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Design of microfluidic channels to prevent negative filtration in implantable hemofiltration devices

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***Abstract*— In order to improve the quality of life of dialysis patients, our group have been developing an implantable hemofiltration device (IHFD) composed of multiple layers of dialysis membranes and microfluidic channels. To improve the hemodialysis performance of IHFD, preventing the negative filtration, which is caused by the oncotic pressure of blood, is mandatory. In this study, we fabricated IHFDs with five different microchannel designs and experimentally investigated the performance of each device in *in vitro* experiment. In addition, the successful IHFD was further evaluated by *ex vivo* experiments with a beagle dog. The experiments verified the effectiveness of the microchannel design, which will be used for the IHFD for *in vivo* experiments with pigs in the future.**

I. Introduction

Kidneys play important roles in removing waste and toxic substances from the blood and regulating the concentration of electrolytes such as sodium and potassium. However, when these functions decline, chronic kidney disease occurs and many symptoms such as swelling, fatigue, proteinuria and high blood pressure appear. There are three popular treatment methods for kidney disease, hemodialysis, peritoneal dialysis and kidney transplantation, but more than 90% of patients choose hemodialysis treatment in Japan. However, hemodialysis treatment requires four hours of treatment once every two days, and patients are forced to restrict drinking water because they cannot regulate the amount of water in their bodies.

In order to solve these problems, we have developed an implantable hemofiltration device (IHFD), as shown in Figure 1[1]. The design will be detailed in the following section. IHFD allows patients to constantly maintain their water balance by discharging the water filtered by the device as urine. The implantation of IHFD has the advantage of enabling patients to urinate on their own, eliminating the restriction of drinking water, and reducing the frequency of hospital visits for hemodialysis. IHFD uses blood pressure for blood filtration, thus there is no need of pumps or dialysis fluid. This makes it possible to minimize the size of the device.

Through the development of IHFD, we have encountered a problem that the filtrate was not sufficiently obtained when the blood pressure was not high. This phenomenon is largely related to the oncotic pressure, which originates from the osmotic pressure caused by the differences in protein concentration between the blood and the filtrate. The filter in IHFD is designed to prevent the proteins in the blood, such as albumin and globulin, to diffuse into the filtrate. The oncotic pressure works to bring the filtrate back to the blood. When the pressure difference between the blood and the filtrate is larger than the oncotic pressure, positive filtration takes place, i.e., filtrate is produced, as shown in Figure 2[2]. However, when the pressure difference is smaller than the oncotic pressure, filtrates are reabsorbed to the blood, i.e., negative filtration occurs. Since the blood pressure decreases along with the microfluidic channels, positive filtration can be taken over by the negative filtration in the microfluidic channels, which is considered to be the reason why the amount of the obtained filtrate was not sufficient.

In the case of IHFD, the blood pressure at the inlet of the device depends on the connected arterial pressure and that at the outlet depends on the venous pressure. Therefore, there is a chance that negative filtration starts to occur at a certain point in the microfluidic channels.

In this study, we propose a mechanism to prevent negative filtration, i.e., we design the microfluidic channels that have the limited areas for hemofiltration. *In vitro* and *ex vivo* experiments are conducted to verify the concept and to deduce the design to maximize the hemofiltration efficiency.

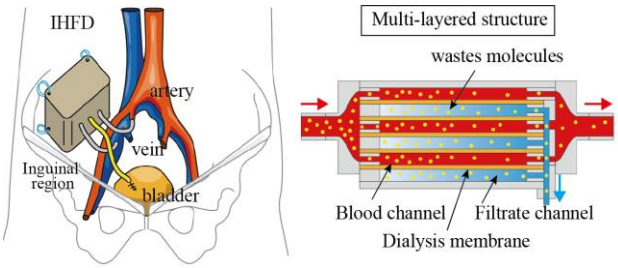

Figure 1 Concept of IHFD system and hemofiltration phenomena

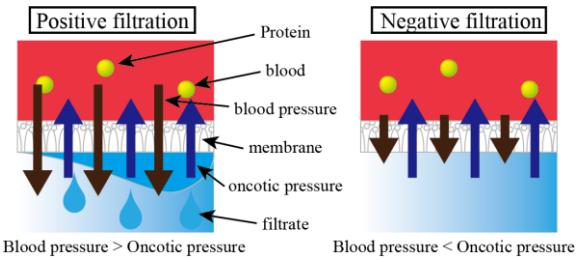

Figure 2 Positive filtration and Negative filtration

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II. Design and Fabrication Process

A. Design

The IHFD utilizes the principle of hemofiltration, in which small molecular-sized waste products are removed from the blood through the dialysis membrane. The device is a multi-layered microfilter composed of blood microchannels 400 µm in height and filtrate microchannels 400 µm in height which are separated with nanoporous membranes. All the materials are selected based on ISO 10993. Blood flows into the device from the artery and returns to the vein by the pressure difference between artery and vein, while the blood is filtered. The filtrate is guided to the bladder and is discharged as urine. To prevent the negative filtration, we highlighted the ratio of the filtrate channel to the blood channel.

The pressure difference between the blood and the filtrate decreases with the channels due to the pressure drop, which may cause negative filtration and the low hemofiltration efficiency. Therefore, our idea is to limit the channel areas for filtration such that positive filtration takes place but negative filtration does not occur (Figure 3). We designed and fabricated five devices with the ratios between the areas for filtration and non-filtration, as shown in Table 1 and Figure 4.

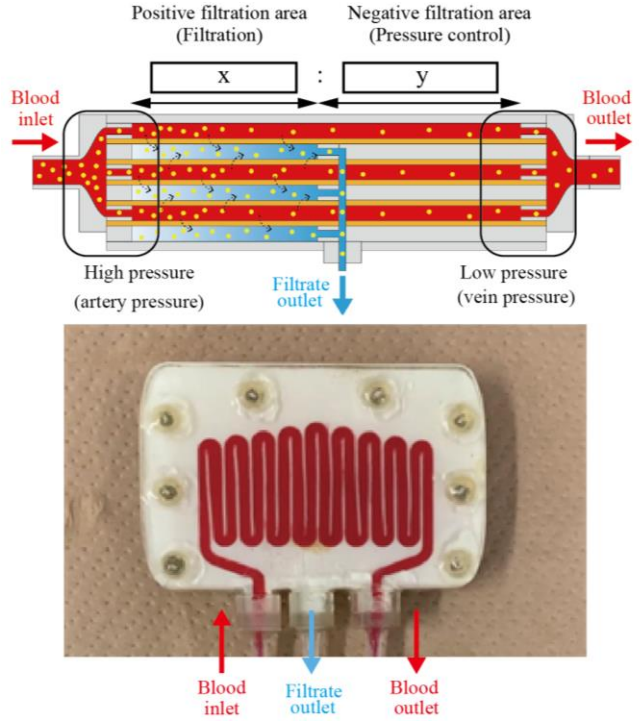

Figure 3 Multi-layered structure Device photo

TABLE I. THE DESIGN OF MICROCHANNELS

	The ratio of microchannel		Effective membrane area
	Filtrate : Non-filtrate = X : Y		*A* [mm2]
C1	100	0	804.5
C2	89.77	10.23	722.3
C3	79.05	20.95	636.0
C4	67.83	32.17	545.7
C5	56.11	43.89	451.4

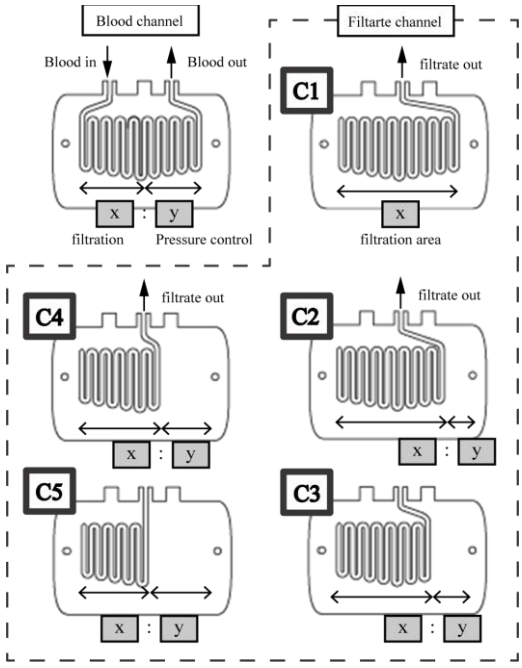

Figure 4 Design of microchannel (channel type C1/C2/C3/C4/C5)

B. Fabrication

IHFD consists of layers of blood microchannels, filtrate microchannels and filtration membranes. The membranes are made from polyether sulfone and formed by depositing solution mixed of polyether sulfone, polyethylene glycol, and dimethylacetamide. Both sides are lapped by PMMA plates as shown in Figure 3. The inlet and outlet for blood and the filtrate outlet are attached with connectors.

C. Filtration efficiency

We used filtration coefficient (L_p [ml/mmHg/hour/m2]) to evaluate the devices. It is a medical index to express the filtration performance of hemofiltration device. The filtration coefficient is determined by dividing the filtrate volume per unit time (V [mL]) by time (T [hour]), transmembrane pressure (TMP [mmHg]), and effective membrane area (A [m2]), and is calculated as in (1) [1].

$$L_p = \frac{V}{T \times A \times TMP} \quad (1)$$

TMP is determined by subtracting the oncotic pressure (P_o[mmHg]) from the average blood pressure at the inlet and outlet of the device. The oncotic pressure is determined by the amount of total protein in the blood (C_{tp} [g/dL]), can be calculated as in (2) for humans, as in (3) for dogs [3] [4]

$$P_o = 0.009\,Ctp^3 + 0.16\,Ctp^2 + 2.1\,Ctp \quad (2)$$

$$P_o = 0.005\,Ctp^3 + 0.22\,Ctp^2 + 1.4\,Ctp \quad (3)$$

Concentration of total protein is measured by Spotchem (EZ SP-4430, Arkray, Inc).

III. *In Vitro* Expeiment

A. Experimental method (in vitro)

In the *in vitro* experiment, a peristaltic pump is used to drive the blood while the pressure at the inlet and outlet is

measured with a pressure gauge, as shown in the Figure 5. We measured the filtrate volume for 5 minutes while the oncotic pressure is deduced from the amount of total protein. Bovine preserved blood (Kohjin Bio Co.,Ltd) was flowed into each device, when the blood pressure applied to the devices was changed by adjusting the flow rate of the peristaltic pump. Since the vein pressure is about 0 to 5 mmHg, the oncotic pressure is about 5 to 25 mmHg, and the arterial pressure is about 80 mmHg in case of beagle dogs, the pressure was controlled from 5 to 100 mmHg in the *in vitro* experiments.

B. Result (in vitro)

The filtration coefficients for each of the five devices(n=3), from C1 to C5, were as shown in Figure 6. The vertical axis represents the filtration coefficient, and the horizontal axis represents the calculated TMP (average pressure applied to the filter minus oncotic pressure). L_p of C1, C2 and C3 were small at low pressure, which indicates that negative filtration occurred during the filtration area. L_p of C4 and C5 were almost constant in the experiments, which indicates that the device is successfully designed such that only positive filtration takes place.

IV. *EX VIVO* EXPERIMENT

A. Experimental method (ex vivo)

In the clinical operation, we directly anastomose the artificial blood vessel to the artery where sufficient blood flow can be secured. However, in *ex vivo* experiments using dogs, we connected the device to the femoral artery and radial cutaneous vein by puncturing the two vessels with indwelling needles, which is thinner than the artificial vessels, as shown in the Figure 7[5]. In this case, the pressure inside the device may be lower than the case *in vivo* due to the pressure loss in the indwelling needle. Therefore, we used the C5 device, which was verified to be capable of stable hemofiltration under low blood pressure. With this setup, we conducted the experiment for 90 minutes, while the filtrate volume was measured every 15 minutes. All animal experiments were approved by the President and by the Institutional Animal Care and Use Committee of Tokyo Medical University and performed in accordance with institutional, science community, and national guidelines.

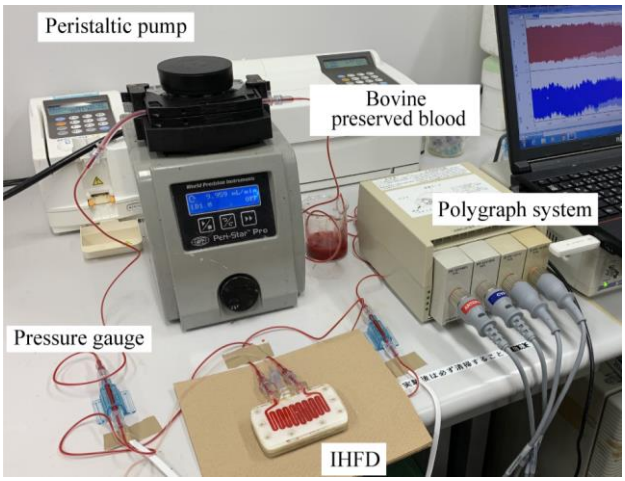

Figure 5 *In vitro* experiment setup.

(Peristaltic pump/Bovine blood/IHFD C1~C5/pressure gauge*2/polygraph system for pressure monitoring)

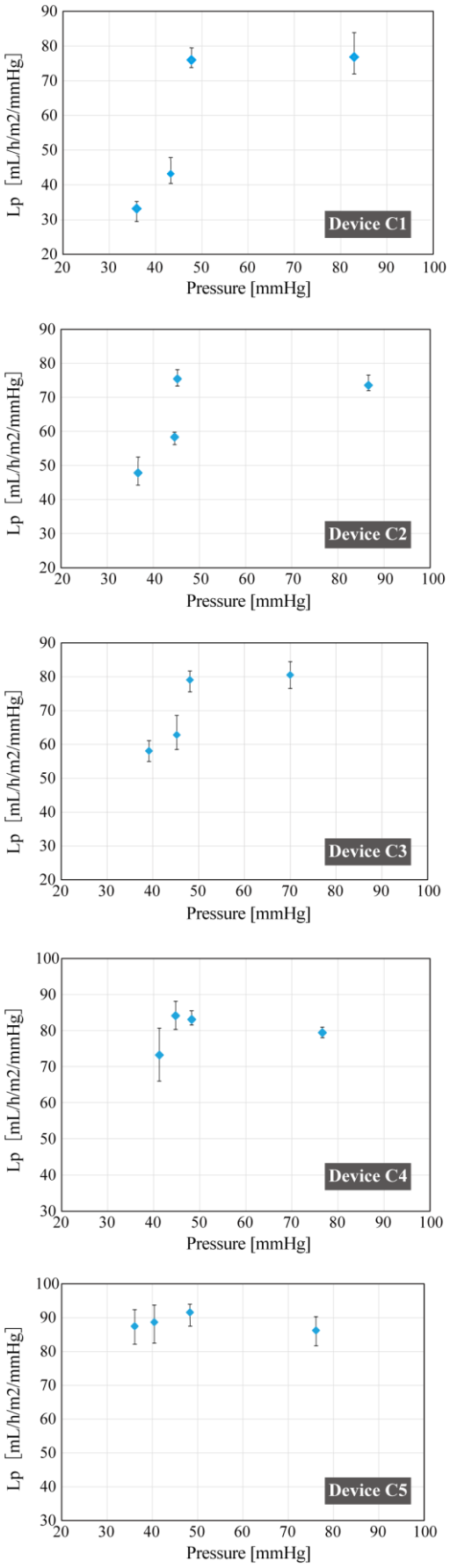

Figure 6 In vitro results(filtration coefficient and TMP)

Figure 7 *ex vivo* experiment setup. Beagle(10.8 kg, Age 4.3, male)/IHFD C5/pressure gauge*2/polygraph system for pressure monitoring

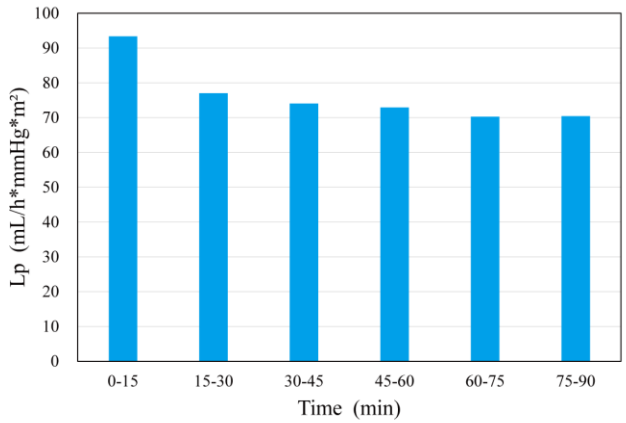

Figure 8 *Ex vivo* results (filtration coefficient and time)

B. Result (ex vivo)

The results of the *ex vivo* experiment, the change in the filtration coefficient every 15 minutes is shown in Figure 8. The vertical axis represents the filtration coefficient and the horizontal axis represents the time. C5 device worked successfully and filtrate constantly. The filtration coefficient was slightly higher in the first 15 minutes, the filtration coefficient remained the same as in the *in vitro* experiment.

V. DISCUSSION

A. In vitro experiments

In the *in vitro* experiments using the C1 and C2 devices, it was difficult to produce filtrate when the transmembrane pressure was near the oncotic pressure. Since the blood pressure supplied by the peristaltic pump rises and falls significantly over time similarly with the actual heartbeat, it is likely that negative filtration occurred temporary even when the average of the pressure difference was above the oncotic pressure. On the other hand, the filtration coefficients of the C4 and C5 devices, in which the filtrate flow path area was less than 80% of the blood flow path area, were found to be constant at all pressures.

Assuming that the pressure drop in the device is linear, the blood pressure in the part of the device conducting filtration is higher than that in the C1 and C2 devices. Therefore, it is considered that negative filtration did not occur in the device and filtrate was constantly produced, which led to the high L_p.

B. Ex vivo experiments

The reason for the high filtration coefficient in the beginning of the experiment could be the effect of the heparin saline solution that was filled in the device before connection of device and vessels.

Normally, the plasma albumin concentration of the beagle dogs is 1.5 to 2.0 g/dL and that of humans in normal state is 4.5 to 7.2 g/dL. In this *ex vivo* experiment, it was 1.2 g/dL. Therefore, humans' oncotic pressure is higher than that of dogs, which can lead to negative filtration in humans. However, in these *in vitro* experiments, the albumin concentration in bovine blood was adjusted according to human conditions, and the effectiveness of C5 device was confirmed [6][7].

In general, the filtration coefficient of commercially available dialyzer is about 10~50 ml/mmHg/hour/m2, C5 device showed 70~80 ml/mmHg/hour/m2. Note that the device is sterilized with gamma rays (10 kGy) after fabrication process [8]. Slight decrease of L_p with time could originate from biofouling to the filtrating membrane.

VI. CONCLUSION

In the *in vitro* experiments by varying the ratio of the areas of the filtrate flow path to that of the blood flow path, it was found that negative filtration due to the osmotic pressure could be prevented. In the *ex vivo* experiments, stable filtration performance was successfully observed at any pressure.

In the future, *in vivo* experiments using medium-sized animals will be conducted to investigate the long-term stability of the device. The device will be designed based on the results obtained in this study.

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