



A β Influx into the Blood Evoked by Different Blood A β Removal Systems: A Potential Therapy for Alzheimer's Disease

Nobuya Kitaguchi¹ 
 Kazunori Kawaguchi¹
 Miwa Sakata¹
 Hiroki Aoki¹
 Kazunori Yamazaki¹
 Megumi Kaneko¹
 Jun Kinomura¹
 Masao Kato²
 Midori Hasegawa¹ 
 Nobuo Suzuki³
 Masao Mizuno⁴
 Yukio Yuzawa²

¹Faculty of Clinical Engineering, School of Medical Sciences, Fujita Health University, Toyoake, Aichi, 470-1192, Japan;

²Department of Nephrology, School of Medicine, Fujita Health University, Toyoake, Aichi, Japan; ³Chiryu Clinic, Chiryu, Aichi, Japan; ⁴Mizuno Clinic, Toyoake, Aichi, Japan

Purpose: Amyloid- β (A β) is a brain protein that causes Alzheimer's disease. We have revealed that extracorporeal blood A β -removal systems evoked a large A β influx into the blood. This study investigated the system that is more effective in evoking A β influx.

Methods: A β removal activities were compared between hexadecyl-alkylated cellulose beads (HexDC) and fragments of polysulfone hollow fibers (PSf-HFs) in mini-columns to eliminate the filtration effect. Then, adsorptive filtration systems were adapted for PSf hemodialyzers to enhance A β adsorption on micropores in the wall of hollow fibers. Plasma A β concentrations of patients with renal failure were analyzed during treatment with PSf hemodialyzers alone for 8 h or tandemly connected HexDC and PSf hemodialyzers for 4 h.

Results: In the in vitro study, A β removal efficiency for HexDC was approximately 100% during the 60 min treatment, whereas the removal efficiency for PSf-HF fragments gradually decreased. However, PSf hemodialyzer in adsorptive filtration systems removed A β s comparably or more than HexDC. A β influx into the blood increases time-dependently. Concomitant use of HexDC and PSf hemodialyzer evoked a larger A β_{1-40} influx than that of PSf hemodialyzer alone. However, A β_{1-42} influx by PSf hemodialyzer alone was similar to or a little larger than influx by the combined system. Both systems evoked almost doubled A β influx than estimated A β s existing in the normal brain during the 4 h treatment.

Conclusion: PSf hemodialyzer alone for a longer period and concomitant use of HexDC and PSf hemodialyzer for a shorter time effectively evoked a larger A β influx. To evoke A β_{1-42} influx, PSf hemodialyzer alone was effective enough. These findings of devices and treatment time may lead to optimal clinical settings for therapy and prevention of Alzheimer's disease.

Keywords: amyloid, blood purification, extracorporeal system, polysulfone hemodialyzer, HexDC, 3D printer

Introduction

Amyloid- β (A β) in the brain is a causative protein of Alzheimer's disease (AD). Harmful proteins primarily include 40 amino-acid A β_{1-40} , 42 amino-acid A β_{1-42} , and abnormally phosphorylated tau.¹ Impaired A β clearance from the brain might increase brain A β , particularly in sporadic AD cases. A β clearance from the brains of patients with sporadic AD was 30% lower than the clearance in normal subjects, although A β production was similar.² The peripheral administration of anti-A β antibodies to increase the clearance of A β s from the brain has been investigated. Unfortunately, most clinical trials using anti-A β antibodies did not meet the endpoint

Correspondence: Nobuya Kitaguchi
 Faculty of Clinical Engineering, School of Health Sciences, Fujita Health University, 4-8-17, Yuzato, Higashimiyoshi-Ku, Osaka, 546-0013, Japan
 Tel +81-6-4392-7087
 Fax +81-6-4392-7087
 Email nkitaguc@fujita-hu.ac.jp

criteria, although brain A β s were reduced. However, a recent re-analysis of the clinical results for Aducanumab, an anti-A β antibody, revealed reduced cognitive decline at the high dose,³ resulting in the accelerated approval of an Alzheimer's drug by the FDA on June 7, 2021. Furthermore, Gantenerumab, an anti-A β antibody used in the dominantly inherited Alzheimer's network trial unit (DIAN-TU), reduced A β s and tau in the brain.^{4,5} Therefore, A β may be the primary causative protein for AD.⁴

We proposed extracorporeal blood A β removal systems (E-BARS) as another method for enhancing A β clearance from the brain (Figure 1).⁶ There are several rationales for blood A β removal systems. First, there is an A β concentration gradient between the brain and blood. A β concentration in the cerebrospinal fluid (CSF) of patients with AD is approximately 100 times higher than in the plasma.^{7,8} Second, A β moves from the brain into the blood via transporters, including low-density lipoprotein receptor-related protein 1 (LRP-1), ApoJ, ApoE, and receptor for advanced glycation end products (RAGE).^{9–11} Pharmaceuticals targeting RAGE and LRP-1 are being developed to increase A β transportation.¹²

We have reported the following evidence to support the efficacy of blood A β removal for AD therapy and prevention. First, we found several medical materials of high efficacy for A β removal from the blood, including hexadecyl alkylated cellulose beads (HexDC)^{6,13} and

hollow fibers in hemodialyzers, such as polysulfone (PSf), polymethylmethacrylate, and polyethersulfone.¹⁴ The A β removal efficiency of PSf dialyzers was as high as 50% for both A β_{1-40} and A β_{1-42} during a 4 h hemodialysis session.^{15,16} The mechanism of blood A β removal by these hemodialyzers is mainly by adsorption.^{14,17} Second, the removal of blood A β evoked a large influx of A β into the blood from certain tissues during hemodialysis.^{15,16,18,19} Third, we showed that A β accumulation in the brains of patients undergoing hemodialysis was significantly lower than A β accumulation in age-matched controls not undergoing hemodialysis.²⁰ Furthermore, we reported more direct evidence showing that hemodialysis decreased A β accumulation in the brain by positron emission tomography (PET)-imaging with Pittsburgh compound B (PiB) as a probe (PiB/PET).²¹ The brain A β accumulation in a chronic renal failure patient suffering from mild cognitive impairment was decreased by -0.19 standard uptake value ratio (SUVr) after hemodialysis for 6 months (4 h/session, three sessions/week). The data suggest that the brain is an origin of A β influx into the blood during hemodialysis. Fourth, A β concentration in the CSF was decreased in rat studies using HexDC columns. Plasma A β concentrations increased during blood A β removal, despite the 90% efficiency of A β removal using HexDC columns.²²

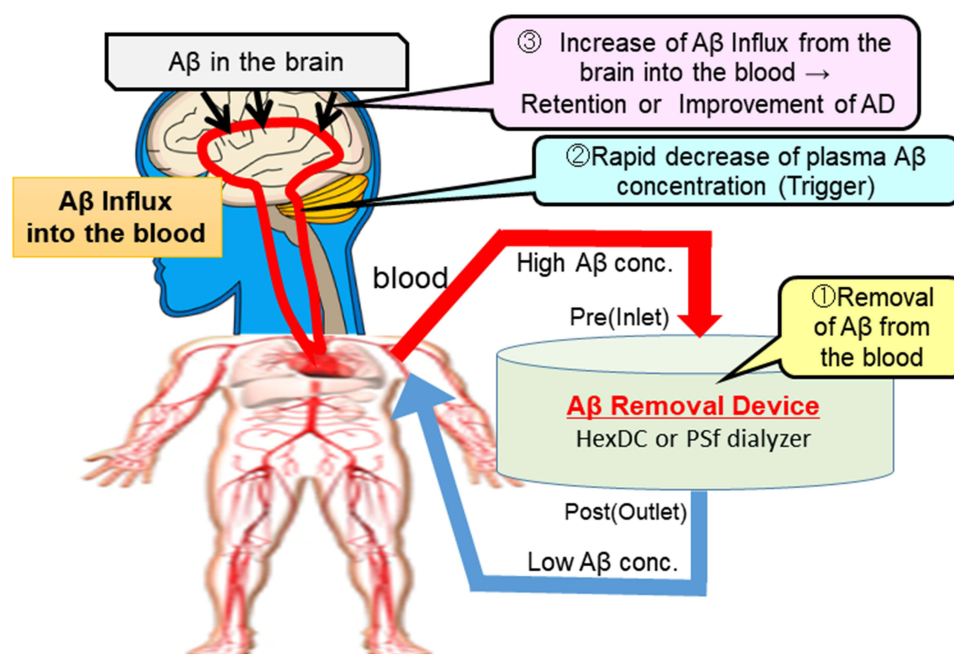


Figure 1 Schematic diagram of the extracorporeal blood A β removal systems (E-BARS) using HexDC or the PSf dialyzer. Postulated mechanisms for the E-BARS include: 1) HexDC and/or PSf hemodialyzer remove blood A β s in an extracorporeal circulation system, 2) rapid decrease in plasma A β s, and 3) it triggers increased A β influx from the brain into the blood, resulting in retention or improvements of Alzheimer's disease.

Finally, the mini-mental state examination scores of hemodialysis patients were maintained or slightly improved in a prospective study.¹⁸ We also reported that longer hemodialysis duration correlated with lower dementia risk in an analysis of more than 200,000 Japanese hemodialysis patients.²³ Furthermore, we recently reported that A β oligomers were effectively removed by size-separation methods with hollow fiber devices of appropriately large pore sizes in vitro and in humans.²⁴

Several other groups also reported that removing blood A β s may be a helpful AD therapy. Peritoneal dialysis, in which peritoneal membranes are used as dialysis membranes instead of hemodialyzers, reduced plasma A β in humans and brain A β in mouse AD models.²⁵ The authors reported that peritoneal dialysis only removed 131.33 ng of A β s,²⁵ whereas hemodialysis removed 7219 ng of A β _{1–40} and 664 ng of A β _{1–42}, totaling 7883 ng of A β s as we reported previously.¹⁹ Furthermore, plasma exchange therapy, which removes plasma A β by discarding the plasma with albumin replacement as A β binding protein, effectively improves cognitive functions in patients with AD.²⁶ This therapeutic plasma exchange discarded all plasma proteins, including coagulation factors and immunoglobulins. Therefore, intravenous immunoglobulin was injected every 4 months.

Thus, the removal of blood A β has attracted attention as a therapeutic strategy for AD.²⁷

Furthermore, regarding A β influx into the blood, we reported that the total amount of A β influx during one hemodialysis session (4 h) was calculated as 7219 ng for A β _{1–40} and 664 ng for A β _{1–42} for 30 patients undergoing hemodialysis.¹⁹ These amounts of A β influx during one hemodialysis session of 4 h are comparable with the reported total A β content of 7760 ng in the brain.²⁸

We found several effective materials suitable for blood A β removal, including HexDC and PSf-HFs. This study aimed to determine which materials are more efficient at removing A β s from the blood (Figure 1). Another and primary objective in this study was what systems are more effective to evoke a larger A β influx into the blood. We compared two systems: one was a system of enhanced A β removal activity by using doubled A β removal devices (concomitant use of HexDC and PSf hemodialyzer) for 4 h, the other was a longer treatment system by using PSf hemodialyzer alone for 8 h.

Materials and Methods

Ethical Approval and Collection of Human Plasma

This study conformed to the Declaration of Helsinki's Good Clinical Practice. This research was comprehensively reviewed and approved by the institutional review board at Fujita Health University (the latest approval number is HM16-266). Patients undergoing blood purification provided written informed consent for collecting blood samples.

Preparation of the A β Solutions

Human plasma remaining in used bags of fresh frozen plasma and discarded plasma from patients was obtained after plasma exchange therapy. The plasma was refrozen at -80°C with additional heparin. Before use, the plasma was thawed and shook in a water bath at 37°C and centrifuged to remove precipitates. Detailed procedures were previously described.²⁴

Preparation of Mini-Columns of HexDC Beads and PSf-HF Fragments

HexDC was chosen for this study because it is one of the most efficient adsorbents for blood A β removal, as described in the Introduction.^{6,13} HexDC beads, shown in Figure 2A, came from a commercially available HexDC device (LIXELLE S-35 containing 350 mL HexDC, Kaneka, Osaka, Japan), which is used to remove β 2-microglobulin from the blood of hemodialysis patients having carpal tunnel syndrome in the clinical circuit with tandem connection to hemodialyzers. Hexadecyl alkyl chains are appropriately hydrophobic, interacting with hydrophobic proteins, such as β 2-microglobulin and A β s. HexDC beads (1.75 mL, 1/200 of LIXELLE S-35) were put into a 2.5 mL polypropylene syringe to form the mini-HexDC column.

PSf-HFs were also used in this study as one of the most efficient adsorbents for blood A β removal.^{14–17} Among various materials of hollow fibers in hemodialyzers, PSf is hydrophobic enough to adsorb hydrophobic proteins, such as albumin and A β s. PSf-HF was obtained from hemodialyzers (APS-13EA, Asahi Kasei Medical, Tokyo, Japan) and cut into 2–5 mm fragments (Figure 2B) to eliminate the filtration effect. The membrane surface area of the fragments in the mini-column of PSf-HF was 0.01 m^2 , which was 1/200 of 2.0 m^2 (a representative membrane area used in clinical hemodialysis). The

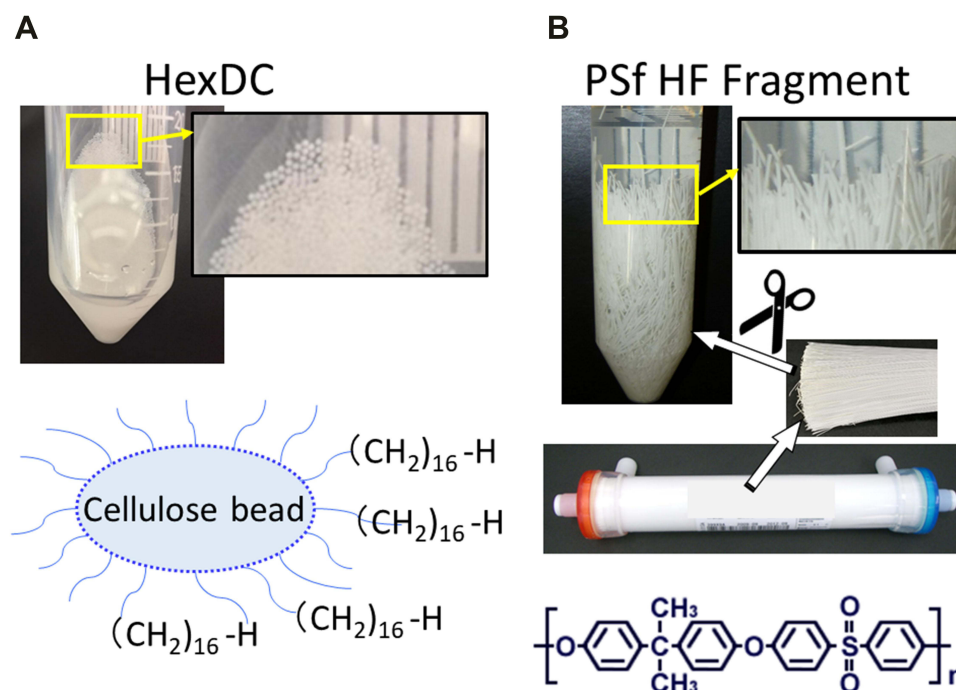


Figure 2 Materials for A β removal: hexadecyl alkylated cellulose beads (HexDC) and polysulfone hollow fibers (PSf-HF) fragments were used for A β removal in this study. **(A)** HexDC: bottom, the chemical structure of HexDC; top left, a photo of HexDC beads; top right, enlarged HexDC photo. **(B)** Fragments of PSf-HF: bottom, the chemical structure of polysulfone; lower middle, PSf hemodialyzer; upper middle, PSf hollow-fiber bundles as main components of the PSf hemodialyzer; top left, a photo of PSf-HF fragments of 2–5 mm length which were cut from PSf-HF bundles; top right, enlarged photo of PSf-HF fragments.

fragments were put into a 2.5 mL syringe to form a mini-column of PSf-HF fragments.

A β Removal with Mini-Columns in vitro

Eighteen milliliters of pooled human plasma was applied continuously to mini-columns of HexDC or PSf-HF fragments and returned to the plasma pool at a flow rate of 240 μ L/min using a Perista pump (ATTO, Tokyo, Japan), as shown in Figure 3A. This plasma flow rate was set to 1/200 of the flow rate in a clinical setting with 50 mL plasma/min (77 mL blood/min when the hematocrit is 35%), determined in our previous study.¹⁴

The A β removal efficiency of the column was calculated as follows:

$$\text{Removal efficiency(\%)} = 100 \times \left\{ 1 - \frac{\text{concentration of A}\beta \text{ leaving the column at after a designated time}}{\text{concentration of A}\beta \text{ before entering the column at that time}} \right\}$$

Eq (1)

The A β reduction rate for the experimental pool solution was defined as follows:

$$\text{Reduction rate(\%)} = 100 \times \left\{ 1 - \frac{\text{A}\beta \text{ concentration in the pool solution at a designated time}}{\text{Initial A}\beta \text{ concentration in the pool solution}} \right\}$$

Eq (2)

A β Removal by One-Pump Adsorptive Filtration Using Hemodialyzers in vitro

The primary mechanism of A β removal using hemodialyzers is adsorption, not filtration.¹⁴ To enhance adsorption to the surface of “micropores in the hollow fiber walls” of hemodialyzers (Figure 3B), we developed “adsorptive filtration” systems with two pumps.¹⁷ One pump is for blood circulation and the other for filtration. In this study, to make adsorptive filtration systems with two pumps easier to use in clinical settings, one-pump adsorptive filtration systems were created with Venturi tubes instead of filtration pumps (Figure 3C). The Venturi tube has a narrow pass in the middle part, which increases fluid pressure before the narrow pass and decreases the pressure after the narrow pass. The increased fluid (blood) pressure enhances filtration

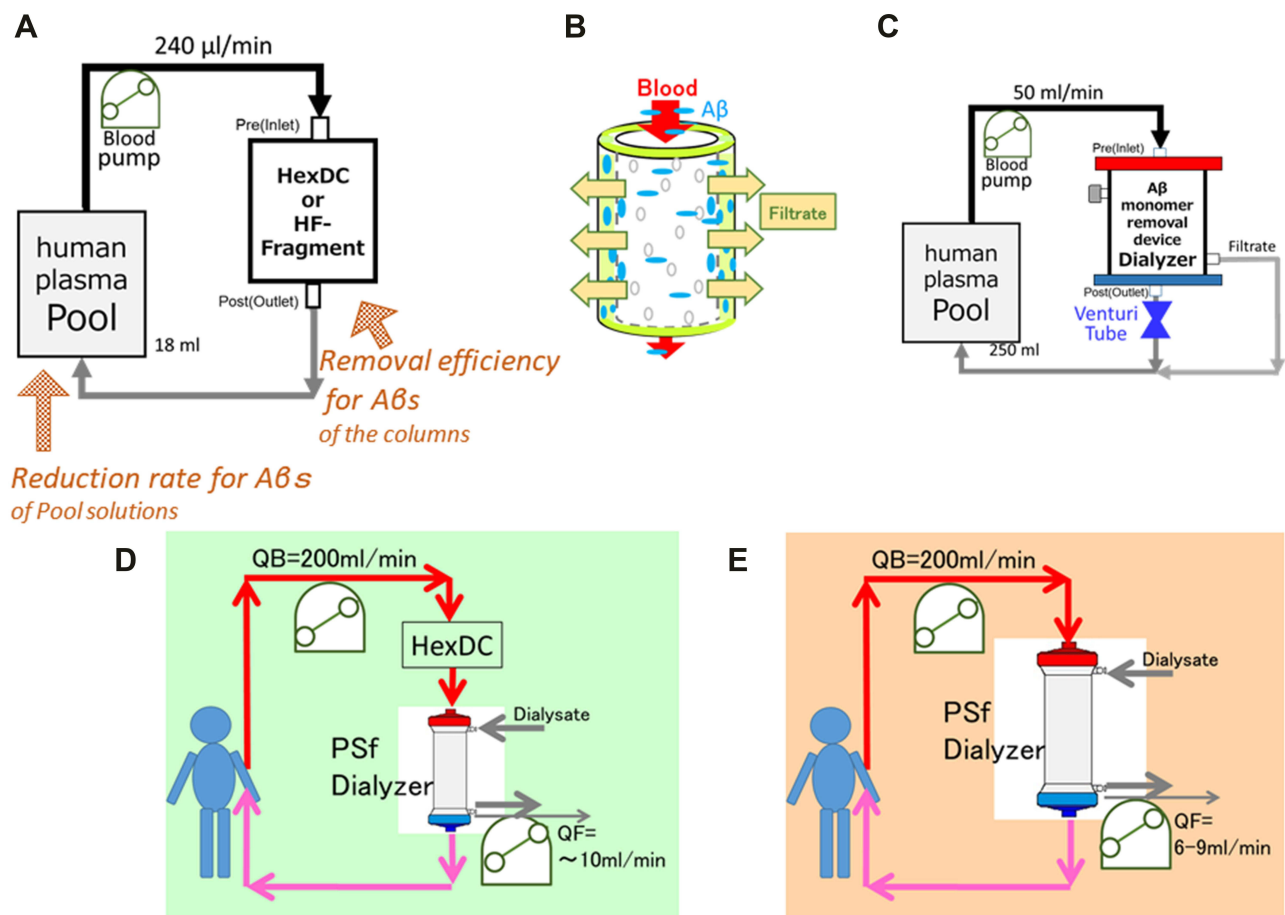


Figure 3 Experimental and clinical circuits of Aβ removal systems. (A) In vitro experimental circuit for Aβ removal with mini columns of HexDC or PSf-HF fragments. Plasma flow rate and the quantities of HexDC or PSf HF were set to 1/200 of the human clinical setting. Aβ removal efficiencies of the columns and reduction rates in the plasma pool are defined in Eqs (1) and (2), respectively. (B) The basic concept of adsorptive filtration system for Aβ removal to enhance adsorption to the inner surface of hollow-fiber walls in hemodialyzers. (C) One-pump adsorptive filtration circuit with a Venturi tube and PSf hemodialyzer. (D) The clinical setting for treatment of renal failure patients suffering from carpal tunnel syndrome as a complication. The PSf hemodialyzer was tandemly connected just after the HexDC column (pale green background). (E) The clinical setting for treatment of renal failure patients with a PSf hemodialyzer (light orange background).

through the wall of hollow fiber membranes in adsorptive filtration systems.

The Venturi tubes were designed with three-dimensional computer-aided design software, DesignSpark Mechanical (RS Components, Yokohama, Japan). Using the designed standard triangulated language (STL) data, Venturi tubes were produced with 1.75 mm filaments of polylactic acid using a fused deposition modeling 3D printer (Replicator 2; MakerBot, NY, USA). In the experimental circuit (Figure 3C), a Venturi tube was added after the polysulfone dialyzer outlet (APS-13EA, Asahi Kasei Medical, Tokyo, Japan) to control the filtration rate. A flowmeter (Coriolis Flow Meter FD-SS02A, Keyence, Osaka, Japan) was placed between the filtrate outlet (one of the dialysate ports) and the junction with the return tube to the pool of 250 mL of human plasma. Human plasma was circulated at a 50 mL/min flow rate using peristaltic pumps (Masterflex Variable-Speed

Drive; Cole-Parmer, IL, USA). This flow rate was determined based on our previous studies of adsorptive filtration.^{14,17}

Aβ Removal in Hemodialysis Patients Using PSf Hemodialyzers and HexDC

Table 1 summarizes the demographics of the blood treatment subjects. All subjects were nondiabetic, as diabetes mellitus is an AD risk factor. Three hemodialysis patients having carpal tunnel syndrome underwent treatment using PSf hemodialyzers (APS-21SA, Asahi Kasei Medical, Tokyo, Japan) and tandemly connected HexDC (LIXELLE S-15, Kaneka, Osaka, Japan). Figure 3D shows the clinical circuit for these treatments. Treatment time was 4 h, and patients were treated during the day. Dialysate flowed outside PSf-HF in the PSf hemodialyzer at a flow rate of 500 mL/min.

Table 1 Demographics of the Subjects Undergoing Blood Purification

Group	Subject	Sex	ApoE4	Age	Smoking History	PSf Hemo-Dialyzer	HexDC	Treatment Time (Hours)	QB	QD
HexDC + Dialyzer	Hex-01	M	-/-	63	Yes	APS21SA	Lixelle	4.0	200	500
	Hex-02	M	+/+	60	Yes	APS21SA	Lixelle	4.0	200	500
	Hex-03	M	-/-	75	No	APS21SA	Lixelle	4.0	200	500
Dialyzer Only	ON-01	M	-/-	55	Yes	APS21SA		8.0	200	400
	ON-02	M	±	55	Yes	APS21SA		8.0	220	400
	ON-03	F	-/-	48	Yes	APS21SA		8.0	180	400

Abbreviations: HexDC, hexadecyl alkylated cellulose; Lixelle, the brand name of HexDC columns produced by Kanaka; PSf, polysulfone; APS21SA, the model name of PSf hemodialyzer produced by Asahi Kasei Medical; QB, blood flow rate (mL/min); QD, dialysate flow rate (mL/min).

This treatment system can be regarded as a kind of E-BARS “with double Aβ-removal devices” (concomitant use of HexDC and PSf hemodialyzer). Furthermore, PSf hemodialyzer in this system worked as an adsorptive filtration system^{14,17} because of water removal by filtration. Hemodialysis patients can pass little or no urine because of renal failure; excess water by drinking and eating should be removed from the blood during hemodialysis. The filtration rate for the removal of excess water from the blood was approximately 10 mL/min (Figure 3D).

Three additional patients were treated using only PSf hemodialyzers (APS-21SA) for 8 h overnight because they had daytime jobs. Figure 3E shows the clinical circuit. Dialysate flowed outside PSf-HF in the PSf hemodialyzer at a flow rate of 400 mL/min. This treatment system can be regarded as “longer time treatment” of E-BARS. The first 4 h of hemodialysis in these patients was regarded as the hemodialyzer-only (without HexDC) control group compared with concomitant treatments with HexDC and hemodialyzer. Filtration rates of the hemodialyzers were 6–9 mL/min for removal of excess blood water (Figure 3E).

Blood samples were obtained at 0, 1, and 4 h (for all patients) and 8 h (for ON1–3 patients in Table 1). The dialysate flow rate was 400 mL/min (24 L/h) for ON1–3 patients (Table 1). Part of the mixture of filtrate and discarded dialysate were collected at the rate of 1 L/h for the periods of 0–4 h and 4–8 h for ON1–3 patients. The accumulated filtrate/dialysate was mixed well before sampling.

Calculation of Estimated Aβ Influx into the Plasma

Aβ influx into the plasma during blood treatment was estimated as the sum of Aβs changed in the plasma during

blood treatments and Aβs removed by dialyzers, HexDC, or both, according to the following equation.

$$\text{Estimated A}\beta \text{ influx} = (\text{plasma volume}) \times (\text{concentration increase of A}\beta \text{ in the plasma during a designated period}) + (\text{sum of A}\beta \text{ removed by a device/devices during the period})$$

Eq (3)

where Aβ removed by a device during the period = (concentration of Aβ at the inlet of a device) X (removal efficiency of the device) X (plasma flow rate during the period) X (minutes of the period)

Decreased plasma concentration is denoted with a minus sign. The period is divided into 0–1, 1–4, and 4–8 h of a treatment session. Aβ concentration at the device’s inlet was set as the average of each period: 0 and 1 h for the 0–1 h period, 1 and 4 h for the 1–4 h period, and 4 and 8 h for the 4–8 h period. The removal efficiency of the devices for the 0–1 h was the removal efficiency at 1 h. The removal efficiency for the 1–4 h period was the average of those at 1 and 4 h, and the removal efficiency for the 4–8 h period was the average of those at 4 and 8 h. The whole blood volume was calculated as 1/13 of the patient’s body weight. The plasma volume was calculated as (whole blood volume) × (1 – hematocrit/100).

Measurements of Blood Concentrations of Aβs

Aβ_{1–40} and Aβ_{1–42} concentrations in the plasma were measured using the High-Sensitive Human β Amyloid (1–40) and (1–42) ELISA Kit Wako II (WAKO Pure Chemical, Osaka, Japan), respectively. ApoE4 was measured by the ApoE4/Pan-ApoE ELISA kit (MBL, Nagoya, Japan).

Statistical Analysis

All data are expressed as the mean \pm standard deviation unless otherwise specified. Differences were determined using a Wilcoxon rank-sum test for nonparametric variables and the Student's *t*-test for parametric variables, unless otherwise specified, using the statistical package JMP14 (SAS Institute Inc., Cary, USA). Values of $p < 0.05$ were considered statistically significant.

Results

Comparison of A β Removal Efficiencies of HexDC and PSf-HF Fragments

The in vitro A β removal efficiencies and reduction rates for HexDC were compared with PSf-HFs using mini-columns. Figure 3A shows the experimental circuit; quantities of HexDC and PSf-HF and the plasma flow rates were set at about 1/200 of the parameters used in clinical patient treatment. PSf-HF fragments of 2–5 nm length

were packed in the column to eliminate the filtration effect and detect adsorption effects only.

A β_{1-40} and A β_{1-42} in the plasma pool were significantly decreased to about half of the initial concentrations by HexDC and PSf-HF fragment columns (solid lines in Figure 4A–D). The A β_{1-40} and A β_{1-42} concentrations at the HexDC columns' outlet (Post) were almost zero during the treatment period, indicating that almost all A β s flowing into the column were removed by the HexDC columns (dotted lines in Figure 4A and C). By contrast, A β concentrations at the outlet (Post) of PSf-HF fragment columns gradually increased after 30 min of treatment, especially the A β_{1-40} (dotted lines in Figure 4B and D). The A β_{1-40} concentrations at the outlet (Post) were similar to those in the plasma pool (Pool) at 60 min (Figure 4B), indicating that PSf-HF fragments removed almost no A β_{1-40} at the end of the treatment.

Figure 5A and B for A β_{1-40} and Figure 5C and D for A β_{1-42} show the removal efficiencies for the mini-columns and reduction rates in the plasma pool. Using HexDC, the

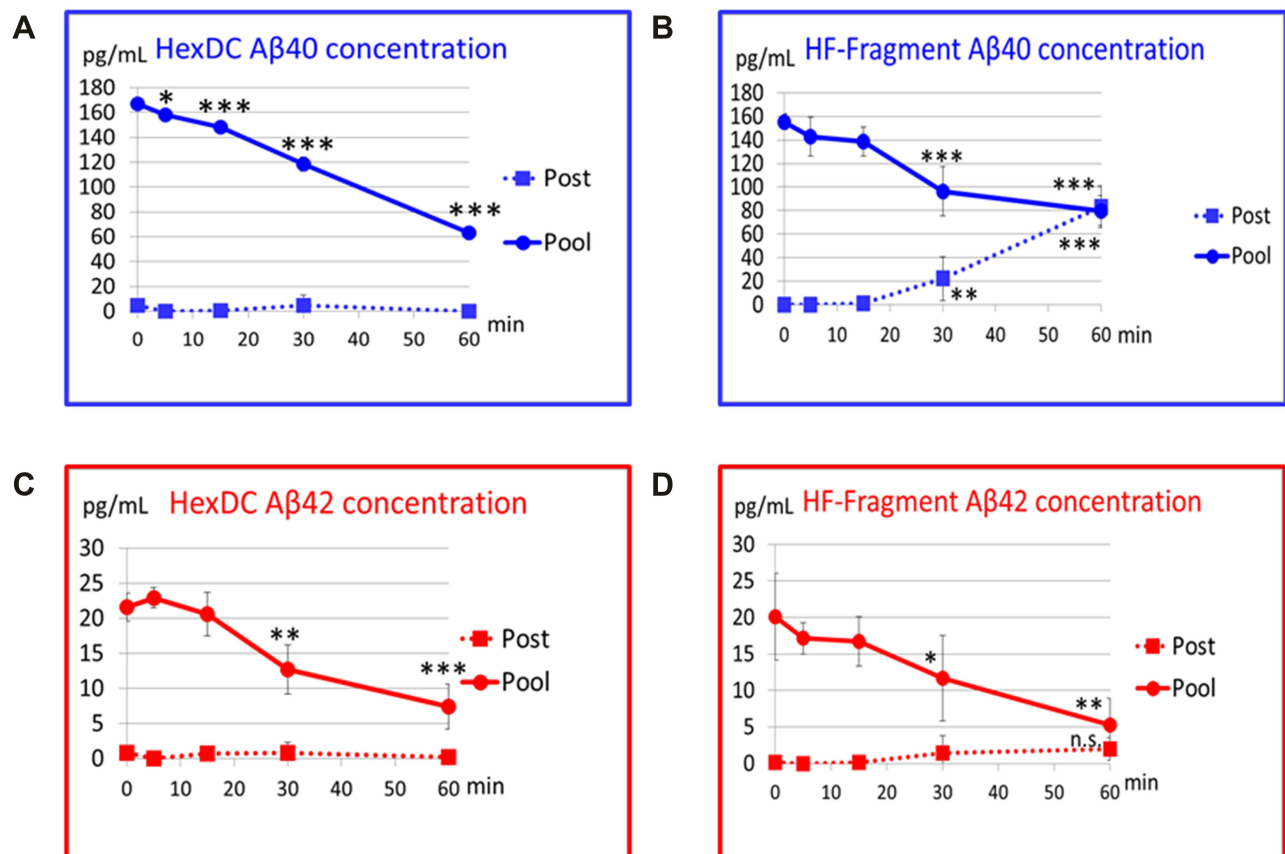


Figure 4 A β concentration changes in the plasma pool and post-filtration for the mini columns in vitro. (A and B) A β_{1-40} (blue) concentration changes with mini columns of HexDC (A) and PSf-HF fragments (B). (C and D) A β_{1-42} (red) concentration changes with HexDC (C) and PSf-HF Fragments (D). Solid lines with circle symbols, in the plasma pool; Dotted lines with square symbols, post-filtration (at the outlet of mini columns). ns, not significant; * $p < 0.05$; ** $p < 0.01$; and *** $p < 0.001$ indicate significant changes compared with 0 min for the plasma pool and with 15 min for the post-filtration measurements).

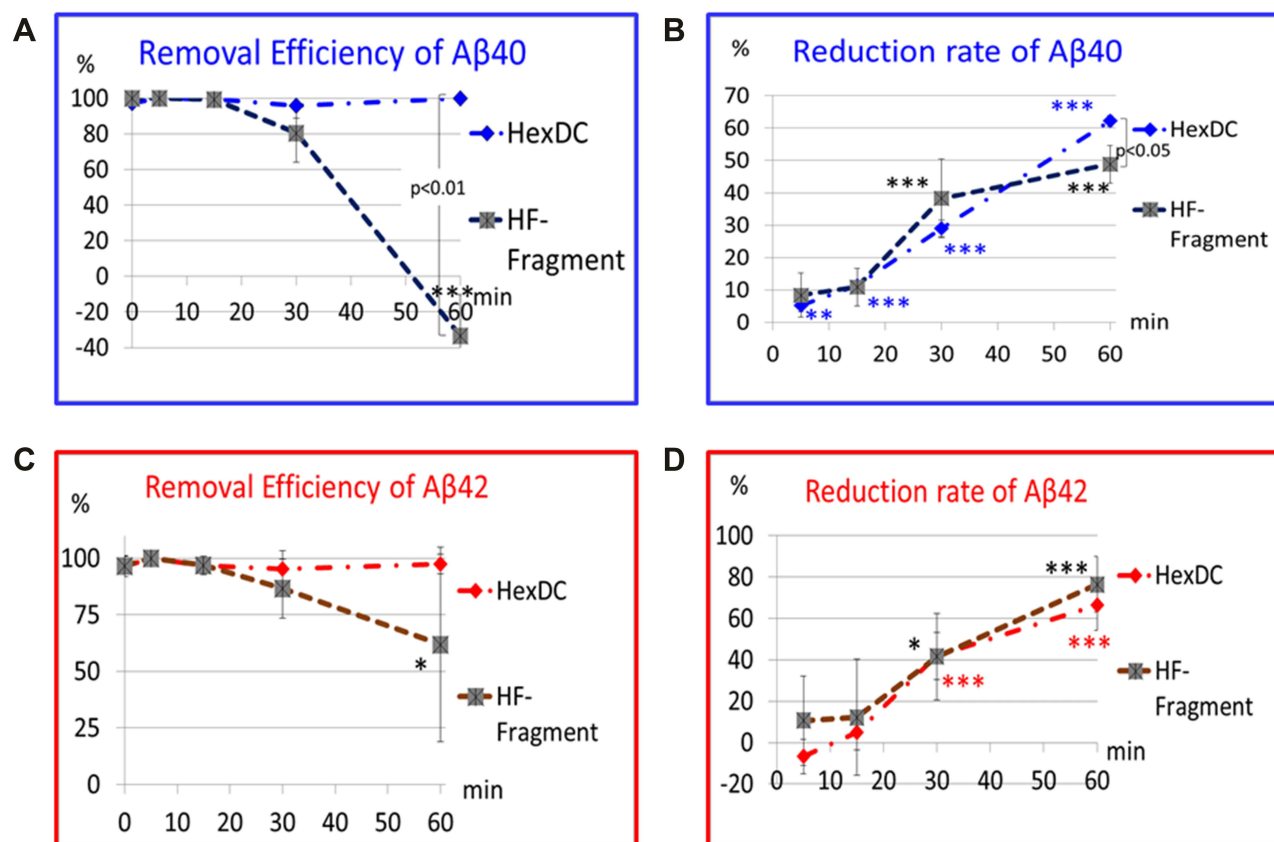


Figure 5 Aβ removal efficiencies and reduction rates for the in vitro systems using HexDC or PSf-HF fragments. (A and B) Aβ₁₋₄₀ (blue) removal efficiency (A) and reduction rate (B). (C and D) Aβ₁₋₄₂ (red) removal efficiency (C) and reduction rate (D). Dashed line with rhombus symbols represent HexDC; dotted line with square cross marks represent PSf-HF fragments. (**p* < 0.05; ***p* < 0.01; and ****p* < 0.001 indicate significant changes compared with 0 min). Removal efficiencies of HexDC were significantly higher than those of PSf-HF fragments for Aβ₁₋₄₀ at 60 min (*p* < 0.01) (A). Reduction rates of HexDC were significantly higher than those of PSf-HF fragments for Aβ₁₋₄₀ at 60 min (*p* < 0.05) (B).

removal efficiencies for both Aβs were approximately 100% during the entire treatment period (dashed line in Figure 5A and C). However, the removal efficiencies and reduction rates decreased after 30 min treatment using the PSf-HF fragments. The Aβ₁₋₄₀ removal efficiency was significantly lower using the PSf-HF fragments than the removal efficiency using HexDC (Figure 5A, *p* < 0.01). The Aβ₁₋₄₀ removal efficiency at 60 min using PSf-HF fragments was below zero, indicating that some adsorbed Aβ₁₋₄₀ was desorbed at the end of the treatment. In contrast to the removal efficiencies, the reduction rates increased for both materials and reached more than 50% after 60 min of treatment (Figure 5B and D). Thus, more than half of the existing Aβs in the plasma pool were removed after 60 min of treatment. The Aβ₁₋₄₀ reduction rates after 60 min of HexDC treatment were significantly higher than the reduction rates when using PSf-HF fragments because of the higher removal efficiency (Figure 5B, *p* < 0.05).

One-Pump Adsorptive Filtration Systems with PSf-HF

Adsorption on the surface of the small inner pores in the walls of hollow fibers was enhanced by filtration to increase the Aβ removal activity of PSf-HF (adsorptive filtration, Figure 3B). The previous adsorptive filtration was conducted using two pumps, a main blood circulation pump and a filtration pump through the hollow fiber walls.¹⁷ The representative clinical setting of the two-pump adsorptive filtration system is similar to that in Figure 3E, but no dialysate. A one-pump system was created to make this adsorptive filtration easy to use. The basic concept of this system was that the pressure changes in the Venturi tubes at the outlet of the dialyzer increase filtration through the hollow fibers' membrane walls. Venturi tubes with various minimum internal diameters were produced using a 3D printer (Figure 6A and B). When melted PLA filaments were piled in the long

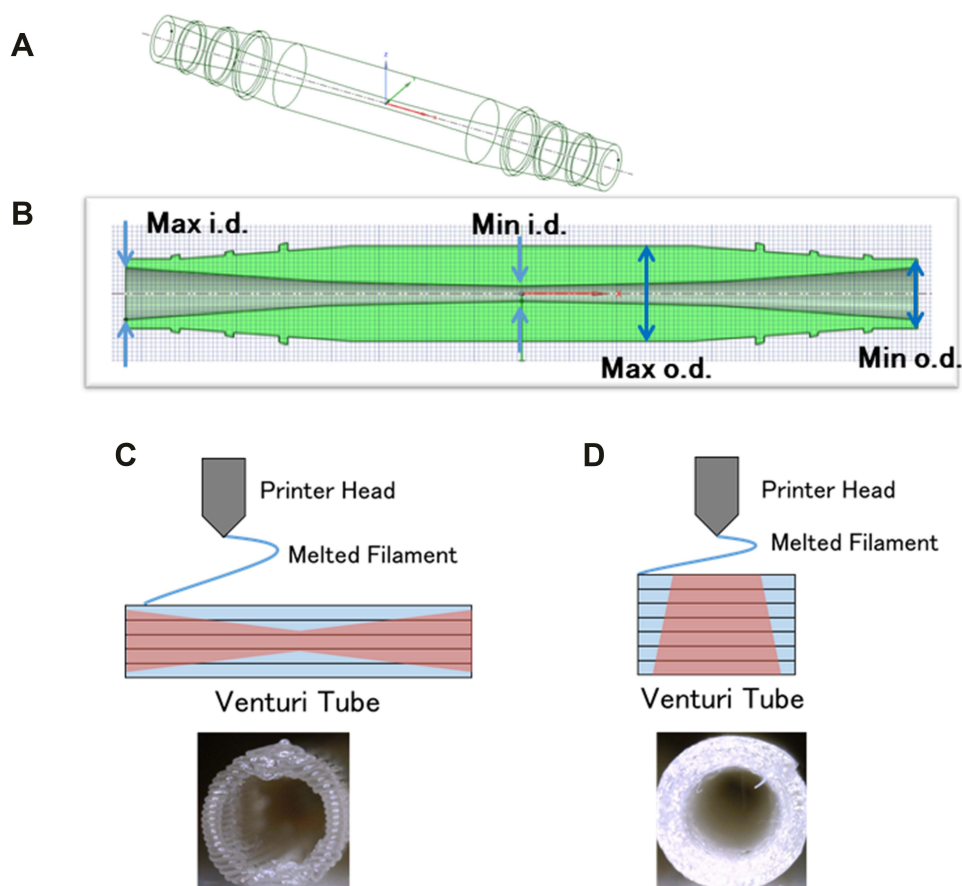


Figure 6 Preparation of Venturi tubes for the one-pump adsorptive filtration system. (A and B) Design and dimensions of the Venturi tubes. Melted PLA filaments were piled in the long axis direction (C) or circumferentially (D). The latter resulted in less leakage.

Abbreviations: o.d., outer diameter; i.d., internal diameter; Min, minimum; Max, maximum.

axis direction (Figure 6C), the cross sections were not circular in parts, resulting in frequent leakage at the circuit tube connections. Melted PLA filaments were then piled circumferentially (Figure 6D), resulting in less leakage.

Circulation analysis using these Venturi tubes was first conducted using water (Figure 7A). As expected, the filtration rate (QF) depended on the tube's narrowest inner diameter and the flow rate (QB) of water. This one-pump adsorptive filtration system was then applied to A β removal from human plasma with PSf hemodialyzers for 60 min (Figure 3C). The pressures before and after the hemodialyzer and at the filtrate outlet were mostly stable throughout the 60 min sessions at 50 mL/min QB (Figure 7B, an example using the Venturi tube "14j-2," whose minimum internal diameter was 1.4 mm). The A β reduction rates in the plasma pool were high, as shown in Figure 7C and D for A β _{1–40} and A β _{1–42}, respectively. Thus, the one-pump system functioned as designed.

A β Removal During Hemodialysis with Concomitant Use of HexDC and PSf Hemodialyzers

To enhance A β influx into the blood, an E-BARS with double A β removal devices seemed effective. We hypothesized that concomitant use of a HexDC column and a PSf hemodialyzer (double efficient A β removal devices^{13,14}) would enhance blood A β removal and increase A β influx from the brain into the blood. Therefore, blood A β changes and A β removal efficiency were investigated in three hemodialysis patients undergoing blood purification with HexDC columns and PSf hemodialyzers (Hex-01–03 in Table 1) as an observational study. These patients underwent blood purification with HexDC columns to remove blood β 2 microglobulin for carpal tunnel syndrome and hemodialysis for renal failure. Figure 3D shows the clinical circuit. During hemodialysis, excess blood water was filtered out at approximately 10 mL/min. This filtration can be considered adsorptive filtration for A β removal.

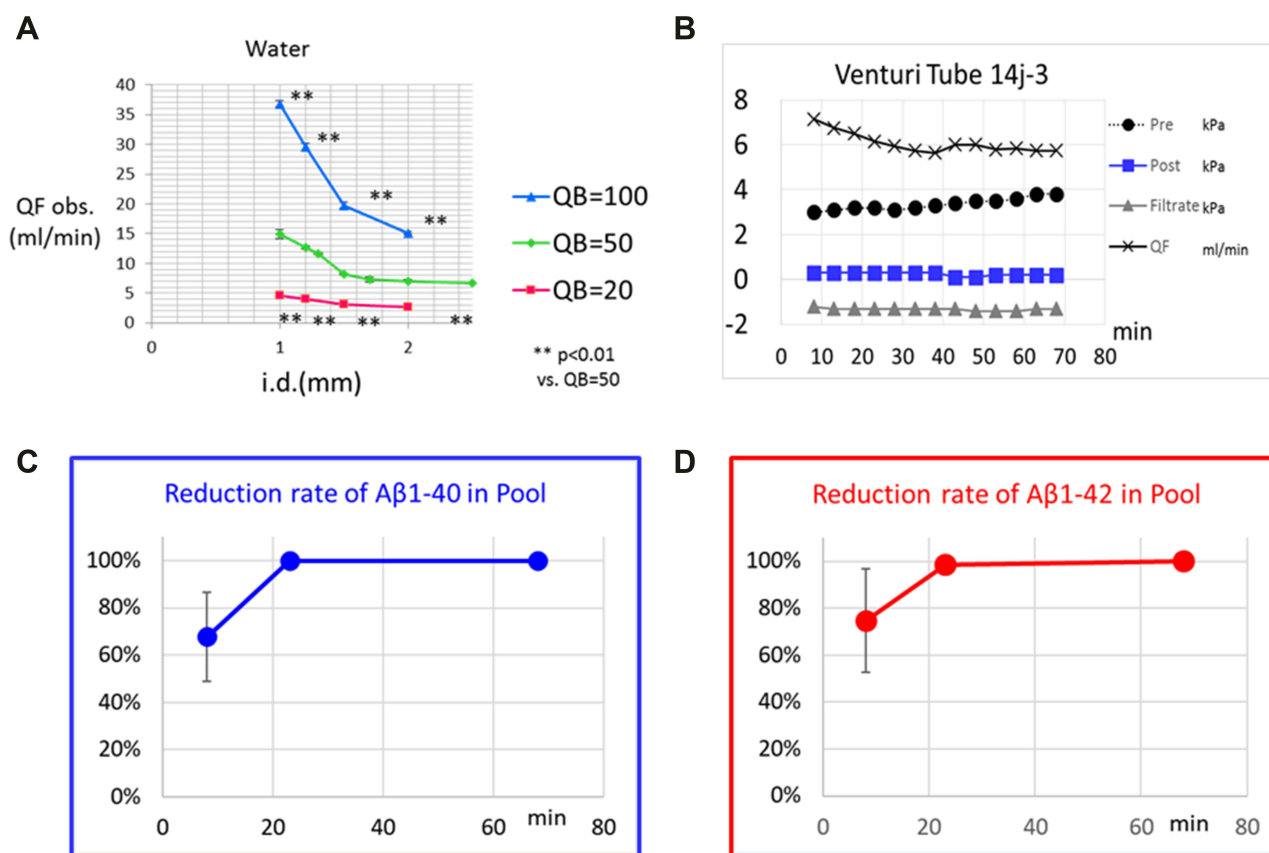


Figure 7 Performance of the one-pump adsorptive filtration system with Venturi tubes. **(A)** Correlation between the narrowest internal diameter (i.d.) and flow rate (QB) measured with water. At 50 mL/min QB, suitable filtration rate (QF) (around 6–10 mL/min) was obtained with an i.d. of 1.4–2.5 mm. **(B)** Representative data for stable QF (mL/min) and pressures (kPa) at Pre (the inlet of hemodialyzers), Post (the outlet of Venturi tubes connected to hemodialyzers), and Filtrate of PSf hemodialyzer during Aβ reduction from human plasma with the 14j-2 Venturi tube of 1.4 mm i.d. **(C and D)** Reduction rates of plasma Aβ₁₋₄₀ **(C)** and Aβ₁₋₄₂ **(D)** in the human plasma pool for three Venturi tubes. **p < 0.01.

Figure 8A shows the plasma concentration changes for Aβ₁₋₄₀ and Aβ₁₋₄₂ in whole-body circulation. Both Aβ₁₋₄₀ and Aβ₁₋₄₂ decreased similarly. Figure 8B and C show the Aβ removal efficiencies of the HexDC column and PSf hemodialyzer, respectively. Aβ₁₋₄₀ and Aβ₁₋₄₂ removal efficiencies for both devices were maintained during the 4 h treatment. The removal efficiencies were lower in this clinical setting than the removal efficiencies in the in vitro experiments (Figures 3A, 5A and C). The plasma flow rates were higher in human treatment (200 mL blood/min, approximately 130 mL plasma/min) than the flow rates in in vitro experiments (equivalent to 50 mL plasma/min in humans). Lower blood flow rates resulted in higher Aβ removal efficiencies, as previously reported.^{14,17}

Aβ Removal in Hemodialysis Patients Using PSf Hemodialyzers Alone for 8 h

Another method of enhancing Aβ influx into the blood, an E-BARS with long-time treatment, was also believed to be

effective. Blood Aβ changes in hemodialysis patients using hemodialyzers alone for 4 h were already investigated in the previous study.^{15,16,18,19} We then hypothesized that longer hemodialysis times, such as 8 h (doubled compared with ordinal 4 h treatment), would enhance Aβ influx into the blood. Three patients suffering from end-stage renal failure underwent overnight hemodialysis for 8 h using a PSf hemodialyzer alone (ON-1–3 in Table 1). Overnight hemodialysis during sleep for 8 h was provided because these patients worked during the day. This was also an observational study. Figure 3E shows the clinical circuit. The blood was partially filtered at a 6–9 mL/min rate during hemodialysis to remove excess water, resulting in enhanced Aβ adsorption on the surface of small pores in the membrane wall (Figure 3B, adsorptive filtration).

Figure 9A shows the plasma concentration changes for Aβ₁₋₄₀ and Aβ₁₋₄₂ in whole-body circulation. Both Aβ₁₋₄₀ and Aβ₁₋₄₂ similarly decreased. The Aβ removal efficiencies using the PSf hemodialyzer were maintained

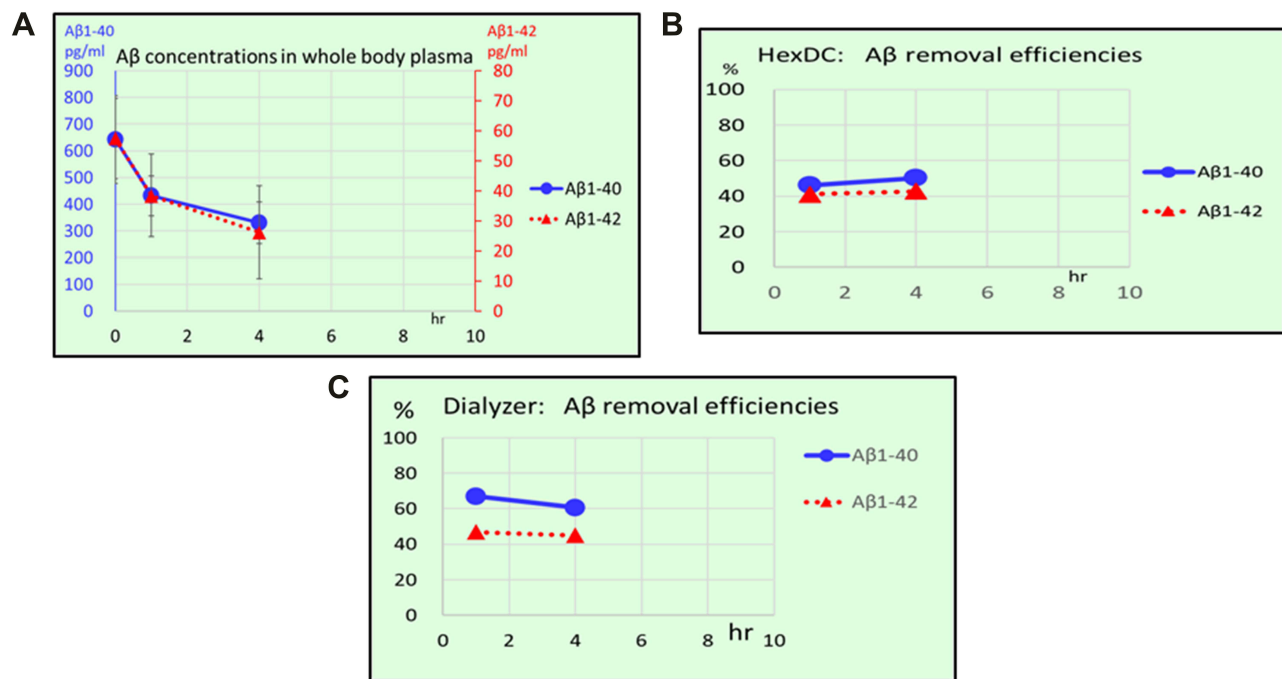


Figure 8 Aβ removal during hemodialysis with concomitant use of HexDC and PSf hemodialyzers for 4 h. (A) Changes in plasma Aβ₁₋₄₀ (left blue vertical axis) and Aβ₁₋₄₂ (right red vertical axis) concentrations in whole-body circulation. (B and C) Aβ removal efficiencies of HexDC (B) or PSf hemodialyzers (C). (Aβ₁₋₄₀, blue solid line; Aβ₁₋₄₂, red dotted line).

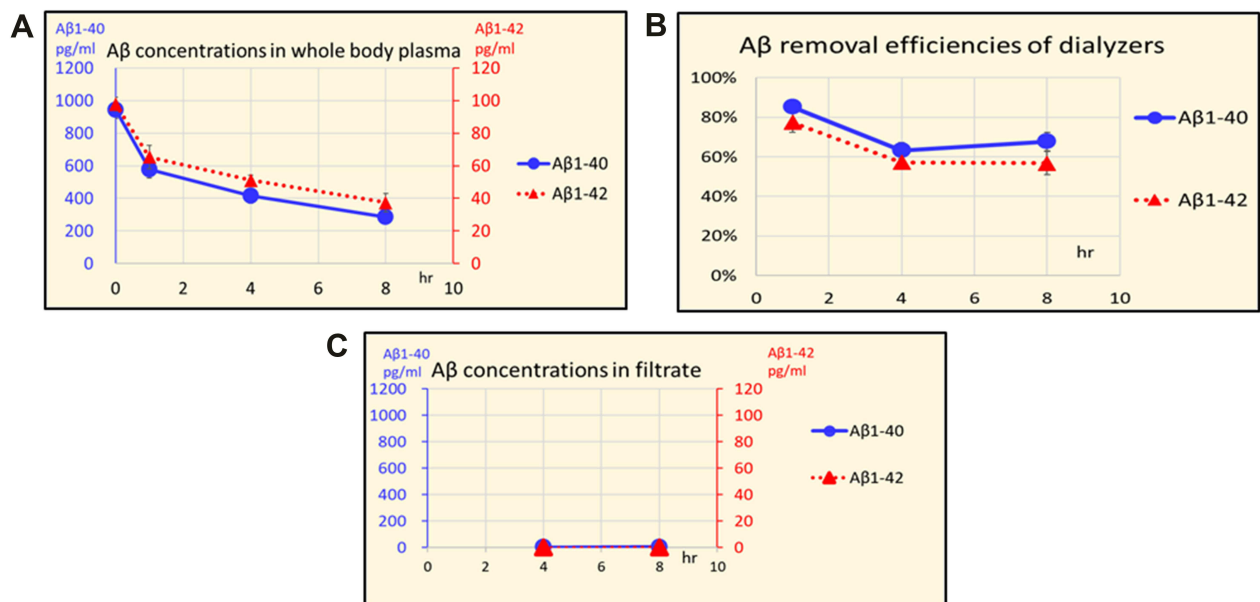


Figure 9 Aβ removal during hemodialysis with PSf hemodialyzer alone for 8 h. (A) Changes in plasma Aβ₁₋₄₀ (left blue vertical axis) and Aβ₁₋₄₂ (right red vertical axis) concentrations in whole-body circulation. (B) Aβ removal efficiencies of the PSf hemodialyzer. (C) Aβs concentrations in the filtrate from the PSf hemodialyzer. (Aβ₁₋₄₀, left blue vertical axis; Aβ₁₋₄₂, right red vertical axis; Aβ₁₋₄₀, blue solid line; Aβ₁₋₄₂, red dotted line).

at over 60% during the 8 h treatment (Figure 9B). Aβ concentrations in the filtrate of the dialyzers were also measured. The flow rate of the mixture of filtrate and waste dialysate was approximately 400 mL/min. The

total volume was up to 192 L, and part of the fluid was collected at a rate of 1000 mL/h for the periods of 0–4 h and 4–8 h. Figure 9C shows the Aβ concentrations in the filtrate and waste dialysate, indicating that

almost all A β s were adsorbed (trapped) on the inner surface of the PSf-HFs.

Comparison of A β Influx into the Blood While Using Different A β Removal Systems

Removing blood A β evokes a large A β influx into the blood,^{15,16,18,19,22} probably from the brain.^{20,22} A β influx into the blood was estimated according to the equation shown in Figure 10 for studies of renal failure patients using the concomitant HexDC and PSf hemodialyzer for 4

h and using the hemodialyzer alone for 8 h (Figure 3D and E, respectively).

Figure 11 shows A β_{1-40} (Figure 11A) and A β_{1-42} (Figure 11B) amounts removed by each device, and A β s decreased in the plasma compared with the starting amounts. The A β amounts are shown separately for the 0–1, 1–4, and 0–4 h periods for both systems and 4–8 and 0–8 h for the dialyzer alone. A β_{1-40} removed by HexDC increased time-dependently (blue diagonal cross lattice in Figure 11A). A β_{1-40} removed by HexDC during the 1–4 h period (3 h) was nearly three times

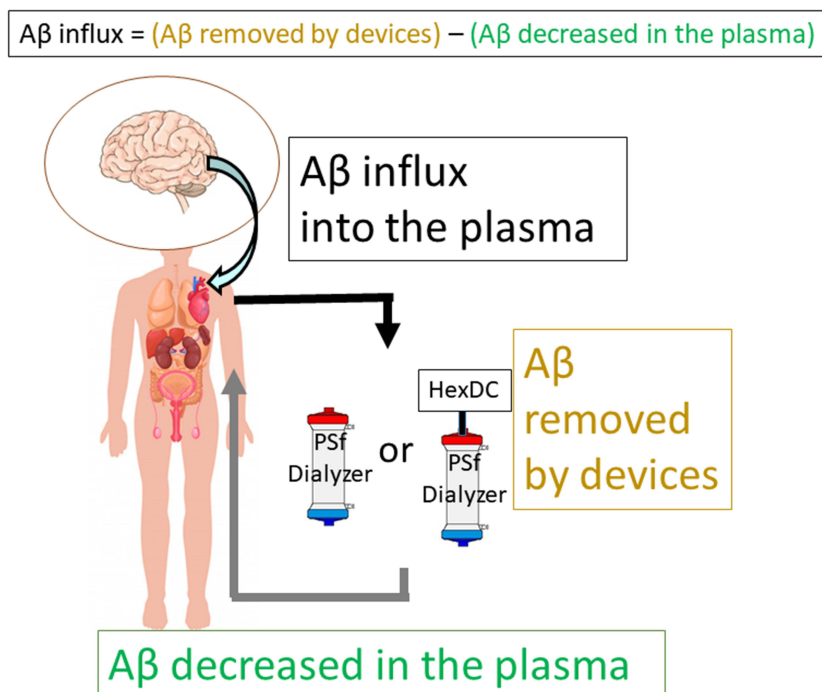


Figure 10 A β influx into the blood was calculated by subtracting the A β amounts decreased in the plasma from the A β amounts removed by the devices.

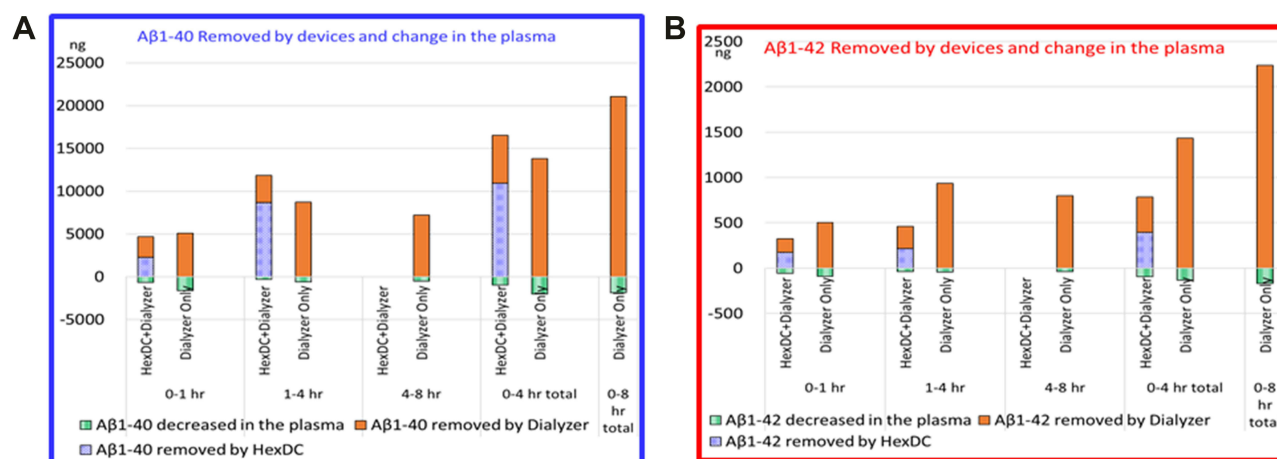


Figure 11 A β amounts removed by HexDC (blue diagonal cross lattice), by PSf hemodialyzer (orange solid bar), and A β amounts decreased in the plasma (green vertical stripe) for each period. (A) A β_{1-40} . (B) A β_{1-42} .

larger than the removal during the 0–1 h period. However, the $A\beta_{1-42}$ removed by HexDC and both $A\beta_{1-40}$ and $A\beta_{1-42}$ removed by PSf dialyzers showed no clear trend over time and were suppressed in later treatment periods.

Figure 12 shows the $A\beta$ influx evoked by the $A\beta$ removal systems, calculated based on the data shown in Figure 11. $A\beta_{1-40}$ influxes (blue diagonal striped bars in Figure 12) during concomitant use of the HexDC and PSf dialyzer were significantly ($p < 0.05$) higher than the influxes during use of the PSf dialyzer alone in the 1–4 h period. By contrast, $A\beta_{1-42}$ influxes (red solid bars in Figure 12) during concomitant use of HexDC and the PSf dialyzer were significantly ($p < 0.05$) lower than influxes during the use of the PSf dialyzer alone in the

0–1, 1–4, and 0–4 h periods. Consequently, the sums of $A\beta_{1-40}$ and $A\beta_{1-42}$ influxes (black horizontal striped bars in Figure 12) were not significantly different between the two systems.

The average $A\beta_{1-40}$ influx for both systems in the 1–4 h (3 h) period was nearly three times higher than the influx in the 0–1 h (1 h) period (11,549 ng vs 4042 ng for the concomitant use of HexDC and the PSf dialyzer and 8132 ng vs 3478 ng for PSf dialyzer alone). On the other hand, $A\beta_{1-42}$ influxes in both systems during the 1–4 h period were larger than those in the 0–1 h period, but not proportional to the treatment time (425 ng vs 256 ng for the concomitant use of HexDC and PSf dialyzer, and 892 ng vs 410 ng for PSf dialyzer-alone system).

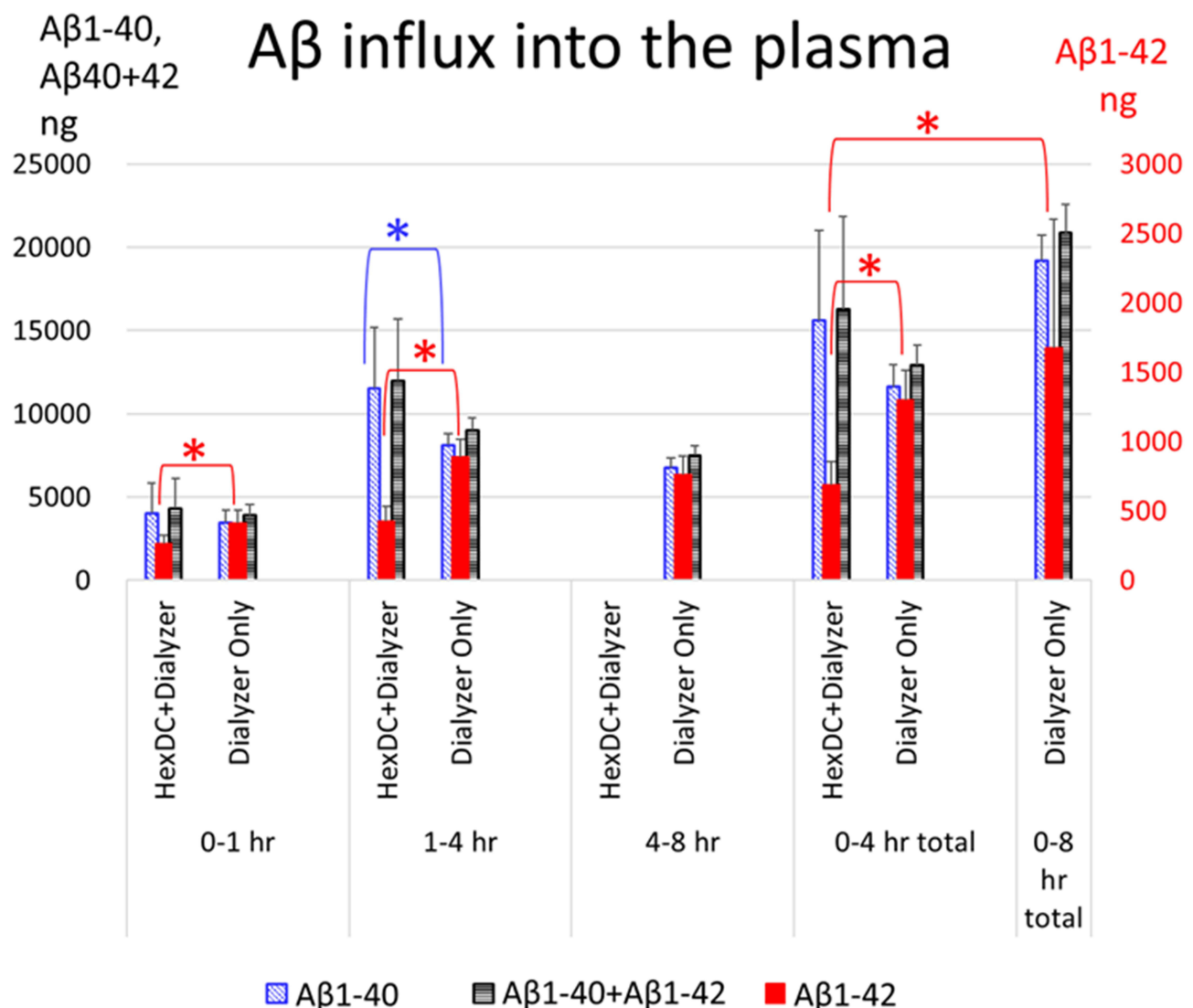


Figure 12 $A\beta$ influx into the plasma evoked by concomitant use of HexDC and the PSf hemodialyzer (HexDC+Dialyzer) and by the PSf hemodialyzer alone (Dialyzer Only). $A\beta_{1-40}$, blue diagonal line (left black vertical axis); $A\beta_{1-42}$, red solid bar (right red vertical axis); summation of $A\beta_{1-40}$ and $A\beta_{1-42}$, black lateral stripe (left black vertical axis). (* $p < 0.05$).

A β influxes for the PSf dialyzer alone during the 0–8 h period were not doubled compared with those in the 0–4 h period, as shown on the right of Figure 12. Thus, the influxes of both A β _{1–40} and A β _{1–42} may decrease over time during the treatment.

Relative A β Influx Normalized to the A β Amounts Existing in the Plasma at the Beginning of Blood Purification

The absolute amounts of A β s removed, those decreased in systemic plasma, and A β influxes are dependent on the beginning plasma A β concentrations of each patient. Therefore, relative values for these A β amounts were calculated relative to the plasma A β amounts at the beginning of the treatment (Figure 13). Interestingly, standard deviations for each relative A β value were far smaller than

expected. Thus, the A β amounts similarly changed for each patient during blood treatments.

Relative A β amounts removed by HexDC and PSf dialyzers (solid lines and dotted lines in Figure 13, respectively) increased time-dependently. This suggests that HexDC and PSf dialyzers had adequate A β adsorption capacity during the 4 and 8 h treatments. However, the changes were smaller in the latter half of the treatment than in the first half. The relative decreases in plasma A β (dashed lines under 0% in Figure 13) seemed to plateau after 1 h of treatment. This indicates that blood A β _{1–40} and A β _{1–42} reached homeostasis, even though large amounts of A β were removed from the blood because of A β influx.

Figure 14 shows the comparison of relative A β influx for the two A β removal systems. As shown in Figure 14A, relative A β _{1–40} influx after 4 h using the combined HexDC

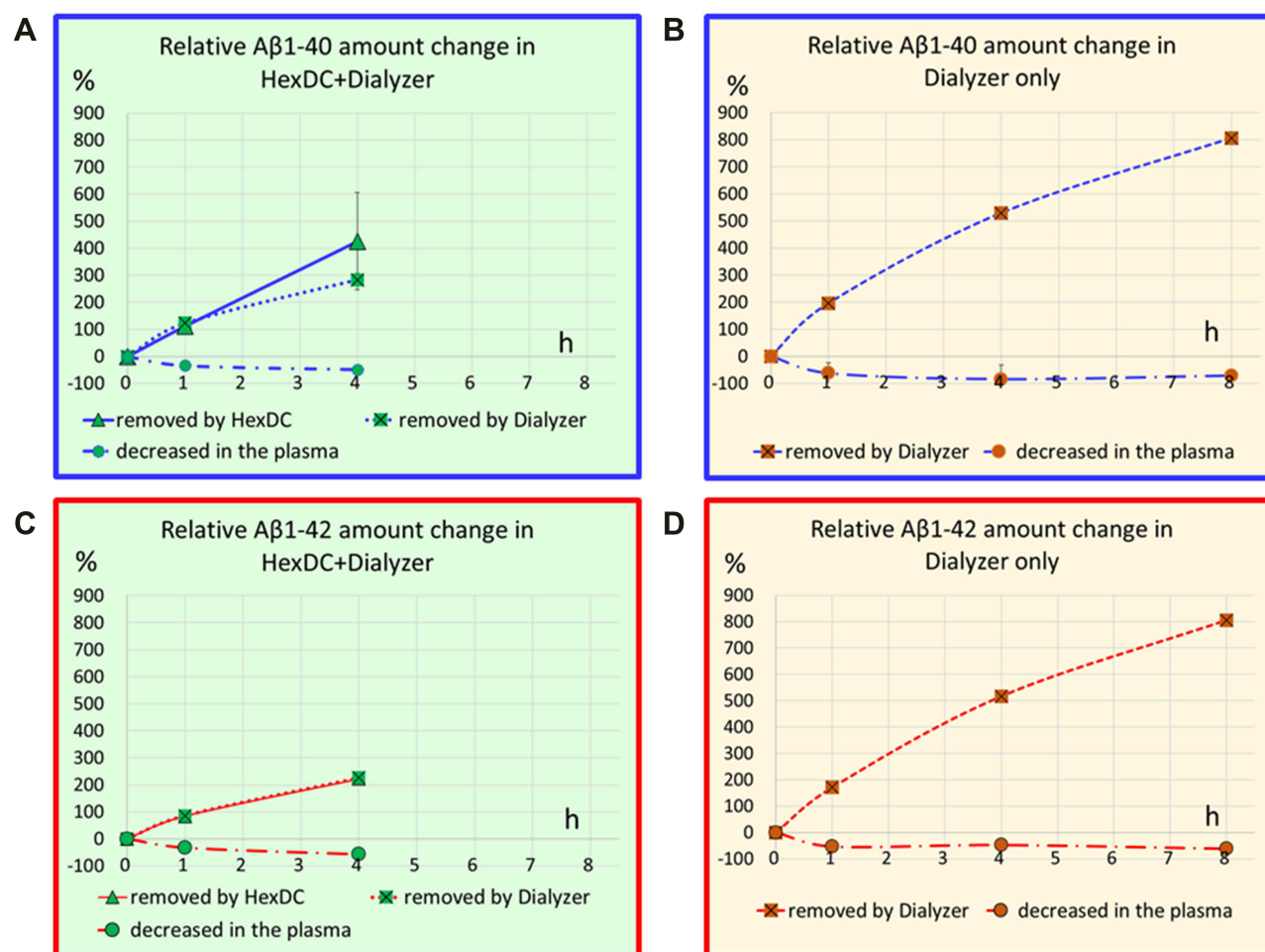


Figure 13 Relative A β amounts normalized to the A β amounts existing in the plasma at the beginning of blood purification. (A and B) A β _{1–40} (blue lines), (C and D) A β _{1–42} (red lines). Relative A β amount changes during treatment with concomitant use of HexDC and the PSf hemodialyzer (HexDC+Dialyzer) (A and C, pale green background). Relative A β amount changes during treatment with PSf hemodialyzer alone (Dialyzer only) (B and D, light orange background). Solid lines with triangle symbols, relative A β amounts removed by HexDC; dotted lines with cross square marks, relative A β amounts removed by PSf hemodialyzer; dashed lines with circle symbols, relative A β amounts decreased in the plasma.

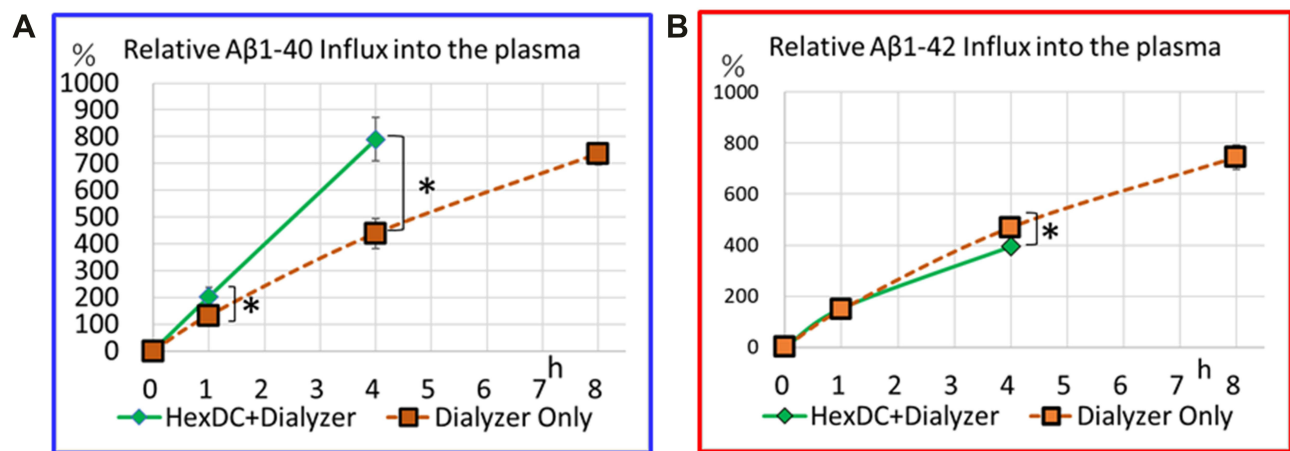


Figure 14 Relative A β influxes normalized to the A β amounts existing in the plasma at the beginning of blood purification. **(A)** Relative A β_{1-40} influx into the plasma, **(B)** relative A β_{1-42} influx into the plasma. Solid green lines with rhombus symbols, relative A β influxes evoked by concomitant use of HexDC and the PSf hemodialyzer (HexDC +Dialyzer); dotted lines with square symbols, relative A β influxes evoked by the PSf hemodialyzer alone (Dialyzer Only). *, $p < 0.05$.

and PSf dialyzer was significantly higher than influx using the PSf dialyzer alone ($p < 0.05$). The total relative A β_{1-40} influx for the PSf dialyzer alone at 8 h was similar to that of HexDC and PSf dialyzer at 4 h. In contrast to A β_{1-40} , relative A β_{1-42} influx after 4 h using the HexDC and PSf dialyzer was slightly, but significantly, lower than that of the PSf dialyzer alone (Figure 14B). A total relative A β_{1-42} influx during 8 h of treatment using the PSf dialyzer alone was almost double the A β_{1-42} influx of the combined HexDC and PSf dialyzer during 4 h.

Discussion

Regarding A β influx into the blood, we have reported that ordinal hemodialysis with hemodialyzers alone for 4 h evoked an influx of 7219 ng A β_{1-40} and 664 ng A β_{1-42} based on analysis of 30 hemodialysis patients.¹⁹ In this study, as shown in Figure 12, A β_{1-40} , A β_{1-42} , A β_{1-40} + A β_{1-42} influx evoked by the concomitant use of HexDC and the PSf hemodialyzer for 0–4 h were $15,591 \pm 5407$ ng, 690 ± 166 ng, and $16,281 \pm 5565$ ng, respectively. Those by PSf hemodialyzer alone were $11,610 \pm 1335$ ng, 1302 ± 211 ng, and $12,912 \pm 1224$ ng for 0–4 h, and $19,198 \pm 1556$ ng, 1673 ± 928 ng, and $20,871 \pm 1699$ ng for 0–8 h, respectively. Thus, compared with E-BARS with hemodialyzers alone for 4 h, E-BARS with double devices of A β removal (HexDC and PSf hemodialyzer) for 4 h evoked nearly doubled A β s (A β_{1-40} + A β_{1-42}) influx: 7219 ng vs 16,281 ng, and E-BARS of longer treatment with PSf hemodialyzer alone for 8 h also evoked more than doubled or nearly tripled A β s (A β_{1-40} + A β_{1-42}) influx: 7219 ng vs 20,871 ng. A β influx in this study was two to three times

larger than the estimated total A β s (7760 ng) in the normal human brain²⁸ and far larger than A β s removed by peritoneal dialysis: 131.33 ng, which was approximately 2% of the total A β in the normal brain.²⁵ Therefore, efficient A β removal systems, such as a combination of HexDC and PSf hemodialyzer or longer treatment time, may be more effective in removing brain A β s than ordinal hemodialysis (hemodialyzers alone) for 4 h.

One aim of our blood A β removal systems was to enhance A β influx (migration) from the brain into the blood, especially A β_{1-42} , which readily forms neurotoxic A β_{1-42} oligomers. Both A β removal systems in this study showed very similar time dependency (Figure 14B) for relative A β_{1-42} influxes. However, PSf dialyzer alone evoked slightly higher ($p < 0.05$) relative A β_{1-42} influx than the combined system of HexDC and PSf dialyzer. Furthermore, the 8 h treatment with the PSf hemodialyzer alone evoked significantly larger, almost doubled, A β_{1-42} influx than the concomitant use of HexDC and the PSf hemodialyzer for 4 h (Figure 14B). Focused on A β_{1-42} removal, PSf hemodialyzer alone may have enough ability to evoke A β_{1-42} influx into the blood.

In contrast to the A β_{1-42} influx, concomitant use of HexDC and the PSf hemodialyzer evoked a larger A β_{1-40} influx (significantly for only 1–4 h) than the PSf hemodialyzer alone (Figures 12 and 14A).

Overall, A β removal systems with concomitant use of HexDC and PSf hemodialyzer evoked similar or less A β_{1-42} influxes and larger A β_{1-40} influx compared with A β influx using the PSf hemodialyzer alone. Although the reason for this difference is unclear at present, it

provides information to establish appropriate systems of E-BARS.

Regarding discrepancy between this and previous studies, A β influx with PSf hemodialyzer in 0–4 h period at night in this study was larger than those we reported previously for ordinal hemodialysis patients for 4 h during the day.¹⁹ 12,912 ng vs 16,281 ng. One possible reason is the variations in hemodialyzer materials used. Hemodialyzer material in this study was only PSf, one of the efficient A β adsorbents. By contrast, some hemodialyzers used in the previous study included less efficient A β removal devices, such as cellulose triacetate. Another reason may be that blood purification was conducted overnight or daytime. In this study, the blood purification with the PSf hemodialyzer alone for 8 h was provided overnight, including when patients were sleeping, whereas 4 h blood purification was provided during the day in the previous study.¹⁹ It was reported that A β concentrations in CSF are higher in the evening (about 18:00–22:00) than during the awake daytime hours and decrease while a patient is sleeping (about 22:00–7:00).^{29,30} Therefore, the differences in A β s concentrations in CSF depending on the time of day might affect this study's results. Thus, blood A β removal during sleeping might be an effective method for brain A β removal.

The amounts of A β _{1–40} and A β _{1–42} removed by the PSf hemodialyzers in concomitant use with HexDC were smaller than the A β amounts removed by PSf hemodialyzers alone in each period of 0–1, 1–4, and 0–4 h, as shown in Figure 11A and B (the solid orange bars of “HexDC + Dialyzer” and “Dialyzer only”). One explanation is that the A β concentrations at the PSf hemodialyzer inlet (Figure 3D) were lower than the A β concentrations for the PSf hemodialyzer directly connected with the blood vessels of patients (Figure 3E) because approximately 50–60% of the A β s in the blood were already removed by the HexDC column (Figure 3D) before PSf hemodialyzer in the system of concomitant use of “tandemly” connected HexDC and PSf hemodialyzer. To use the total A β removal activity capacity of PSf hemodialyzer, blood should be introduced “in parallel” to the HexDC and PSf hemodialyzer systems. However, such parallel systems require doubled blood flow rates, which are unsuitable for Japanese hemodialysis patients because of blood outflow limitations.

Figure 15 summarizes the factors that may affect blood A β removal. The key factors are not only A β removal efficacy of the device but also the treatment period, blood flow rates into the devices, A β concentrations in the blood, A β concentrations in CSF that change depending on the time of day and A β production/degradation

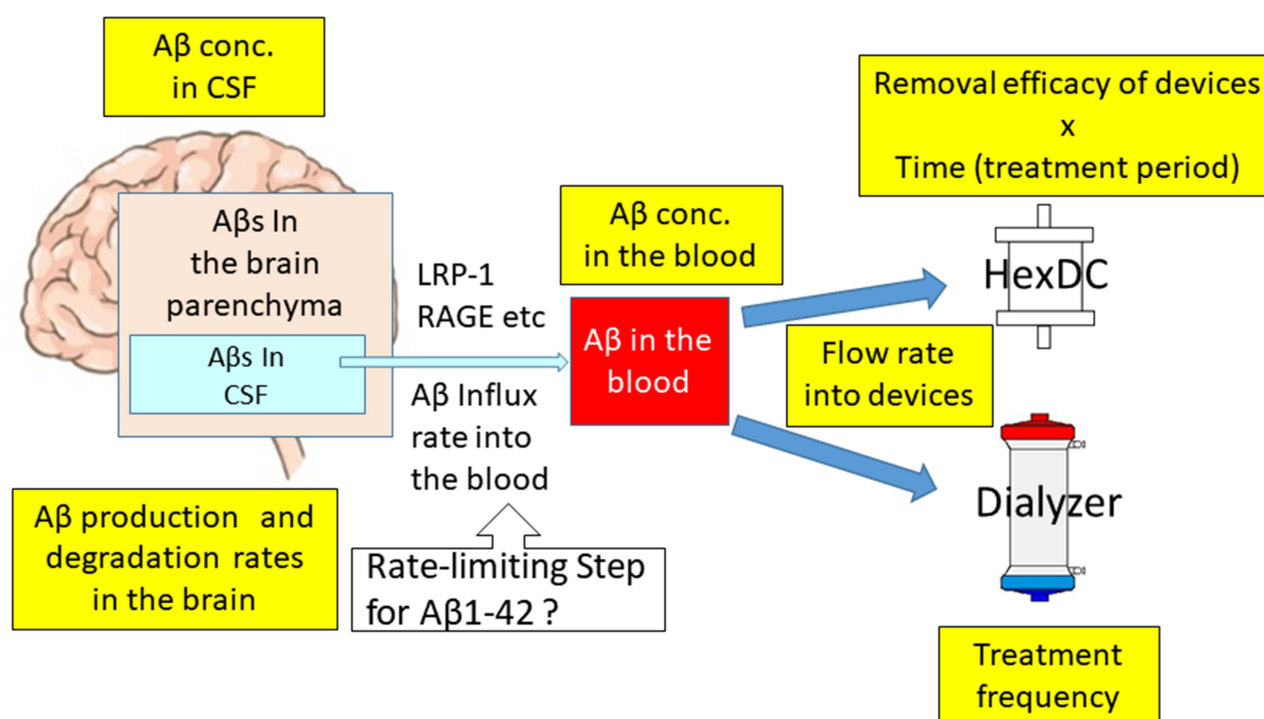


Figure 15 A β transportation pathway from the brain to A β removal devices. Key factors affecting A β influxes and removal are also shown.

rates in the brain, the activity of A β transporters (for example, LRP-1 and RAGE), and frequency of treatment (for example, three times a week, or once a month?) of A β removal. When comparing dual A β removal devices with a single A β removal device, the relative A β_{1-42} influx was similar (Figure 14B). Therefore, the rate of A β influx to the blood from the brain, especially A β_{1-42} , might be the rate-limiting step for brain A β_{1-42} removal, even if more effective devices are used for A β removal.

Conclusions

As blood A β removal devices, PSf hemodialyzer in adsorptive filtration methods and HexDC showed comparable adsorption capacity for plasma A β s. Doubled A β removal devices consisting of tandemly connected HexDC and PSf hemodialyzer for 4 h evoked a larger A β_{1-40} influx into the blood than PSf hemodialyzer alone for the same period. However, both systems evoked similar A β_{1-42} influx for 4 h. These systems evoked A β s (A β_{1-40} + A β_{1-42}) influx nearly two times larger than A β s existing in the normal brain. Furthermore, longer A β removal evoked more influxes of A β_{1-40} and A β_{1-42} . These findings of blood A β removal systems may lead to an optimal clinical setting for therapy and prevention of AD.

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Disclosure

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The other authors declare that they have no conflict of interest.

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