Competitive plasma protein adsorption onto fluorinated polyimide surfaces

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Abstract: A series of fluorinated polyimides cured at different temperatures was prepared, and plasma protein adsorption and platelet adhesion onto the polyimide films were evaluated *in vitro* using scanning electron microscopy, a micro-bicinchoninic acid protein assay, and a gold–colloid-labeled immunoassay. In particular, we focused on competitive plasma protein adsorption onto polyimide film because elucidation of the competitive adsorption mechanism is needed for a good understanding of *in vivo* biocompatibility of polyimide. Interestingly, the trend of IgG adsorption onto the polyimide surface measured in human plasma was completely contrary to that observed with IgG dissolved in PBS, and the adsorption increased with an increase in the curing temperature. We propose that the human plasma F_c region in IgG might selectively adsorb onto polyimide film cured at high temperatures because of competitive plasma protein adsorption to the surface. © 2003 Wiley Periodicals, Inc. J Biomed Mater Res 67A: 1393–1400, 2003

Key words: fluorinated polyimide; competitive plasma protein adsorption; platelet adhesion; hydrophobicity; electrical repulsive force

INTRODUCTION

Aromatic polyimides are a thermally stable class of high-performance polymers that have a high glass transition temperature and a relatively low dielectric constant.[1] Various polyimides have become increasingly important in a variety of technologic applications, such as semiconductor devices, high-temperature adhesives, and high-performance composite materials. On the other hand, we have clarified that polyimides containing a fluorinated group are promising materials for medical devices.[2,3] Recently we reported the gas exchange and blood compatibility of polyimide hollow fibers fabricated from soluble fluorinated polyimides synthesized with a chemical imidization at ambient temperature.[4] The polyimide fibers show not only a high gas exchange (O_2 transfer and CO_2 removal) but also suppression of platelet adhesion, suggesting the possibility of a novel membrane oxygenator with the advantage of both increased gas exchange and excellent biocompatibility. In addition, we demonstrated that fluorinated polyimide suppresses neutrophil adhesion and complement activation.[5]

It is well known that neutrophils are a predominant subpopulation of leukocytes and that their stimulation with an inflammatory mediator activates the release of reactive oxygen species (ROS), resulting in cell and tissue damage. Activation of the complement system also appears as a key event, eliciting secondary production and inflammatory mediators. And *in vivo* leukocyte and complement activation often are observed during cardiopulmonary bypass and hemodialysis.[6,7]

Interestingly, neutrophil adhesion and complement activation for polyimide films significantly depended on the curing temperature in preparing the films, and they decreased with an increase in the temperature. For the advancement of a novel membrane oxygenator that has been used clinically for a long time, we need to elucidate the effect of the curing temperature on the interaction between a biomolecule and the polyimide surface.

In this study, a series of fluorinated polyimides cured at different temperatures was prepared, and plasma protein adsorption and platelet adhesion on the polyimide films were evaluated using scanning electron microscopy, a micro-bicinchoninic acid protein assay, and a gold–colloid-labeled immunoassay.

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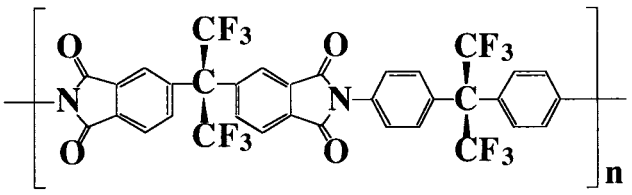


Figure 1. Chemical structure of 6FDA–6FAP.

It generally is accepted that the initial adsorption of plasma protein from blood onto a material's surface has a significant influence on several biologic responses, such as the formation of a thrombus, platelet adhesion and activation, and complement activation. Therefore, in particular, we focused on competitive protein adsorption to polyimide surfaces in human plasma to elucidate several biologic responses observed on polyimide surfaces.

MATERIALS AND METHODS

Materials

We purchased 2, 2′-bis(3,4-dicarboxyphenyl)hexafluoropropane dianhydride (6FDA) from the Japanese Hoechst Co. (Tokyo), and purified it by sublimation prior to use; and 2,2′-Bis(4-aminophenyl)hexafluoropropane (6FAP) was purchased from the Central Glass Co., (Saitama, Japan) and recrystallized twice in methylene chloride solution prior to use.

Fluorinated polyimide, 6FDA–6FAP, was synthesized by chemical imidization of the poly(amic acid) precursors, as reported in the literature.[8] The structure of the synthesized 6FDA–6FAP is presented in Figure 1. Polyimide films were prepared using a solvent-casting method from a tetrahydrofuran solution on a glass plate, and they were cured at 50°, 150°, or 250°C. The obtained films were optically clear. Films of approximately 50 μm in thickness were prepared by the solvent-casting method. Polydimethylsiloxane (PDMS) films, kindly supplied by Create Medic Co. (Kanagawa, Japan), were used as a control material.

A glow discharge reactor was used (Samco Corp., Kyoto, Japan) for the surface modification of the fluorinated polyimide. The frequency applied was 13.56 MHz. The polyimide films were exposed to an Ar-plasma for 20 s, and following the Ar-plasma treatment, air was introduced into the reactor.

Protein adsorption

The amounts of proteins adsorbed onto the dense flat films were determined by a micro-bicinchoninic acid protein assay (PIERCE, Inc., Micro BCA Protein Assay) at 36.5°C in PBS, as reported in the literature.[5] Bovine serum albumin (BSA) was purchased from Nacalai Tesque, Inc. (Tokyo), and g-globulins (IgG) and fibrinogen (Fbg) were purchased from the Sigma Chemical Co. (St. Louis, MO). These proteins were used without further purification. PBS (pH = 7.4) was purchased from the Yatoron Co. (Tokyo). The concentrations of BSA, IgG, and Fbg were 1.0 mg/mL, 0.3 mg/mL, and 0.1 mg/mL, respectively. The polyimide films were rinsed with deionized water and ethanol prior to use. The film was contacted with each protein solution for 2 h at 36.5°C. The proteins adsorbed onto the film were rinsed with 1% sodium dodecyl sulfate, and the amounts of protein then were determined at 562 nm with a spectrophotometer (Ubest-55, JASCO, Tokyo).

The amount of adsorption and distribution of a specific protein from human plasma onto the films was evaluated by gold–colloid-labeled immunoassay (British Bio Cell, Cardiff, UK), as reported previously.[9]

The 10 mm-in-diameter polyimide films were contacted with human plasma for 2 h at 37°C. After the films were rinsed with PBS solution, they were kept for 16 h at 4°C. After having been rinsed with PBS solution, the films were incubated with gold–colloid-conjugated anti-human plasma proteins, such as albumin (HAS), γ-globulin (IgG), and fibrinogen (Fbg) for 15 h at 37°C. Anti-human IgG (F_{ab}) (Rockland Inc., New York) also was used. The gold–colloid that remained after rinsing was enhanced to 200–300 nm with silver (Silver Enhancer Kit, Sigma, St. Louis, MO). Finally, the gold–colloids on the films were examined using scanning electron microscopy (SEM, JXP-6100P, JEOL Ltd., Tokyo).

Platelet adhesion

Blood was withdrawn from the carotid of several volunteers into a siliconized glass tube containing 3.8% trisodium citrate aqueous solution. Platelet-rich plasma (PRP) and platelet-poor plasma (PPP) were prepared from the blood by centrifugation, as reported in a previous paper.[3] The platelet counts (approximately 2×10^5/mL) in PRP were adjusted by diluting the PRP with the PPP and determined by a Coulter counter (Coulter Electronics, Inc. Tokyo).

The films were soaked in PRP suspension and incubated at 37°C for 2 h. After being rinsed with a phosphate-buffered saline (PBS), the films were fixed with 2.5% glutaraldehyde saline solution for 2 days. The morphologic deformation of platelets adhered onto the films was observed by scanning electron microscopy (SEM, JXP-6100P, JEOL, Ltd., Tokyo). The amounts of plasma protein and total protein adhered onto the film soaked in the PPP and PRP, respectively, were determined by an amino acid analyzer (HITACHI 835, Hitachi, Ltd., Tokyo), which is able to detect by hydrolysis the least amount of adhered proteins. The amounts of adhered platelets were expressed by the platelet proteins adhered onto the film ($\mu g/cm^2$) because a close correlation between them has been clarified.[10] The platelet proteins were determined by subtracting the amounts of adhered plasma protein from that of adhered total protein.

Surface analysis

To determine the ζ-potential of a polyimide film, the electrophoretic mobility of the film was measured using an electrophoresis apparatus (Otsuka Electronics Co. Ltd., ELS-8000, Tokyo). The ionic strength was 0.001, and the temperature was 25°C.

The contact angles of water on the dry films were determined by a contact angle measurement (Kyowa Co. Elma GI, Tokyo).

AFM analysis

The surface morphology of the film was visualized using an atomic force microscope (AFM; Seiko SPI3700, Tokyo) in air at room temperature.[11] The cantilevers (Seiko SN-AF01), with a spring constant of 0.021N/m, were microfabricated from silicon nitride. The surface was continuously imaged in the feedback mode with a scan area of 500 × 500 nm and a constant scan speed of 2 Hz. The surface roughness profile was analyzed using the parameter R_a, the arithmetic mean of the departure of the roughness profile from the mean line.

RESULTS

Characteristics of fluorinated polyimide films

The fluorinated polyimide, 6FDA–6FAP, had a molecular weight of 4.8×10^5 with a polydispersity index of 2.6. This means that a high molecular weight polyimide with a narrow molecular distribution can be prepared by a chemical imidization. The polyimide films were prepared by a solvent-casting method and were cured at 50°, 150°, or 250°C for 15 h. The solvent in the film was measured using thermogravimetric analysis (Seiko, TG/FDTA300, Tokyo) and was completely removed by the curing treatment.

The surface roughness and area of 500 × 500 nm of the films cured at 50°, 150°, and 250°C were calculated using AFM. The roughness is evaluated by R_a, which is the arithmetic mean of the departure of the roughness profile from the mean line. The values of the films cured at 50°, 150°, and 250°C were 0.22, 0.21, and 0.20 nm, respectively, indicating that the curing treatment did not influence the roughness of the polyimide film. In addition, the surface areas of the films cured at 50°C 150°, and 250°C were 2.770×10^5, 2.768×10^5, and 2.767×10^5 nm^2, respectively, indicating that there also was no difference in surface area among the films cured at the different temperatures. These findings indicate that the surface area and morphology of a fluorinated polyimide film do not influence protein adsorption and platelet adhesion.

Table I presents the contact angle of water and the ζ-potential value on 6FDA–6FAP films cured at 50°, 150°, and 250°C. The contact angle for the polyimide films increased with an increase in the curing temperature, and the polyimide surface displayed a stronger hydrophobic nature after the curing. In contrast, the ζ-potential value decreased with the curing temperature.

TABLE I
The Contact Angle of Water and ζ -Potential of Polymer Surfaces

Polymer	ζ-Potential[a)] [mV]	Contact Angle of Water [deg.]
PDMS	−28	103
6FDA–6FAP at 50°C	−42	74
6FDA–6FAP at 150°C	−53	78
6FDA–6FAP at 250°C	−64	81

Ionic strength : 0.001.

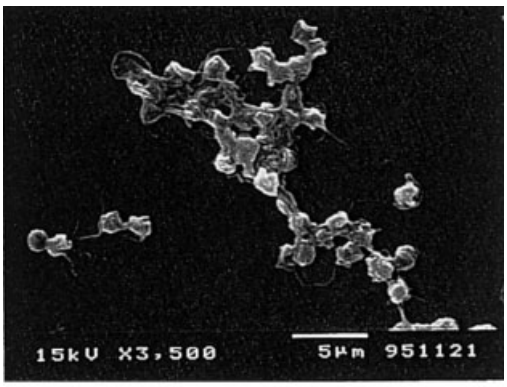
Platelet adhesion

Figure 2 shows SEM photographs of platelets adhering to 6FDA–6FAP films prepared at different curing temperatures. The films were cured at 50°, 150°, or 250°C. The films were soaked in a PRP suspension and incubated at 37°C for 2 h. After having been rinsed with PBS, the films were fixed with 2.5% glutaraldehyde saline solution for 2 days. Interestingly, the amounts of adhered platelets on the films decreased with an increase in the curing temperature. The platelets on the polyimide film cured at 250°C hardly changed shape, and deformation and aggregation were not observed. These results indicate that fluorinated polyimide cured at high temperature suppresses platelet adhesion and activation.

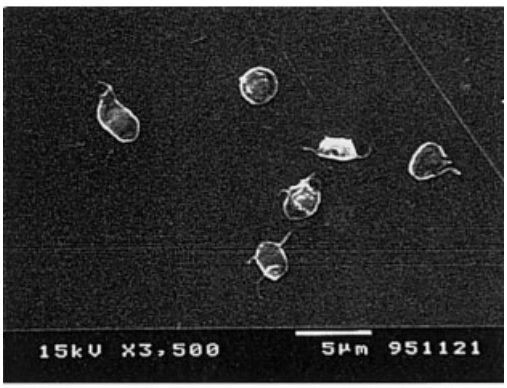
Figure 3 shows the numbers of platelets adhering to 6FDA–6FAP and PDMS films after contact with PRP for 2 h. Platelet adhesion to the polyimide surfaces effectively was reduced compared with that found on the PDMS surface. In addition, the numbers of platelets adhered onto the polyimide film decreased with an increase in the curing temperature, as observed in Figure 2. We clarified that fluorinated polyimide surfaces cured at high temperatures showed excellent *in vitro* blood compatibility.

Protein adsorption

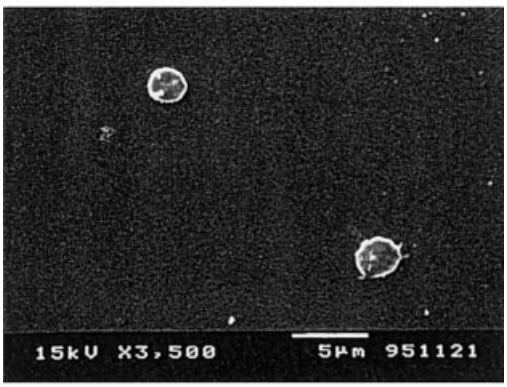
Table II presents the amount of BSA, IgG, or Fbg adsorbed onto 6FDA–6FAP films cured at 50°, 150°, and 250°C. Each protein adsorption was determined using a micro-bicinchoninic acid protein (BCA) assay. What is interesting to note is that the polyimide sup-



50°C



150°C



250°C

Figure 2. Scanning electron micrographs of platelets adhering to 6FDA–6FAP films prepared at different curing temperatures: 50°, 150°, and 250°C.

pressed the protein adsorption compared with PDMS. In particular, the adsorption of each protein on the polyimide cured at 250°C was approximately one-half that of PDMS.

Interestingly, significant differences in protein adsorption among the polyimide films also were observed. Protein adsorption on the polyimide films

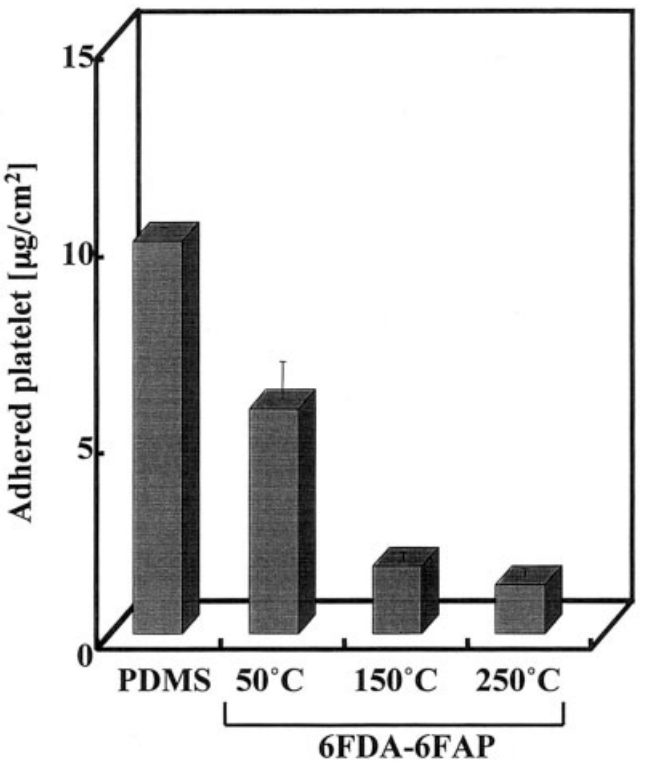


Figure 3. The amount of platelets adhering to 6FDA–6FAP films prepared at different curing temperatures: 50°, 150°, and 250°C. Error bars = means ± SD (n = 3).

strongly depended on the curing temperature, and the amounts decreased with increasing temperature. Proteins showed the greatest adsorption on the polyimide surfaces cured at 50°C and the smallest adsorption on the surfaces cured at 250°C.

Figure 4 shows SEM photographs of plasma protein adsorption patterns on 6FDA–6FAP films cured at 50°, 150°, and 250°C as determined using gold–colloid-labeled immunoassay. The amount of a specific protein's adsorption from human plasma onto the films was evaluated by immunoassay. The white particles observed on the surface of the film correspond to the specific proteins adsorbed onto the surface. On the film cured at 50°C, nonselective adsorption of plasma proteins was observed. On the other hand, the amounts of albumin (HSA) and fibrinogen (Fbg) on the polyimide film cured at 250°C had decreased sig-

TABLE II
Amount of Plasma Protein Adsorbed onto 6FDA–6FAP Surfaces at 36.5°C

Curing Temp.	BSA [µg/cm²]	Fbg [µg/cm²]	IgG [µg/cm²]
PDMS	0.237 (±0.0010)	0.364 (±0.0140)	0.456 (±0.0093)
50°C	0.158 (±0.0059)	0.272 (±0.0078)	0.314 (±0.0088)
150°C	0.119 (±0.0045)	0.239 (±0.0037)	0.260 (±0.0070)
250°C	0.083 (±0.0088)	0.165 (±0.0022)	0.190 (±0.0026)

Mean ± SD; n = 3.

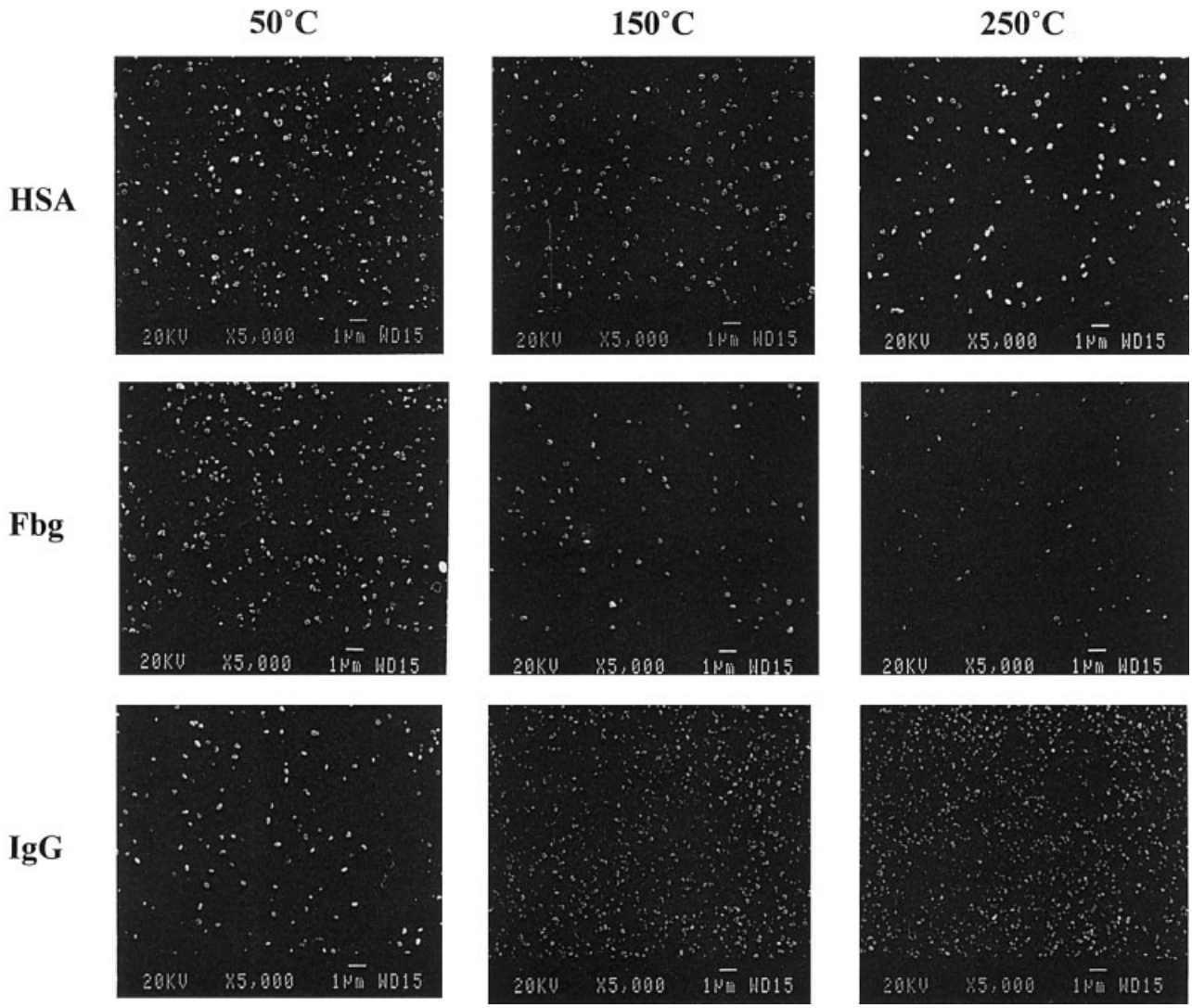


Figure 4. Scanning electron micrographs of plasma proteins adsorbed on 6FDA–6FAP films prepared at different curing temperatures, 50°, 150°, and 250°C, determined using gold–colloid-labeled immunoassay. The films were contacted with human plasma for 2 h at 37°C.

nificantly compared with those on the film cured at 50°C; and HSA and Fbg adsorption on the films decreased with an increase in curing temperature. In contrast, IgG adsorption increased with increased curing temperature.

Figure 5 shows SEM photographs of IgG adsorption patterns on 6FDA–6FAP films cured at 250°C as determined using gold–colloid-labeled immunoassay. There was no great difference in white particle numbers on the film observed after an incubation time of 5 or 30 min, which indicates that IgG adsorption on the polyimide surface was almost finished within a short time. These results may mean that the specific adsorption surface for IgG is formed by the curing process.

Figure 6 shows SEM photographs of IgG adsorption patterns on 6FDA–6FAP films modified with or without Ar glow discharge. The polyimide film shown in Figure 6 [see (1)] had been exposed to an Ar plasma for 20 s, and following the Ar-plasma treatment, air was introduced into the film. On the other hand, the film shown in Figure 6 (2) had not been treated by the plasma. The films were incubated with the gold–colloid-conjugated anti-human IgG (F_{ab}) for 15 h at 37°C. The white particle numbers on the polyimide film observed in the photographs correspond to the gold–colloid-conjugated anti-IgG (F_{ab}) adsorbed onto the surface. The particle numbers shown in (1) are fewer than those in (2), which were almost equal to the amount of IgG adsorbed onto the film cured at 250°C (see Fig. 5).

DISCUSSION

First, we demonstrated that the surface roughness and area of polyimide films cured at different temper-

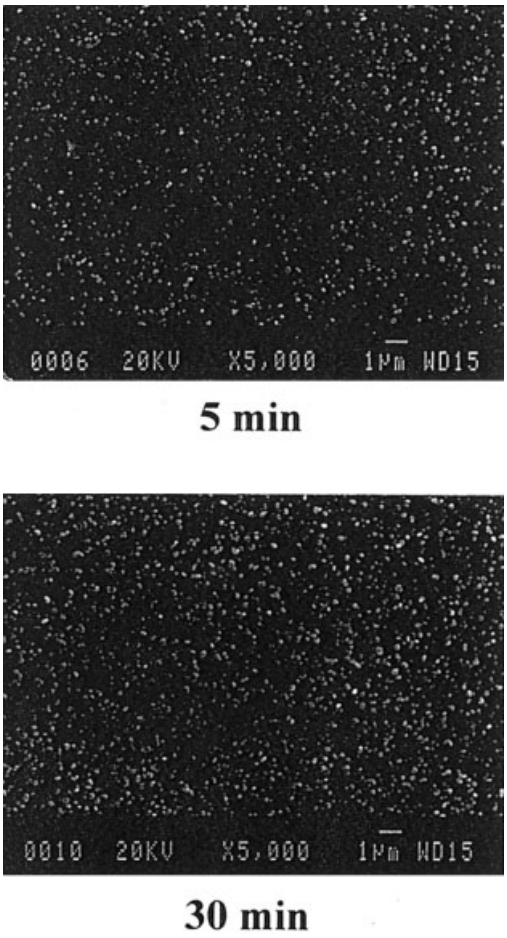


Figure 5. Scanning electron micrographs of IgG adsorbed on 6FDA–6FAP films cured at 250°C, determined using gold–colloid-labeled immunoassay. The films were contacted with human plasma for 5 or 30 min at 37°C.

atures does not influence protein adsorption and platelet adhesion onto surfaces. The surface roughnesses of the polyimide films were negligible relative to protein or platelet size. The differences in surface areas between films cured at 50° and 250°C was only 0.11%. That is, factors other than surface morphology of polyimide films influence protein adsorption and platelet adhesion onto their surfaces.

It is well known that the initial adsorption of plasma protein from blood onto a material surface has a significant influence on several biologic responses, such as the formation of a thrombus and platelet adhesion and activation.[12] Fbg is one of the important plasma proteins that dominate biologic responses, and it has an RGD sequence that is involved in platelet adhesion and activation. As shown in Table II, Fbg adsorption onto polyimide surfaces decreased with an increase in the curing temperature, which may be responsible for the temperature-dependence observed in platelet adhesion on the polyimide surface.

The results obtained from the BCA method indicate the interaction of only one kind of protein with the polyimide surface. However, in actuality, the competitive adsorption among many proteins, such as albumin, fibrinogen, and globulin, to the polyimide surface should occur before the platelet adheres to the surface. Therefore we evaluated the amount of adsorption and distribution of specific proteins from human plasma on the polyimide film using a gold–colloid-labeled immunoassay.

Figure 4 showed SEM photographs of the plasma protein adsorption patterns on the polyimide films cured at different curing temperatures as determined using the gold–colloid-labeled immunoassay. Results of Fbg adsorption obtained from the immunoassay were in accordance with those in the BCA method, indicating that decreased Fbg adsorption on polyimide film cured at 250°C is responsible for suppression of platelet adhesion and activation. In contrast, it was clear that the amounts of IgG adhered on the film cured at 250°C had increased dramatically and that the IgG adsorption increased with an increase in the curing temperature. Interestingly, the results of IgG adsorption onto the polyimide surface, determined using the immunoassay, were completely contrary to those obtained from the BCA assay.

As described above, the protein adsorption in the BCA method indicated only the interaction between the single purified protein and the polyimide surface. On the other hand, the adsorption in the gold–colloid-labeled immunoassay indicated competitive adsorption among albumin, fibrinogen, and globulin onto the polyimide surfaces. It is well known that competitive protein adsorption to material surfaces induces displacement or conformational changes of protein and that a dynamic protein adsorption phenomenon, such as the Vroman effect, occurs.[13] We consider that there may be a great difference in IgG adsorption between the BCA assay and the immunoassay due to competitive protein adsorption to the polyimide surfaces.

Next, we investigated the orientation of IgG adsorbed onto polyimide surfaces to elucidate the mechanism of selective IgG adhesion onto surfaces cured at high temperatures. It is well known that IgG is a 150-kD glycoprotein and that its structure often is classified by its major enzymatic fragments, F_{ab} and F_c.[14,15] We measured the orientation of IgG by evaluating the interaction between the polyimide surface and the F_{ab} region.

Figure 6 showed SEM photographs of anti-human IgG (F_{ab}) adsorption patterns on polyimide films cured at 250°C. The polyimide film shown in Figure 6 (1) was treated by Ar plasma, and the film in Figure 6 (2) was without the plasma treatment. We believe that the orientation of IgG on the polyimide surface is shown by the pictures in Figure 6 because there were many more white particles apparent in (2) than in (1). These results may mean that in the case of the polyimide surface without Ar-plasma treatment, the F_c

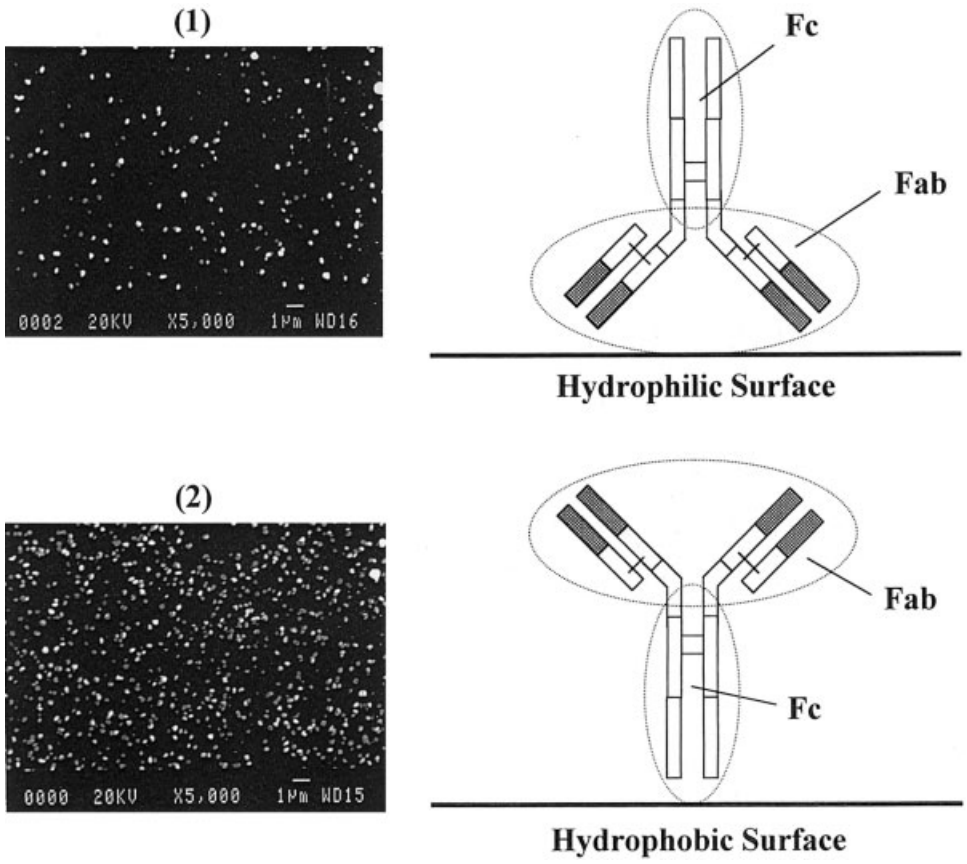


Figure 6. Scanning electron micrographs of IgG (F_{ab}) adsorbed on 6FDA–6FAP films cured at 250°C, determined using gold–colloid-labeled immunoassay. The films were contacted with human plasma for 2 h at 37°C. (1) Plasma-treated film; (2) untreated film.

region selectively makes contact with the surface. In contrast, F_{ab} may favor the polyimide surface modified by Ar plasma. The water contact angle of the plasma-treated polyimide film was 19° and the surface displayed a hydrophilic property.

It has been reported that both neutrophil and complement (C_{1q}) have the F_c receptors and that F_c-mediated activation would occur on the F_c region.[16] Recently we reported that neutrophil adhesion and complement activation for polyimide surfaces significantly depend on the curing temperature, decreasing with an increase in temperature.[5] The results obtained in a previous paper also suggest that the F_c region in IgG may adsorb selectively onto film cured at high temperatures.

In addition, we investigated the correlations between the surface characteristics of the polyimide and the curing temperature. Table I presents the contact angle of water and the ζ-potential values on polyimide films cured at different temperatures. The contact angle for the polyimide films increased with an increase in the curing temperature, and the polyimide surface displayed a stronger hydrophobic nature after the curing. In general, physical and chemical factors have a great influence on the contact angle.[17] The physical factor involves changes in surface morphology, such as surface roughness, and the contact angle of water is more susceptible to the magnitude of surface roughness. However, we demonstrated that the change in the surface roughness on the polyimide film was so small that we could ignore it. Therefore, the chemical factor appears to contribute significantly to the change in the contact angle of water.

We already have demonstrated that the values of polar and hydrogen bonding components on the fluorinated polyimide film, calculated using the Kitazaki-Hata equation, strongly depend on curing temperature.[11] This occurs because, due to curing, more polar and hydrogen-bonding groups in the polyimide exist on the polymer side than on the air side; thus the more hydrophobic groups, such as CF_3, move to the surface because of curing.[11] We believe the results of this study indicate that the rearrangement of the polyimide by curing occurs at the outermost surface, which induces a decrease in the polar and hydrogen-bonding components on the surface and an increase in hydrophobicity. The rearrangement of the polyimide induced at the outermost surface may influence plasma protein adsorption and platelet adhesion.

Interestingly, the ζ-potential value on the polyimide

surface also decreased with an increase in the curing temperature. We believe that electrolyte cations in blood play an important role in competitive protein adsorption onto polyimide surfaces because surfaces with low ζ-potential values can adsorb many electrolyte cations so that a strong electrical double layer is formed on the surface. In particular, double layers formed on surfaces cured at 250°C are considered to be compressed compared with those of other polyimide surfaces cured at lower temperatures.

As a result, a strong electrical repulsive force is formed between the polyimide surface with a low ζ-potential value and plasma proteins with positive charges at a lower pH, such as HAS [isoelectric point (iep); pH 4.7] or Fbg (iep; pH 5.8), which might suppress the plasma adsorption on the polyimide surface. On the other hand, the electrical repulsive force formed between the polyimide surface and IgG with an iep at pH 6.3–7.3 was relatively weak, suggesting that IgG adsorption onto surfaces might be facilitated in human plasma because they would win the competition with HAS and Fbg. However, it is clear that further study is needed to elucidate the effect of polyimide surface on plasma protein adsorption.

CONCLUSIONS

The purpose of this study was to elucidate the mechanism of competitive plasma protein adsorption on fluorinated polyimide films cured at different temperatures. A series of fluorinated polyimides cured at different temperatures was prepared, and plasma protein adsorption onto polyimide films was evaluated *in vitro* using a micro-bicinchoninic acid protein assay and a gold–colloid-labeled immunoassay.

Interestingly, the amounts of plasma protein adsorbed onto polyimide surfaces strongly depended on the curing temperature. The amounts of BSA, Fbg, and IgG adsorbed onto surfaces, determined using a BCA assay, decreased with an increase in the temperature. On the other hand, the amounts of IgG adsorption, determined using an immunoassay in human plasma, increased with the temperature while those of HSA and Fbg decreased. These results indicate that competitive plasma protein adsorption on polyimide films undoubtedly occurs and that specific plasma adsorption surfaces for IgG are formed by the curing process.

Contact angle of water and ζ-potential values on the polyimide surfaces also strongly depended on the curing temperature, indicating that hydrophobicity and electrical repulsive force formed on the surface have a significant influence on competitive plasma protein adsorption.

We earlier reported that a polyimide hollow fiber not only has a high gas exchange (O_2 transfer and CO_2 removal) but also biocompatibility. We consider that the competitive plasma protein adsorption on polyimide surfaces observed in this study is an important factor in an elucidation of the mechanism of *in vivo* biocompatibility of fluorinated polyimide.

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