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Development of a New Antithrombogenic Continuous Ultrafiltration System

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Abstract: By interfacing a polyacrylonitrile (PAN)–polyethyleneoxide (PEO) membrane with an ionically heparin-bound catheter, tubing, and module header, a totally antithrombogenic continuous ultrafiltration system (ACUS) was developed and its performance, persistent antithrombogenicity, and well-maintained ultrafiltration level were confirmed through animal experiments. Although the amount of heparin released and accumulated in vitro from those heparinized parts was very low and stable (on the order of 1×10^{-2} U/cm^2/min), partial thromboplastin time evaluated in vivo was not elongated during passage through the ACUS. Extracorporeal circulation time with the ACUS in unheparinized dog model was 458 ± 302 min (n = 24), whereas those of partially modified (antithrombogenic) system did not exceed 100 min. As compared with that in a conventional continuous arteriovenous hemofiltration system, an extracorporeal circulation with the ACUS in an unheparinized dog model revealed significantly less fluctuation of platelet count, and no adherent platelets were observed on the surface of the PAN–PEO membrane. An ACUS consisting of a PAN–PEO membrane and heparinized parts was thus demonstrated to have good platelet compatibility. An ACUS with a surface area of 0.25 m^2 was applied to two patients with acute renal failure. Hemofiltration without systemic heparinization lasted for 44 h per hemofilter, and a stable level of ultrafiltration was maintained. This system seems to be applicable for the clinical management of volume overload, especially in patients with bleeding tendencies or postoperative bleeding. **Key Words:** Antithrombogenicity—Hemofiltration—Heparinized surface—PAN–PEO membrane.

Anticoagulation is one of the three essential factors that allowed the first clinical trial of the artificial kidney in 1937 (1). Since that time, continuous advances in the field of extracorporeal therapy in general and in hemodialysis in particular have made this lifesaving treatment available to more than a quarter of a million patients with end-stage renal failure (1). Anticoagulation has also played a similar role in other extracorporeal circulation therapies such as lung assist devices. However, the most common anticoagulation method used, namely, systemic heparinization, often conflicts with an increased bleeding tendency in patients undergoing those therapies. Several approaches to design a totally antithrombogenic system, therefore, have been tried thus far. For example, the trial performed by Schmer and colleagues (2,3), in which heparin was grafted on the dialysis membrane, was proposed as a modified dialysis system that avoided anticoagulation systemically. However, the leaching of cetylpyridinium chloride, which was used for heparin binding, seemed to discourage further clinical application. Surface heparinization of lung assist devices was also developed by a group from the Karolinska Hospital (4), based on new techniques of heparin surface coating (5), which highlighted the renewed concern and desire to develop a nonthrombogenic system without the use of systemic anticoagulation.

The demonstration of a new therapeutic mode called continuous arteriovenous hemofiltration (CAVH) by Kramer and colleagues (6), and the further development and clinical application of this

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technique by Paganini (7), encouraged many clinicians to treat patients with acute renal failure with this system. However, this therapy also revealed a high incidence of hemorrhagic complications, and several methods for optimal regional heparinization were explored (8).

By making use of various antithrombogenic materials (9,10) and technologies (11–13) developed and accumulated by Toray Industries, Inc., through their collaboration with medical institutions, we attempted to design a new, totally antithrombogenic system for the management of fluid states of patients, especially those with bleeding complications such as postoperative acute renal failure or multiorgan failure.

MATERIALS AND METHODS

Basic designing of an antithrombogenic device

Elementary technologies and parts, which were considered to be needed for designing a totally antithrombogenic continuous hemofiltration system and were actually evaluated, are summarized in Fig. 1. As shown in this figure, two kinds of antithrombogenic materials/surfaces were employed: polyacrylonitrile (PAN)–polyethyleneoxide (PEO) polymer (PAN–PEO) and a heparinized surface. A partially hydrophilic and antithrombogenic PAN–PEO membrane (14) was fabricated from the spinning solution containing a copolymer of acrylonitrile and methoxy polyethyleneglycol methacrylate and a homopolymer of acrylonitrile. To render the surfaces of catheter, tubing, header, and potting material antithrombogenic, ionic binding of heparin (9,11–13) was applied. The elution rate of heparin from those heparinized parts was assayed in vitro by measuring heparin thrombin time (15) with fresh plasma taken from rabbits. The effect of released heparin on the coagulation cascade was determined in vivo by measuring partial thromboplastin time (PTT) (16).

Second, hemodynamic modification was attempted. Because our preliminary trials revealed that the shape of a header at the inlet side was critical, a tangential header was designed instead of a conventional vertical one, and each connection between any part was attempted to be made as smooth as possible. Furthermore, careful manipulation, such as the insertion of catheters, was devised. Namely, instead of deep cannulation, an attempt was made to limit insertion of the antithrombogenic catheter into blood vessels to ~10–20 mm in the dog model, which contributed to the prevention of thrombus formation around the catheter inserted in the blood vessels. The catheters were then fixed by ligation. Because of dialysis shunt-like cannulation with the antithrombogenic catheter, the blood flow rate was stabilized.

A schematic diagram of the totally antithrombogenic system thus designed in this study is shown in Fig. 2, where smooth surfaces and interfaces to eliminate uneven structure are emphasized. A commercially available hemofiltration membrane made with PAN combined with an unheparinized catheter (polyurethane) and tubing (polyvinyl chloride) was used as a conventional control CAVH system.

Evaluation in animal models

Unless otherwise stated, animal experiments were performed with unheparinized beagle dogs (body weight ~10 kg) that were under intravenous pentobarbital sodium anesthesia. Connecting a system for evaluation between the femoral artery and vein, extracorporeal circulation without a blood pump was attempted. The blood flow rate was monitored by using an ultrasonic flowmeter (T101: Transonic Systems Inc., Ithaca, NY, U.S.A.), while the platelet count was measured by the con-

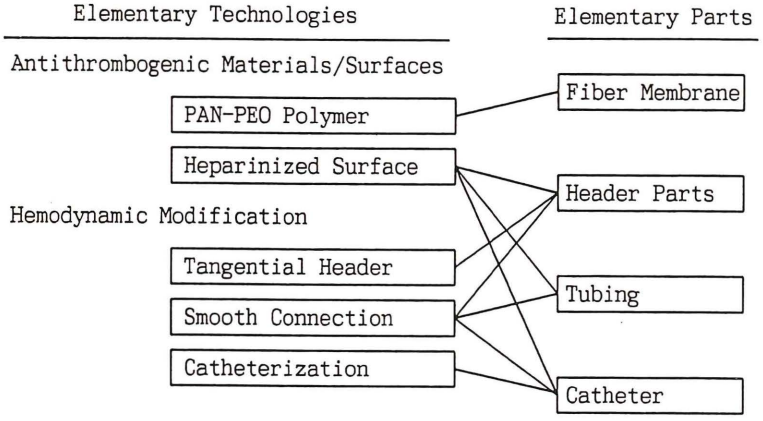

FIG. 1. Designing of antithrombogenic continuous ultrafiltration system. PAN–PEO, polyacrylonitrile–polyethyleneoxide.

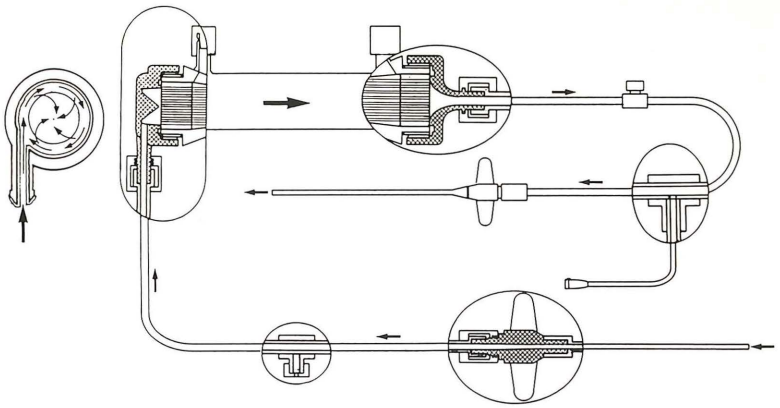

FIG. 2. Totally antithrombogenic continuous ultrafiltration system that was newly designed by combining various antithrombogenic materials and surfaces with hemorheological devices. Arterial blood flows through the heparinized catheter (inner diameter/outer diameter: 2.4/3.3 mm) and heparinized tubing (inner diameter: 3.8 mm) and then into a polyacrylonitrile–polyethyleneoxide hemofilter with a surface area of 0.25 m^2. The header of the inlet side of the hemofilter module is tangential. Passing through the module and then through similarly heparinized tubing and catheter, blood returns back into the vein. Total priming volume is ~30 ml.

ventional method. To measure the effect of the extracorporeal circulation on the coagulation system in test animals, PTT was monitored. No heparin was used either initially or during extracorporeal circulation, and if the blood flow rate decreased below 80 ml/min, the circulation was terminated. After the test, the total system was rinsed with saline solution and then fixed with 3 wt % glutaraldehyde saline solution. The amount of adherent platelets and adsorbed protein was observed by scanning electron microscopy and by an amino acid analyzer, respectively.

Because the ultrafiltration rate primarily depends on the blood flow rate, the latter should be stabilized to obtain stable and reproducible data on the former under a fixed condition. Therefore, only for the measurement of the ultrafiltration rate, we used 3–4 kg heparinized rabbits placed under peritoneal pentobarbital sodium anesthesia, and fiber modules with tubing were connected between the carotid artery and the jugular vein through a blood pump. A bolus shot of heparin, 60 U/kg, followed by the continuous infusion of 30 U/kg body weight per hour was applied, and the ultrafiltrate was returned into the venous side with another pump to maintain the fluid state of the rabbits.

Clinical evaluation

Two patients were studied without systemic heparinization and a blood pump by connecting a total system between the femoral artery and vein, after obtaining informed consent.

Data analysis

All data were expressed as mean ± SD, unless otherwise stated, and statistical analysis was performed by Student's *t* test.

RESULTS

Basic designing of a total system

Table 1 summarizes the results of the dog experiments carried out to determine the optimum parameters and the basic design of a totally antithrombogenic ultrafiltration system as well as the number of experiments. It is seen that significant prolongation in the extracorporeal circulation time without the use of heparin infusion was achieved only when the three modified elements, namely (a) the catheter

TABLE 1. *Comparison of extracorporeal circulation time in dog model*

Description	Combination of elements: Elements I	II	III	Extracorporeal circulation time without heparinization (min): Mean ± SD	n	Correlation of results with those of totally modified version
Control	C	C	C	30, 40	2	—
Partially modified	C	C	M	55 ± 21	6	$p < 0.005$
	C	M	C			
	M	C	C	45 ± 21	5	$p < 0.005$
	C	M	M	50 ± 23	3	$p < 0.005$
	M	C	M	70 ± 49	6	$p < 0.05$
	M	M	C	99 ± 82	4	$p < 0.05$
Totally modified	M	M	M	458 ± 302	24	—

C, conventional; M, modified. Elements: I, catheter and tubing; II, header (inlet, outlet) and surface of potting material; III, fiber membrane.

and tubing, (b) the header part of a hemofilter module, and (c) the fiber membrane were all present. For example, as long as conventional unheparinized catheter and tubing were used, mean extracorporeal circulation time without heparinization did not exceed 60 min. Even when a PAN–PEO membrane filter was combined with a heparinized catheter and tubing, the use of a conventional vertical header at the inlet side of the module caused thrombus formation, as shown in Fig. 3, and mean circulation time was 70 min as listed in Table 1.

Figure 4 depicts the in vitro elution rates of heparin from heparin-bound parts designed for this study. It is noted that the elution rates were all very low and stable on the order of 1×10^{-2} U/cm^2/min. Even if the heparin thus released was accumulated

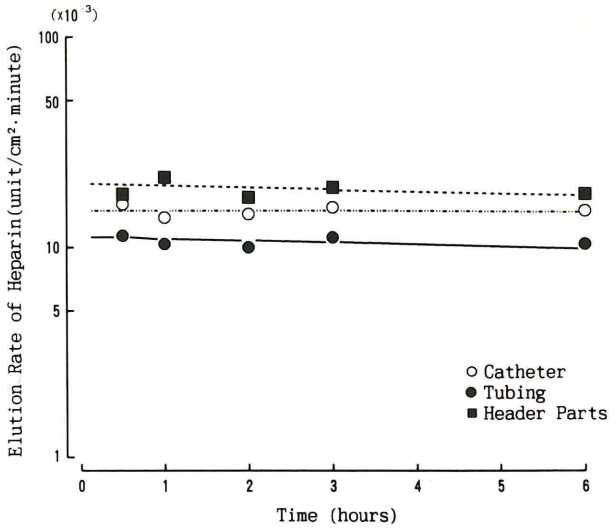

FIG. 4. Elution rate of heparin from heparinized parts of the antithrombogenic continuous ultrafiltration system assayed by measuring heparin thrombin time.

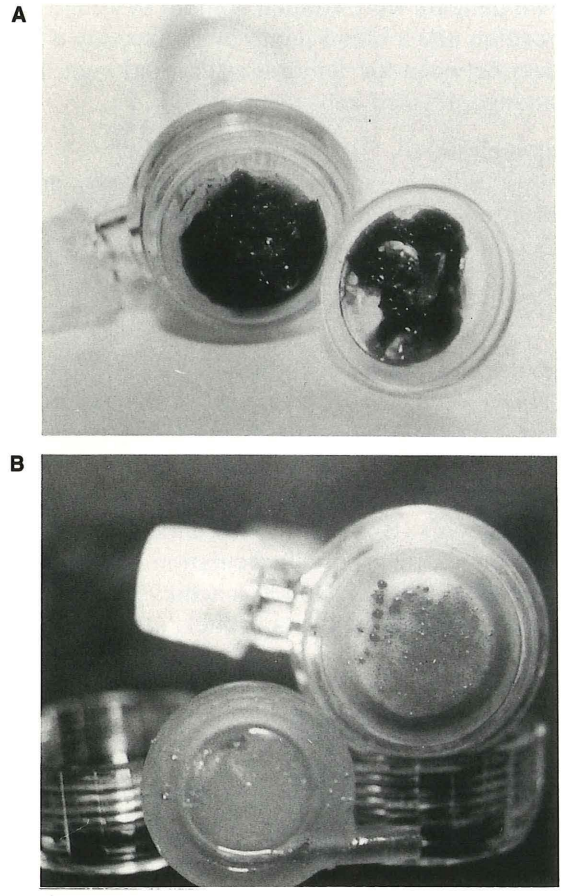

FIG. 3. Thrombus formed at the inlet side of the hemofilter module during an extracorporeal circulation without heparin infusion. **A:** Heavily formed thrombus at the conventional vertical header connected with heparinized catheter and tubing, where extracorporeal circulation lasted for 45 min. **B:** Slight thrombus formation at the heparinized tangential header in the antithrombogenic continuous ultrafiltration system, where the heparin-free circulation lasted for 360 min.

without being metabolized, the estimated amount of heparin released from this totally modified system [antithrombogenic continuous ultrafiltration system (ACUS)] was ~3 U/min, which is far less than the level of conventional systemic heparinization. As shown in Fig. 5, any significant release of heparin from the totally modified system (ACUS) so as to cause a difference in PTT between before and after passing the system was ruled out by in vivo PTT measurement during the 9-h circulation with the ACUS.

For more detailed comparison between a conventional CAVH system and the newly designed and totally modified one (ACUS), further animal experiments with unheparinized dogs and heparinized rabbits were performed. Figure 6 depicts contrasting change in the extracorporeal blood flow rate between the conventional CAVH system and the ACUS in the unheparinized dog model. An extracorporeal blood circulation rate of >100 ml/min was maintained for 7 h with the ACUS, whereas it rapidly decreased with the conventional system.

Figure 7 shows the relative PTT and platelet count, both of which strongly suggest less damage on the coagulation and platelet systems by the ACUS as compared with the conventional system. In contrast to the conventional membrane (PAN), no adherent platelets were observed on the PAN–PEO membrane surface as shown in Fig. 8. In this experiment, the amount of protein adsorbed on the fiber membranes was 25 ± 5.4 (n = 3) and 682 ± 251 (n = 3) μg/cm^2 for PAN–PEO and PAN mem-

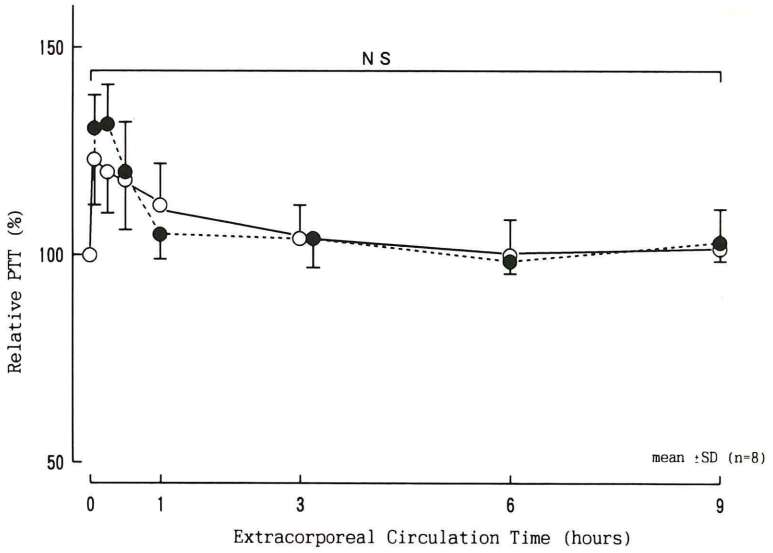

FIG. 5. Partial thromboplastin time (PTT) of the blood entering (open circles) and leaving (closed circles) the antithrombogenic continuous ultrafiltration system (ACUS). Changes in PTT are expressed in percentage and mean ± SD. It is noted that any significant change in PTT during passage through the ACUS is not observed in the total 9-h extracorporeal circulation.

branes, respectively. The results of these observations seem to coincide with those demonstrated in Fig. 7.

In Fig. 9, the time course of the relative ultrafiltration rate in the heparinized rabbit model, which was needed for the well-controlled comparison of the ACUS with a nonantithrombogenic conventional system, is shown. Again it is noted that the level of ultrafiltration rate was well maintained with the ACUS, whereas a fairly rapid decrease was observed with the conventional one.

Clinical application of the newly designed system

This newly designed and totally antithrombogenic ultrafiltration system (ACUS) with a membrane surface area of 0.25 m^2 was clinically applied to two cases, in both of which a hemorrhagic tendency was observed and, therefore, systemic anticoagulation was considered to be very risky. In these cases, the catheter was fixed at the points where the tip of the catheter was inserted into the blood vessels by ~50 mm, based on the results in animal experiments, and the hemofilter was horizontally set at the level of the heart of the patients so as not to create additional static pressure.

A 27-year-old man (Case 1), in whom bone marrow transplantation was performed for control of acute myeloblastic leukemia, became anuric 20 days later because of acute renal failure associated with sepsis. Treatment with an ACUS without heparin infusion and a blood pump was initiated. The ultrafiltration rate was maintained at 207 ± 32 ml/h

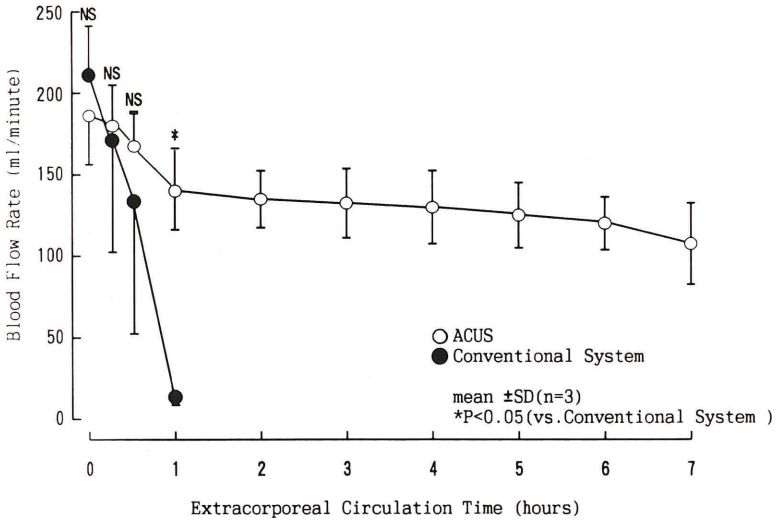

FIG. 6. Change of blood flow rate in extracorporeal circulation with unheparinized dog. Because of thrombus formation, the blood flow rate with the conventional system (closed circles) rapidly decreased whereas the extracorporeal circulation lasted with the antithrombogenic continuous ultrafiltration system (ACUS) (open circles). Student's *t* test was used for statistical analysis.

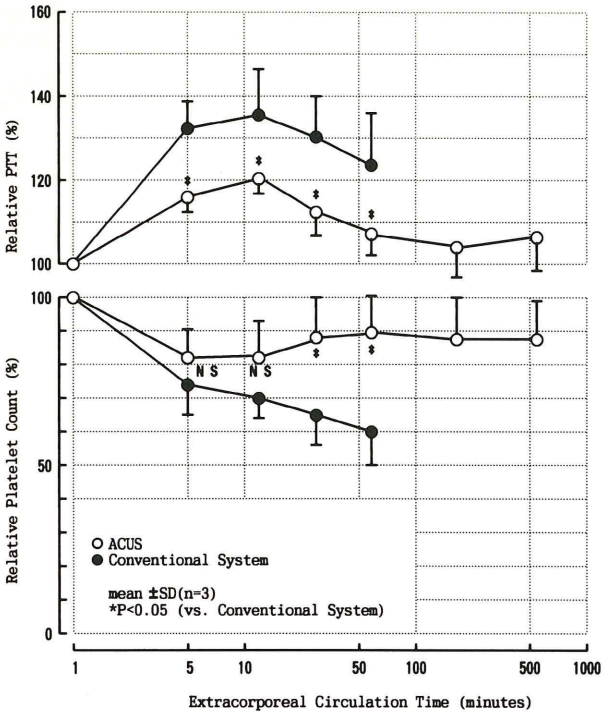

FIG. 7. Changes in relative partial thromboplastin time (PTT) and platelet count in unheparinized extracorporeal circulation. As compared with the conventional system, less activation of the coagulation cascade and less variation of platelet count were observed with the antithrombogenic continuous ultrafiltration system (ACUS).

for the first 24 h. To stabilize the ultrafiltration rate and to exert a negative pressure, a vacuum pump was inserted in the ultrafiltrate line, which enabled the ultrafiltration level of 331 ± 29 ml/h to be maintained for a further 30 h, as shown in Fig. 10. After a total 54-h treatment with the ACUS, the patient died of shock caused by deteriorated sepsis. No clotting was observed in the device during the 54-h treatment and, as shown in Figure 11, no adhesion of cellular components such as platelets and leukocytes on the membrane surface was seen by scanning electron microscopy. It is also noted that a fairly high level of ultrafiltration was obtained despite low blood pressure, as shown in Figure 10.

The second clinical case to which this device was applied was a 17-year-old girl with systemic lupus erythematosus. She became anuric because of septic shock resulting from severe pneumonia caused by the mixed infections of *Aspergillus* and cytomegalovirus. Although the mean blood pressure remained very low at ~50 mm Hg, a persistent level of ultrafiltration of 188 ± 27 ml/h for 33 h was observed, as shown in Fig. 12. During this period, only one hemofilter was used and no thrombus formation was detected.

DISCUSSION

Total heparinization of an extracorporeal circulation system is limited but the most practical approach thus far tried to allow the use of a totally antithrombogenic system. In this study, however, we designed an anticoagulant-free, partially hydrophilic antithrombogenic membrane instead, although other elements with smaller surface areas such as the catheter, tubing, and header were coated with heparin by ionic binding. In general, application of heparin or other antithrombogenic materials after the manufacture of a device or membranes is not easy, because the surface area of the membrane is large and occupies the major part of the inner surface that comes in contact with blood, and because careful attention should be paid not to cause any damage to the permeability or ultrafiltration characteristics. We therefore tried to design an inherently antithrombogenic membrane by modifying the spinning condition of the blended polymer solution, in which a PEO chain-containing acrylonitrile copolymer and an acrylonitrile homopolymer

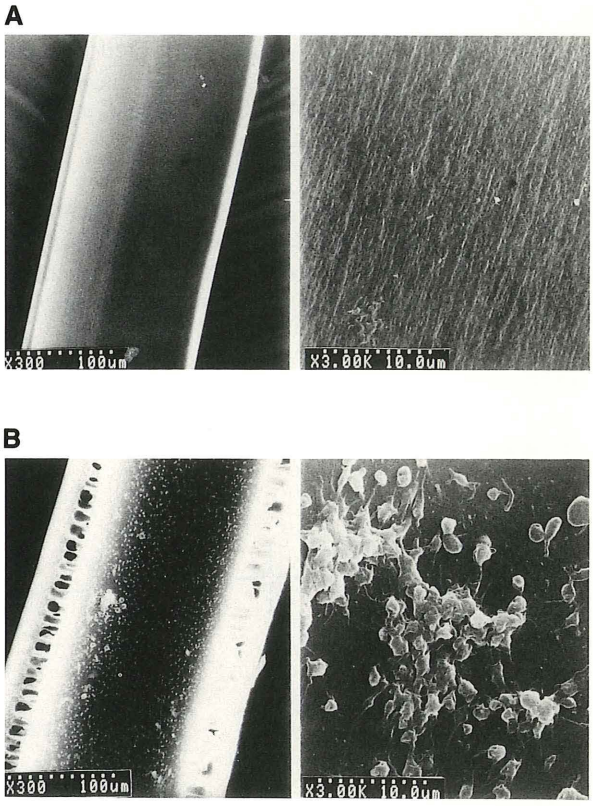

FIG. 8. Scanning electron micrographs of the surfaces of the modified (polyacrylonitrile–polyethyleneoxide: **A**) and the conventional (polyacrylonitrile: **B**) membranes after extracorporeal circulation in an unheparinized dog model. The magnification is shown in each micrograph.

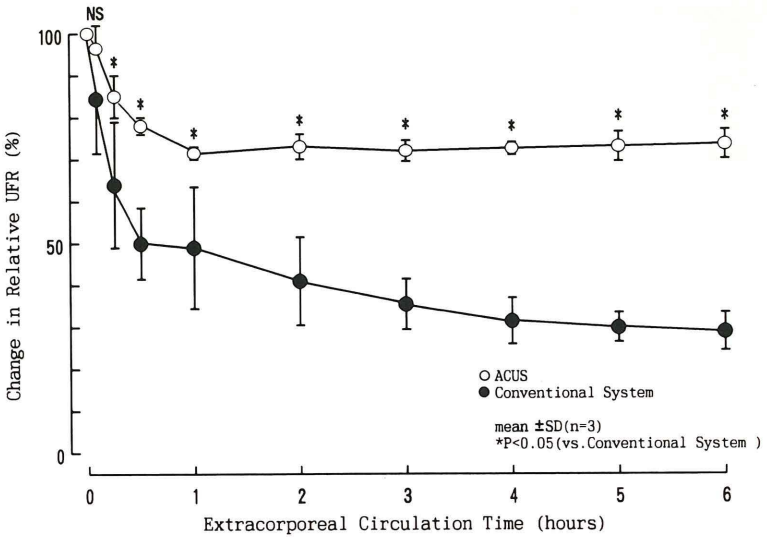

FIG. 9. Change in relative ultrafiltration rate (UFR) in heparinized rabbit model. A higher level of UFR was maintained longer with the modified system as compared with the conventional one.

were dissolved. This membrane is characterized by its very low tendency of platelet adhesion and protein adsorption. As described above, neither platelets nor other cellular components were seen on the membrane surface either in the animal experiments or in the clinical trials, whereas numerous cellular components were found to adhere on the conventional membrane. Adsorption of proteinaceous substances on the modified antithrombogenic surface was also shown to be less than that found on the conventional surface.

It should be noted that even the most biocompatible and antithrombogenic membrane could not prolong the extracorporeal circulation time without heparin infusion unless it was combined with the modified and antithrombogenic elements such as the catheter, tubing, and header as summarized in Table 1. That is, only when all three antithrombogenic elements were connected without any nonuniformity structures was substantial elongation of the heparin-free circulation time achieved. In the modifications of the materials and surfaces, the hemodynamic considerations—typified by the tangential header to reduce the dead space to a minimum and by the smooth connections of parts—were found to avoid flow separation, which can occur at various places in an extracorporeal circuit (17).

As the safety and significance of the ACUS was thus validated through animal experiments, this system was clinically applied to two severe anuric patients to support their fluid management. Severe hypotension and bleeding tendency due to their original diseases were observed for these two cases and, therefore, it was difficult to prescribe conventional hemodialysis for them. As compared with peritoneal dialysis, ACUS treatment was considered to be more effective for controlled and programmed removal of fluid from these patients. Thus, we applied an ACUS to them without heparin infusion and pumping with a machine and could man-

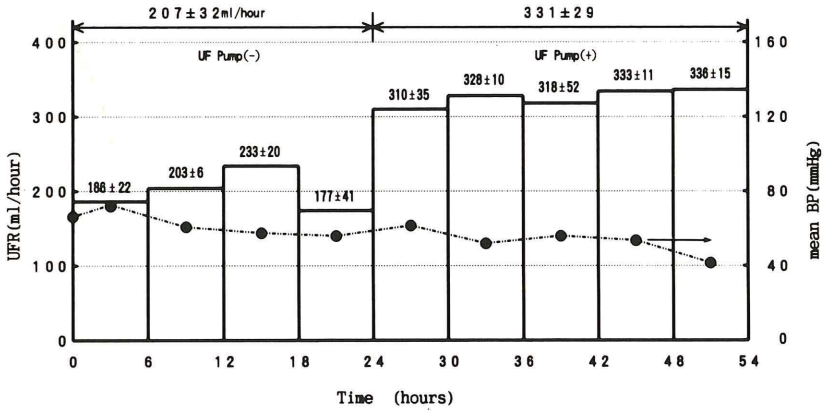

FIG. 10. Time course of ultrafiltration rate (UFR) and mean blood pressure (BP) in the clinical trial, Case 1.

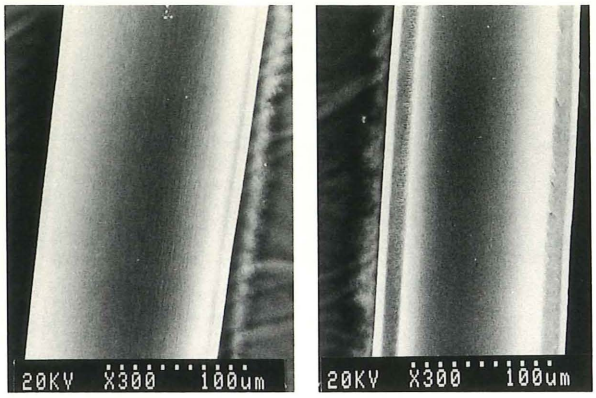

FIG. 11. Scanning electron micrographs of the surfaces of a polyacrylonitrile–polyethyleneoxide membrane as clinically used (Case 1). The left and right panels are the surfaces near the inlet and outlet of the hemofilter module, respectively. No cellular adhesion is demonstrated, which is very consistent with that of the animal experiments.

age fluid removal from them without further deteriorating the bleeding tendency, which can be considered to be clinically effective.

Recently, various anticoagulant agents such as low-molecular-weight heparin (18) and a protease inhibitor (19) have been developed and introduced in clinical practice to overcome the defects of heparin, especially its relatively long half-life due to its slow metabolism. However, infusion of any anticoagulant agents requires special care and attention to optimize the dose even if the metabolic reaction is fast. The ACUS does not require any anticoagulation and, therefore, critical cases to whom the application of conventional hemodialysis is difficult may be easily treated with this system. Recently, Weiss et al. reported the clinical significance of CAVH (20), in which the necessity of controlling a bleeding tendency is described. Although more careful evaluations are needed, this totally antithrombogenic ultrafiltration system may open a new era in the field of extracorporeal circulation therapies.

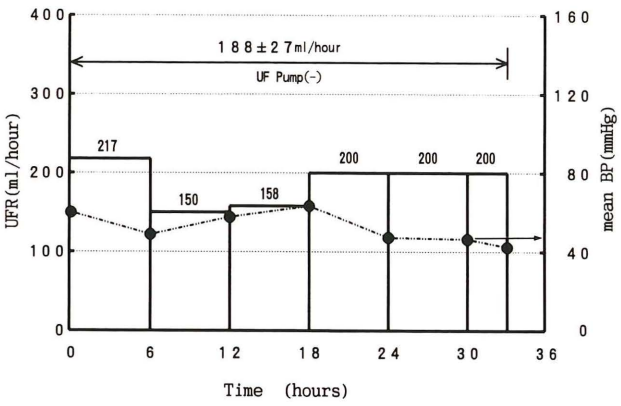

FIG. 12. Time course of ultrafiltration rate (UFR) and mean blood pressure (BP) in the clinical trial, Case 2.

It is concluded that a newly designed antithrombogenic ultrafiltration system, which consists of a PEO chain-containing filtration membrane (PAN–PEO) and heparinized catheter, tubing, and header parts, can be used as a continuous and mild arteriovenous hemofiltration system without systemic anticoagulation for control of acute renal failure, especially for the cases with bleeding tendencies or postoperative bleeding.

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