



Eluted Substances From Hemodialysis Membranes Elicit Positive Skin Prick Tests in Bioincompatible Patients

*†Shuji Konishi, ‡Atsushi Fukunaga, *Hayato Yamashita, †§Masahiro Miyata,
and *Makoto Usami

**Division of Nutrition and Metabolism, Department of Biophysics, Kobe University Graduate School of Health Sciences;*

‡Division of Dermatology, Department of Internal Related, Kobe University Graduate School of Medicine, Kobe;

†Department of Clinical Engineering, Hattori Hospital, Miki; and §Department of Biomedical Engineering, Osaka Electro-Communication University, Osaka, Japan

Abstract: Recently, hypotension and malaise during hemodialysis using polysulfone (PS) membranes have been reported. This study aimed to evaluate the bioincompatibility of eluted substances from PS hemodialysis membranes that can induce hypotension, malaise, and anaphylactic shock. Polyvinylpyrrolidone (PVP) elution from five hemodialysis membranes was measured in an in vitro experimental circulation. Skin prick tests (SPTs) with PVP or the priming fluid of hemodialysis membranes were carried out for seven PS membrane-incompatible patients and seven healthy volunteers. Skin reactivity for histamine was compared in patients and healthy volunteers. The symptoms of PS membrane-incompatible cases were hypotension, dyspnea, nausea, or vomiting.

One patient had gone into shock. PVP was eluted from hemodialysis membranes, but the SPT for PVP was negative in all patients. SPTs with priming fluid (or priming fluid effluxed during priming) were positive in four out of six patients. However, the SPT with bisphenol A was positive in one patient. The area of the flare reaction against histamine in patients was smaller than that of healthy subjects. In conclusion, eluted substances apart from PVP from hemodialysis membranes could cause bioincompatibility with PS membranes. **Key Words:** Polyvinylpyrrolidone—Skin prick test—Hemodialysis—Priming fluid—Polysulfone—Hemodialysis membrane—Polymethyl methacrylate.

Polyvinylpyrrolidone (PVP) is present in hair-sprays, cosmetics, povidone-iodine, and tablets. PVP can have adverse effects in humans, such as allergies and anaphylactic shock (1–3). Some patients may show a positive reaction upon a skin prick test (SPT) with PVP. Adachi et al. reported that PVP could cause an anaphylactic reaction after exposure to povidone-iodine (4) and that the SPT or histamine-release test indicated a positive reaction against PVP.

Polysulfone (PS) membranes are present in >50% of hemodialyzers. Recently, hypotension and malaise during hemodialysis treatment using PS membranes have been reported (5,6). Bacelar et al. reported nine occasions when hemodialysis using PS membranes was carried out with no abnormalities, followed by a tenth occasion when hemodialysis induced anaphylactic shock immediately (5). In their study, changing to a cellulose diacetate membrane without PVP contributed to improvements in symptoms. Namekawa et al. reported elution of a measurable amount of PVP from the PS membrane using the Müller method (7). The authors hypothesized that PVP in the PS membrane could cause hypotension and malaise.

In nonhemodialysis studies, SPTs have shown that PVP is allergenic. However, the association between PVP and PS membrane-incompatible patients undergoing hemodialysis has not been investigated.

doi:10.1111/aor.12392

Received March 2014; revised June 2014.

Address correspondence and reprint requests to Prof. Makoto Usami, Division of Nutrition and Metabolism, Department of Biophysics, Kobe University Graduate School of Health Sciences, 7-10-2, Tomogaoka, Suma-ku, Kobe, Hyogo 654-0142, Japan. E-mail: musa@kobe-u.ac.jp

It is suspected that substances other than PVP eluted from hemodialysis membranes could cause bioincompatibility (8). Some reports have shown that bisphenol A (BPA) is eluted from hemodialyzers (9–11). Also, BPA in raw materials such as epoxy and polycarbonate resins is suspected to disrupt the endocrine system (9).

We hypothesized four possibilities in this clinical study: (i) PVP is eluted from hemodialysis membranes; (ii) PVP causes bioincompatibility; (iii) eluted substances apart from PVP cause bioincompatibility; and (iv) BPA causes bioincompatibility. We investigated substances that can cause bioincompatibility by measuring PVP elution from hemodialysis membranes using an experimental circulation system and conducting SPTs of PVP, priming fluid, and BPA in patients in whom bioincompatibility was induced during hemodialysis.

PATIENTS AND METHODS

The study protocol was approved by the Ethics Committee of Kobe University (Kobe, Japan). All participants provided written informed consent to be included in the study.

Subjects

Patients who underwent hemodialysis in Hattori Hospital (Miki, Japan) from April 2009 to April 2013 formed the study cohort. Seven of 463 patients had hypotension, malaise, or symptoms suggestive of anaphylactic shock during hemodialysis using PS membranes. We measured the levels of bacteria and endotoxin in the dialysate monthly, according to the Japanese Society for Dialysis Therapy guidelines (12). The demographic data of patients are shown in Table 1. Seven healthy volunteers (three female and four male; 24–58 years old) were the controls.

Definitions

Hypotension was defined as a sudden decrease in systolic blood pressure (SBP) >30 mm Hg during hemodialysis (13). Malaise was defined as lassitude, dyspnea, pressure in the chest, or nausea without hypotension. If hypotension, decrease in blood flow, or decrease in the ultrafiltration rate was observed, 100 mL saline was administered to reverse these symptoms, and this intervention was termed “treatment.”

In vitro PVP elution from hemodialyzers

To measure PVP elution from hemodialysis membranes, five hemodialyzers were used: a Toraylight NV-16U (Toray, Tokyo, Japan), a Kawasumi RENAK PS-1.6 (Kawasumi, Tokyo, Japan), a VitabranE VPS-15HA (Asahi Kasei Medical, Tokyo, Japan), a Polynephron PES-15Sα eco (Nipro, Osaka, Japan), and a Hollow Fiber Dialyzer FD series FDX-150GW (Nikkiso, Tokyo, Japan). These dialyzers are hemodialysis membrane materials that contain PVP and are sold in Japan. The membrane data of hemodialyzers are shown in Table 2 and the in vitro experimental circulation system is shown in Fig. 1. The dialysis-fluid sides of the hemodialyzers were primed using dialysate at a flow rate of 500 mL/min for 5 min. The blood sides of the hemodialyzers were primed with saline at a flow rate of 100 mL/min for 10 min. Saline (0.9%, 1 L) at 37°C was circulated through the blood side at a flow rate of 200 mL/min for 240 min while keeping the dialysis fluid stationary. Iodometry was carried out to quantify PVP (14). A calibration curve was obtained from the absorbance at 470 nm of PVP (grade = K90; Wako Pure Chemical Industries, Osaka, Japan) at various concentrations measured using an ultraviolet (UV)–visible spectrophotometer (UV-1700PC; Shimadzu, Kyoto, Japan) (7). A sample (2.5 mL) was mixed with 1.25 mL of 0.2 M citric acid (Wako) and 0.5 mL

TABLE 1. Demographic data

Patient number	Sex	Age (years)	Months*	Primary disease	Hemodialyzer at treatment onset	Symptoms	Hemodialyzer use
1	F	77	43	Polycystic kidney	CS-1.3U [†]	Hypotension, malaise	Continual use
2	M	79	2	Chronic glomerulonephritis	PS-1.3UW [‡]	Hypotension	Continual use
3	F	75	36	Polycystic kidney	CS-1.3U [†]	Hypotension	Continual use
4	F	61	4	Diabetic nephropathy	PS-1.3UW [‡]	Shock	First use (but with previous experience of use)
5	F	63	2	Diabetic nephropathy	CS-1.3U [†]	Hypotension, malaise	Continual use
6	M	65	2	Diabetic nephropathy	PS-1.6UW [‡]	Hypotension	Continual use
7	M	76	2	Diabetic nephropathy	PS-1.3UW [‡]	Hypotension	Continual use

*Time period using a polysulfone hemodialyzer. [†]Toraylight CS-1.3U. Currently not manufactured or sold. [‡]Fresenius Dialyzer PS-1.3UW and PS-1.6UW. Currently not manufactured or sold.

TABLE 2. Technical data of hemodialyzers

Name of hemodialyzer (type)	Manufacturer	Membrane material	Contains bisphenol A
Toraylight NV-16U (moist)	Toray	Polysulfone*	Yes
Kawasumi RENAK PS-1.6 (wet)	Kawasumi	Polysulfone†	Yes
VitabranE VPS-15HA (wet)	Asahikasei	Polysulfone	Yes
Polynephron PES-15Sα eco (dry)	Nipro	Polyethersulfone	No
Hollow Fiber Dialyzer FD series FDX-150GW (wet)	Nikkiso	Polyester polymer alloy	Yes

All membranes contain polyvinylpyrrolidone. * Successor product to Toraylight CS-1.6U, with membrane materials the same as in Toraylight CS-1.3U. † Successor product to the Fresenius Dialyzer PS-1.3 and PS-1.6UW.

of 0.02 N iodine solution (Wako). Ten minutes after mixing, the absorbance of samples was measured at 470 nm using the UV–visible spectrophotometer, and the PVP concentration was calculated from the calibration curve (14).

SPTs with PVP and povidone–iodine

To assess the influence of PVP on the human body, SPTs were carried out using PVP or 10% povidone–iodine solution including 1% iodine and 9% PVP. PVP of grades K30, K60, and K90 was used (K30: molecular weight 60 000; K60: molecular weight 400 000, K90: molecular weight 1 300 000; ISP Japan Corporation, Tokyo, Japan) (15,16). The grade and molecular weight of PVP included with hemodialysis membranes are not reported; thus, we chose three kinds of PVP that might be included in hemodialysis membranes based on information from the companies. Concentrations of PVP in 0.9% saline for SPTs were 10, 100, 1000, and 10 000 mg/L. The 10% povidone–iodine solution (Push Swab P) was obtained from Hakuzo Medical Corporation (Tokyo, Japan).

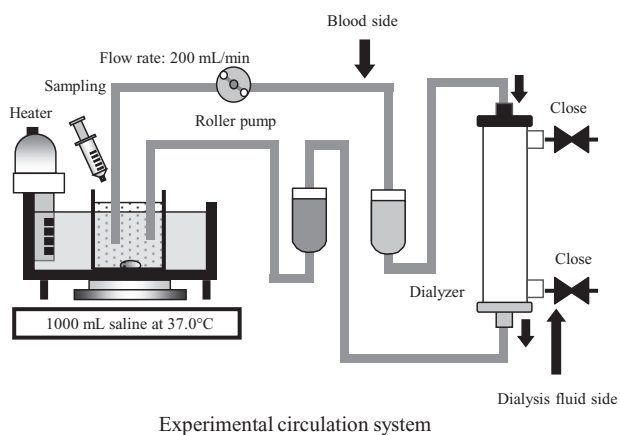


FIG. 1. Experimental circulation for the elution of polyvinylpyrrolidone from hemodialyzers. Saline (0.9%, 1 L) at 37°C was circulated through the blood-side compartment at a flow rate of 200 mL/min for 240 min while maintaining dialysis fluid stationary.

SPT with priming fluid

To evaluate the influence of eluted substances (except PVP) from hemodialysis membranes, SPTs were carried out using priming fluid or priming fluid effluxed during priming. Priming fluid was collected from the wet-type hemodialyzers detailed in Table 2. Priming fluid effluxed during the priming process was also collected from dry- and moist-type hemodialyzers. We refer to both types of fluid as “priming fluid” in this study.

SPT with BPA

To assess the influence of BPA on the human body, SPTs were carried out using BPA in the solution (10 000 mg/L of BPA with 1% petrolatum) used as the established method for standard skin tests (17). BPA was obtained from TROLAB Patch Test Allergens (Almirall Hermal, Reinbeck, Germany).

SPT score

Prick lancetters (Ewo Care AB, Gislaved, Sweden) were used in SPTs. SPTs were carried out following standard methods (4). Saline and histamine (10 mg/mL, Hollister-Stier Laboratories, Spokane, WA, USA) were used as controls. The responses were then compared with those of the positive histamine controls (10 mg/mL) and were scored as follows: 0, no positive area compared with the wheal on the histamine-positive control; 1+, 25% (false positive); 2+, 50% (positive); 3+, >100% (strongly positive). Pruritus was scored as “clear reaction” (+), “weak reaction” (±), or “could not feel” (–). The area of the wheal-and-flare reaction was calculated by multiplication of the long-side radius, narrow-side radius, and π (3.14). The control histamine reaction in two series of SPTs was compared between seven patients and seven healthy subjects to evaluate differences in skin reactivity.

Statistical analyses

Data are given as the mean $\pm$ standard error of the mean (SEM). The Tukey–Kramer post hoc test and the two-factor factorial analysis of variance were

performed to compare the PVP elution. Student's *t*-test was carried out for the area of the wheal-and-flare reaction caused by histamine in the SPT.

$P < 0.05$ was considered significant. All statistical analyses were performed using JMP 10 (SAS Institute, Tokyo, Japan).

RESULTS

Case studies in which bioincompatibilities owing to hemodialyzers were suspected

Patient 1

A 77-year-old female underwent hemodialysis for polycystic kidney disease using a hemodialyzer containing a PS membrane (Fresenius Dialyzer PS-1.0UW and PS-1.3UW [Kawasumi] and Hollow Fiber APS-13MD [Asahi Kasei Medical]) from June 12, 2006. The hemodialyzer was changed to a PS membrane (Toraylight CS-1.3U, Toray, Tokyo, Japan) on March 29, 2009. SBP decreased to 108 mm Hg, and malaise was observed on June 8, 2009. After the hemodialyzer was changed to a cellulose triacetate membrane (Triacetate Hollow Fiber Dialyzer FB-130Pβ, Nipro, Osaka, Japan) the symptoms disappeared.

Patient 2

A 79-year-old male was hemodialyzed for chronic glomerulonephritis using a cellulose triacetate membrane (FB-130Pβ) from June 16, 2009. The hemodialyzer was changed to a PS membrane (PS-1.3UW) on July 10, 2009. After this change, hypotension was induced thrice (August 8, 11, and 13). On August 11, SBP decreased to 66 mm Hg at 10 min after hemodialysis was started (Fig. 2A). After the hemodialyzer was changed to a polymethyl methacrylate (PMMA) membrane (Filtrizer BG-1.3PQ, Toray, Tokyo, Japan), hypotension disappeared.

Patient 3

A 75-year-old female had been hemodialyzed for polycystic kidney disease using PS membranes (APS-13MD and PS-1.3UW) from April 14, 2006. The hemodialyzer was changed to a PS membrane (CS-1.3U) on March 28, 2009. Without ultrafiltration, her SBP decreased from 180 to 130 mm Hg just after the initiation of hemodialysis on November 9, 2009. There were no subjective symptoms. After the hemodialyzer was changed to a PMMA membrane (BG-1.3PQ), hypotension disappeared.

Patient 4

A 61-year-old female had been hemodialyzed for diabetic nephropathy using PS membranes (PS-

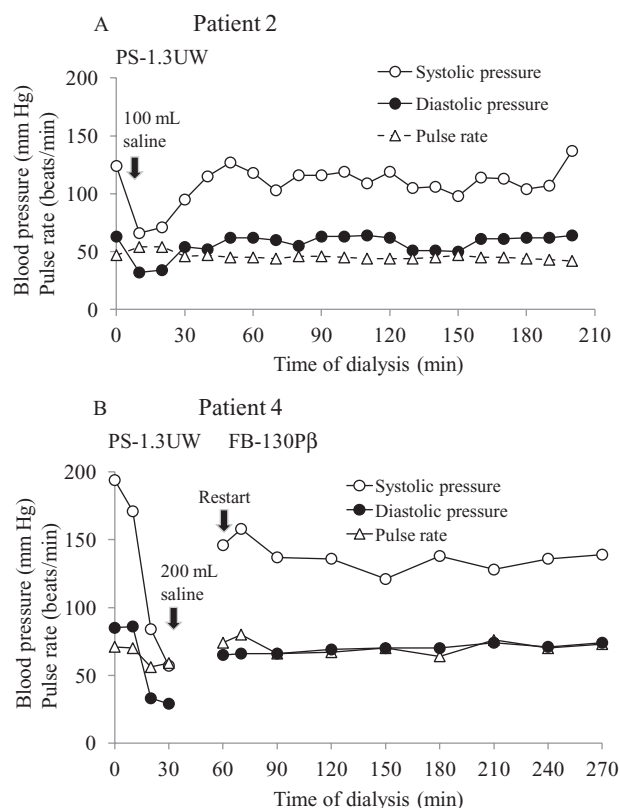


FIG. 2. Change in blood pressure and pulse rate in each patient during hemodialysis. (A) Hemodialysis chart for Patient 2 on August 11, 2009, using PS-1.3UW. (B) Hemodialysis chart for Patient 4 on January 11, 2010 (changing from PS-1.3UW to FB-130Pβ).

1.3UW and CS-1.3U) and a cellulose triacetate membrane (FB-130Pβ) from February 4, 2009. The hemodialyzer was changed to a PS membrane (PS-1.3UW) on January 11, 2010. SBP decreased to 57 mm Hg just after the initiation of hemodialysis on January 11, 2010, and she lost consciousness (Fig. 2B). Cessation of hemodialysis enabled her to recover consciousness, and SBP increased to 146 mm Hg. Hemodialysis was restarted with a cellulose triacetate membrane (FB-130Pβ) 30 min later, and her symptoms disappeared.

Patient 5

A 63-year-old female had been hemodialyzed for diabetic nephropathy using a cellulose triacetate membrane (Triacetate Hollow Fiber Dialyzer FB-90Pβ, Nipro) from January 5, 2010. The hemodialyzer was changed to a PS membrane (CS-1.3U) on January 8, 2010. On January 25, 2010, SBP was 155 mm Hg, but nausea and dyspnea appeared just after the initiation of hemodialysis. Oxygen saturation (SpO_2) was 91% upon inhalation of 2 L

oxygen. However, 20 min later, SBP decreased to 137 mm Hg, and the patient vomited. On January 27, 2010, nausea appeared 10 min after hemodialysis was started with inhalation of 1 L oxygen. SBP decreased from 148 to 106 mm Hg just after ultrafiltration was stopped. After the hemodialyzer was changed to a PMMA membrane (BG-1.3PQ), her symptoms disappeared.

Patient 6

A 65-year-old male had been hemodialyzed for diabetic nephropathy using a cellulose triacetate membrane (FB-130P β) from September 1, 2009. The dialyzer was changed to a PS membrane (Fresenius Dialyzer PS-1.6UW, Kawasumi) on December 19, 2009. Upon hemodialysis on January 25, 2010, malaise appeared, and SBP decreased from 167 to 130 mm Hg after 20 min. Dyspnea developed 1.5 h thereafter, so ultrafiltration was stopped. SpO₂ was 91% upon inhalation of 2 L oxygen, but SBP decreased to 95 mm Hg. After the hemodialyzer was changed to a PMMA membrane (Filtrizer BG-1.6PQ, Toray), his symptoms disappeared.

Patient 7

A 76-year-old male had been hemodialyzed for diabetic nephropathy using a PS membrane (PS-1.3UW) from December 28, 2010. On February 1, 2011, SBP decreased from 168 to 107 mm Hg after 30 min of hemodialysis, and he complained of tightness in the chest (Fig. 3A). On February 5, 2011, SBP decreased from 154 to 113 mm Hg after 1 h of hemodialysis. During the hemodialysis carried out on February 8, 2011, dyspnea developed without hypotension. Ultrafiltration was stopped but symptoms did not improve. Simultaneously, SpO₂ was 96%. After the hemodialyzer was changed to a PMMA membrane (BG-1.3PQ), his symptoms disappeared. However, the hemodialyzer was changed again to a polyester polymer alloy membrane (FDX-150GW) on August 21, 2012. Then, dyspnea and general malaise developed 1 h after hemodialysis was started, and blood flow and ultrafiltration rate decreased. He requested interruption of hemodialysis, so we stopped hemodialysis (Fig. 3B).

At that time, hematology data showed 63.4% neutrophils, 18.5% lymphocytes, 3.4% monocytes, 14.3% eosinophils, 0.4% basophils, and 96 IU/mL nonspecific IgE. The eosinophil count was high, but allergic symptoms were not observed. Symptoms improved after stopping hemodialysis. We restarted hemodialysis using a cellulose triacetate mem-

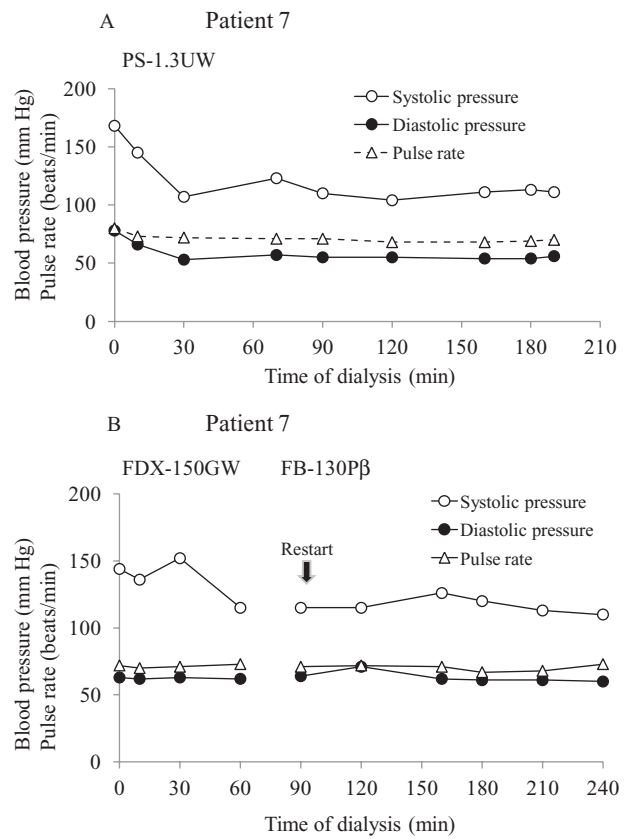


FIG. 3. Change in blood pressure and pulse rate in each patient during hemodialysis. (A) Hemodialysis chart for Patient 7 on February 1, 2011, using PS-1.3UW. (B) Hemodialysis chart for Patient 7 on August 21, 2012 (changing from FDX-150GW to FB-150P β).

brane (Triacetate Hollow Fiber Dialyzer FB-150P β eco, Nipro, Osaka, Japan) and his symptoms disappeared.

PVP elution from hemodialyzers

We evaluated PVP elution from hemodialysis membranes in vitro (Fig. 4). PVP elution in NV-16U and RENAK PS-1.6 hemodialyzers was not detected 10 min after circulation. However, PVP elution in VPS-15HA, PES-15S α eco, and FDX-150GW was 0.02 ± 0.01 , 0.14 ± 0.06 , and 0.79 ± 0.08 mg/L at 10 min after circulation, respectively. After 240 min, PVP elution in NV-16U, RENAK PS-1.6, VPS-15HA, PES-15S α eco, and FDX-150GW was 0.73 ± 0.18 , 0.56 ± 0.46 , 1.26 ± 0.76 , 1.45 ± 0.21 , and 1.11 ± 0.14 mg/L, respectively. The PVP elution in PES-15S α eco 180 and 240 min after circulation was significantly higher compared with the elution before and 10 min after circulation. The PVP elution in FDX-150GW was significantly higher at all time points after circulation than before circulation. Sig-

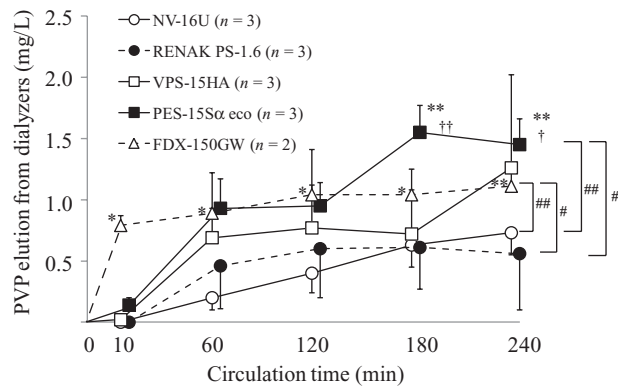


FIG. 4. Polyvinylpyrrolidone elution from hemodialyzers in the experimental circulation system. * $P < 0.05$, ** $P < 0.01$ versus 0 min; † $P < 0.05$, †† $P < 0.01$ versus 10 min (Tukey–Kramer post hoc test). # $P < 0.05$, ## $P < 0.01$ by the two-factor factorial analysis of variance.

nificantly higher levels of PVP were eluted from both PES-15S α eco and FDX-150GW than from NV-16U and RENAK PS-1.6.

SPTs with PVP or povidone-iodine

PVP K30, K60, and K90 (10–10 000 mg/L) and 10% povidone-iodine solution were negative in all patients. In healthy subjects, PVP was positive (2+) only in K30 (10 000 mg/mL) of healthy volunteer number 5 (Table 3).

SPT with priming fluid

NV-16U and RENAK PS-1.6 in patient 2, NV-16U in patient 3, NV-16U and RENAK PS-1.6

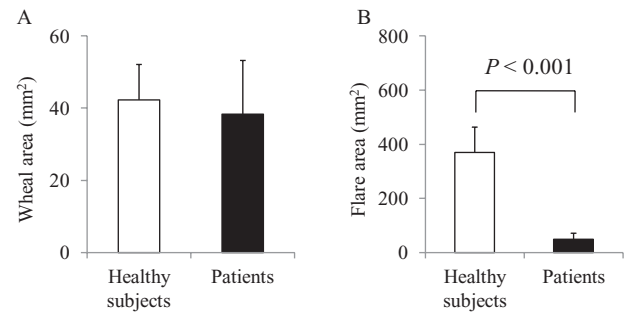


FIG. 5. Histamine reaction in the skin prick test. (A) Wheal area (patients: $n = 12$, control: $n = 14$). (B) Flare area (patients: $n = 12$, control: $n = 14$). Student's t -test was done to compare the area of the wheal and flare to that of the reaction to histamine in the skin prick tests. $P < 0.001$ was considered significant.

in patient 5, and NV-16U in patient 6 were positive (2+). VPS-15HA and FDX-150GW in patient 2 and RENAK PS-1.6 in patient 6 were strongly positive (3+). In contrast, all healthy subjects were negative (Table 4).

SPT with BPA

SPT with BPA was positive only in patient 2. The other patients were all negative (Table 5).

Wheal and flare area after the histamine reaction in SPTs

The wheal area in the histamine reaction was not significantly different between patients and healthy subjects (Fig. 5A). However, the flare area was significantly smaller in patients compared with healthy subjects ($P < 0.001$) (Fig. 5B).

TABLE 3. Skin prick tests with PVP or povidone-iodine

Patients		1	2	3	4	5	6	7
Histamine (mm)	Wheal	5 × 5	8 × 7	N/A	—	7 × 6	10 × 9	7 × 6
	Flare	5 × 5	8 × 7	N/A	—	7 × 6	50 × 32	7 × 6
	Pruritus	—	—	N/A	—	—	+	—
Saline		—	—	N/A	—	—	—	—
K30		—	—	N/A	—	—	—	—
K60		—	—	N/A	—	—	—	—
K90		—	—	N/A	—	—	—	—
Povidone-iodine		—	—	N/A	—	—	—	—
Healthy subjects		1	2	3	4	5	6	7
Histamine (mm)	Wheal	8 × 8	9 × 7	5 × 5	9 × 8	6 × 7	6 × 6	10 × 7
	Flare	25 × 25	12 × 12	17 × 20	25 × 22	30 × 25	24 × 22	25 × 20
	Pruritus	+	—	—	+	+	+	+
Saline		—	—	—	—	—	—	—
K30		—	—	—	—	2+	—	—
K60		—	—	—	—	—	—	—
K90		—	—	—	—	—	—	—
Povidone-iodine		—	—	—	—	—	—	—

N/A, not available. K30, K60, and K90 were used in concentrations of 10 000 mg/L.

TABLE 4. Skin prick test with priming fluid

Patients		1	2	3	4	5	6	7
Histamine (mm)	Wheal	N/A	7 × 7	8 × 7	—	12 × 10	6 × 7	9 × 7
	Flare	N/A	12 × 12	8 × 7	—	12 × 10	20 × 18	9 × 7
	Pruritus	N/A	+	+	—	±	+	+
Saline		N/A	—	—	—	—	—	—
NV-16U		N/A	2+	2+	—	2+	2+	—
RENAK PS-1.6		N/A	2+	—	—	2+	3+	—
VPS-15HA		N/A	3+	—	—	—	—	—
PES-15Sα eco		N/A	—	—	—	—	—	—
FDX-150GW		N/A	3+	—	—	—	—	—
Healthy subjects		1	2	3	4	5	6	7
Histamine (mm)	Wheal	9 × 4	10 × 10	5 × 5	6 × 6	7 × 9	7 × 6	8 × 10
	Flare	22 × 25	10 × 10	15 × 15	24 × 22	22 × 24	20 × 25	25 × 31
	Pruritus	+	+	+	+	+	+	+
Saline		—	—	—	—	—	—	—
NV-16U		—	—	—	—	—	—	—
RENAK PS-1.6		—	—	—	—	—	—	—
VPS-15HA		—	—	—	—	—	—	—
PES-15Sα eco		—	—	—	—	—	—	—
FDX-150GW		—	—	—	—	—	—	—

N/A, not available.

DISCUSSION

We found that (i) PVP was eluted from five hemodialysis membranes; (ii) PVP in SPTs was negative for PS-incompatible patients; (iii) priming fluid was positive in the SPTs of four patients; (iv) a positive reaction was observed in the SPT with BPA in one of seven patients. These data suggested that eluted substances from PS membranes other than PVP could be the cause of bioincompatibility of PS membranes. In addition, BPA was suspected to be one of the causative substances.

First, PVP elution from PVP-containing hemodialysis membranes in our study was in accordance with other reports (7,18). Also, the change to hemodialysis membranes that did not contain PVP improved allergic symptoms in all seven patients, suggesting that PVP could be a cause of those symptoms. This result is in accordance with reports in nonhemodialysis research (1–4). PVP was suggested not to be an allergen because the SPTs of all patients were negative. Also, positive reactions

were not observed with the priming fluid of PES-15Sα eco (from which the highest PVP elution was observed in our experimental circulation). Hence, these results conflicted with our second hypothesis that PVP causes PS membrane bioincompatibility.

Third, we hypothesized that eluted substances other than PVP from hemodialysis membranes affected patients. SPTs suggested that priming fluid could be an allergen for hemodialysis patients. These results supported the notion that PVP did not cause bioincompatibility but that other eluted substances did.

Fourth, we suspected BPA to be a bioincompatibility-causing substance because BPA was contained in the housing or membrane materials of the hemodialyzers except for PES-15Sα eco. In patient 2, the SPT suggested BPA to be an allergen. BPA is eluted from hemodialysis membranes and is known to disrupt the endocrine system (9–11). In the other three patients, influences of eluted substances other than PVP or BPA from hemodialysis

TABLE 5. Skin prick test with BPA

Patients		1	2	3	4	5	6	7
Histamine (mm)	Wheal	5 × 5	9 × 9	5 × 5	—	3 × 4	7 × 7	4 × 4
	Flare	5 × 5	9 × 9	5 × 5	—	3 × 4	30 × 28	4 × 4
	Pruritus	+	±	±	—	±	±	+
Saline		—	—	—	—	—	—	—
BPA		—	2+	—	—	—	—	—

BPA, bisphenol A.

membranes were suggested. This result supported our third and fourth hypotheses. Heegard et al. reported that the hemodialysis membrane itself can cause allergic reactions (19). However, owing to SPTs, we believe eluted substances from hemodialysis membranes other than PVP or BPA to be the causes of bioincompatibility for hemodialysis in the other three patients.

Additionally, we showed that the flare areas of all patients aged >60 years were significantly smaller than those of younger, healthy subjects. This finding is in agreement with reports suggesting that histamine reactivity is decreased age-dependently, as well as in subjects with renal insufficiency and those undergoing hemodialysis and peritoneal dialysis (20–22). Conversely, with regard to the wheal area, a significant difference was not observed in comparison with healthy subjects. Yoshida et al. (3) reported that the SPT with PVP was negative but observed a positive reaction in the histamine-release test. Detailed studies are required with respect to other evaluation systems (including the histamine-release test).

Since April 2013, patient bioincompatibility with PS membrane has not appeared in our hospital. In modern Japan, new-generation hemodialysis membranes are used, and priming of hemodialyzer using dialysate backfiltration is widespread (23). We believe that these advances in technology may have reduced elution of substances from PS membranes, leading to the reduction of bioincompatibility. CS-1.3U, PS-1.3UW, and PS-1.6UW induced bioincompatibility in this study. To our knowledge, the NV-16U and RENAK PS-1.6, with the lowest measured elution of PVP in this study, have not yet been reported to induce bioincompatibility; they are new-generation hemodialyzers (succeeding, respectively, the CS-1.3U and the PS-1.3UW and PS-1.6UW). However, larger studies, such as a multicenter study, are needed to determine the causes of the bioincompatibility during hemodialysis that appeared in this study.

CONCLUSION

We showed that eluted substances from polysulfone membranes (but not polyvinylpyrrolidone), including bisphenol A, could be causes of bioincompatibilities in hemodialysis membranes. We hope that suitable hemodialysis membranes can be developed in the near future to reduce such bioincompatibilities.

Acknowledgments: We are very grateful to Dr. Chika Onoe (Department of Medicine, Hattori Hos-

pital, Miki, Japan) and Professor Koichi Ukimoto (Department of Biomedical Engineering, Osaka Electro-Communication University, Osaka, Japan) for their cooperation.

Author contributions: S. Konishi, H. Yamashita, and M. Usami carried out study and drafted the manuscript. A. Fukunaga designed the study. M. Miyata carried out the data collection and sample analyses.

Conflict of Interest: There is no financial conflict of interest for any of the authors.

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