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Push/Pull Based Renal Replacement Treatments

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1. Introduction

The incidence of kidney disease is rapidly increasing worldwide [1], accompanied by widespread research and development resulting in remarkable improvements in the technologies used for treatment in end-stage renal disease (ESRD) patients. Polymeric membranes are better at preventing the transfer of pyrogenic substances into the blood stream and membrane biocompatibilities are much improved [2]. The sharp molecular cut-offs of these membranes also prevents further loss of albumin during high-dose convective treatment [3]. These membrane technology advancements have been accompanied by the evolution of varied choices for renal replacement treatment. Particularly, better outcomes achieved by convective treatment have encouraged the use of synthetic membranes with high water permeability and sieving characteristics in clinical setups worldwide [4, 5].

Maintenance hemodialysis (HD) nevertheless remains a standard protocol for treating ESRD patients, despite the development of renal replacement modalities. This process is a result of two physical phenomena that facilitate mass transfer in purifying blood. Diffusion caused by a concentration gradient between blood and dialysate contributes to the removal of uremic solutes, particularly small-sized, water-soluble molecules. Excess water and mid-sized molecules are removed primarily by convective mass transfer, resulting from the transmembrane pressure gradient [6]. Plasma water flow through a membrane leads to the simultaneous movement of a solute through the membranes. Thus, volume-controlled high-flux HD adequately clears mid-size solutes without sterile fluid infusion because forward filtration exceeding the desired volume removal is compensated for by backfiltration [7], and this modality can provide a simpler form of dialysis treatment than other treatment methods. However, although the convective dose delivered during high-flux HD has been shown to



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reduce mortality in patients at risk [8], overall patient survival remains comparable to that of low-flux HD [9]. This is presumably caused by the limited amount of internal filtration involved due to limitations imposed by fluid dynamics and the geometric nature of the he-modialyzer.

In contrast, hemodiafiltration (HDF) is characterized by a large filtration volume that far exceeds the desired volume removal. Given that, the dehydration must be corrected in real time by infusing exogenous sterile replacement fluid. HDF has been reported to deliver better dialysis outcomes than high-flux HD, because of the improved middle-to-large size molecular removal, better control of EPO and inflammation [10-13], resulting in less patient mortality [14, 15]. However, HDF use is limited globally because the requirement of exogenous fluid infusion raises concerns about water quality, safety and cost. This has led to modifications of HDF strategies to increase convective mass transfer without the need for exogenous replacement fluid infusion. This is achieved by spontaneous fluid reinfusion at a rate that matches convection. Backfiltration and regenerated ultrafiltrate can be the methods of spontaneous fluid restoration.

Push/pull strategies have also been examined to increase total filtration volumes without the exogenous replacement fluid infusion. The push/pull technique uses the entire membrane as the forward filtration domain for a period of time. However, backfiltration must accompany the forward filtration to compensate for the fluid depletion that occurred due to the forward filtration, and as a result, making it necessary to switch the membranes to a backfiltration domain. In other words, push/pull systems rely on alternate repetitions of forward and backward filtration during dialysis treatment and the repetitive filtration contributes to the increased total filtration volume.

In this chapter, the trials of push/pull-based renal supportive treatments are reviewed in terms of their technical description, hemodialytic efficacy and applicability for clinical use. In addition, the fluid management accuracy of the push/pull dialysis method will be discussed in depth.

2. Backfiltration and push/pull operation

Precise volume control is a crucial pre-requisite in renal replacement therapy. With kidney malfunction, the accumulation of uremic toxins and surplus water is a consistent fact in ESRD patients, and appropriate, timely renal supportive treatment must be conducted to avoid deadly uremic conditions. It has been recently reported that dialysis outcomes are considerably improved with enhanced convective mass transfer during hemodialysis, and techniques to maximize the convective volume exchange have been extensively explored. As the volume depletion exceeds the prescribed amount, it must be promptly compensated. A straightforward way is to infuse sterile fluid after calculating the desired fluid level. However, the external infusion of sterile dialysate raises concerns like high standard water quality and treatment-related cost. Reverse movement of dialysate within a hemodialyzer has been tried as an alternative approach.

Backfiltration is the phenomenon that dialysate moves into the blood stream across membranes, in the area where dialysate pressures are higher than hydraulic blood and osmotic pressures. A pressure drop is inevitable as fluid flows through a cylindrical tube, and blood and dialysate pressures decrease along the dialyzers. In a normal countercurrent dialysis setup, because blood and dialysate flow in opposite directions, these pressure drops occur with opposing gradients, and in some regions hydraulic blood and dialysate pressures overlap. Thus, the sum of hydraulic and osmotic pressures, termed transmembrane pressure (TMP), is positive in the proximal region of a hollow fiber dialyzer, and plasma moves to the dialysate compartment across the membranes (forward filtration). However, fluid movement occurs in the opposite direction in the distal region because TMP becomes negative, and backfiltration occurs. This backfiltration compensates for fluid loss in the proximal region (Figure 1) [16].

While backfiltration method could provide fluid restoration easily, the amount of forward filtration in the normal countercurrent dialysis setup is limited, because (1) a small area of the membranes is used for the filtration inside the hemodialyzer and (2) the increase of pressure gradients through the hemodialyzer is limited in a particular hemodialyzer geometry and flow conditions. These limitations have led to investigations for techniques to increase the blood-to-dialysate pressure gradients. As fluid pressure drop through a cylindrical tube is proportional to the tube length, but is inversely proportional to the 4th power of tube diameter, hemodialyzers with reduced fiber diameters or elongated hemodialyzers have been developed [17-19]. In addition, a unique design for the hemodialyzer was also introduced [20-22] in which forward and backward filtration regions are separated longitudinally, instead of horizontally, giving the independent control of blood or dialysate pressures in each region.

Additionally, push and pull actions were devised for an infusion-free HDF technique. Differently from other methods, forward filtration and backfiltration repeat in the push/pull technique. During a given period of time, the entire membrane is used as the forward filtration domain, as in the HDF method, by regulating blood pressure higher than dialysate. Thus, the filtration rates necessarily exceed prescribed rates. Immediately after the forward filtration, the pressure gradients through the hemodialyzer are reversed, the fluid movement is switched to the opposite direction. This opposite fluid movement compensates for the excessive fluid loss during the previous filtration phase. The alternate repetition of forward filtration and backfiltration constitutes a cycle of fluid movement and the difference of the forward and backward filtration rates, i.e., net-filtration rates, is regulated at the desirable level.



Figure 1. Transmembrane Pressure Gradient along Dialyzer Length.

3. Push/pull hemodiafiltration

The concept for repetitive use of forward and backward filtration during conventional dialysis treatments was first introduced in Japan in the early 1980's, in an effort to simplify the infusion-free HDF technique, using a serial arrangement of two hemodiafilters [23-25]. However, that system requires a means of repeating backfiltration [26]. Thus, a redundant dialysate bag is integrated downstream of the hemodialyzer and connected to the dialysate stream by a bidirectional peristaltic pump [27]. The push/pull action accomplished by this bi-directional pump alternates the evacuation and replenishment of the bag. During normal operation, dialysate flow rates upstream and downstream of the hemodialyzer are maintained in balance and the desired volume removal is achieved by a separate ultrafiltration pump. Therefore, when the bidirectional push/pull pump pulls a portion of dialysate into the bag (e.g., 70 ml/min for 3 minutes), hydrostatic pressures through the dialysate compartment decrease, because the dialysate compartment is closed and has a fixed volume, and water flux occurs from blood to the dialysate compartment (ultrafiltration) at the same rate as dialysate removal from the dialysate compartment. Soon after the ultrafiltration completes, the pump reverses and pushes the dialysate in the bag into the dialysate stream, causing a volume overload in the dialysate compartment. The surplus dialysate in the closed dialysate compartment is then moved to the blood compartment (backfiltration). Another bag and an additional bidirectional peristaltic pump is also integrated into the venous chamber, and conducts the pulling and pushing of blood, although in this case, the actions of the blood-side pump are 180° out of phase with those of the dialysate side pump to keep blood flow returning to the patient constant.

When pure dialysate is pushed into the blood stream, solute concentrations in blood are immediately equilibrated and decreased by dilution. Soon after, the blood-to-dialysate pressure gradient reverses from negative to positive, and plasma fluid in blood is forced to move into the dialysate compartment, which removes various molecules from the plasma. This repetitive ultrafiltration contributes to convective mass transfer and increases the removal of small-sized (urea) or mid-sized (beta-2-microglobulin) molecules compared to hemofiltration (HF) or hemodialysis method, respectively [28]. On the other hand, repetitive backfiltration during push/pull HDF prevents volume depletion. In addition, the repetitive backflushing of dialysate also helps prevent membrane bindings of various blood components [26].

However, the disposable bags and separate bidirectional peristaltic pumps make this unit notably complicated. To overcome these shortcomings, a double-chamber cylinder pump was devised. The double cylinder pump includes two independent chambers and a reciprocal piston, and each chamber is connected to either dialysate or the blood stream [29], as seen in Figure 2. When the piston squeezes the chamber on the dialysate side, the dialysate compartment, which has a fixed volume, is pressurized and backfiltration begins. At this time, the chamber on the blood side expands and blood in the venous chamber starts flowing in the direction of the cylinder pump. Since the blood volume that returns to the bloodside chamber of the pump is equal to the backfiltration volume, blood flow returning to patients remains constant. The piston then moves in the opposite direction and squeezes the blood-side chamber, the dialysate compartment begins to expand, and the dialysate compartment is depressurized, leading to ultrafiltration. However, despite the large amount of ultrafiltration, blood flow in the venous line is maintained, because the ultrafiltrate removed in the hemodialyzer is replenished in the venous chamber.

The reciprocating movement of the piston is regulated by pressure differences between the two chambers of the cylinder pump (i.e., Pb-Pd). The rotation torque of the driving motor attached to the piston can be adjusted in accord with TMP (i.e., torque = TMPxSxLxsin θ). Voltage applied to the motor is adjustable, allowing the TMP to be set at 400 mmHg during forward filtration, but at -400 mmHg during the backward filtration phase. Pressure-controlled push/pull HDF can maintain transmembrane pressures at the maximum permissible level throughout treatment [30]. In addition, contrary to the original push/pull HDF, in which one cycle of filtration and backfiltration takes approximate 4~5 minutes, the pressure controlled push/pull HDF unit can repeat one cycle in1.5~1.7 seconds.



Figure 2. Push/Pull HDF and Double-Chamber Cylinder Pump

This optimized use of transmembrane pressure and more frequent alternations of forward and backward filtration in the revised push/pull HDF unit are obviously accompanied with a markedly larger total filtration volumes and higher solutes clearances [30]. The push/pull HDF unit tends to relieve symptoms like arthralgia (joint pain), irritability, pruritus, and insomnia more rapidly than conventional HD mode [27, 31, 32]. Furthermore, the optimal maintenance of membrane permeabilities by prompt backfiltration has the added benefit of considerably inhibiting albumin loss while increasing convection and diffusion [33]. Some albumin loss is unavoidable when using membranes with high water permeabilities and sieving characteristics [34]. Since convective therapy is based on larger amounts of fluid exchange and solvent drag during fluid exchange occurs randomly, albumin permeation becomes more worrisome during convective treatments [3]. In addition, filtration-induced elevated albumin concentration at the inner membrane wall also aggravates the albumin loss [35]. Protein concentration polarization develops quickly after sudden TMP development and the hydraulic permeabilities of the membrane decrease rapidly in about 2 seconds. However, during push/pull HDF, backward flushing of dialysate takes place within the time frame required for the protein layer to fully develop (i.e., 1.5~1.7 seconds), and thus, it can effectively wash out the inner lumen and inhibit excessive albumin leakage [33]. This dialysate backflushing eventually allows membrane hydraulic capabilities to be better maintained throughout the treatment.

In summary, push/pull HDF was developed in an effort to perform infusion-free, simultaneous HD and HF by using a single hemodialyzer. Thus, it alternates between ultrafiltration and backfiltration instead of dividing ultrafiltration and backfiltration regions. Pressurecontrolled push/pull HDF can maintain TMPs at maximal levels and the total filtration volumes achieved are far greater than that of any other treatment modality. In addition to the filtration quantity, repetitive cycles in a shorter time than the time required for a protein layer to be established ensure superior membrane use throughout treatment, further inhibiting albumin loss. Push/pull HDF is assumed to be close to pre-dilution mode HDF because the repetitive dilution exceeds blood flow rates [36]. Even though post-dilution HDF is more efficient in terms of solute removal, the substantial amount of total filtration and the optimal use of membrane offered by the push/pull HDF technique probably translate to outstanding hemodialytic outcomes. Therefore, a prolonged prospective study on push/pull HDF may be worthwhile to determine the benefits of this modality versus other forms of convective renal replacement.

4. Pulse push/pull hemodialysis

Flow patterns have been an obvious research avenue for treatments requiring extracorporeal blood circulation. Blood pulsation has been accepted, although with controversy, as beneficial during cardiopulmonary bypass, because it achieves greater perfusion to peripheral vessels and end-organs [37, 38]. Blood pulsation in a pediatric CRRT animal model delivers adequate performance over a 2-hour period in terms of ultrafiltration rates and cross-filter blood pressure drops [39, 40]. It was further found that the pulsatile flow tends to enhance ultrafiltration rates versus non-pulsatile flow [41, 42], attributable to increased rheological power of pulsatile flow. However, little evidence is available clinically or experimentally that explains the efficacy of pulsatile flow on dialysis outcomes. Pulse push/pull HD (PPPHD) is a convection-enhanced dialysis treatment, using pulsatile devices for blood and dialysate to achieve the cyclic repetition of forward and backward filtration. During an early trial, a T-PLS pump (Twin Pulse Life Supporter, AnC Bio Inc., Seoul, Korea) was used as the pulsatile pump [43]. The T-PLS consists of blood and dialysate sacs, a reciprocating actuator and a motor-cam assembly [44], with the actuator between the blood and dialysate sacs (Figure 3). When the actuator squeezes the blood sac, blood can move forward due to one-way check valves. At the same time, the dialysate sac expands and is filled with fresh dialysate. In the same manner, dialysate also moves forward when the sac is squeezed and the blood sac is filled with blood. These reciprocating movements create pulsatile flow. By setting their phase difference at 180° degrees, the pushing phases of blood and dialysate pumps alternate, and TMPs cycle between positive and negative, driving consecutive periods of ultrafiltration and backfiltration.

The hemodialytic efficiencies of PPPHD have been demonstrated, and studies show that PPPHD substantially improves uremic marker molecules clearance, particularly for midsized molecules (Table 1) [43]. Increased filtration volumes in the PPPHD unit may also be due to reduced membrane fouling. In an *in vivo* setup on PPPHD, one cycle of ultrafiltration and backfiltration took 3 seconds at a pulse frequency of 20 bpm [45]. When ultrafiltration and backfiltration times were defined as the durations of positive and negative TMPs, respectively, ultrafiltration and backfiltration times for the PPPHD unit were approximately 1.7 and 1.3 seconds, respectively. Since protein concentration polarization on the blood-side membrane develops during forward filtration and is reduced by backfiltration, membrane convective capacity could be better maintained during PPPHD than during CHD, showing smaller reductions in post-dialysis hydraulic permeabilities [45].



Figure 3. T-PLS pump for the original PPPHD

| Group | BPM | QB | QD | Clearance (ml/min) | | | | | |
|------------|-----|---------|-------|--------------------|------------|-------------|----------|--|--|
| Group | | | | BUN | Creatinine | Vitamin b12 | Inulin | | |
| CHD | - | 236±3.6 | 420±3 | 161.1±4.3 | 127.2±3.9 | 37.5±6.3 | 25.3±5.1 | | |
| PPPHD | 40 | 234±3.1 | 419±3 | 166.2±3.8 | 136.9±4.2 | 55.7±5.0 | 37.8±3.9 | | |
| % Increase | | - | - | 3.2 | 7.6 | 48 | 49 | | |
| P-value | | NS | NS | 0.053 | <0.05 | <0.001 | <0.001 | | |

Table 1. Solutes Clearances. (CHD, conventional high-flux HD; PPPHD, pulse push/pull HD; BPM, beats per minute; QB, blood flowrate; QD, dialysate flowrate; BUN, blood urea nitrogen; NS, not significant) (Reproduction was permitted by a publisher)

5. Modified pulse push/pull hemodialysis

Pulsatile circulation of blood and dialysate offers a simple and efficient strategy for the repetitive cycle of filtration and backfiltration. However, blood pulsation during extracorporeal renal replacement treatment is potentially problematic. Specifically, instant suction generated by a pulse pump through a narrow catheter may cause blood damage, vessel narrowing, or vessel collapse. In addition, instantaneous negative pressures generated upstream of a pulsatile blood pump not only introduce the possibility of circuit aeration, but could lead to a failure to maintain predetermined blood flow rates [46, 47].

Hence, PPPHD unit was revised, and while many facets of the original PPPHD were retained, including the alternating water flux across the membrane, blood pulsation was excluded. This was achieved by employing dual pulsation in the dialysate stream, that is, pulsatile devices in the dialysate stream upstream (a dialysate pump) and downstream (an effluent pump) of the dialyzer [48]. Backfiltration occurs when the sum of the cross-membrane pressures is negative, but ultrafiltration when the sum is positive. The hydraulic pressures of blood and dialysate were both manipulated in the original PPPHD, but since blood pulsation was eliminated, dialysate pressure alone regulates TMP in the revised unit. Therefore, the following two assumptions were made; (1) dialysate compartment pressures must be far higher than blood-side pressures when pure dialysate is forced into the dialyzer, and (2) dialysate pressures drop to lower than blood pressures during effluent pump expansion. Given these assumptions, the dialysate and effluent pumps are replaced with a dual pulse pump [49].



Figure 4. Dual Pulse Pump (DPP). DPP is composed of a base plate, a unidirectional electric motor, a cam, and four actuators. It contains two separate silicone tubes. Pulsatile flow is generated by squeezing each dialysate and effluent tubing segments. (A1~A4, actuators 1 to 4; p1~p6, silicone tubing segments at positions 1 to 6, respectively) (Reproduction was permitted by a publisher)

The dual pulse pump (DPP) is a pulsatile device that was developed to eliminate the one-way valves that are generally required for pulsatile devices to prevent retrograde flow. Instead, time-delayed tube openings and closings constitutes a cycle of pulse generation (Figure 4). In other

words, two separate silicone tubes in the DPP are periodically opened or closed. Pulse generation with DPP can be described in terms of four phases as determined by cam rotation, which translates motor rotation to actuator linear displacement. As the cam rotates, the four actuators periodically push on the tubing segments at the positions shown in Figure 4. Actuator 1 pushes on the tubing segments at positions 1 and 6 (p1 and p6) simultaneously, and actuator 3 squeezes the tubing segments at positions 3 and 4. Actuators 2 and 4 squeeze tubing segments at p 2 and p5, respectively, and cause the dialysate in the tube to move in the required direction. For pulse generation by the dialysate pump, as the cam rotates from $\theta=0^{\circ}$ to 90°, the p2 tubing segment opens and p1 closes, and these processes overlap such that pure dialysate fills p2 tubing. While p2 expands, p3 remains closed, acting as an upstream valve to prevent retrograde dialysate. These tube openings and closings are depicted diagrammatically in Figure 5. During the first phase, with p3 closed, p2 tube openness increases whereas p1 tube openness decreases. During the 2nd phase (θ =90°~180°), with p1 closed, p2 begins to be squeezed and simultaneously p3 begins to open, and pure dialysate is driven into the hemodialyzer. Closure of p1 fulfills the same function as atrioventricular valve closure during left ventricular systole, which prevents retrograde flow. Likewise, during the 3rd phase (θ =180°~270°), p3 is closed, while p1 and p2 remain closed and in the final phase (θ =270°~360°), p1 is open, and p2 and p3 remain closed in preparedness for the next filling phase. These time-delayed tube openings and closures constitute one cycle of pulse generation. In the same manner, effluent pulsations were also generated through the effluent tube, although in this case, the actions of actuators 1 and 3 were reversed, and the pulsatile flow pattern was 180° out of phase with that in the dialysate tube.



Figure 5. Changes in DPP Tube Openness at p1~p3 for Dialysate Pump (top) and at p4~p6 for Effluent Pump (bottom). Tube openness is defined as the ratio of compressed to original tube cross-sectional area. Tube openness at p1 (p6) and p3 (p4) during cycles ranged between 94% and 0%, corresponding to fully opened and completely closed, respectively. The p2 and p5 had an openness that ranged from 99% to 17%. (p1~p6, tubing segments at positions 1 to 6, respectively, as shown in Figure 4) (Reproduction was permitted by a publisher)

Theoretically, forward and backward filtration rates during one cycle of PPPHD are identical to effluent and dialysate flow rates, respectively. The moment when pure dialysate is driven to the dialyzer (i.e., during p2 squeezing), the effluent dialysate path is closed at p6. At the same time, p1 is also closed, and thus, the pure dialysate pushed into dialyzer moves into the blood stream (backfiltration), because the whole dialysate compartment is fixed and closed. Immediately after the backfiltration is completed, the effluent tubing (p5) begins to expand (i.e., p5 expansion during the 3rd phase), and since the dialysate and effluent pathways are still closed at p1 and p6, respectively, dialysate pressures in the hemodialyzer drop steeply and ultrafiltration takes place at a rate determined by effluent stroke volume.

During experiments using the revised PPPHD, the animals remained stable without any procedurally related complications. Molecular removals were satisfactory while total protein levels, albumin concentrations, and glucose levels were preserved uniformly throughout sessions (Table 2) [50]. As stated before, the DPP is additionally characterized by a lack of valves, which makes the pulsatile device simple and inexpensive, and thus, any medical-grade silicone tubes can be used as dialysate and effluent sacs. With the exception of small tubing sections at p1, p3, p4, and p5, most of the tubing is operated non-occlusively, reducing the chances of tubing rupture and spallation [51, 52].

| PPPHD | | | | | | | | | | | |
|-------|---------|---------|----------|----------|---------|---------|--------|----------|---------|---------|--|
| (h) | aPTT | PT | WBC | Hct | TP | ALB | Glu | Ca2+ | Na+ | K+ | |
| 0 | 16±14 | 6.0±2.6 | 10.5±6.1 | 28.5±4.6 | 5.3±0.4 | 3.1±0.1 | 119±7 | 12.4±0.8 | 136±5.7 | 5.7±0.6 | |
| 1 | 48±48 | 3.9±2.1 | 6.9±2.6 | 27.8±4.0 | 5.3±0.4 | - | - | - | - | - | |
| 2 | 166±149 | 4.8±1.9 | 8.0±3.1 | 28.0±3.6 | 5.6±0.7 | 3.1±0.2 | 111±4 | 11.5±0.8 | 134±4.2 | 5.1±0.6 | |
| 3 | 317±220 | 4.4±1.3 | 8.7±2.8 | 28.5±2.9 | 5.6±0.7 | - | - | - | - | - | |
| 4 | 205±69 | 3.8±0.7 | 9.2±2.7 | 27.3±3.5 | 5.3±0.4 | 3.1±0.2 | 126±44 | 10.8±0.5 | 132±3.1 | 4.3±0.5 | |
| | CHD | | | | | | | | | | |
| (h) | aPTT | PT | WBC | Hct | TP | ALB | Glu | Ca2+ | Na+ | K+ | |
| 0 | 16±6 | 3.2±1.1 | 9.3±4.1 | 30.3±6.8 | 5.7±0.4 | 3.2±0.3 | 124±10 | 11.7±0.4 | 138±4.9 | 5.9±0.2 | |
| 1 | 170±93 | 3.8±0.6 | 6.9±4.4 | 27.3±5.5 | 5.7±0.1 | - | - | - | - | - | |
| 2 | 232±125 | 4.5±0.5 | 7.8±4.8 | 28.3±6.1 | 5.6±0.2 | 3.2±0.3 | 111±8 | 11.3±0.3 | 136±5.5 | 4.2±2.4 | |
| 3 | 154±50 | 4.3±2.3 | 7.5±4.2 | 28.0±5.6 | 5.5±0.3 | - | - | - | - | - | |
| 4 | 248±150 | 6.0±1.6 | 9.1±4.7 | 26.3±5.1 | 5.2±0.3 | 3.1±0.3 | 108±10 | 10.7±0.2 | 137±5.2 | 4.9±0.7 | |

Table 2. Physiologic Parameters and Electrolytes Balance during PPPHD and CHD. (aPTT, activated partial thromboplastin time in sec; PT, prothrombin time in sec; WBC, white blood cell in 10³/µl; Hct, hematocrit %; TP, total protein in g/dl; ALB, albumin in g/dl; Glu, glucose in mg/dl) (Reproduction was permitted by a publisher)

6. Pulse push/pull hemodialysis with dual piston pump

Pulse push/pull HD is conceptually similar to the push/pull HDF method. Both modalities were devised to increase total filtration level by alternating forward and backward filtration. However, the underlying design of PPPHD significantly differs from push/pull HDF. The supplementary component required to switch from ultrafiltration to backfiltration phases or vice versa used in push/pull HDF is not needed for PPPHD because the alternating bimodal pulsation in the dialysate stream creates the cyclic repetition. In addition, the dual pulsatile device in the PPPHD unit serves as a flow equalizer.

Maintaining pre-determined flow rates and precise volume control are pre-requisites of extracorporeal renal replacement treatments for ESRD patients, particularly when using membranes with high-water permeability. Accordingly, the dual pulsatile pump integrated into the dialysate stream has been remarkably improved to achieve substantially more accurate fluid balancing, and the dual pulsation system acting on the PPPHD dialysate compartment was replaced with a dual piston pump. Figure 6 is a schematic diagram for the PPPHD system as combined with the dual piston pump. This modification allows pulse generation and push/pull actions to be achieved, not only by the novel design of the piston pump, but also by the unique control of piston movements offered. As the dialysate piston compresses the cylinder, pure dialysate is forced into the dialyzer, but at this time, the effluent stream is functionally closed at the effluent piston pump, thereby increasing dialysate compartment pressures rapidly and backfiltration occurs ($a \rightarrow b$ in Figure 7). The effluent piston then begins to expand and dialysate moves into the effluent cylinder, while the dialysate supply line remains closed at the dialysate pump. Because of effluent suction, dialysate compartment pressures fall sharply and water flux from blood lumen to dialysate occurs ($b \rightarrow c$). During the final step $(c \rightarrow a)$, pure dialysate fills the dialysate cylinder, and simultaneously used dialysate is drained.

In an *in vitro* test of PPPHD with the dual piston pump, in which bovine blood was circulated, the phenomena of push (backfiltration) and pull (ultrafiltration) were well sustained throughout, and their levels perfectly balanced those of stroke volumes of the dialysate and effluent pumps. In addition, dialysate and effluent piston pumps served as a means of controlling isovolumetic dialysate flow rates upstream and downstream of the dialyzer. Results showed the balancing error between dialysate and effluent piston pumps was less than 0.09% of total dialysate volume. During the 4-hour session, total dialysate volume supplied to the dialyzer is 95.8L, and 95.7L of the used dialysate was collected during the same period. Furthermore, TMPs clearly cycled positive and negative due to huge fluctuations in hydraulic dialysate pressures (Figure 8). Despite the use of a peristaltic roller pump for blood, the blood pressures acquired during PPPHD showed an obvious fluctuation which was perfectly synchronized with dialysate pressure pulsation. Generally, peristaltic roller pumps create small fluctuations in flow and pressure because of the way they squeeze tubing. However, the blood pressure fluctuations acquired during PPPHD were much larger than that observed with peristaltic roller pumps during conventional HD, providing clear evidence of dialysate flux to the blood stream. Hydrostatic dialysate pressures were approxi-



Figure 6. Circuit Diagram for PPPHD with Dual Piston Pump.

mately 620~660 mmHg during the backfiltration phase and -480~-520 mmHg during the ultrafiltration phase, which correspond to the positive and negative TMPs of 400~420 mmHg and -460~-506 mmHg, respectively.

In addition, the optimal use of transmembrane pressures and enhanced convective mass transfer translates into a significant increase of molecular removal. Even though no significant difference was observed with respect to clearances of low molecular weight substances, the inulin clearances were increased significantly for the PPPHD versus the conventional high-flux HD (CHD) mode. In addition, there is a clear tendency that the proportionate increase (%increase) of solutes clearances between the PPPHD and CHD was increased as the molecular weights increase.

PPPHD with the dual piston pump is also versatile and can be easily converted to conventional high-flux HD mode. Time-controlled piston operations perform the push and pull operations, but when the two piston movements are synchronized alternately (that is, dialysate piston compression and effluent piston expansion or dialysate piston expansion and effluent piston compression occur simultaneously), dialysate passes through the hemodialyzer without significant volume exchange. In this situation, the two piston pumps serve as a flow equalizer only and dialysis is largely achieved by diffusive mass transfer.



Figure 7. Three Phases for Push/Pull Generation for the PPPHD with Dual Piston Pump.



Figure 8. Pressure Profiles during PPPHD treatment (mBP, mean blood pressure; mDP, mean dialysate pressure; TMP, transmembrane pressure defined by mBP-mDP)

7. Conclusion

Much evidence shows that HDF delivers better dialysis outcomes than high-flux HD, and these benefits have been attributed to the higher convective doses permitted during HDF. In addition, advances in water treatment allow ultrapure replacement fluid to be prepared in real time, which further inhibits the inflammation risk in the ESRD patients [53]. In this chapter, the author reviews HDF techniques that are based on the push/pull operation. Push/pull based HDF techniques were derived by considering the time-split phase separation, which is based on the notion that the repetitive ultrafiltration contributes to the increase in the total filtration volume and convective mass transfer. While the push/pull HDF requires the use of a separate device so that dialysate pressures are regulated instantaneously, the pulse push/pull method employs the pulsatile circulation of dialysate and effluent to effect the repetitive procedures. In addition, the devised dual piston pump in the most advanced PPPHD unit not only offers unmatched fluid balancing accuracy, but also the maximal permissible level of convective volume exchange, and the entire dialysis system for PPPHD could be substantially simplified. Based on these features of the devised PPPHD, the author believes that the PPPHD system should be further improved by being equipped with features that simplify overall dialysis treatment and enable dialysis to be performed in free-standing clinics. A dialysis unit equipped with these features may also provide treatment alternatives beyond the current thrice weekly 4-hour practice, and perhaps allow even daily home dialysis for ESRD patients.

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