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Improved Hemolytic Performance of Blood Pump with Fluorine-Doped Hydrogenated Amorphous Carbon Coating

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ABSTRACT

Fluorine-doped hydrogenated amorphous carbon (a-C:H:F) film was deposited on a flow-straightener, impeller and diffuser surface (SUS 304) of an enclosed-impeller type flow blood pump using the ionization deposition method with a source gas of C_6F_5H. The surface characteristics of the a-C:H:F film were examined using atomic force microscopy, X-ray photoelectron spectroscopy, and measurements of surface roughness, friction and surface potential. The a-C:H:F film tends to increase surface roughness and the negative surface charge. In addition, the surface energy and friction decrease with fluorine dopant in the a-C:H film. To estimate the hemolytic performance of a blood pump with the a-C:H:F film coating, the amount of hemolysis was measured using a mock circulatory system (*in vitro* test) with 500 mL of pig blood containing sodium citrate. *In vitro* test was conducted for 180 min with the blood flow and pump head maintained at 5 L/min and 100 mmHg, respectively. The a-C:H:F film coating reduced the amount of hemolysis and improved the hemolytic performance. Decreasing the surface energy and negative surface charge of the a-C:H:F film contributes to the improvement of the hemolytic performance. The a-C:H:F film coating is thus expected to be utilized in medical technology as a surface coating technology for artificial heart blood pumps.

Keywords: Fluorine-Doped a-C:H Film; Hemolytic Performance; Artificial Heart Blood Pump

1. Introduction

A ventricular assist device (VAD) is an important instrument in treating heart failure. With the development of heart surgery, VADs have been used as a bridge-to-transplant or destination therapy [1-3]. The VAD provides effective blood circulation support until a donor heart becomes available for transplant, improves other organ function, improves exercise performance, and enables participation in cardiac rehabilitation [4]. In recent years, the VAD has also been considered for long-term implantation as a destination therapy. The circulatory support can provide symptomatic relief and improved survival for those who do not have access to cardiac transplantation [5-7]. A VAD generally consists of a pump unit that is either implanted in the abdomen or is outside the body, a control system and an energy supply. VADs can be divided into two main categories: displacement pumps and rotary pumps [1,8,9]. Energy transfer in displacement pumps is characterized by periodic changes of the working space as a pulsation, whereas in rotary pumps, the energy transfer to the fluid is established by velocity changes within the impeller vanes. Rotary pumps are designed to work in a constant speed mode of mechanical circulatory support, thus, in principle, produce non-pulsatile flow. Compared with displacement pumps, the rotary type pumps have advantages of compactness, no valves, simpler control aspects, lower power consumption, lower relative cost, and a more simplistic design, which results in smaller size and increased reliability [2,8,10]. However, the fluid dynamic forces in centrifugal blood pump impellers contribute to the destruction of red blood cells because the rotational speed leads to harsh interactions between the impeller and red blood cells [11-13]. Thus, hemolysis is caused by

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the high-speed rotation of the impeller in mechanical circulatory support devices, and the damage is mainly due to the interaction with solid surfaces. Therefore, an important factor in the development of devices, such as artificial heart blood pumps is the reduction of hemolysis and thrombus formation; and minimizing the level of hemolysis is a key development task to avoid thrombus formation [11].

Hydrogenated amorphous carbon films (a-C:H), including diamond-like carbon (DLC), have been the focus of considerable research efforts due to their electrical, mechanical, and chemical properties [14,15]. The properties of a-C:H films are mainly determined by sp^3 and sp^2 bonding hybridization of the carbon atoms and the relative concentration of these bonds [16]. The combination of these properties makes many applications available for a-C:H film coatings. a-C:H films have also shown promising results in hemocompatible coating technology. To date many types of a-C:H films have been applied to medical devices [17-24].

A thrombus is formed by platelet adhesion followed by aggregation and spreading. Therefore, the low surface energy of a-C:H films has prompted investigation of such coatings for improvement of medical devices that require anti-thrombogenic properties. Hasebe and colleagues reported that fluorine-doping of a-C:H (a-C:H:F) films results in a significant reduction of Young's modulus and the surface free energy, meaning these films could be useful for blood contacting medical devices [20,23]. The numbers of platelets adhering to a-C:H:F films were reported to be significantly lower than that with a-C:H films, and the number and activation of adherent platelets was reduced with a-C:H:F films [23].

In this study, a-C:H:F film coatings were investigated for an enclosed-impeller type axial flow blood pump that circulates blood under high speed rotation of an impeller. The purpose of such a coating is to improve the hemolytic performance of the blood pump. However, the impeller of an axial flow type blood pumps requires continuous rotation at high speed to perform blood circulation as a primary function. Therefore, to apply a-C:H:F film coatings to the impeller, it is necessary to investigate the effect of improvement of the hemolytic performance and applicability to the high-speed rotation of the impeller.

2. Materials and Methods

2.1. Film Deposition

A schematic diagram of the ionization deposition method is shown in **Figure 1**. The direct current ion source consists of a tantalum filament, a tungsten anode electrode and a molybdenum reflector. The ionization method was used to deposit a-C:H:F onto SUS 304 substrate (753513, The Nilaco Corporation, Tokyo, Japan; 200 × 200 mm^2, 1 mm thick). The characteristics of the a-C:H:F films were compared with a conventional a-C:H film deposited under the same conditions to determine the effect of fluorine doping. C_6F_5H and C_6H_6 source gases were decomposed to produce a-C:H:F and a-C:H films, respectively. Each film was deposited using a gas flow of 3 sccm and a substrate bias of 2.0 kV. The resultant films were approximately 1 μm thick (**Table 1**). The surface morphology and friction of the films was investigated using atomic force microscopy (AFM; JSPM-5200, Jeol Ltd, Tokyo, Japan) and a friction tester (FPR-2100, Rhesca Co., Ltd, Tokyo, Japan). The friction test was conducted using an aqueous glycerol solution with the viscosity adjusted to simulate human blood (33 wt%, 20˚C). In addition, the surface characteristics were measured using surface potential meter (KSV SPOT1, KSV Instruments Ltd., Helsinki, Finland) and X-ray photoelectron spectroscopy (XPS; JPS-9000MC, Jeol Ltd, Tokyo, Japan) with Mg *Kα* radiation.

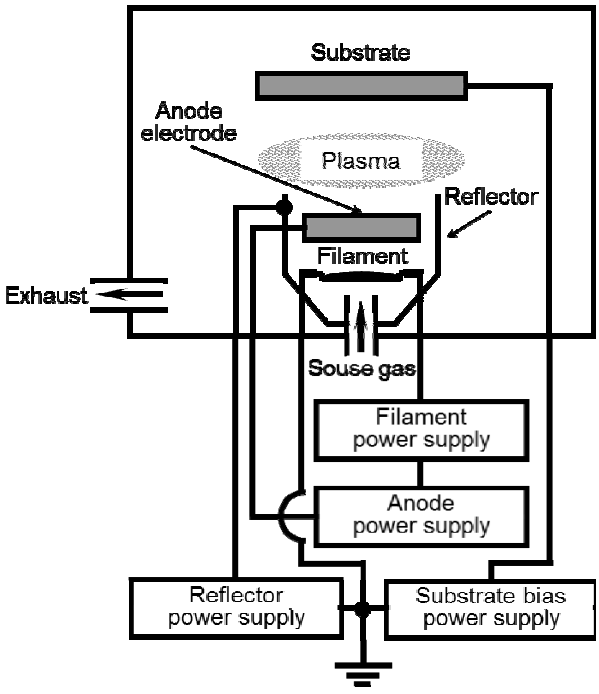

Figure 1. Schematic diagram of the ionization deposition method used to prepare a-C:H:F and a-C:H film coatings.

Table 1. Deposition of a-C:H:F and a-C:H film preparation conditions employed for the ionization method.

	Sauce gas	Gas pressure (Pa)	Substrate bias (kV)	Thickness (μm)	Substrate
a-C:H:F film	C_6F_5H	6.7×10^{-4}	3	1	SUS 304
a-C:H film	C_6H_6				

2.2. Immersion Test

As a preliminary experiment, blood adhesion at the a-C:H:F film surface was investigated under static conditions. The a-C:H:F sample was fully immersed in 50 mL of pig blood containing 5 mL sodium citrate for 180 min under static conditions at 37˚C (**Figure 2**). After immersion, the sample was rinsed in distilled water and the amount of protein accretion at the sample surface was estimated by the adenosine triphosphate (ATP) bioluminescence method using a lumitester (PD-20, Kikkoman Food Products Company, Tokyo, Japan). Monitoring of the amount of ATP is typically used as a surface cleaning test [25] and the amount of luminescence is proportional to the amount of ATP and adenosine monophosphate (AMP) present in the sample. The luminescence was measured with the lumitester and the results are given in relative light units (RLU) [25,26].

2.3. Hemolysis Test

Figure 3 shows the enclosed-impeller type flow blood pump, a schematic diagram of the driving parts for circulation, and the hemolysis test system with mock circulation. The *in vitro* test system with mock circulation consists of a flow-straightener, impeller, diffuser, a flexible tube, and a flow meter (T402, Transonic Systems Inc., New York, USA). Maruyama, *et al.* reported that the threshold surface roughness obtained for rapid increase in hemolysis was 0.8 μm or greater [11,27]. In this experiment, to avoid the influence of surface roughness on hemolysis, the surface roughnesses of the flow-straightener, impeller, and diffuser, which were made of SUS 304, were treated to less than 0.6 μm by electrolytic polishing. After electrolytic polishing, a-C:H:F was deposited on the parts by the ionization method (**Table 1**). The film thickness was controlled to 1 μm and the surface roughness was measured using a surface roughness tester (SJ 400, Mitsutoyo Co., Kanagawa, Japan). The mock circulation circuit was filled with 500 mL of pig blood containing 50 mL sodium citrate and *in vitro* testing was conducted for 180 min with a blood flow rate of 5 L/min, a pump head of 100 mmHg, and an impeller speed of *ca*. 1,100 rpm. After the circulation test, the total hemoglobin concentration in the pig blood was determined by the cyanmethemoglobin method based on a standard hemoglobin concentration curve from UV-vis absorption measurements (U-1500, Hitachi, Ltd., Tokyo, Japan) at an absorbance wavelength of 540 nm.

3. Results and Discussion

3.1. Film Deposition

a-C:H:F was successfully deposited on SUS 304 substrates. The surface roughness of the a-C:H:F was measured using AFM and was determined to be uniform and smooth on the SUS 304 substrate. The surface roughness results shown in **Table 2** indicate the a-C:H:F film was significantly rougher than the a-C:H film, but similar to the SUS 304 substrate. Yu, *et al*. reported that the increased surface roughness of fluorinated amorphous carbon films was possibly caused by preferential etching of fluorine because the films were not ideally isotropic [28]. The surface roughness was reported to increase with the amount of fluorine dopant in the a-C:H film [29]. The growth of fluorinated a-C:H films is dependent on the competing deposition and etching processes. In the present work, the surface roughness of the a-C:H:F film showed the same tendency as that reported by Yu, *et al*.

The friction coefficient of the a-C:H:F film surface is shown in **Table 2**. The friction coefficient of the SUS 304 surface was reduced from 0.18 to 0.14 by coating with the a-C:H:F film. The reduction of the friction coefficient by C_6F_5H plasma deposition on the SUS 304 surface is due to a substantial decrease in the polar component of the surface energy.

The chemical composition of the a-C:H:F film surface

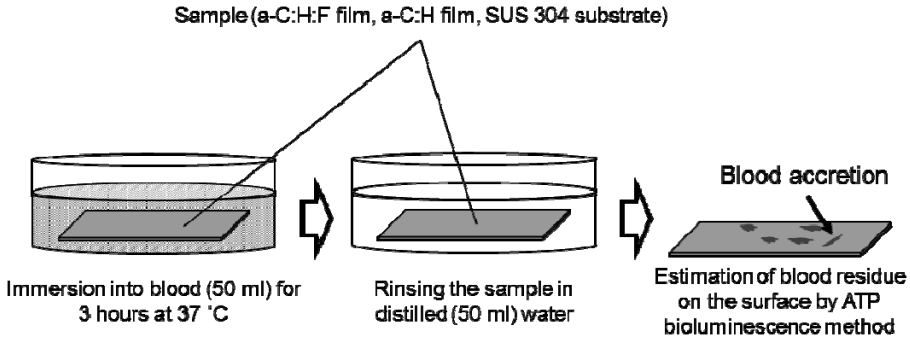

Figure 2. Schematic diagram of the immersion test. The a-C:H:F and a-C:H films, and the SUS 304 substrate (without coating) were fully immersed in 50 mL pig blood containing 5 mL sodium citrate for 180 min under static conditions at 37˚C. After immersion, the samples were rinsed in distilled water and the amount of protein accretion at the sample surface was estimated using the adenosine triphosphate (ATP) test.

Table 2. Surface characteristics of a-C:H:F and a-C:H films, and the SUS 304 substrate surface.

	Substrate roughness (nm)	Friction	Contact angle (deg)	Surface potential (mV)
a-C:H:F film	16.14 ± 2.69	0.14	105.9 ± 5.0	-0.75
a-C:H film	7.79 ± 3.51	0.17	99.6 ± 3.1	-0.31
SUS 304 substrate (without coating)	18.34 ± 4.37	0.18	101.6 ± 3.6	-0.17

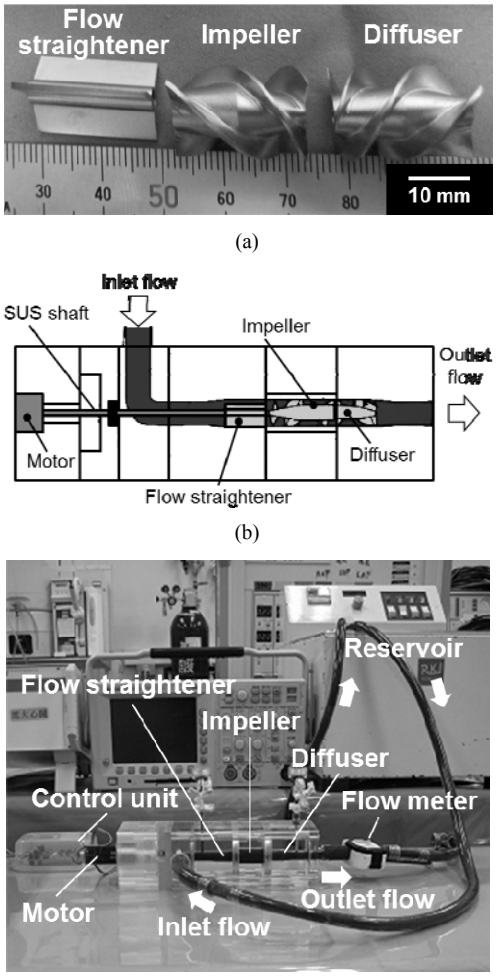

Figure 3. (a) Enclosed-impeller of axial flow blood pump. (b) Schematic diagram of the driving parts for blood circulation. (c) Hemolysis test system employed for mock circulation.

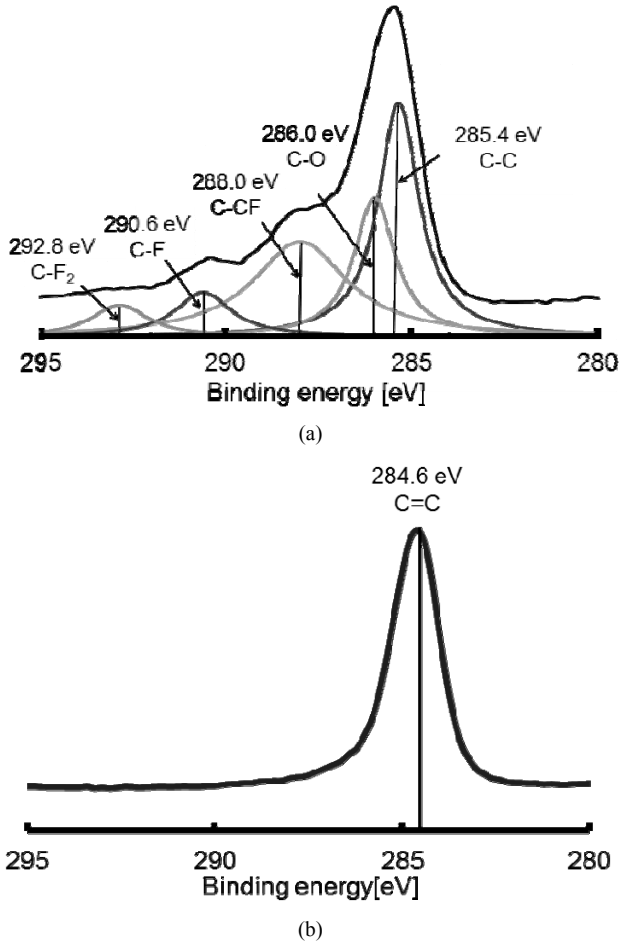

Figure 4. Decomposed XPS C_{1s} spectrum for (a) a-C:H:F film. (b) XPS C_{1s} spectrum for a-C:H film.

was estimated using XPS. **Figure 4(a)** and **(b)** show the XPS C_{1s} spectra for the a-C:H:F and a-C:H films deposited on SUS 304 substrates, respectively. The main feature of the a-C:H film was an asymmetric peak at 284.6 eV, which indicates π-bonding. The C_{1s} spectrum of the a-C:H:F film was decomposed into 5 peaks corresponding to C-F_2 (292.8 eV), C-F (290.6 eV), C-CF (288.0 eV), C-O (286.0 eV), and C-C (285.4 eV). The surface free energy of the a-C:H:F film was reported to be reduced with increasing fluorine content, which is due to changes in the bonding within the film as C-CF bonds decrease and CF and CF_2 bonds increase [29,30]. Water contact angle measurement was carried out using the $\theta/2$ method with a digital camera. The contact angles for the a-C:H:F and a-C:H films, and the SUS 304 substrate were 105.9˚ ± 5.0˚, 99.6˚ ± 3.1˚ and 101.6˚ ± 3.6˚, respectively. The surface roughness generally affects contact angle measurements. Yu, *et al*. reported a decrease in the contact angle (larger surface energy) with increasing surface roughness [28]. However, in the present work, the surface roughness increased with increasing contact angle (smaller surface energy). Hasebe, *et al*. and Yu, *et al*. reported that the surface roughness and microstructure have a negligible influence on the surface energy [23,28],

which is consistent with the present results.

Fluorine is a termination radical in C-C networks and consequently decreases cross-linking, which leads to new, more open structural arrangements that can lead to a decrease in the density of a film [29-31]. The addition of fluorine also results in a decrease in the hardness and stress of a film [29,30]. These results indicate that a-C:H:F film becomes more graphitic with increasing fluorine concentration [28]. In addition, fluorine atoms are very electronegative and so will carry some degree of negative charge. The surface of the a-C:H:F film was increased to more negative potentials, as shown in **Table 2**.

3.2. Immersion Test

Figure 5 shows the ATP bioluminescence for protein accretion on the a-C:H:F and a-C:H films, and on the SUS 304 substrate after the immersion test. The surface of a-C:H:F film had a low luminescence level, and thus a low ATP concentration, which indicates that the a-C:H:F film tends to weaken the protein adhesion of blood compared with the other samples is due to negative charge polarity. The high electronegativity of fluorine gives carbon-fluorine bonds a significant polarity or dipole moment. Therefore, it was expected that the van der Waals interaction of the pig blood with the a-C:H:F surface is reduced by the carbon-fluorine bonds. Platelet adhesion and activation on the surface of a biomaterial is the most important factor in determining the hemocompatibility of a biomaterial, and low platelet adhesion denotes good hemocompatibility, while a higher degree of platelet adhesion tends to result in the formation of a thrombus [20].

3.3. Hemolysis Test

a-C:H:F film was deposited on the surface of the flow-straightener, enclosed-impeller, and the diffuser. The surface roughness of these parts was 0.48 μm, while that for the SUS 304 substrate and the a-C:H film were 0.47 and 0.46 μm, respectively (**Table 3**). Therefore, it was expected that there was no influence of surface roughness on the hemolytic performance. The hemolytic performance of a blood pump with a-C:H:F film coating was determined according to the amount of hemolysis measured for a mock circulatory system (*in vitro* tests). **Figure 6** shows the amount of free hemoglobin in the blood that was released in a hemolysis reaction for the blood pump with a-C:H:F and a-C:H film coatings, and the SUS 304 without a coating. The rotational speed of the impeller in the blood pump was around 11,000 rpm. The amount of hemolysis was reduced from 1110 mg/dL to 925 mg/dL with the a-C:H:F film coating. There was a significant difference between the a-C:H:F film coating and the SUS 304 surface without a coating ($P < 0.05$). According to the ATP bioluminescence of the a-C:H:F film surface, it was expected that the amount of hemolysis was reduced by 20% with the decrease in the surface energy of the blood contact surface. In addition, the a-C:H:F film had good stability during the *in vitro* test.

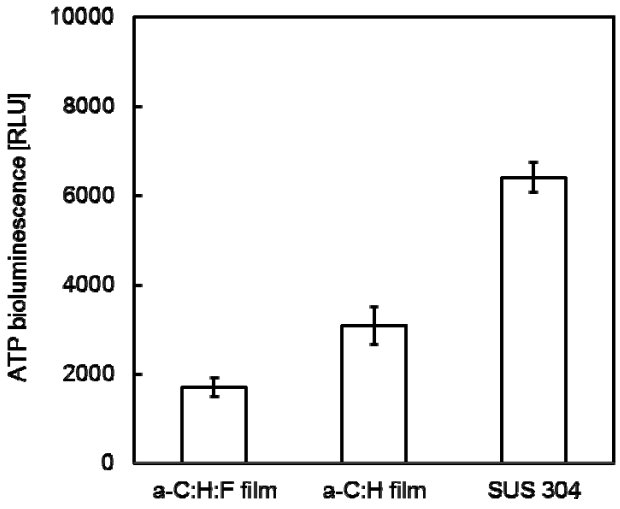

Figure 5. ATP bioluminescence results for the a-C:H:F and a-C:H films, and the SUS 304 substrate.

The negatively charged polarity suppresses platelet adhesion and fibrinogen adsorption as the platelets and proteins tend to have a net negative zeta potential [20,23]. In this study, the a-C:H:F film surface resulted in a higher degree of negative charge polarity. Roy, *et al*. [20] studied the effect of fluorine incorporation into a-C:H films on hemocompatibility. They reported that platelet adhesion was suppressed as the fluorine concentration increased and the surface charge became more negative. This observation is closely related with the $C\text{-}F_2$, C-F, and C-CF surface bonds, because the negative charge of the surface increased with the fluorine concentration [20,29]. Yu, *et al*. also reported that the polar component of the surface energy was reduced with increasing fluorine concentration [28]. Thus, it is possible to have higher surface polarization in films with higher fluorine concentration. Their observations support the present suggestion that the negatively charged polar component caused by $C\text{-}F_2$, C-F and C-CF surface bonds improves the hemolytic performance under dynamic high-speed rotation of the impeller.

4. Conclusion

In this study, the effect of a-C:H:F film coating on the hemolytic performance of a blood pump was investigated. The results indicate that the a-C:H:F film tends to increase the surface roughness and negative charge of the surface. In addition, the surface friction is decreased with respect to fluorine doping in the a-C:H film. In *in vitro* test, it has been indicated that fluorine in the a-C:H film

Table 3. Surface roughness of flow-straightener, the enclosed-impeller, and the diffuser.

	Surface roughness (μm)
a-C:H:F film	0.48
a-C:H film	0.47
SUS 304 substrate (without coating)	0.46

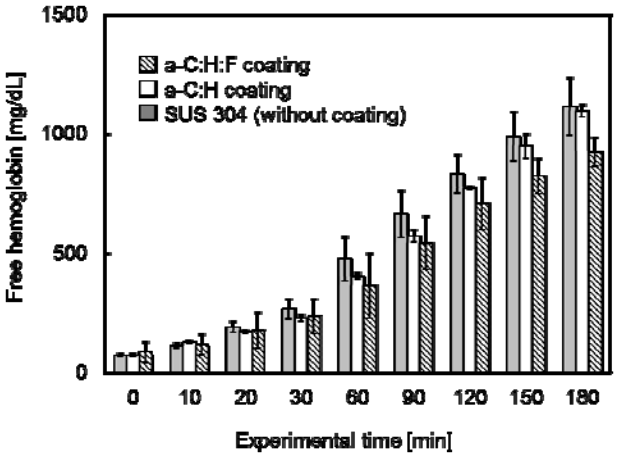

Figure 6. Hemolytic performance for an axial flow type blood pump with a-C:H:F film coating, a-C:H film coating, and without coating.

tends to weaken the protein adhesive properties of blood. In addition, the hemolytic performance of the blood pump with a-C:H:F film coating was improved because the a-C:H:F film coating reduced the amount of hemolysis. Decreasing the surface energy and negative charge of the surface by coating with the a-C:H:F film was a contributing factor for improvement of the hemolytic performance. The a-C:H:F film coating is thus expected to be utilized in medical technology as a surface coating technology for artificial heart blood pumps. However, the level of hemolysis is still relatively high. Therefore, further investigations are required to understand the hemolysis process in blood circulation with dynamic high-speed rotation of the impeller.

5. Acknowledgements

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