diaphragm hernia, and acute myocarditis, meconium aspiration syndrome. In adult cases, most of the ECMO procedures are post-cardiotomy shock or severe pulmonary dysfunction against mechanical ventilation and other medical treatments. Recently adult and pediatric populations treated with ECMO have increased rapidly, and the outcome has significantly improved.

Recent Progress

Even though ECMO is an effective life saving treatment, the equipment being used in the United States today is outdated (Kolobow oxygenator,[8] 1972 model), expensive and very difficult to use. In addition, the high-pressure drop and limited blood flow cannot be compromised for long-term ECMO usage. Plasma leakage is a major concern during ECMO with traditional hollow fiber oxygenators built from microporous membrane as mentioned above. There is no hollow fiber membrane oxygenator for ECMO available. Presently, membrane oxygenators for ECMO need to have frequent module exchanges (average: 4.5 days). Consequently, the need to develop a second-generation ECMO oxygenator is desperately needed.

To solve this problem, this author's group started to develop a membrane oxygenator using a novel fine silicone hollow fiber in 1995. Theoretically, to achieve long-term ECMO usage, ideal oxygenators should be the true membrane (to prevent plasma leakage) and hollow fiber type. The final goal of our group is to develop a membrane oxygenation system that has a two-week capability without plasma leakage, with high anti-thrombogenitic properties, and low hemolytic characteristics.[9-17]

Silicone material

One of the limitations of conventional silicone hollow fiber oxygenators compared with microporous membrane oxygenators is poor gas permeability. However, gas exchange performance across the silicone membranes mainly is dependent on resistance to gas transfer in proportion to the membrane thickness. Thus, it is necessary to develop a new silicone hollow fiber with reduced wall thickness to obtain good gas permeability. However, it has been difficult to fabricate a fine, thin hollow fiber for reduction of resistance to gas permeability because of the poor mechanical strength of conventional silicone materials. This author's group successfully developed a novel silicone material that has sufficient mechanical strength for fabrication of a fine hollow fiber.[9]

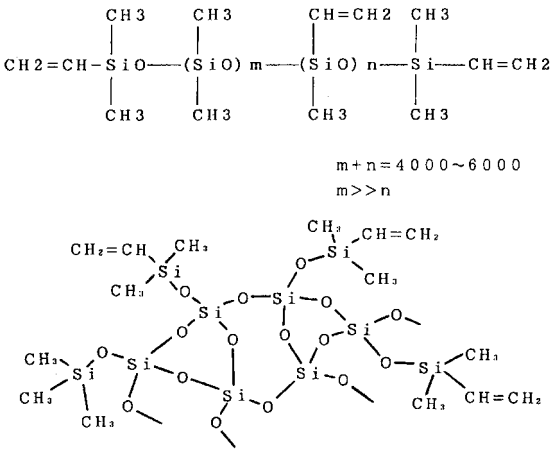


Fig. 1. Structure of the base polymer and vinyl resin.

A new silicone material was developed from methylvinylsiloxane as the base polymer, vinyl resin, and hydrogen siloxane. The base polymer and vinyl resin were cross-linked by hydrogen siloxane. Silica was used as the surface treatment reagent. The complex three-dimensional structure of methylvinylsiloxane and vinyl resin provides improved mechanical strength of the silicone material. Figure 1 shows the structure of the base polymer and vinyl resin. Fine silicone hollow fibers were fabricated using this newly developed material, with an outside diameter of 300 μm and wall thickness of 50 μm, which is approximately half that of the conventional silicone hollow fiber. Its mechanical strength is 950-1,200 g/mm^2, which is two times greater than that of conventional silicone hollow fibers.

New hollow fiber silicone membrane oxygenator for ECMO

Using this newly developed silicone hollow fiber, this author's group developed a compact extracapillary flow membrane oxygenator. Based on the results of many experimental models,[9-12] two types of pre-clinical models were fabricated (Fig. 2). Table 1 shows the characteristics of each oxygenator. This oxygenator is an extra-capillary flow type, in which blood flows outside the hollow fibers. The hollow fibers were cross-wound to augment the secondary flow (Fig. 3).

Fig. 2. The photograph shows the prototype silicone hollow fiber membrane oxygenators designed for ECMO (PPM-03 and PPM-04).

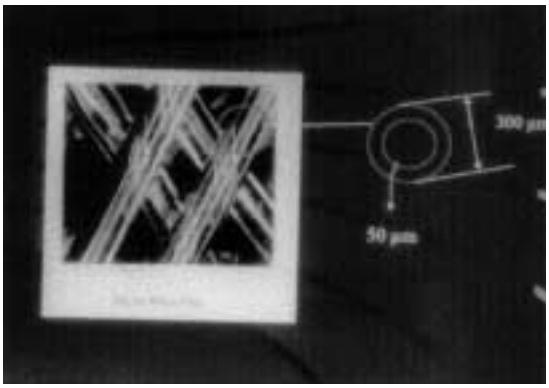


Fig. 3. Photograph of the mechanically cross-wound ultrathin silicone hollow fiber membrane used in the prototype oxygenator.

Table 1. The characteristic of the new hollow fiber silicone membrane oxygenators for ECMO

	PPM-03	PPM-04
Surface area (m^2)	0.8	1.0
Height of the housing (mm)	200	220
Fiber length (mm)	100	150
Packing density (%)	45	40
Priming volume (ml)	140	200
Flow distributor	4-chamber	1-chamber

PPM-03 type oxygenator

The first prototype silicone membrane oxygenator (preproduction model: PPM-03) consisting of these silicone hollow fibers into a housing made of polycarbonate (inner diameter: 80 mm) was fabricated (Fig. 2, left). In vitro studies[13] and ex vivo studies using bovine[14] were performed.

In vitro study: The gas transfer performance and biocompatibility of this oxygenator simulating ECMO conditions were evaluated. Fresh bovine blood was used for the in vitro studies. According to the established Baylor laboratory method, a mock circuit was assembled. Guidelines from the Association for Advancement Medical Instrumentation (AAMI) and the recommended practice for assessment of hemolysis as described by the American Society of Testing and Materials (ASTM) were followed during this study.[18,19] The test circuit for the gas transfer evaluation contained two membrane oxygenators (a test oxygenator and a de-oxygenator), a centrifugal pump, a roller pump, the appropriate polyvinylchloride tubing, and connectors with stopcocks for blood sampling. Two polyvinylchloride reservoirs with a sampling port were attached. The Cobe Optima® oxygenator (Cobe Cardiovascular, Inc., Amada, CO, U.S.A.) was employed as the de-oxygenator, and the Gyro C1E3® (Kyocera Corporation, Kyoto, Japan) was used as the centrifugal pump.[20,21] A Sechrist oxygen/air blender (Sechrist Industries, Inc., Anaheim, CA, U.S.A.) was connected to the de-oxygenator with tubing. Temperature was maintained at 37±2°C with a heat exchanger for the de-oxygenator that was connected to the water bath. For the hemolysis test and pressure drop measurement, the test circuit contained a pump, oxygenator, appropriate polyvinylchloride tubing, and connectors with stopcocks for blood sampling and pressure measurements. A polyvinylchloride reservoir with a sampling port was attached. The Gyro C1E3® was used as the centrifugal pump. The pressure of the distal side of the oxygenator was controlled at 100 mmHg. The blood flow was monitored with an ultrasonic flowmeter (Transonic System T108, Ithaca, NY, U.S.A.).

Gas transfer performance tests were performed at a blood flow rate of 0.5-6 L/min and V/Q (V is gas flow rate, Q is blood flow rate) ratio of 2-4. Blood gas samples, taken from the inlet and outlet sampling ports, were analyzed using a System 1306 pH/blood gas analyzer (Instrumentation Laboratories, Lexington, MA, U.S.A.). The O_2 content and O_2 transfer rate and the CO_2 content and transfer rate were calculated by the following standard

formulas:

O_2 content (Vol%)=(Hb×1.34×%O_2 saturation)/100+PO_2×0.003

O_2 transfer rate (ml/min)=(CaO_2–CvO_2)×blood flow rate

Total CO_2 (mmol/L)=HCO_3^-+0.03×PCO_2

CO_2 transfer rate (ml/min)=22.4×(tCO_2v–tCO_2a)×blood flow rate

where Hb is hemoglobin (g/dl), PO_2 is partial pressure of oxygen (mmHg), CaO_2 is arterial oxygen content (Vol%), CvO_2 is venous oxygen content (Vol%), the blood flow rate represents pump flow rate (L/min), HCO_3^- is plasma bicarbonate ion concentration (mmol/L), PCO_2 is CO_2 partial pressure (mmHg), tCO_2v is venous total CO_2 (mmol/L), and tCO_2a is arterial total CO_2 (mmol/L). Hemolysis tests were performed at a blood flow rate of 1 and 5 L/min. The plasma free hemoglobin (fHb) concentration was measured spectrophotometrically with a Sigma assay kit (kit No. 527, Sigma Chemical Co., St. Louis, MO, U.S.A.). The Normalized Index of Hemolysis (NIH) was calculated according to the following formula with linear regression analysis:

$$\mathrm{NIH\,(g/100\,L)} = \frac{\Delta \mathrm{fHb} \cdot \mathrm{V} \cdot \left(1 - \left(\frac{\mathrm{HT}}{100}\right)\right) \cdot 100}{\Delta \mathrm{t} \cdot \mathrm{Q}}$$

where ΔfHb is the increase in free plasma hemoglobin concentration (g/L) during the testing period, Δt is the testing time (min), Ht is the hematocrit (%), V is the blood volume of each circuit (L), and Q is the flow rate expressed as L/min. ΔfHb/Δt was obtained from the slope of the regression line between the free plasma hemoglobin and the test time. The sampling times were plotted on the X-axis, and the free plasma hemoglobin values were plotted on the Y-axis. The slope of the regression line between them was derived from the graph using computer software. The obtained slope indicated the value of ΔfHb/Δt. This authors' group previously reported on the hemolysis studies from the oxygenator.[22,23] The Normalized Index of Hemolysis for Oxygenator (NIHO) has been modified according to the ASTM standards.[19] The NIH value, which was obtained from the circuit without an oxygenator was subtracted from the primary NIH value, which was obtained from the circuit with an oxygenator to eliminate the effects of the centrifugal pump or other artifacts. This value was defined as the value of NIHO. The blood pressure drop was also measured. Pressure differences between the inflow and outflow ports were measured while testing the oxygenator using a pressure monitor (Living Systems Instrumentation, Burlington, Vermont, U.S.A.) at blood flow rates incrementally from 0.5 L/min until reaching 200 mm Hg.

The NIHO value could be determined as 0.0112 (g/100 L) and 0.0152 (g/100 L) at flow rates of 1 L/min and 5 L/min, respectively. This pre-clinical model demonstrated a good gas transfer rate per unit surface area, which is superior to the Kolobow oxygenator.[13] However, the gas transfer rates per total unit were marginal from the clinically acceptable level.

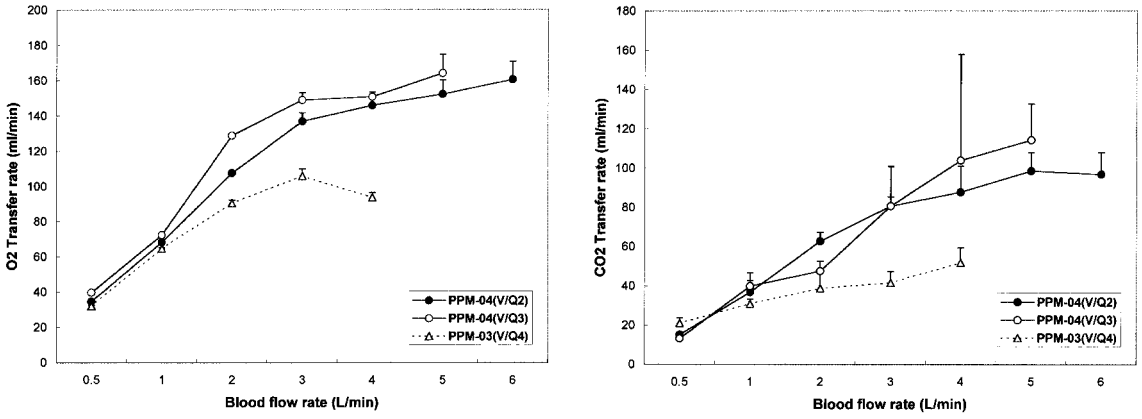
Ex vivo study: Ex vivo long-term durability tests for ECMO were performed using healthy miniature calves. A 15 cm longitudinal incision was made along the jugular vein on the left side of the neck, and the left carotid artery and jugular vein were dissected. The arterial cannula was inserted through a small arterotomy and threaded proximally into the artery; the venous cannula was inserted through the jugular vein in the proximal direction in the same manner. After placing the arterial and venous cannulae, both were externalized and connected to the extracorporeal circuit, and the pump circuit was activated. The Gyro C1E3® was used for the centrifugal pump. The Gyro C1E3® has been determined to have good biocompatibility and hydraulic performance characteristics.[20,21] Pressure differences between the inflow and outflow ports were monitored to assess the pressure drop in the oxygenator throughout the experiment. The O_2 and CO_2 gas transfer rates and pressure drop were evaluated for one week.

The stable gas transfer rates at a blood flow rate of 1 L/min and V/Q=4 were maintained for the entire experiment. However, in spite of a high dose of heparin, a high-pressure drop and occlusion was discovered during some ex vivo studies.[14] That is why the improved oxygenator was necessary to be developed.

PPM-04 type oxygenator

The major changes of the new improved model (PPM-04) (Fig. 2, right) are as follows: 1) increase the fiber length (from 100 to 150 mm) and the surface area (from 0.8 to 1.0 m^2) to increase the gas transfer rate, 2) decrease the packing density (from 45 to 40%) to decrease the pressure drop, and 3) a specially designed blood flow distributor (from 4-chamber to 1-chamber) was incorporated into the center of the module to prevent blood stagnation.

In vitro study: At a blood flow rate of 1 L/min and V/Q=3, the O_2 and CO_2 gas transfer rates were



A B

Fig. 4. Gas transfer performance changes of O_2 transfer rate (A) and CO_2 transfer rate (B) for an in vitro study (n=6). Sufficient gas transfer levels were revealed. Data are expressed as mean±SD. (from Ref. No. 15)

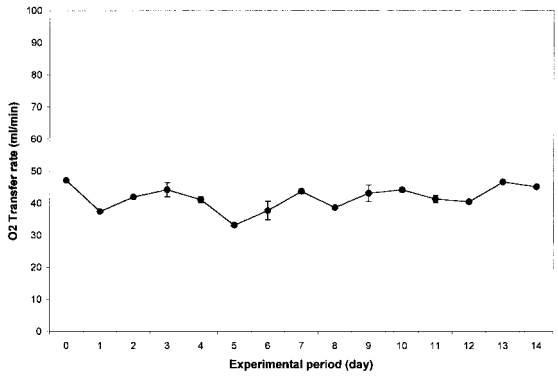
72.45±1.24 (mean±SD) ml/min and 39.87±2.92 ml/min, respectively. At a blood flow rate of 2 L/min and V/Q=3, the O_2 and CO_2 gas transfer rates were 128.83±1.09 ml/min and 47.49±5.11 ml/min (Fig. 4). Clearly, these data were superior to those obtained with previous models (PPM-03, V/Q=4). As for the pressure drop and hemolytic performance, remarkable improvements were also demonstrated.[15] The pressures of the PPM-04 were lower than the pressures of the PPM-03. The NIHO value could be determined as 0.0098 (g/100 L) and 0.0117 (g/100 L) at flow rates of 1 L/min and 5 L/min, respectively.

Ex vivo study: A short-term[16] and a two-week long-term[17] ex vivo experiment were successfully performed without exchanging the oxygenator. The stable and reliable performance of this new oxygenator was demonstrated for the entire experiment. Figure 5 shows the results of the gas exchange performance and hemolysis tests. The O_2 and CO_2 gas transfer rates at a blood flow rate of 1 L/min and V/Q=3 were maintained at 41.72±4.13 ml/min and 40.97±14.49 ml/min, respectively, for two weeks. The plasma free hemoglobin was maintained at 5.50±2.20 mg/dl for two weeks. The pressure drop in the blood chamber was kept from 20 to 40 mmHg. After the experiment, no blood clot formation was observed in the module and no abnormal necropsy findings were found.

These data suggest that this newly improved oxygenator has superior efficiency, less blood trauma, and may be suitable for long-term ECMO usage. However, the value of plasma free hemoglobin increased abruptly at the eighth day after experiment. Hemolysis is one of the most critical blood reaction of blood in contact with circulatory assist devices. Hemolysis from the oxygenator is dependent upon several physical factors, including pressure drop, wall thickness of the membrane functioning as resistance, surface characteristics (surface roughness and coating). In this study, as the pressure drop also increased at the same time, we guess one possible reason is the increase of shear stress due to the micro thrombus formation in the oxygenator. On the other hand, however, we cannot eliminate the effects of the centrifugal pump or other artifacts, too. For further high performance and antithrombogenicity, this pre-clinical model will be modified, and a final model will be developed soon.

Conclusion

Today in the United States, ECMO applications are annually increasing due to excellent clinical results. Unfortunately, there are no good ECMO oxygenators available. During the last seven years, these authors and team members at Baylor College of Medicine have been pursuing the development of a better hollow fiber membrane oxygenator for ECMO. This group will continue advancing with further development. It is believed that the long-term ECMO support using the reliable and durable oxygenator has led us to a new field of treatment for respiratory failure patients. Now we are in the final stage of development.



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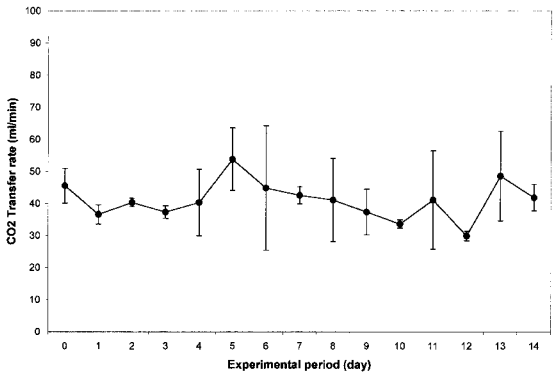

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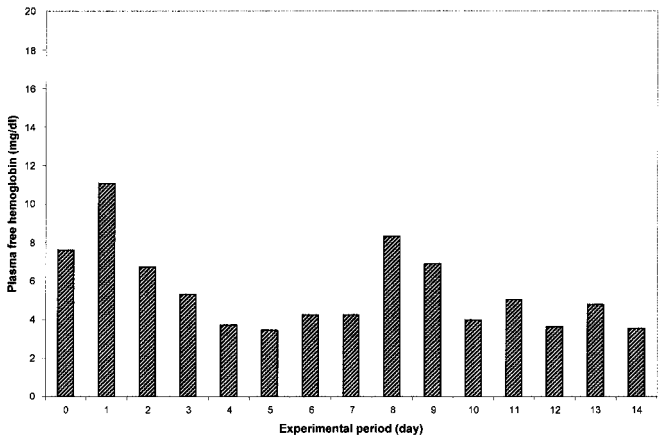

C

Fig. 5. Gas transfer performance changes of O_2 transfer rate (A) and CO_2 transfer rate (B) for a two-week ex vivo study. Stable and sufficient gas transfer levels were revealed. Data are expressed as mean±SD. The change of plasma free hemoglobin during the two-week ECMO study (C). (from Ref. No. 17)

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