

# Preclinical Evaluation of a New Hollow Fiber Silicone Membrane Oxygenator for Pediatric Cardiopulmonary Bypass: Ex-vivo Study

Shinji Kawahito, MD, PhD, Tomohiro Maeda, MD, PhD, Tadashi Motomura, MD, Tamaki Takano, MD, Kenji Nonaka, MD, Joerg Linneweber, MD, PhD, Seiji Ichikawa, MD, Masaki Kawamura, PhD, Hiroshi Ishitoya, MD, PhD, Julie Glueck, Koshiro Sato,\* and Yukihiro Nosé, MD, PhD

**Based on the results of many experimental models, a hollow fiber silicone membrane oxygenator applicable for long-term extracorporeal membrane oxygenation (ECMO) was developed. For further high performance and antithrombogenicity, this preclinical model was modified, and a new improved oxygenator was successfully developed. In addition to ECMO application, the superior biocompatibility of silicone must be advantageous for pediatric cardiopulmonary bypass (CPB). An ex vivo short-term durability test for pediatric CPB was performed using a healthy miniature calf for six hours. Venous blood was drained from the left jugular vein of a calf, passed through the oxygenator and infused into the left carotid artery using a Gyro C1E3 centrifugal pump. For six hours, the O<sub>2</sub> and CO<sub>2</sub> gas transfer rates were maintained around 90 and 80 ml/min at a blood flow rate of 2 L/min and V/Q=3, respectively. The plasma free hemoglobin was maintained around 5 mg/dl. These data suggest that this newly improved oxygenator has superior efficiency, less blood trauma, and may be suitable for not only long-term ECMO but also pediatric CPB usage. (Ann Thorac Cardiovasc Surg 2002; 8: 7–11)**

**Key words:** hollow fiber, silicone membrane, oxygenator, pediatric, cardiopulmonary bypass, ex-vivo study

## Introduction

Today in the United States, extracorporeal membrane oxygenation (ECMO) applications are increasing annually due to the excellent clinical results.<sup>1)</sup> Unfortunately, there are no good ECMO oxygenators available, except for the Kolobow spiral coil membrane oxygenator (Medtronic Inc., Anaheim, CA, U.S.A.) which was developed almost 30 years ago.<sup>2)</sup> Consequently, the need to

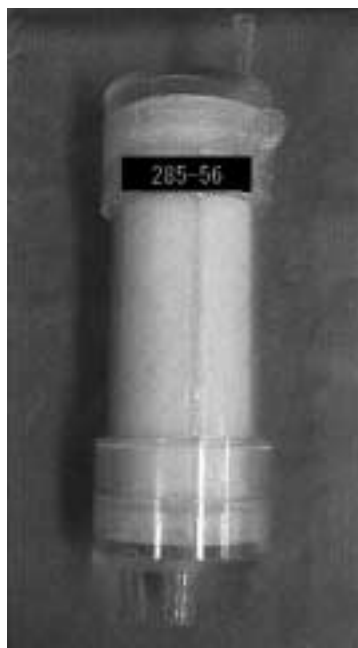
develop a second-generation ECMO oxygenator is desperately needed.

This author's group started to develop a membrane oxygenator for ECMO application using a novel fine silicone hollow fiber in 1995, and successfully made a preclinical model.<sup>3-6)</sup> For further high performance and antithrombogenicity, this preclinical model was modified (increase of the fiber length and the total surface area, decrease of the packing density, modification of the flow distributor etc.), and a new improved oxygenator was successfully developed. Acceptable gas performance and hemolytic features of this improved model during in vitro studies have already been reported.<sup>7)</sup> It is well known that silicone rubber is good blood biocompatible material. In addition to the ECMO application, the superior biocompatibility of silicone must be advantageous for pediatric cardiopulmonary bypass (CPB) usage. The purpose of this ex vivo study is to evalu-

---

*From the Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, USA, and \*Fuji Systems, Inc., Tokyo, Japan*

Received May 28, 2001; accepted for publication August 1, 2001.  
Address reprint requests to Shinji Kawahito, MD PhD.: Department of Anesthesiology, Tokushima University School of Medicine, 3-18-15, Kuramoto, Tokushima 770-8503, Japan.  
Presented in part at the 8th Congress of the International Society for Rotary Blood Pumps, September 6-9, 2000, in Aachen, Germany.



**Fig. 1.** This photograph shows the new prototype silicone hollow fiber membrane oxygenator.

ate the gas transfer and hemolytic performances of this newly improved model during pediatric CPB condition using calves.

## Materials and Methods

The Animal Research Committee of Baylor College of Medicine approved the study protocol, and the calves were treated humanely according to the Baylor Animal Protocol Review Committee's regulations.

### Membrane oxygenator (Fig. 1)

A new silicone hollow fiber membrane oxygenator (preproduction model PPM-04, Fuji Systems Inc., Tokyo, Japan) was fabricated for long-term ECMO application based on the results of a previous model (PPM-03).<sup>7)</sup> The major changes of the newly improved model (PPM-04) are as follows: 1) increase the fiber length (from 100 to 150 mm) and the surface area (from 0.8 to 1.0 m<sup>2</sup>) to increase the gas transfer rate, 2) decrease the packing density (from 45 to 40%) to decrease the pressure drop, 3) and a specially designed blood flow distributor (from a 4 chamber to 1 chamber) was incorporated into the center of the module to prevent blood stagnation.

Consequently, the new ECMO oxygenator module was 220 mm long and contained in silicone coated acrylic

housing. The priming volume of this module was 200 ml. This prototype oxygenator is a cross-flow type, and the blood flows outside the hollow fiber, while the gas flow is inside the fibers.

### Surgical procedure

A healthy miniature female calf (Dexter strain) weighing 90 kg was used for this acute ex vivo study. Anesthesia was induced using 4% halothane with 50% nitrous oxide through a special mask. When the animal was anesthetized, endotracheal intubation was performed and anesthesia was maintained by 1-2% halothane with 100% oxygen. 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 arteriotomy 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<sup>®</sup> (Kyocera Corporation, Kyoto, Japan) was used for the centrifugal pump. Mean arterial pressures were maintained at more than 80 mmHg. Throughout the experiment, heparin diluted with saline (500 units/ml) was continuously administered intravenously to maintain an activated clotting time at approximately 400 sec.

### Measurements

**Gas transfer rate:** At a blood flow rate of 2 L/min and V/Q=3 (V=gas flow rate; Q=blood flow rate), the O<sub>2</sub> and CO<sub>2</sub> gas transfer rates were evaluated for 6 hours (pediatric CPB condition). Blood gas samples, taken from the inlet and outlet sampling ports, were analyzed every hour using a System 1306 pH/blood gas analyzer (Instrumentation Laboratories, Lexington, MA, U.S.A.). The O<sub>2</sub> content and O<sub>2</sub> transfer rate and the CO<sub>2</sub> content and transfer rate were calculated by the following standard formulas:

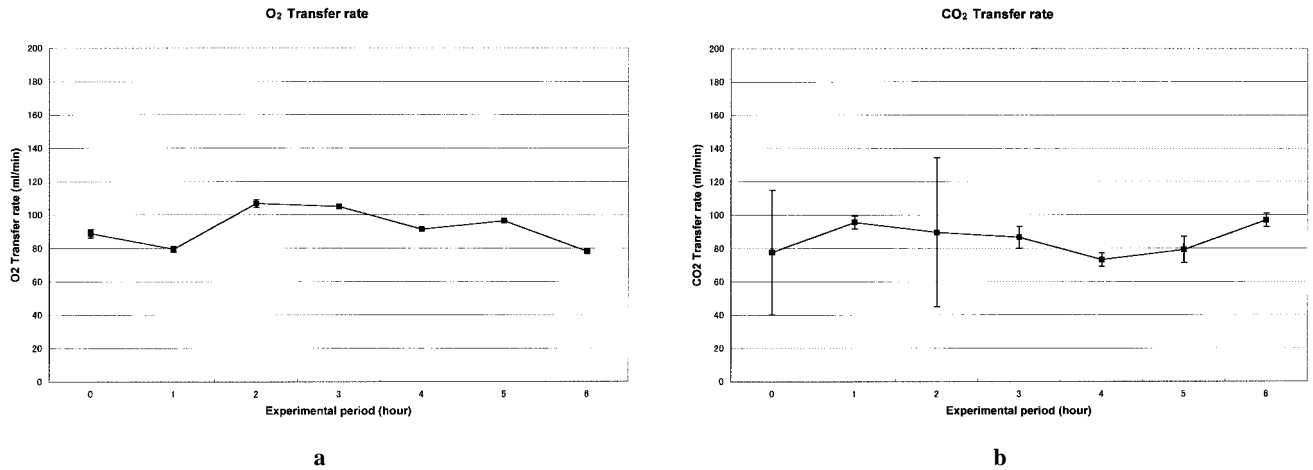
$$\text{O}_2 \text{ content (vol\%)} = (\text{Hb} \times 1.34 \times \% \text{O}_2 \text{ saturation}) / 100 + \text{PCO}_2 \times 0.003$$

$$\text{O}_2 \text{ transfer rate (ml/min)} = (\text{CaO}_2 - \text{CvO}_2) \times \text{blood flow rate}$$

$$\text{Total CO}_2 \text{ (mmol/L)} = \text{HCO}_3^- + 0.03 \times \text{PCO}_2$$

$$\text{CO}_2 \text{ transfer rate (ml/min)} = 22.4 \times (\text{tCO}_2 \text{v} - \text{tCO}_2 \text{a}) \times \text{blood flow rate}$$

where Hb is hemoglobin (g/dl), PO<sub>2</sub> is oxygen partial pressure (mmHg), CaO<sub>2</sub> is arterial oxygen content (vol%),



**Fig. 2.** Gas transfer performance changes of O<sub>2</sub> transfer rate (a) and CO<sub>2</sub> transfer rate (b) for acute 6-hour studies in pediatric cardiopulmonary bypass condition. Sufficient gas transfer levels were revealed. Data are expressed as mean ± SD.

CvO<sub>2</sub> is venous oxygen content (vol%), the blood flow rate represents pump flow rate (L/min), HCO<sub>3</sub><sup>-</sup> is plasma bicarbonate ion concentration (mmol/L), PCO<sub>2</sub> is CO<sub>2</sub> partial pressure (mmHg), tCaO<sub>2</sub>v is venous total CO<sub>2</sub> (mmol/L), and tCO<sub>2</sub>a is arterial total CaO<sub>2</sub> (mmol/L).

**Hemolytic characteristics:** Plasma free hemoglobin was measured every hour. The method of measuring plasma free hemoglobin has been described by Mizuguchi et al.<sup>8)</sup>

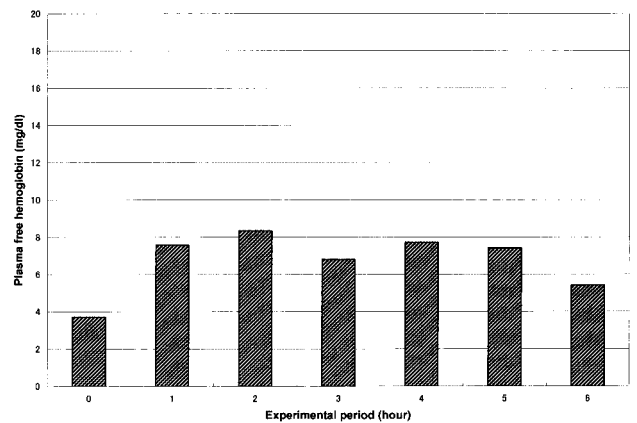
**Pressure drop measurement:** Pressure differences between the inflow and outflow ports were monitored to assess the pressure drop in the oxygenator throughout the experiment using a pressure monitor (Living Systems Instrumentation, Burlington, VT, U.S.A.).

**Results**

**Gas transfer performance:** Figure 2 (a, b) shows the results of gas exchange performance tests. The O<sub>2</sub> and CO<sub>2</sub> gas transfer rates at a blood flow rate of 2 L/min and V/Q=3 were maintained at 91.53±10.67 (mean ± SD) ml/min and 85.34±27.94 ml/min, respectively, for the entire experiment.

**Hemolysis test:** As shown in Fig. 3, the plasma free hemoglobin was maintained at 6.71±1.61 mg/dl for 6 hours.

**Pressure drop study:** The pressure drop in the blood chamber gradually increased, and reached 180 mmHg in 5 hours. However, more increase was not observed.



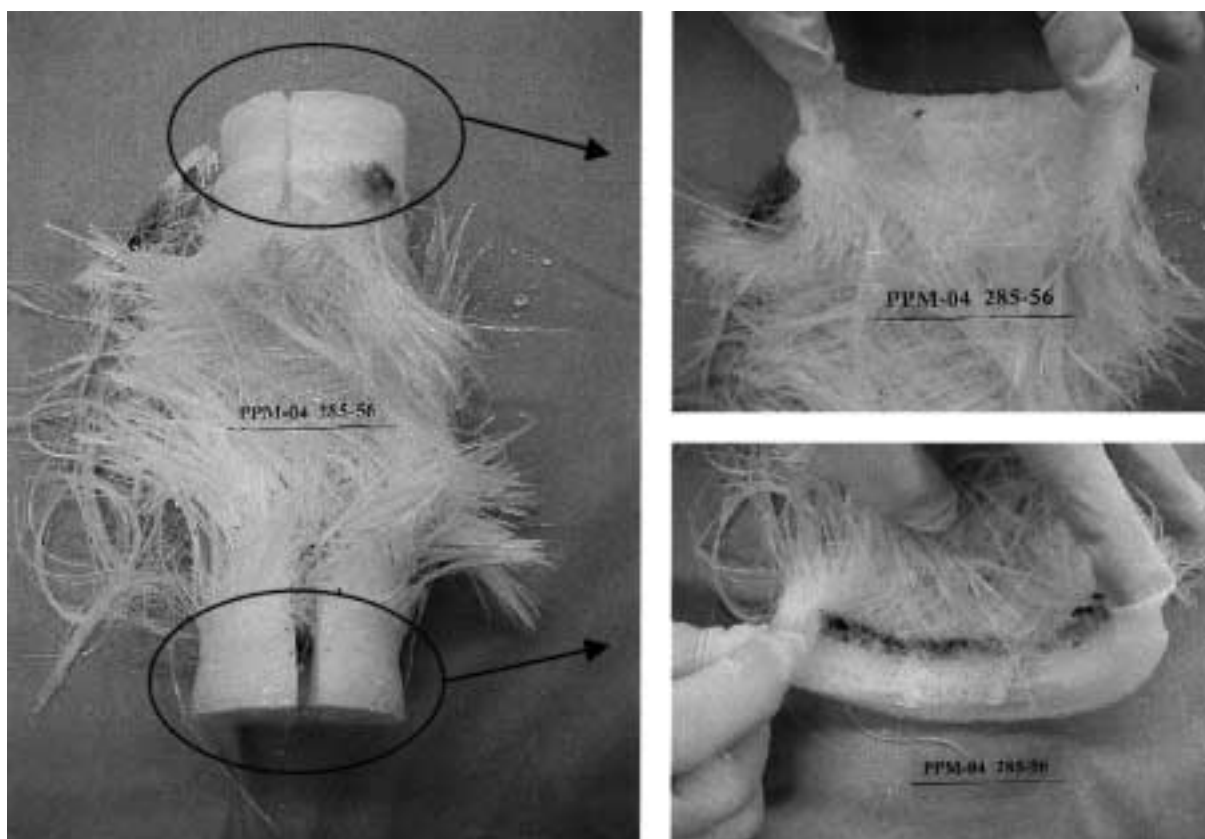
**Fig. 3.** The changes of plasma free hemoglobin for 6-hour acute studies in pediatric cardiopulmonary bypass condition.

**Visual inspection:** Visual inspection after the experiment revealed no obvious blood clot formation in the oxygenator (Fig. 4).

**Discussion**

In the United States, each year many adults and over 6,000 newly born babies suffer from severe lung disease, which requires emergency respiratory support. More than 80% of these non-adult patients are saved by an artificial lung system called ECMO. Even though ECMO is an effective life saving treatment, the equipment being used in the United States today is outdated (1972 model), expensive and very difficult to use. There is no hollow fiber membrane oxygenator for ECMO available.

A silicone hollow fiber membrane oxygenator for long-



**Fig. 4.** This is a photograph of the oxygenator after an experiment.

term ECMO was developed in our laboratory (PPM-03) using an ultra-thin silicone hollow fiber.<sup>3-6)</sup> The equipment we have developed is cheaper, easier to use and can safely support the patient for a longer period of time with better efficiency. However, the marginal gas transfer performances and a high-pressure drop in some cases were demonstrated in the initial models. In order to improve its performances the following features were incorporated in the most recent oxygenator model (PPM-04), increasing the fiber length and total surface area, decreasing the packing density, and modifying the flow distributor. Hence, this newly developed oxygenator was improved.

In this study, this newly improved oxygenator was evaluated simulating pediatric CPB condition with an ex vivo experiment. The change in  $O_2$  and  $CO_2$  gas transfer rates at a blood flow rate of 2 L/min and  $V/Q=3$  were maintained around 90 ml/min and 80 ml/min, respectively. Clearly, these data were superior to those of our previous model.<sup>6)</sup> Comparing the results of our in vitro data,  $O_2$  transfer rate is a little lower, and  $CO_2$  transfer rate is a little higher.<sup>7)</sup> However, stable and sufficient gas transfer performance during pediatric CPB condition was

proven in this ex-vivo experiment.

In short-term usage such as in CPB, the effects of plasma leakage may be less than in long-term usage. Especially for pediatric usage, good biocompatibility and less blood trauma is essential. Excellent biocompatibility of our silicone membrane oxygenator has already been reported.<sup>7)</sup> Also in this ex vivo study, plasma free hemoglobin levels and pressure drop were within acceptable levels. Even though a little blood clot formation occurred inside the oxygenator, it was at the orifice portion (flow distributor chamber) of the device. This oxygenator is advantageous especially for pediatric CPB application in terms of less blood trauma.

## Conclusion

Good gas transfer and hemolytic performances were kept with a newly improved silicone membrane oxygenator for 6 hours under pediatric CPB condition. These data suggest that this oxygenator will be suitable for pediatric CPB usage, as well as long-term application such as ECMO.

## References

1. Ichiba S, Bartlett RH. Current status of extracorporeal membrane oxygenation for severe respiratory failure. *Artif Organs* 1996; **20**: 120–3.
2. Kolobow T, Spragg RG, Pierce JE, Zapol WM. Extended term (to 16 days) partial extracorporeal blood gas exchange with the spiral membrane lung in unanesthetized lambs. *Trans ASAIO* 1971; **17**: 350–4.
3. Funakubo A, Higami T, Sakuma I, et al. Development of a membrane oxygenator for ECMO novel fine silicone hollow fiber. *ASAIO J* 1996; **42**: M837–40.
4. Niimi Y, Yamane S, Yamaji K, Tayama E, Sueoka A, Nosé Y. Protein adsorption and platelet adhesion on the surface of an oxygenator membrane. *ASAIO J* 1997; **43**: M706–10.
5. Yamane S, Ohashi Y, Sueoka A, Sato K, Kuwana J, Nosé Y. Development of a silicone hollow fiber membrane oxygenator for ECMO application. *ASAIO J* 1998; **44**: M384–7.
6. Maeda T, Iwasaki A, Kawahito S, et al. Preclinical evaluation of a hollow fiber silicone membrane oxygenator for extracorporeal membrane oxygenator application. *ASAIO J* 2000; **46**: 426–30.
7. Kawahito S, Maeda T, Motomura T, et al. Development of a new hollow fiber silicone membrane oxygenator: in vitro study. *Artif Organs* 2001; **25**: 494–8.
8. Mizuguchi K, Damm GA, Aber GS, et al. Does hematocrit affect in vitro hemolysis test results?: preliminary study with Baylor/NASA prototype axial flow pump. *Artif Organs* 1994; **18**: 650–6.