J. Biomed. Eng. Res : 455-460, 2007

Diffusion-Enhanced Modified Hemodialyzer

Kyungsoo Lee[1,4,5], Sa-Ram Lee[1,4,5], Cho-Hae Mun[1,4,5], Byoung-Goo Min[2,3,4,5]

[1]*Interdisciplinary Program in Biomedical Engineering Major, Seoul National University, Seoul, Korea*
[2]*Department of Biomedical Engineering, College of Medicine, Seoul National University, Seoul, Korea*
[3]*Institute of Medical Engineering, Medical Research Center, Seoul National University, Seoul, Korea*
[4]*Korea Artificial Organ Center, Seoul, Korea*
[5]*Cancer Research Institute, Seoul National University Hospital, Seoul, Korea*
(Received April 24, 2007. Accepted June 9, 2007)

Abstract

Flow mismatch between blood and dialysate is invariably encountered during conventional hemodialysis, and this deteriorates diffusive mass transfer. A modification of a conventional dialyzer was conceived to prevent this mismatch. The modified dialyzer includes two independent blood flow regions (central and peripheral regions), which were achieved by redesigning the dialyzer cap. Resultantly, the blood stream was divided into two concentric dialyzer regions. Solutes clearances obtained using the modified dialyzers were compared with those of conventional dialyzers. Solutes clearances by conventionaldialyzers were uniform, but solutes clearances by modified dialyzers were found to be dependent on the simulated blood split into dialyzer central and peripheral regions. Maximal clearances using the modified dialyzer were improved by up to approximately 7.6% for urea and 7.3% for creatinine, as compared with those of conventional dialyzers. More optimizations are required for clinical applications, but the finding that blood flowrates through central and peripheral fiber bundles can be easily regulated is encouraging.

Key words : hemodialysis, diffusion, flow mismatch, blood flow distribution, dialysate flow distribution, channeling

I. INTRODUCTION

Maintenance renal replacement therapies (RRT), whether intermittent or continuous, are essential for patients with renal failure. Blood flows through a bundle of hollow fibers while dialysate flows around these fibers, which causes the transfer of lower molecular weight species through the fiber walls. Two physical phenomena, i.e., diffusion and convection, facilitate this mass transfer, which effectively purifies blood. Diffusion caused by a concentration gradient between blood and dialysate contributes to the removal of small-size uremic solutes, while the removal of excessive water and mid to large-sized molecules depends primarily on convective mass transfer, which is driven by hydraulic and osmotic pressure gradients [1].

This study was supported by the Korea Health 21 R&D Project, Ministry of Health & Welfare, Republic of Korea (#02-PJ3-PG6-EV09-0001), and by the Brain Korea 21 Project.
Corresponding Author : Byoung Goo Min
Department of Biomedical Engineering, College of Medicine, Seoul National University 28 Yungun-dong, Chongno-gu, Seoul, 110-744, KOREA
Tel : +82-2-2072-3126 / Fax : +82-2-2072-7870
E-mail : bgmin@plaza.snu.ac.kr

The effectiveness of hemodialysis for the treatment of chronic renal failure is determined by the mass transfer characteristics of the hemodialysis unit. Diffusive mass transferis strongly affected by blood and dialysate side flow distributions, which play an important role in determining the optimal use of the dialyzer. Previous investigations have revealed that blood and dialysate flow distributions across a hemodialyzer are not uniform[2]. Blood usually flows through the central region of a hollow fiber bundle, whereas a large portion of dialysate runs through the peripheral region of hollow fibers, a phenomenon referred to as channeling[3, 4]. Consequently, diffusive molecular removal is inevitably hampered. Therefore, we conceived a simple modification of a conventional dialyzer in order to reduce blood-to-dialysate flow mismatch. The fiber bundles in modified dialyzers were separated into central and peripheral regions of blood flow, under the assumption that an increase in peripheral blood flowrate would boost diffusive mass transfer. Thus, the present work was aimed at proving the dialytic performance of the modified dialyzer in terms of uremic solutes clearances. The experimental results obtained were also compared with the results of a conventional dialyzer.

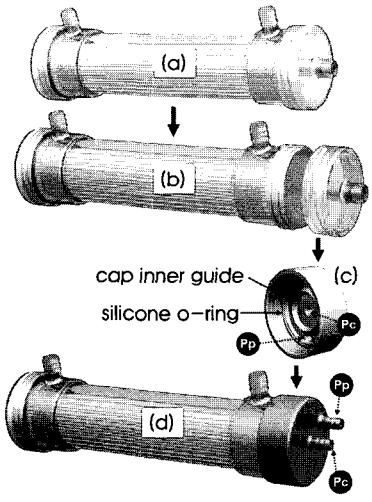

Fig. 1. Assembly Steps for the Modified Dialyzer. (a) Conventional high-flux dialyzer, (b) A dialyzer cap was removed from the conventional dialyzer. (c) The modified dialyzer cap, (d) The modified dialyzer assembled with the new cap. (Pc, central blood port Pp, peripheral blood port)

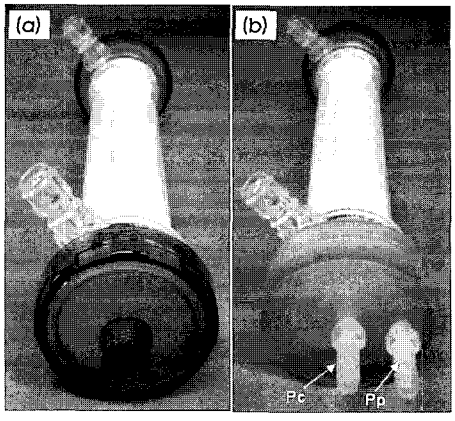

Fig. 2. Picture of a conventional HF50S Dialyzer (a) and of the modified HF50S Dialyzer (b). (Pc, central blood port Pp, peripheral blood port)

II. MATERIALS AND METHODS

A. Modified Dialyzer

The dialyzer as modified contains two blood flow regions, which were achieved by redesigning the dialyzer cap. The new cap shown in Fig. 1c includes an inner guide which partitions the exposed fibers of the dialyzer into two concentric regions, i.e., central and peripheral regions. Two modified caps with inner guide diameters (IGD) of 28 and 30 mm were manufactured. Details on assembly of the modified dialyzer are provided in Fig. 1. A dialyzer cap at the blood inlet was removed from a conventional dialyzer (HF50S, FMC, Germany) and the new cap was then placed onto the dialyzer body. The dialyzer was then inspected to determine whether the central and peripheral regions were properly partitioned by the new cap. Pictorial appearances and detailed specifications of the conventional and modified dialyzers are provided in Fig. 2 and Table 1, respectively. A small reduction in mass transfer area was observed for the modified dialyzers because the inner guides of the modified dialyzers occluded several hollow fibers.

B. Experimental Setup

The dialysis circuit included blood and dialysate pumps, a flowmeter (T206, Transonic Sys, USA) and a hemodialyzer. A conventional dialyzer (HF50S, FMC, Germany) and its modified versions were used throughout dialysis sessions. Thus, the experimental protocol involved three groups; the conventional dialyzer group, the IGD=30 modified dialyzer group, and the IGD=28 modified dialyzer group. Excluding the hemodialyzer,

Table 1. Hemodialyzer Details. Mass transfer areas of the central and peripheral dialyzer regions were calculated from the cross sectional areas of exposed fibers and the dimensions of inner guides. It was assumed that hollow fibers were uniformly distributed in a hemodialyzer. Blood priming volume was defined as the total volume collected from the blood lumen of dialyzers.

	Conventional Dialyzer	Modified Dialyzer	
		IGD=30	IGD=28
Membrane thickness (㎛)	40	40	40
Materials (membrane)	polysulfone	polysulfone	polysulfone
Sterilization	Steam	ETO	ETO
Mass transfer area (m^2)	1.0	0.97 (central 0.52, peripheral 0.45)	0.97 (central 0.45, peripheral 0.52)
Kuf (mL/(h×m^2×mmHg))	30	29.1	29.1
Blood priming volume (mL)	65.1	69.5	69.4

(ETO, Ethylene Oxide : IGD, inner guide diameter of the modified cap)

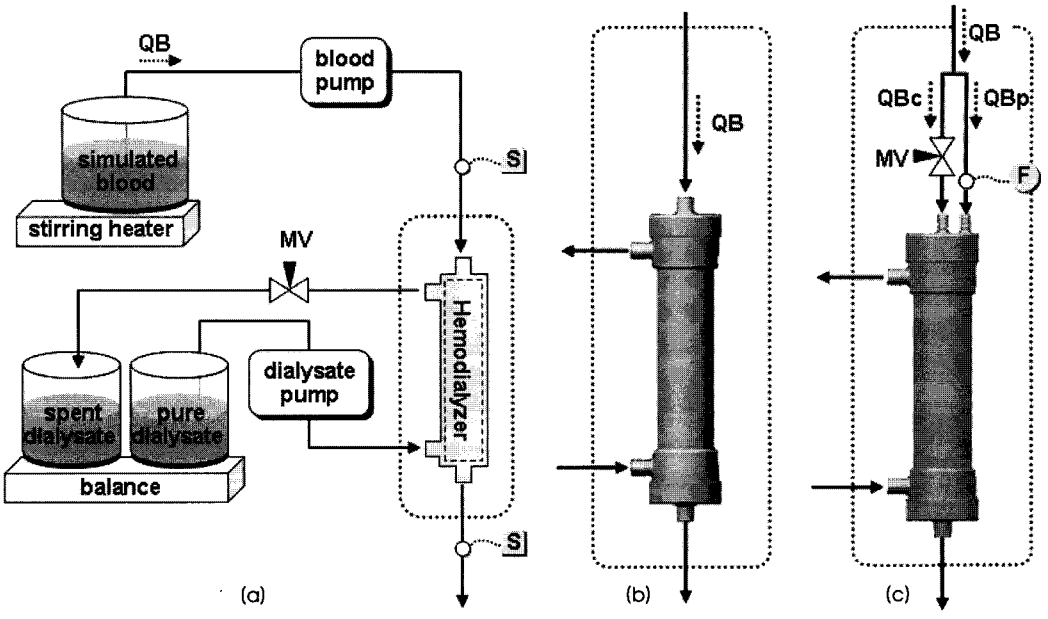

Fig. 3. (a) Experimental Diagram. Zero net-filtrations were preserved by regulating dialysate pressures by manually adjusting a metering valve on the dialysate lumen exit. (b) The conventional hemodialyzer contains a single path for blood and dialysate. (c) Modified dialyzers contained two separate regions for blood flow, thus blood stream was split and directed into the inner and outer concentric regions. The ratio of blood flows into these two regions was regulated by adjusting a metering valve at the inlet of the central region. Flowrates were measured at the peripheral region inlet, and blood flow distributions, i.e., QBp/QB, were determined. (MV, metering valve; F, flowmeter; S, sampling sites; QBc, central blood flowrate; QBp, peripheral blood flowrate; QB, total blood flowrate, QB=QBc+QBp)

all other conditions were preserved identically in all groups. Prior to starting each hemodialysis, the fitted hemodialyzer was properly primed with isotonic normal saline. This priming was performed to remove any surfactants and air bubbles present inside the unit. A diluted solution of urea and creatinine was used as a simulated blood. This was prepared by dissolving 21.4 mg of urea and 1 g of creatinine in 10 liters of isotonic saline solution. The simulated blood was circulated at a flow rate of 120 mL/min using an AK-95S roller pump (Gambro, Sweden). Pure saline solution was also circulated through the dialysate compartment using a peristaltic pump (Cole-Parmer, Illinois, USA) at 250 mL/min. The total priming volume of the dialysis circuit was approximately 300 mL. Single pass of the blood and dialysate flows were used in experiments (Fig. 3a).

All experiments were performed with zero net-filtration, which was inspected during all dialysis sessions. Spent dialysate was collected in a pre-weighed reservoir to determine dialysate flowrates downstream of the dialyzer. Upstream dialysate flowrateswere also determined in a similar manner and net-filtration rates were calculated by subtracting upstream dialysate flowrates from downstream dialysate flowrates. Zero net-filtration was achieved by regulating dialysate pressures (Fig. 3).

The distribution of simulated blood into central and peripheral regions was crucial in the present study, and a fine regulation of blood flow division was achieved by adjusting a metering valve on blood lumen inlet of the central region (Fig. 3c). In addition, the ratio of blood flowrates into the two regions was monitored by measuring blood flowrates through the peripheral region (QBp). Data on QBp were obtained by recording them for five minutes, and time-averaged values were regarded as instantaneous blood flowrates. When QBp values were obtained, blood samples were drawn from the pre- and post-dialyzer blood streams. Samples were analyzed for urea and creatinine, and solutes clearances were then calculated as follows.

$$\text{Clearance (mL/min)} = QB \times (1 - C_O/C_I) \quad (1)$$

Where, QB is the simulated blood flowrate (mL/min),and C_I and C_O are solute concentrations at blood flow inlet and outlet (mg/dL), respectively. Solute clearance was introduced to clarify comparisons between groups in terms of their abilities to remove solutes. Experimental hemodialysis sessions were repeated for five times per group and data are expressed as means±SD.

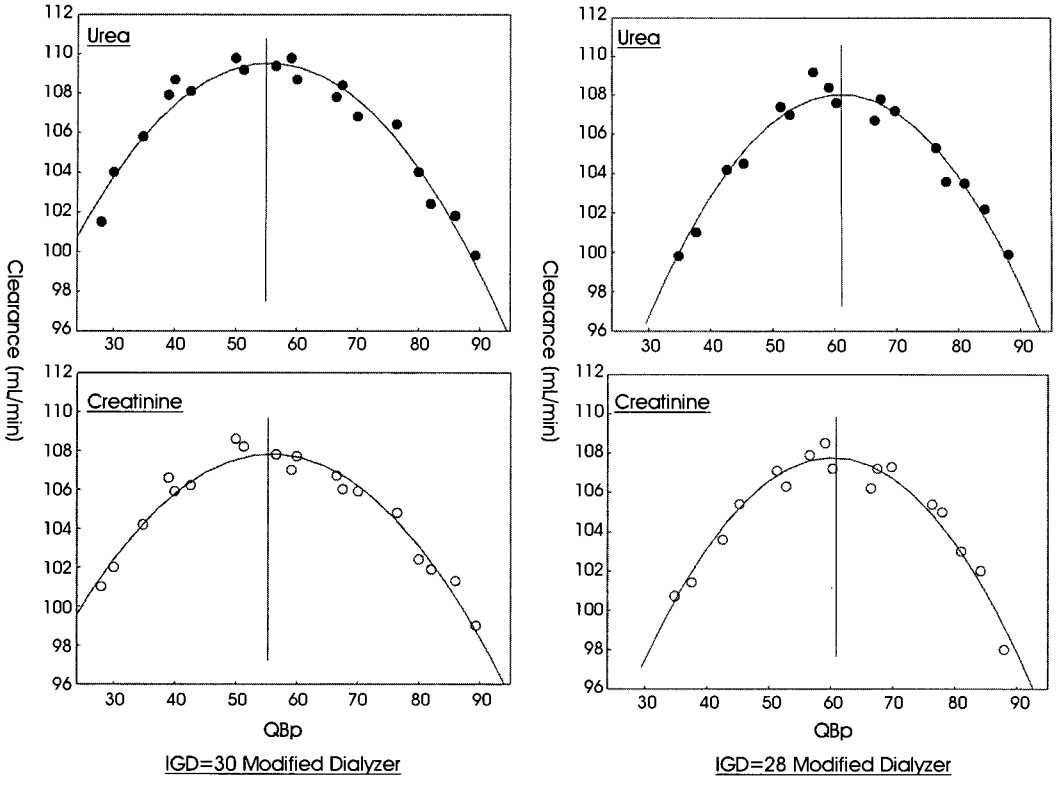

Fig. 4. Solutes Clearances for the IGD=30 (left) and IGD=28 Modified Dialyzer (right). Urea and creatinine clearances were distributed parabolically as QBp increased, whereas they were uniform with conventional dialyzers, 102±2.1 mL/min for urea and 92.1±1.6 mL/min for creatinine. The vertical line represents the peripheral flowrates at highest clearances. (QBp, peripheral blood flowrate in mL/min)

III. RESULTS

No technical problems occurred when using the modified dialyzers and net filtration rates were preserved at zero for all sessions. Solutes clearances in the conventional dialyzer group were uniform, 102±2.1 mL/min for urea and 92.1±1.6 mL/min for creatinine. On the other hand, solute clearances for the modified dialyzers were found to be dependent on simulated blood distribution to central and peripheral regions. Due to the highly diffusive characteristics of small-sized solutes, urea and creatinine clearances were parabolically distributed as the QBp increased (Fig. 4 and 5). Optimization of the blood flow distribution through central and peripheral regions is believed to prevent impairment of dialyzer efficiency by increasing the diffusive mass transfer of solutes. The modified dialyzer with a 30 mm of inner guide diameter, i.e., IGD=30 dialyzer,resulted in highest clearance at approximately 54 mL/min of QBp, which corresponded to 45% of total blood flowrate (Fig. 4). Likewise, solutes clearances were maximized at 62 mL/min of QBp in case of the modified dialyzer with a 28 mm of inner guide diameter, i.e., IGD=28 dialyzer (Fig. 4). In addition, solutes clearances by the modified dialyzers were always higher than those of conventional dialyzers, for which QBp values ranged between 45 and 70 mL/min. Clearances with the modified dialyzers were greater by approximately 7.6% for urea and 7.3% for creatinine than those of conventional dialyzers.

IV. DISCUSSION

Hemodialysis systems have been much improved over recent decades and technical innovations continue to enhance dialysis outcomes for renal failure patients.These developments include dialyzer designs that reduce resistance to mass transfer ratios[5-6]. However, several lines of evidence indicate that blood-to-dialysate flow mismatch hampers the optimal use of diffusive mass transfer in a hemodialyzer. MRI studies and numeric simulations show that dialysate flow distribution in a hemodialyzer is not uniform[7-8]. Although the spacing of fibers can reduce this nonuniformity[9], the channeling may still result in a dialysate flow maldistribution, which causes solutes clearances at central bundles to differ from those at peripheral fiber bundles[10]. A new experimental approach to

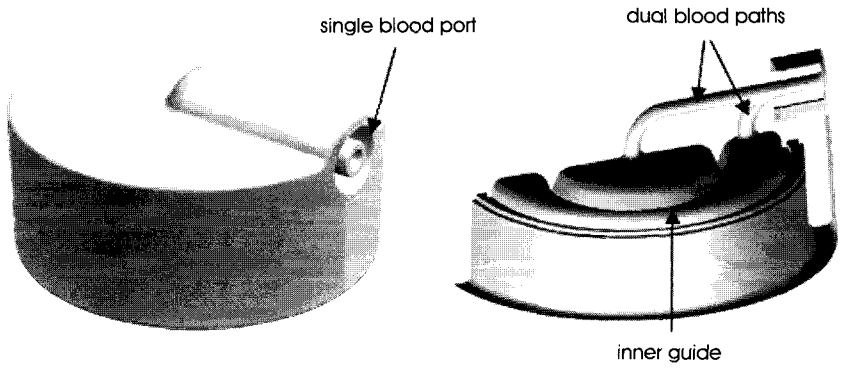

Fig. 5. Conceptual Design of the Modified Cap. External view with a single blood port (left), and internal view with dual blood paths (right).

quantifysolutes clearances contributed by hollow fibers in different hemodialyzer regions also revealed that local clearances increased on moving from inner to outer regions of the fiber bundle[11]. In addition, blood flow is also distributed nonproportionally across dialyzer cross-sections, and this is strongly affected by hematocrit levels[2, 12]. Higher hematocrit levels reduce blood flowrates in peripheral region, supporting the hypothesis that flow mismatch between blood and dialysate is a major cause of dialyzer malfunction. Conventional hemodialyzers were therefore redesigned in the present study to prevent flow mismatch between blood and dialysate by increasing peripheral blood flowrates, and as a result, diffusive molecular removal was significantly improved as compared with conventional dialyzers.

Given the assumption that hollow fibers are uniformly distributed in a hemodialyzer, the inner guide diameter of the modified cap determines the mass transfer areas of the respective central and peripheral regions, and in turn the optimal ratio of blood flow distribution to the two regions is determined. Our experimental results indicate that molecular clearances are dependent on blood flow distributions into these regions. Maximal clearances were achieved at different ratios of blood distribution (QBp/QB) in modified dialyzers with different inner guide diameters. To achieve highest clearances, the IGD=28 dialyzer required larger peripheral blood flowrates (QBp) than those required by the IGD=30 dialyzer.

Conditions other than the dialyzers used were identical in the three study groups. Simulated blood was prepared in an identical manner for all experiments. These procedures allowed all experiments to be performed with no notable differences in pre-dialyzer soluteconcentrations in all groups. The modified dialyzers used are still experimental prototypes, and optimizations of cap design and assembly continue. Blood flow optimization in caps will reduce blood priming volumes and blood damage[13]. In addition, when the cap design is optimized in terms of blood flow distribution, these caps are likely to simplify assembly and treatment set-up for example, it is likely that a unit could be devised with a single external blood port, but dual internal blood paths, as depicted in Fig. 5.

The present study indicates that the use of the devised dialyzers warrants further investigation, and this should include the in-vivo investigation of dialytic performance and the quantification of blood trauma. Viscous blood flow in the in-vivo situation will probably aggravate blood-to-dialysate flow mismatch, because nonproportional blood distribution within a dialyzer is likely to be exacerbated by hematocrit increases. However, whole blood has quite different manner from the non-viscous artificial blood used in the present study. In addition, blood damage is a crucial issue in terms of clinical applications, and therefore a detailed investigation on blood damage likely to occur during clinical dialysis is also required.

V. CONCLUSIONS

This in-vitro study on diffusion-enhanced modified hemodialysis was conducted with a focus on the effects of modified dialyzers on solutes clearances. The modified dialyzers are characterized by a separation of blood flow into the central and peripheral regions of dialyzers. Optimal flow distribution was determined to obtain the highest clearances withthe modified dialyzers. Observed solutes clearances were significantly improved versus conventional dialyzers, which are attributed principally to increase blood flow through peripheral fiber bundles.

REFERENCES

[1] J. T. Daugirdas and J. C. Van Stone, *Physiologic Principles and Urea Kinetic Modeling. In: Daugirdas JT, Blake PG, Ing TS, eds. Handbook of dialysis*, Lippincott Williams & Wilkins, 2000, pp.15-45.

[2] C. Ronco, A. Brendolan, C. Crepaldi, M. Rodighiero and M. Scabardi, "Blood and dialysate flow distributions in hollow-fiber hemodialyzers analyzed by computerized helical scanning technique," *J. Am. Soc. Nephrol.*, vol.13, Suppl 1, pp.S53-61, 2002.

[3] T. Osuga, T. Obata and H. Ikehira, "Detection of small degree of nonuniformity in dialysate flow in hollow-fiber dialyzer using proton magnetic resonance imaging," *Magn Reson Imaging*, vol.22, no.3, pp.417-420, 2004.

[4] C. Ronco, A. Brendolan, C. Crepaldi, M. Rodighiero, P. Everard, M. Ballestri, G. Cappelli, M. Spittle and G. La Greca, "Dialysate flow distribution in hollow fiber hemodialyzers with different dialysate pathway configurations," *Int. J. Artif. Organs.*, vol.23, no.9, pp.601-609, 2000.

[5] A. Brendolan, F. Nalesso, A. Fortunato, C. Crepaldi, M. De Cal, S. Cazzavillan, D. Cruz, N. Techawathanawanna and C. Ronco, "Dialytic performance evaluation of Rexeed: a new polysulfone-based dialyzer with improved flow distributions," *Int. J. Artif. Organs.*, vol.28, no.10, pp.966-975, 2005.

[6] F. Gastaldon, A. Brendolan, C. Crepaldi, P. Frisone, S. Zamboni, V. d'Intini, S. Poulin, R. Hector, A. Granziero, K. Martins, R. Gellert, P. Inguaggiato and C. Ronco, "Effects of novel manufacturing technology on blood and dialysate flow distribution in a new low flux "alpha Polysulfone hemodialyzer," *Int. J. Artif. Organs.*, vol.26, no.2, pp.105-112, 2003.

[7] C. K. Poh, P. A. Hardy, Z. Liao, Z. Huang, W. R. Clark and D. Gao, "Effect of spacer yarns on the dialysate flow distribution of hemodialyzers: a magnetic resonance imaging study," *Asaio J.*, vol.49, no.4, pp.440-448, 2003.

[8] Z. Liao, E. Klein, C. K. Poh, Z. Huang, P. A. Hardy, S. Morti, W. R. Clark and D. Gao, "A modified equivalent annulus model for the hollow fiber hemodialyzer," *Int. J. Artif. Organs.*, vol.27, no.2, pp.110-117, 2004.

[9] C. Ronco, M. Scabardi, M. Goldoni, A. Brendolan, C. Crepaldi and G. La Greca, "Impact of spacing filaments external to hollow fibers on dialysate flow distribution and dialyzer performance," *Int. J. Artif. Organs.*, vol.20, no.5, pp.261-266, 1997.

[10] W. R. Clark and J. H. Shinaberger, "Effect of dialysate-side mass transfer resistance on small solute removal in hemodialysis," *Blood Purif.*, vol.18, no.4, pp.260-263, 2000.

[11] Z. Huang, E. Klein, B. Li, C. Poh, Z. Liao, W. R. Clark and D. Gao, "A new method to evaluate the local clearance at different annular rings inside hemodialyzers," *Asaio J.*, vol.49, no.6, pp.692-697, 2003.

[12] J. K. Unger, A. J. Lemke and C. Grosse-Siestrup, "Thermography as potential real-time technique to assess changes in flow distribution in hemofiltration," *Kidney Int.*, vol.69, no.3, pp. 520-525, 2006.

[13] M. C. Yang and C. C. Lin, "Influence of design of the hemodialyzer inlet chamber on red blood cell damage during hemodialysis," *Asaio J.*, vol.47, no.1, pp.92-96, 2001.