DEVELOPMENT OF A MICRO DIALYSIS SYSTEM FOR EVALUATION OF RENAL CLEARANCE

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ABSTRACT

A cardiovascular microchip for assay of renal clearance was developed. The chip consisted of a peristaltic pump (heart), dialysis component (kidney), and connecting microchannels (blood vessel). By using the system, renal clearance of samples could be assayed.

KEYWORDS

Dialysis, Peristaltic Pump, Renal Clearance, Kidney

INTRODUCTION

In drug development, absorption, distribution, metabolism, and excretion (ADME) of the drugs are very important properties to be assayed other than the bioactivity to the target cells. We have proposed a fundamental concept of a micro total bioassay system and showed preliminary results of microchip-based bioassay of anticancer agents with digestion at stomach and intestine, intestinal absorption and hepatic metabolism [1, 2]. In this study, we developed a microchip-based assay system of the latter half of the ADME, i.e., circulation and excretion components. Low molecular weight drugs are excreted at Bowman capsule in a kidney by ultra filtration, and macromolecule drugs and drugs bound to some proteins (albumin etc.) cannot be excreted. We employed dialysis membrane to mimic the process.

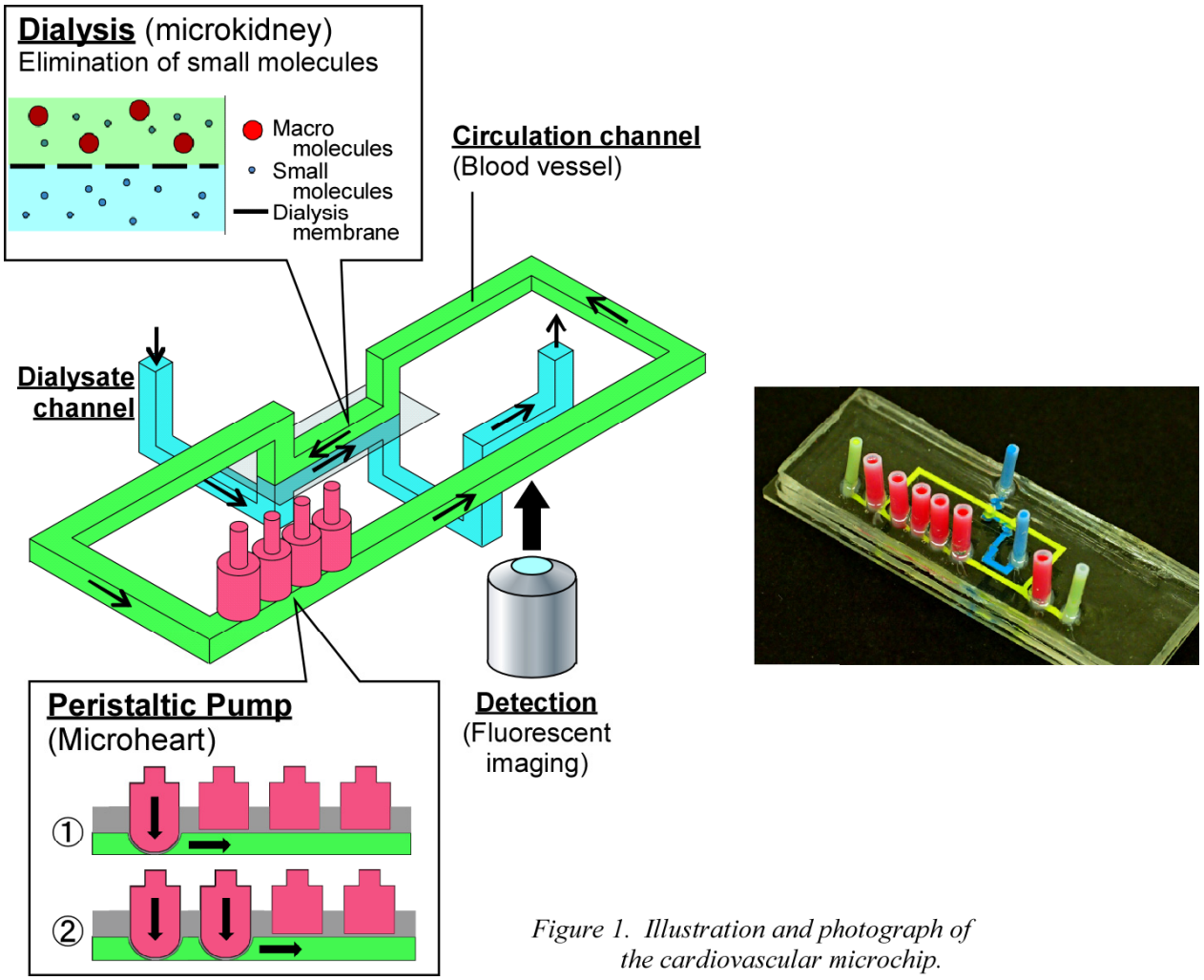

Figure 1. Illustration and photograph of the cardiovascular microchip.

EXPERIMENTAL

The microchip was composed of a glass slide and four PDMS sheets which had microchannels (Fig. 1). Dialysis membrane was laminated between the third and the fourth PDMS sheets for separation of two channels. In the top and the second PDMS sheets, pneumatic valves were fabricated to control a micro peristaltic pump. Air pressure was regulated with PC-controlled solenoid valves. Fluorescein or FITC-albumin was used as a sample, which was circulated in the microchannel by the micro peristaltic pump (microheart) and transferred to the dialysis component (microkidney). Their concentration changes in both circulation and dialysate channels were periodically monitored with a fluorescent microscope.

RESULTS AND DISCUSSION

First, performance of the micro heart was tested by particle image velocimetry (PIV). Average linear flow rate could be controlled ranged from 10 μm/s to 10 mm/s (0.3 μL/min to 300 μL/min) by changing the drive frequency (Fig. 2). Excretion rate of fluorescein is shown in Fig. 3. Higher flow rate of the dialysate showed higher excretion rate, because large concentration difference could be kept in the entire dialysis component in case of the higher flow rate.

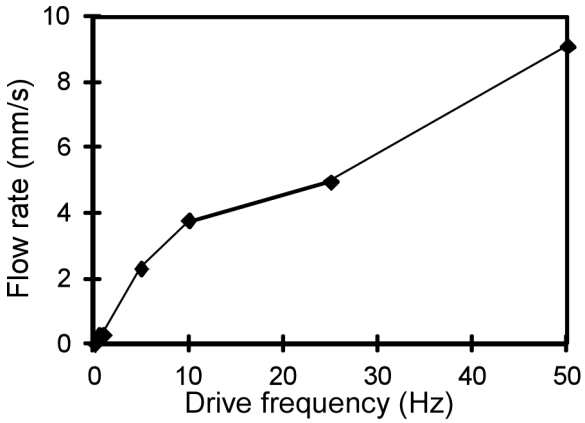

Figure 2. Property of the micro peristaltic pump.

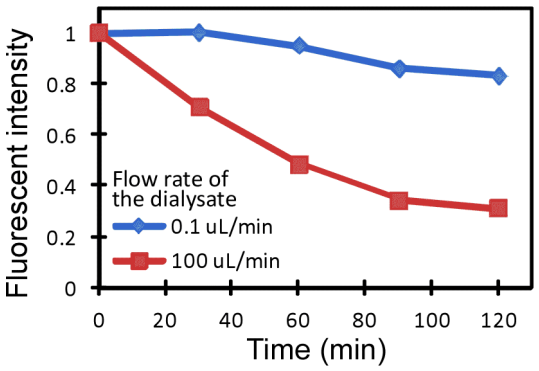

Figure 3. Excretion of fluorescein. Flow rate of the circulation channel was 100 μL/min.

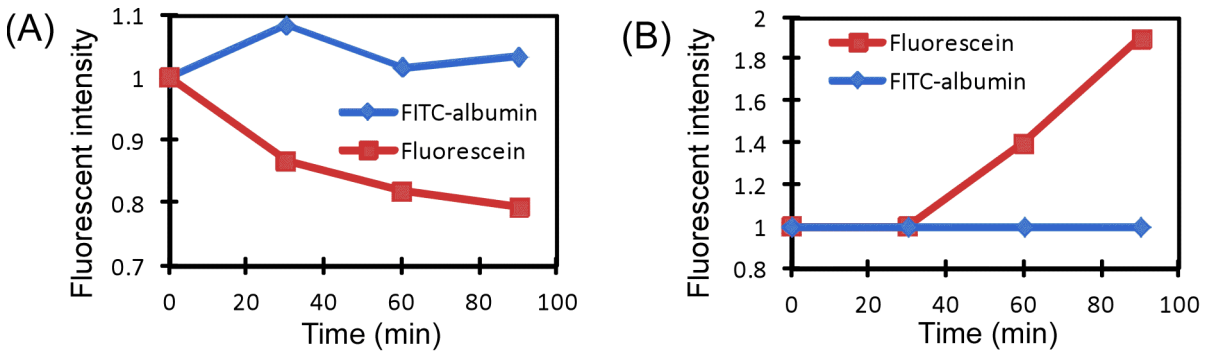

Figure 4. Excretion of fluorescein and FITC albumin.
Fluorescent intensity in the circulation channel (A) and the dialysate channel (B).
Flow rate: circulation channel, 100 μL/min; dialysate channel, 0.1 μL/min.

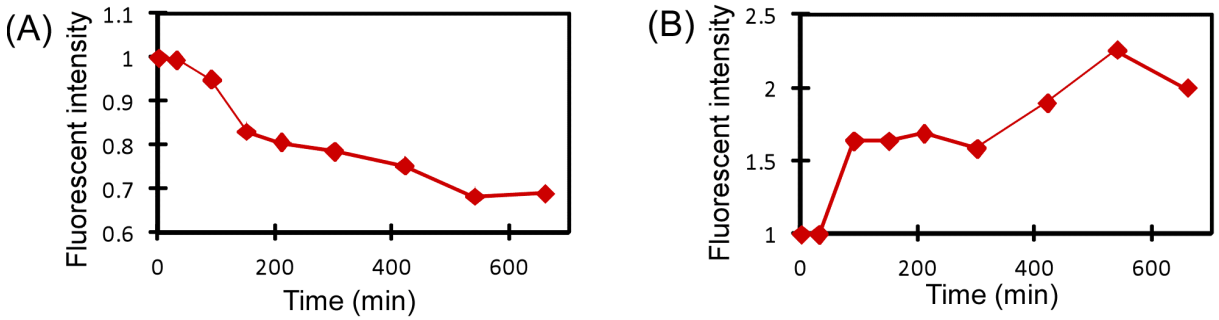

Figure 5. Long-term excretion of fluorescein.
Fluorescent intensity in the circulation channel (A) and the dialysate channel (B).
Flow rate: circulation channel, 100 μL/min; dialysate channel, 0.1 μL/min.

Molecular size dependence of the excretion rate is shown in Fig. 4. Fluorescein was excreted into the dialysate, while FITC-albumin was remained in the circulation channel. Increase in fluorescent intensities in the dialysate channel was delayed more than 30 min (Fig. 4b), because of the travel time of the excreted fluorescein from the dialysis component to the detection point. The results show that the system has an ability to eliminate only small molecules from the circulation channel. Figure 5 shows the results of the long-term excretion experiment in which the system could work more than 10 h.

CONCLUSIONS

The system realized the dialysis of very small amount sample solution, and it is useful for renal excretion assay. We concluded that the developed system had an ability to evaluate the drug activity coupled with renal excretion.

REFERENCES

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