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Emergency Life Support System aiming preprimed oxygenator*

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Abstract— **Development have been achieved of a new blood pump for next generation Percutaneous Cardio-Pulmonary Support (PCPS) system and a novel surface coating method for silicone membrane hollow fiber by physical adsorption using a copolymer composed of a 2-Methacryloyloxyethyl phosphorylcholine (MPC) unit and a hydrophobic unit. The new blood pump, named the Troidal Convolution Pump (TCP), is based on the principle of a cascade pump and perfused 5 L/min and 350 mmHg at 2450 rpm. The novel copolymer composed of 30% MPC unit and 3-(methacryloyloxy) propyltris (trimethylsiloxy) silane (MPTSSi) unit (PMMSi30) was the most suitable molecular design on a silicone surface. The PMMSi30 coated surface adsorbed 7.2 % as much protein a non-coated surface adsorbed.**

I. Introduction

A Percutaneous Cardio-Pulmonary Support (PCPS) system has steadily established its lifesaving effectiveness and significantly contributes to cardiopulmonary resuscitation (CPR) for suffers of acute myocarditis, myocardial infarction, acute respiratory distress syndrome (ARDS) including pulmonary thromboembolism, and the accidental hypothermia. Especially for treatment of ARDS caused by novel influenza, extracorporeal membrane oxygenation (ECMO) is also effective [1]. What are required for future PCPS and ECMO devices are downsizing of the blood circuit, integration of blood pump and oxygenator, shortening of the setup time, usage out of hospitals, prevention of mixture of air bubbles, and long-term support.

Recently, two integrated extracorporeal life support systems (ECLS) have been commercialized as portable heart-lung machines that enable a sick heart and/or lung to recover. LIFEBRIDGE B2T is the world's first CE certified and FDA-cleared mobile ECLS with polypropylene (PP) hollow fiber oxygenator and a semiautomatic priming system [2]. MAQUET CARDIOHELP is the world's smallest CE certified and FDA-cleared mobile ECLS that consists of a polymethylpentene (PMP) hollow fiber oxygenator and an integrated blood pump [3].

The authors have mainly been researching and developing a total artificial heart (TAH) [4] and ventricular assist device (VAD) [5] until now, and one reason for this study is that we have accumulated knowledge and skills while designing and developing the blood pumps and biomedical device technology [6].

Figure 1 shows a picture using computer graphics of the urgent life-support equipment named the Emergency Life Support System (ELSS), which we aim to fabricate in the near future. It consists of an oxygenator, a rotary blood pump, a magnet coupling unit, a motor that drives the blood pump, and a rechargeable battery in an all-in-one console. Two major features of this system are a preprimed oxygenator and long-term use. A preprimed blood circuit including the oxygenator and blood pump decreases setup time. The characteristics of no plasma leakage and biocompatible surface at the hollow fiber in oxygenator enable not only long-term support over one month but also long-term storage time in preprimed condition.

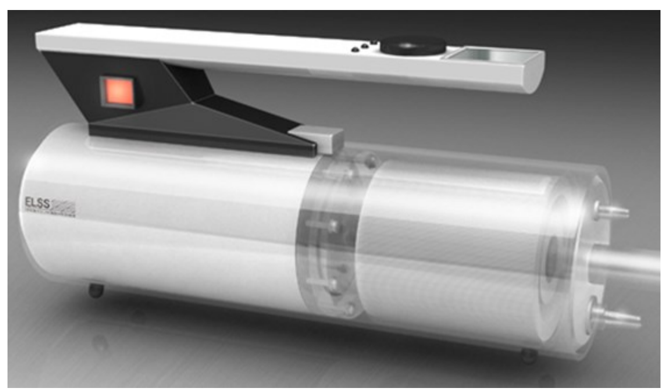

Figure 1. Emergency Life Support System. *(concept illustration)*

In this article, we focus on two components in ELSS. One is the new rotary blood pump with suitable hydrodynamic performance in the case of thin percutaneous cannulae usage and endurance for long-term use. The other is the new biocompatible surface coating method for the hollow fiber in oxygenator.

II. Materials and Methods

A. Troidal Convolution Blood Pump (TCP)

We designed a new blood pump named Troidal Convolution Pump (TCP) that has proper hydraulic performance against the high pressure loss in the case of PCPS application. The pump principle is similar to the cascade pump. The blood is

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given static pressure by the multiple centrifugal forces during spiral turning in the pump room (Figure 2). The inlet of the blood pump is located on the side wall of the pump housing. There are two semicircular blood pump rooms to keep equilibrium in the axis symmetry. There are two pump outlets located at the top surface of the pump in the axial direction to perfuse the blood to the oxygenator.

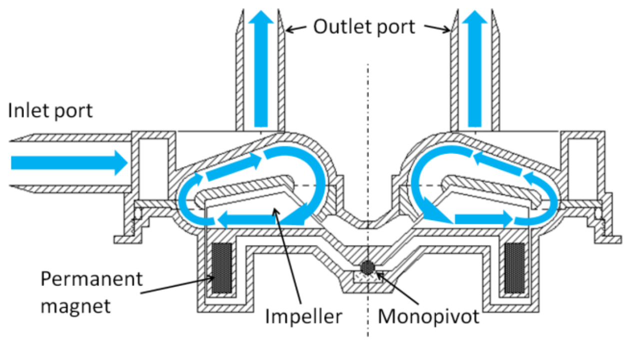


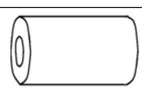
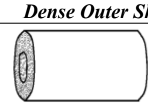
Figure 2. Sectional drawing of TCP.

The impeller is suspended by a monopivot bearing for long-term use and driven by magnet coupling using permanent magnets.

B. Hollow fiber for oxygenator and surface coating

The oxygenator consists of thousands of thin hollow fibers for gas exchange. Microporous hollow fiber used to be common in short-term applications such as open heart surgery, but plasma leakage is observed. The microporous hollow fiber with thin dense outer skin layer is a special membrane for long-term use that eliminates plasma leakage. The membrane hollow fiber made from dense silicone is conventional with its natural high gas permeability and no plasma leakage, and it is especially effective for long-term ECMO application (Table 1).

TABLE I. COMPARISON OF HOLLOW FIBERS FOR OXYGENATOR

Hollow fiber	**Structure of Hollow Fiber**		
	Dense	***Microporous***	***Microporous with Dense Outer Skin***
Schematic view			
Material	Silicone	Polypropelene	Polymethylpentene
Plasma leakage	None	Obserbed	Plasma tight
Main target	Long-term ECMO	Open heart surgery	Short to long term

The materials are shown widely used.

In this study, we employ the dense silicone hollow fiber (Fuji Systems Corporation, Tokyo) from the viewpoint of long-term use and no plasma leakage [7]. However, the surface of silicone hollow fiber is hydrophobic in its natural state, which leads to it adsorbing proteins. Additionally, filling the oxygenator using silicone membrane with aqueous buffer solution is unsuitable because of the generation of bubbles on the surface of silicone hollow fiber.

The 2-Methacryloyloxyethyl phosphorylcholine (MPC) polymer is a well-known hydrophilic and biocompatible surface coating material [8]. MPC polymer coating is one of the most popular biocompatible coatings, especially in long-term use medical devices such as implantable VAD [9]. However, MPC itself was difficult to coat on the surface of silicone.

Recently, poly (MPC-*co*-3-(methacryloyloxy) propyltris (trimethylsiloxy) silane (MPTSSi)) was reported as a coating material for poly (dimethylsiloxane) (PDMS) [10]. Poly (MPC-*co*-MPTSSi) (PMMSi) with several composition ratios of an MPC unit and an MPTSSi unit was synthesized by radical polymerization. Nii et al. reported that the PMMSi30 coating 30% hydrophilic MPC unit was the most suitable molecular design in terms of the stability of the coated membrane of PDMS surface [11]. Figure 3 shows the molecular structure of PMMSi30.

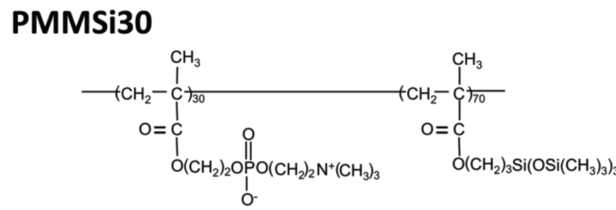


Figure 3. Chemical structuer of PMMSi30.

Surface coating was performed as follows. PMMSi30 was dissolved in ethanol at 30 mg/mL. A silicone hollow fiber was put into the polymer solution for 10 minutes and naturally dried in a clean air box for one hour. The dried sample was aged in water for one hour before having its protein adsorption measured using fluorescein isothiocyanate (FITC)-labeled bovine serum albumin (BSA) (Sigma-Aldrich, St. Louis, MO).

To compare the efficiency of surface coating, commercially available coating material Pluronic F127 (10wt % in water) was coated on the surface of silicone hollow fiber for 24 hours after O_2 plasma treatment (85W, 30s). Figure 4 shows the molecular structure of Pluronic F127(Sigma-Aldrich, St. Louis, MO).

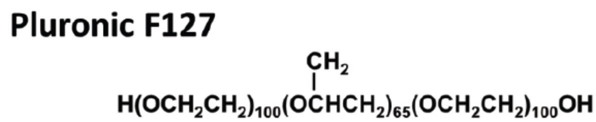


Figure 4. Chemical structuer of Pluronic F127.

A protein adsorption test was performed as follows. The coated silicone hollow fiber was soaked in phosphate buffered saline (PBS) with FITC-labeled BSA (4.5 mg/mL. FITC-labeled BSA: BSA = 1 : 9) for one hour. After the hollow fiber was washed with fresh PBS to remove the protein solution, the hollow fiber was observed by using a fluorescence microscope (Axioskop2 plus, Carl Zeiss, Jena, Germany) at an exposure level of 1/3.5 s.

III. Results

A. Troidal Convolution Blood Pump (TCP)

The main components of prototype TCP are shown in Figure 5. The upper housing with inlet and outlet ports was made of epoxy resin, and the lower housing and impeller were made of polymethacrylate. The impeller consisted of 20 vanes, and its diameter was 66 mm.

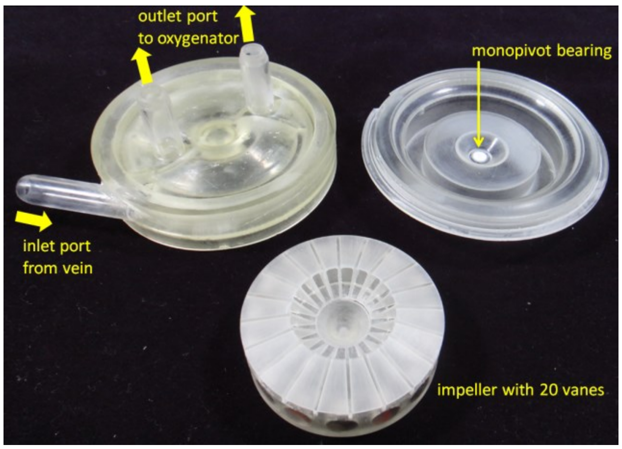


Figure 5. Actual model of TCP.

Figure 6 shows the relationship between the pressure head and the flow rate of the prototype TCP in the mock circulatory system with saline solution. The pump perfused 5 L/min against 350-mmHg pressure head at 2450-rpm motor rotation.

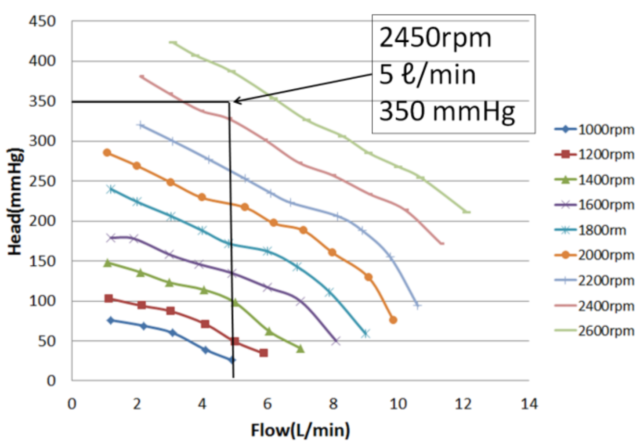


Figure 6. Hydrolic performance of TCP.

B. Hollow fiber for oxygenator and surface coating

The outer and inner diameters of silicone hollow fiber were 0.4 mm and 0.3 mm, respectively. Figure 7 shows the fluorescence microscopy images obtained after the protein adsorption test using the FITC-labeled BSA solution. Fluorescent intensity of the non-coating hollow fiber was strong; indicating that a significant amount of protein was adsorbed on the surface. Protein adsorption was also observed on Pluronic F127 coated hollow fiber. On the other hand, the amount of protein adsorption was significantly decreased almost to the background level when the hollow fiber was coated with PMMSi30.

Relative intensity was calculated for 0 at the fluorescence intensity of no-adsorption-test hollow fiber and 100 at the intensity of non-coating hollow fiber. The relative intensity of PMMSi30 coated hollow fiber was 7.2 (Figure 8).

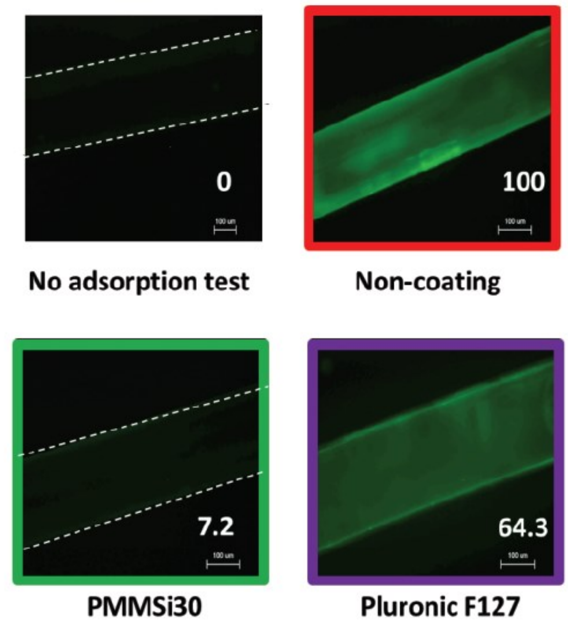


Figure 7. Fluorescence microscopy images obtained after the FITC-labeled BSA adsorption test. The number in each picture is relative intensity of protein adsorption. Dotted line is a virtual line expressing the external form of the hollow fiber. All scale bars 100 μm

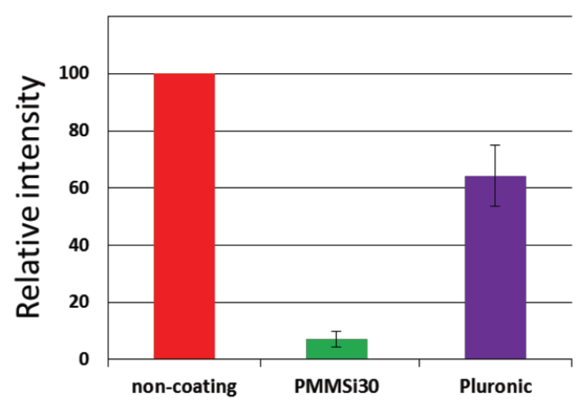


Figure 8. Relative intensity of protein adsorption.

IV. Discussions

An all-in-one ECLS system is an ideal device that promises to be easy to handle, use, and carry on vehicles. LIFEBRIDGE B2T and MAQUET CARDIOHELP realized these features, and they are commercially available in the European Union and United States. A preprimed blood circuit including blood pump and oxygenator is a target at which the next-generation ECLS system should aim. Tatsumi et al. have continued to develop an all-in-one system and reported the trial for preprimed setup using polyolefin hollow fiber [12].

We describe the present status of component technology development for ELSS.

A. *Blood pump*

Most other ECLS systems employ centrifugal blood pumps because they have lower blood trauma, are more compact, and can be used for longer than roller pumps as well as having no excessive pressure. TCP is a cascade pump utilizing multiple centrifugal forces by spiral turning in the pump room. One advantage of TCP is that it operates in relatively low rotation in the same impeller diameter as a centrifugal pump. That means low shear stress for the blood and eliminating wear of monopivot. Another advantage is the equilibrium of the impeller in the axis symmetry thanks to the configuration of two blood pump rooms. The other advantage is the high flexibility of the port placement on pump housing. We could locate the outlet ports on the top of the pump housing in order to connect them to the oxygenator component.

B. *Hollow fiber and surface coating*

Plasma leakage is a major limitation in the application of microporous membrane oxygenators for long-term support. Senko Medical Instrument Manufacturing developed a special surface coating process by the vacuum deposition of cyclosiloxane. A dense skin layer of Tetramethylcyclotetrasiloxane (TMCTS) was formed on the outer surface of polypropylene microporous hollow fiber and performed plasma tight characteristics [13]. The authors employed a dense silicone membrane hollow fiber in this study because of its no-plasma-leakage nature. Additionally, PMMSi30 coated silicone hollow fiber demonstrated low protein adsorption. The relative intensity of protein adsorption using PMMSi30 was 7.2 % of that using non coating and 11 % of that using Pluronic F127. We are now further evaluating by using a prototype oxygenator using PMMSi30 coated silicone hollow fiber to realize high blood compatibility and long-term support.

C. *Prepriming*

A preprimed oxygenator is one of the final goals in ECLS application [14]. However, preprimed dialyzers are common as wet devices in hemodialysis application because dialyzers are used when both sides of hollow fiber are filled with liquid. However, the outside and inside of hollow fiber in a common outside perfusion oxygenator are filled with blood and air (oxygen), respectively. It is difficult for preprimed oxygenators to keep dry inside the hollow fiber during storage period. We should find some solutions to keep preprimed oxygenators dry or to blow off the liquid inside the hollow fiber before use.

V. CONCLUSION

A new TCP showed suitable hydrodynamic performance for a PCPS system in a high pressure loss condition using thin cannulae. The PMMSi30 coated silicone hollow fiber effectively suppressed protein adsorption. We believe that the hollow fiber with no plasma leakage will contribute to the next-generation portable, preprimed, and long-term support ECLS.

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