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Pulse Push/Pull Hemodialysis: Convective Renal Replacement Therapy

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1. Introduction

The incidence of kidney disease is rapidly increasing worldwide, fueled by the increasing incidences of diabetes and obesity (Centers for Disease Control and Prevention, 2010), and thus, more patients with hypertension and diabetes develop end-stage renal disease (ESRD). Maintenance hemodialysis has become an established protocol for treating ESRD patients. This process is facilitated by two physical phenomena that facilitate mass transfer in purifying blood during maintenance hemodialysis. Diffusion caused by a concentration gradient between blood and dialysate contributes to the removal of uremic solutes, particularly small-size molecules. The removal of excess body water and mid-size molecules depend primarily on convective mass transfer, which results from hydraulic and osmotic pressure gradients (Daugirdas & Van Stone, 2000).

Remarkable improvements have been made in the technologies used for renal supportive dialysis treatment in ESRD patients. Polymeric membranes better prevent the transfer of pyrogenic substances into the blood stream and membrane biocompatibilities are much improved (Weber et al., 2004). The sharp molecular cut-offs of these membranes also prevent further loss of albumin during high-dose convective treatment (Ahrenholz et al., 2004). Narrow pore size distributions and improved hydraulic properties in the membranes field are matched by the evolution of various modalities for renal supportive treatment. Furthermore, better outcomes achieved by convective treatment have encouraged the use of synthetic membranes with high water permeability and sieving characteristics in clinical setups (Woods & Nandakumar, 2000), to the extent that hemodiafiltration (HDF) and volume-controlled high-flux hemodialysis (HD) are now regarded as preferred forms of convective therapy, because the retention of middle to large-sized molecules by chronic renal failure patients is closely related to renal-failure associated mortality (Leypoldt et al., 1999).

Volume-controlled high-flux HD adequately clears mid-size solutes without sterile fluid infusion. Forward filtration exceeding desired volume removal is compensated for by backfiltration (Ofsthun & Leypoldt, 1995), and thus, this modality can provide a simpler form of dialysis treatment than other treatment methods. The convective dose delivered during high-flux HD has been shown to reduce mortality in patients at risk, as defined by a serum albumin level of <4 g/dl (Locatelli et al., 2009). However, overall patient survival remains comparable to that of low-flux HD (Eknoyan et al., 2002), which presumably is caused by the limited amount of internal filtration involved due to limitations imposed by fluid dynamics and the geometric nature of the hemodialyzer.

Therefore, HDF is considered the gold standard for high-dose convective therapy, and has even been reported to reduce mortality risk as compared with high-flux HD (Canaud et al., 2006). HDF, which describes an intermittent renal supportive therapy of combined simultaneous diffusive and convective solute transport, is characterized by a large filtration volume that far exceeds the desired volume removal, and hence, external substitution is essential. In early HDF trials, a large number of sterile bags were used to supply substitution fluid, which was costly and complicated (Ledebor, 2007). However, technical advances made in the production of pyrogen-free ultrapure water allow sterile dialysate to be readily produced, which enables on-line based HDF to be used on a clinical basis. Several types of on-line HDF are clinically available that differ in terms of the ways in which external replacement fluid is administered, such as, by pre- or post-dilution. Due to their unique benefits, mixed forms of pre- and post-infusion have also been devised, such as, mixed-dilution or mid-dilution HDF (Krieter & Canaud, 2008, Pedrini & De Cristofaro, 2003). However, the inevitable complexities associated with HDF machines and patient monitoring, and the requirement for the exogenous infusion of replacement fluid is still problematic. Therefore, various modifications of HDF strategies have been proposed to integrate HDF and HD modes, that is, to increase convective dose without the requirement for external infusion. These modifications can be classified into three developmental categories; (1) to increase the internal filtration rate by increasing pressure gradients along the hemodialyzer, (2) to use independent domains for forward filtration and backfiltration, or ultrafiltration and diffusion, and (3) to alternate forward and backward filtration procedures.

In this chapter, the trials on HDF strategies undertaken without exogenous substitution infusion will be discussed in terms of their technical aspects, *in vivo* and *in vitro* efficacies and applicabilities for clinical use. This is followed by an in-depth review on pulse push/pull hemodialysis (PPPHD), a recently introduced pulsatile technique that provides infusion-free HDF.

2. HDF strategies that do not require exogenous substitution infusion

Hemodiafiltration is an intermittent renal supportive therapy that involves the process of convection and diffusion. Total filtration volumes invariably exceed desired amounts and this dehydration must be corrected in real time. Despite various modifications of the HDF techniques based on infusion modes, the need for external replacement fluid infusion has not been eliminated. Accordingly, efforts continue to be made to eliminate exogenous sterile fluid infusion during HDF sessions. 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.

2.1 Internal Filtration Enhanced HDF (iHDF)

Internal filtration (IF) is defined as the total water flux across membranes within the closed blood and dialysate compartments of a dialyzer (Dellanna et al., 1996). Volume controlled high-flux HD is a representative modality to use the internal filtration phenomenon, and provides a straightforward means of achieving enhanced convection by augmenting internal filtration rates, i.e., forward filtration and backward filtration rates. The amount of internal filtration is directly regulated by pressure gradients through the hemodialyzer. A pressure drop is inevitable, as fluid flows through a cylindrical tube, and it is expressed by Poiseuille's equation:

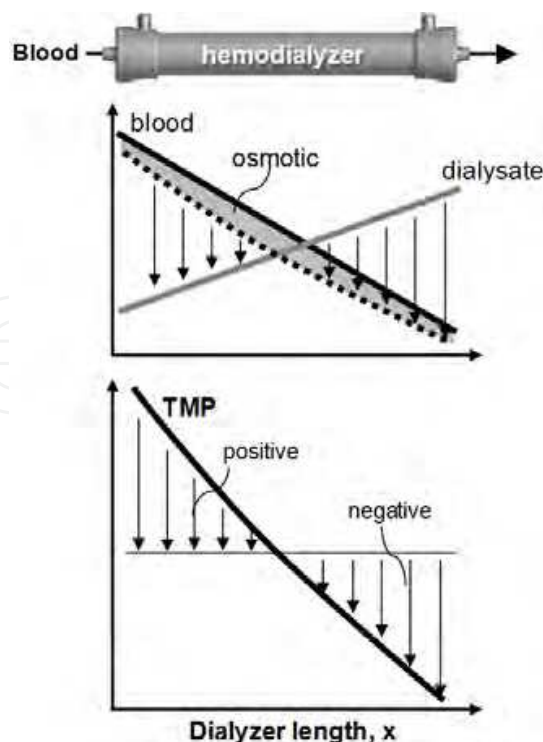


Fig. 1. Blood and Dialysate Pressure Gradient along Dialyzer Length. The sum of hydraulic and osmotic pressures is termed TMP, as $TMP = \Delta P_b - \Delta P_d - \Delta \pi$. Here, ΔP_b represents the average value of arterial and venous blood pressure, ΔP_d for average hydraulic dialysate pressures, and $\Delta \pi$ is oncotic pressures.

$$\Delta P \propto \frac{\mu L}{d^4} Q \quad (1)$$

Where, ΔP is the pressure drop, μ is the fluid viscosity, L and d are the length and diameter of the flow path, and Q the flow rates. Thus, blood and dialysate pressures drop along the dialyzers. However, because blood and dialysate flow in opposite directions, these pressure drops occur with opposing gradients, and in some region, hydraulic blood and dialysate pressures overlap (Fig. 1). In a normal countercurrent dialysis setup, 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 hydraulic blood pressures are below the sum of dialysate compartment pressure and osmotic pressure, and thus, backward filtration occurs and compensates for fluid loss in the proximal region.

2.1.1 Factors influencing internal HDF

Even though forward and backward filtration rates are highly dependent on membrane permeabilities and the degree of membrane fouling, they remain directly proportional to the positive and negative TMPs, respectively. As shown in Fig. 1, resulting TMP gradients can be readily increased by increasing blood and/or dialysate pressure drops (Fiore & Ronco, 2004, 2007). For blood, the pressure drop is proportional to blood viscosity and tube length in accord with Poiseuille's equation (Eq. 1), which shows that tube length increases pressure

differential. Likewise, blood hematocrit and total protein levels also affect the pressure drop through viscosity.

The diameter of the flow path is another important factor. Poiseuille's equation shows that the pressure drop is inversely proportional to the 4th power of tube diameter, which means that membrane (a bundle of hollow fibers) lumen diameter is the predominant factor for governing blood pressure drops, and therefore, many investigations of internal HDF have focused on dialytic efficiencies using hemodialyzers with smaller membrane diameters. In early clinical studies, beta-2 microglobulin (β 2M) removal was found to be significantly increased when membrane diameter was reduced. A 175 μ m diameter dialyzer was found to enhance β 2M clearances by factors of two and four, respectively, over 200 and 250 μ m diameter hemodialyzers (Dellanna et al., 1996). Clearances of inulin and vitamin b12 were also significantly greater with 175 μ m dialyzer than a 200 μ m dialyzer, without changing the clearances of low molecular weight solutes (Ronco et al., 2000). In addition, a mathematical model showed that internal filtration rates increase rapidly with membrane diameter, and this theoretical result was also confirmed experimentally (Mineshima, 2004, Mineshima et al., 2000). Myoglobin clearance was increased by 34% when a membrane of diameter 150 μ m, rather than 200 μ m, with the same surface area was used at the same blood flow rates. These benefits in dialytic efficiency afforded by reducing membrane lumen diameter allow internal filtration enhanced hemodialyzers to be used clinically (Lucchi et al., 2004, Righetti et al., 2010).

However, the underlying risk of hemoconcentration due to high levels of forward filtration may not be negligible. Pressure-driven filtration causes large volume losses from blood and promptly increases blood viscosity, which deteriorates membrane sieving and hydraulic capabilities. Membrane-binding by blood components like plasma proteins and clots is a major cause of permeability reductions, and inevitably diminish membranes efficiencies, particularly in the forward filtration region. Nevertheless, membrane fouling, which tends to be more of an issue during the early stage of iHDF treatment, tends to have little effect on overall membrane transfer capacity during iHDF (Yamamoto et al., 2005).

Dialysate pressure is also regulated by increasing the flow resistance on the dialysate stream. Several techniques can be used to increase dialysate flow resistances, such as increasing membrane packing density, lengthening the hemodialyzer, or placing obstacles in the dialysate flow path. Obviously, dialyzer length effectively regulates dialysate pressure drops. In one study conducted to clarify the effect of dialyzer length on solute clearance, middle-to-large uremic molecules, such as β 2M and alpha-1 microglobulin (α 1M), were shown to be better cleared by a 250 mm dialyzer than a 195 mm dialyzer (Sato et al., 2003). Dialysate pressure drop can also be manipulated by modulating membrane packing density. The higher the packing density of membrane fibers, the greater the resistance to dialysate flow, because the effective cross-sectional area available for dialysate flow decreases. Analytical and experimental studies revealed myoglobin clearances using a hemodialyzer with 71.3% packing density were slightly higher than hemodialyzers with packing densities of 52% or 60.1% (Mineshima, 2004). However, high hemodialyzer packing densities cause substantial degrees of dialysate channeling, and flow mismatch between blood and dialysate. This unmatched flow distribution leads to a loss of effective surface area and impairs the diffusion process (Gastaldon et al., 2003). Flow visualization studies in a dialyzer with a high packing density (75%) reconfirmed this disproportionate flow pattern of dialysate, as compared with standard packing density dialyzers (68%), and consequent reductions in urea clearance (Fujimura et al., 2004, Yamamoto et al., 2005). Nevertheless, a

unique design of housing wall, involving addition of a short taper to the inner housing surface effectively prevented the dialysate from being channeled (Fujimura et al., 2004).

2.1.2 Internal filtration quantification

The beneficial effects of internal HDF, such as increased middle-size solute clearances, may be quantified by evaluating internal filtration rates, because the internal filtration level is directly related to delivered convective dose. The flux across a membrane (Q) at a local region of the hemodialyzer (x) can be expressed by membrane hydraulic permeability (K_{uf} measured in ml/h/mmHg) and TMP (mmHg), as follows:

$$Q(x) = K_{uf}(x) * TMP(x) = K_{uf}(x) * (\Delta P_b - \Delta P_d - \Delta \pi) \quad (2)$$

Where, P_b , P_d and π represent the blood, dialysate and osmotic pressures. However, the flow dynamics inside the hemodialyzer are so complex that precise determinations of internal filtration rates are not available clinically. This is principally because K_{uf} across membranes is neither linearly related to the pressure gradient, nor constant at any position in the hemodialyzer (Ficheux et al., 2010). K_{uf} values are also substantially lowered by membrane fouling, which is remarkably affected by blood viscosity, coagulation, the abilities of membrane materials to bind plasma proteins, and treatment modalities. Hence, fluxes and permeabilities across membranes become parameters beyond the operator's control. Alternatively, a semi-empirical model based on clinical data has been developed to determine internal filtration rates. Using this model, internal filtration volumes and reinfusion rates were determined during internal HDF and post-dilution HDF modes, and revealed that differences between total convections (4.1 and 5.4 L/h for iHDF and HDF) well reflected differences between β_2M clearance rates (123 ± 11 and 149 ± 26 ml/min for iHDF and HDF, respectively) (Lucchi et al., 2004). In a study conducted using *in vitro* scintigraphy method to verify this semi-empirical model, the model was found to show excellent accuracies of around 97% and a prediction error of only 3% (Fiore et al., 2006).

In addition to the mathematical model, methods for performing indirect measurements of the internal filtration have also been proposed. Changes in non-permeable molecular concentrations occur in response to the water content of blood, and thus, the kinetics of water transport across membrane can be evaluated by measuring the cumulative concentration changes of non-permeable molecules (Ronco et al., 1992). Radiolabeled albumin (a non-permeable molecule) has been employed to determine the amounts of convection for hemodialyzers with reduced fiber diameters or an obstacle in dialysate stream (Ronco et al., 2000, 1998). A series of *in vitro* experiments proved that this scintigraphic method was accurate for measuring internal filtration rates, but despite its precision, its clinical application is not plausible due to the safety issue raised by the use of radio-labeled molecules and the complexities of the procedures and equipment.

Another approach to determine internal filtration is offered by Doppler ultrasonography, which measures changes in blood velocity within dialyzers. In the absence of net-filtration, blood volume depletion in the proximal portion of a hemodialyzer leads to a reduction in blood flow velocity, and after the lowest point has been reached, the blood velocity gradually increases due to backfiltration. Thus, changes in blood velocity along a dialyzer provide information on blood volume changes and on amounts of forward and backward filtration. In one study, the internal filtration rate of a 250 mm dialyzer was found to be 37.7

ml/min by Doppler ultrasonography, but only 11.1 ml/min for a standard 195 mm dialyzer (Sato et al., 2003). Doppler ultrasonography is straightforward, non-invasive, and easily used at bedside (Mineshima, 2011). However, the method is still incapable of measuring blood flow velocity precisely, particularly blood velocity deep within the membrane fiber bundle. In other words, this method is based on velocities measured in peripheral membranes, which are quite different from velocities within centrally located fibers, and as a result, deviations from true values are unavoidable.

Other techniques have also been explored in an effort to quantify the filtration phenomena, or to visualize flow distributions inside hemodialyzers, these techniques include magnetic resonance imaging (Hardy et al., 2002), computed tomography (Frank et al., 2000, J. C. Kim et al., 2008) and a computerized scanning technique (Ronco et al., 2000, 2002). However, the quantification of internal filtration using these techniques is not available clinically, due to concerns of patient safety and technical requirements.

Summarizing, internal HDF can provide a means of convective treatment by increasing internal filtration rates using specifically designed hemodialyzers, and at the same time spontaneous backfiltration compensates for fluid loss, and hence, this technique is simpler than other modalities. The hemodialyzer design for internal HDF must be optimized based on specified structural factors and on the filtration characteristics of membrane fibers. The literature suggests superior dialysis outcomes for iHDF, but the precise quantification of internal filtration remains to be determined.

2.2 Double high-flux HDF

Solute removal during extracorporeal hemodialysis, particularly for low-flux HD, is mainly facilitated by diffusion which is driven by the concentration gradient across membrane. Thus, solute clearances are highly dependent on their molecular weights. On the other hand, hemofiltration (HF) is purely convective. Thus, it could be speculated that HF delivers higher middle- to large-size solutes clearances than HD, but poorer small-size mass transfer. The additional advantages of this convective treatment include better maintenance of cardiovascular instability in ESRD patients or in ICUs. These benefits of hemofiltration encouraged investigations aimed at compensating for the inferior diffusive clearances of HF, and a hybrid configuration based on multiple membranes was introduced (Cheung et al., 1982).

Double high-flux HDF was first introduced in the early 1980's as a means of combining HD and HF. This technique was particularly aimed at significantly increasing small (diffusion) and middle-size molecular removal (convection) in order to shorten overall treatment time, and therefore, much larger surface areas were used by arranging two high-flux hemodialyzers in series, in conjunction with a extremely high blood (400-500 ml/min) and dialysate flow rate (800-1000 ml/min) and a bicarbonate dialysate (Miller et al., 1984, von Albertini et al., 1984).

This arrangement of two hemodialyzers enabled flow resistances through the two hemodialyzers to be manipulated, which permitted TMP gradients (both positive and negative) to be adjusted. A flow restrictor, placed on the intermediate blood line of two hemodialyzers, serves as a means of increasing blood pressures in the arterial-side hemodialyzer, which cause positive TMPs through this dialyzer and ultrafiltration (Fig. 2). On the other hand, blood pressure drops below dialysate pressures at the venous-side dialyzer and TMPs become negative, which leads to backfiltration (Shinzato et al., 1982).

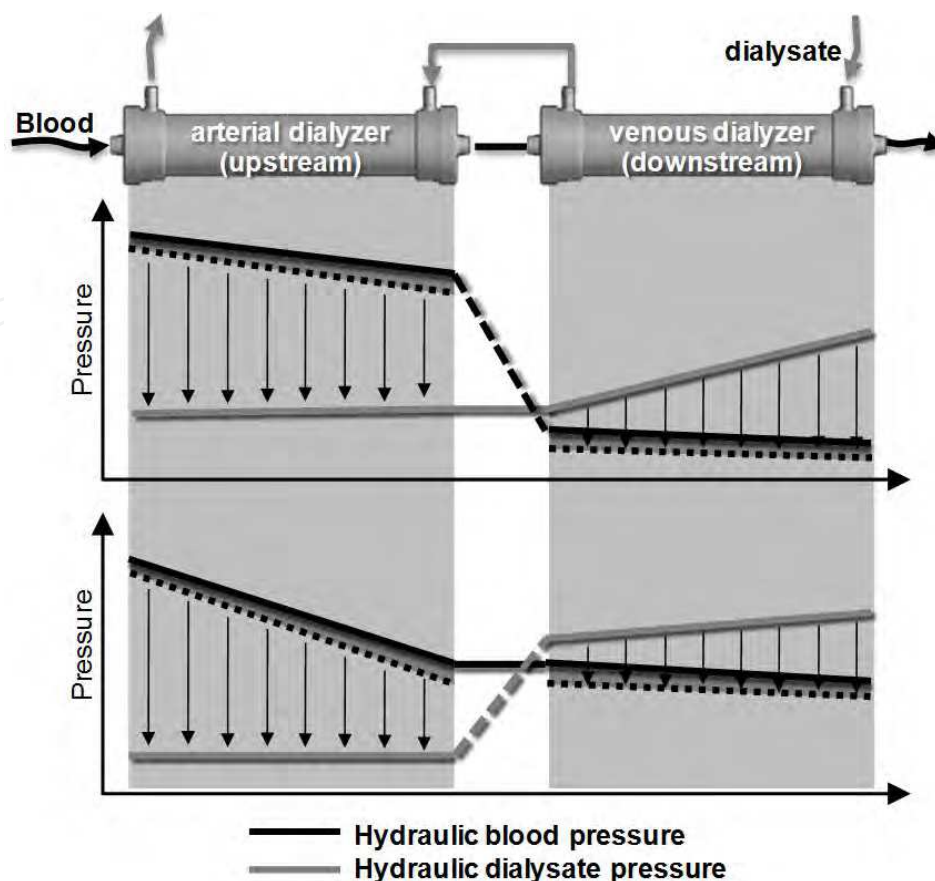


Fig. 2. Schematic Pressure Profiles during Double HDF, when a flow restrictor is placed on blood tube (upper) and on dialysate tube (below) of the two hemodialyzers.

TMP regulation is also achieved by regulating dialysate pressure. Flow resistance applied to the dialysate tubing between the two dialyzers promptly increases dialysate pressures at the venous dialyzer because blood and dialysate flow in opposing directions. Hydraulic dialysate pressures exceed blood pressures, which leads to backfiltration in the venous dialyzer. However, dialysate pressures rapidly fall in the arterial dialyzer due to flow restriction, which causes ultrafiltration in the arterial dialyzer. In addition, the high blood and dialysate flow rates used are also associated with larger pressure gradients. Hence, ultrafiltration at the arterial dialyzer at levels of exceeding those required can be promptly compensated for by backfiltration at the venous dialyzer, and thus, exogenous replacement infusion is not required for this method.

The flow resistance placed on the dialysate stream was originally made from a gauge needle assembled with a bypass line in parallel. A clamp on the bypass line forced the dialysate into the gauge needle, and created flow resistance in dialysate stream. The flow resistance in this configuration is fixed, and the amounts of ultrafiltration and backfiltration cannot be adjustable externally. Hence, the means of creating resistance to dialysate flow was improved in the advanced version, termed convection-controlled double high-flux HDF, in which variable and controllable flow resistances were integrated (Pisitkun et al., 2004).

Therefore, together with these features, this modality achieved unmatched depurative outcomes, as demonstrated by far higher uremic molecular clearances regardless of molecular size (Cheung et al., 1982, Shinzato et al., 1982, von Albertini et al., 1985). Furthermore, increased clearances allowed treatment times to be shortened (Miller et al.,

1984, von Albertini et al., 1984). Solute removal in a relatively short time (e.g., 2 hours) may cause greater rebound of uremic solute levels after post-dialysis equilibrium, thus solute removal rates in trials of double HDF far surpassed the removal rates desired during hemodialysis, achieving two and half times higher clearances over 2 hours as was achieved over 4 hours in conventional HD mode. These results were also confirmed by comparing treatment modalities. Double high-flux HDF attained significantly greater $\beta_2\text{M}$ reduction and Kt/V_{UREA} values than high-flux HD, and showed comparable $\beta_2\text{M}$ clearance to that of on-line HDF (Susantitaphong et al., 2010, Tiranathanagul et al., 2007). Furthermore, the beneficial effect of this technique on patient survival was also suggested in a long-term assessment. In this study, double high-flux HDF was compared with high-efficiency or high-flux HD modes in terms of treatment time, Kt/V and standardized mortality ratio over 6 years. Kaplan-Meier Survival analysis revealed a significantly lower mortality ratio for double HDF versus USRDS (0.41 and 1, respectively) despite the shortened treatment time (Bosch et al., 2006).

However, concerns have been raised regarding the use of two hemodialyzers in this double HDF technique, such as, possible increases in treatment cost and system complexity. One possible way of overcoming these issues involves the reuse of dialyzers, although regulatory guidelines on renal replacement practices in some countries do not permit reuse. Another concern arises from the large amount of cross-membrane flux. In particular, a large quantity of backfiltration should be assured by the strict and regular verification of water quality (Bosch & Mishkin, 1998), although this too could increase treatment-related costs. One positive aspect is that the venous dialyzer acts as a final barrier to pyrogen transfer.

Double high-flux HDF emerged as a result of an effort to increase treatment efficiencies and shorten treatment times by maximizing both diffusive and convective mass transfer. Many observations have confirmed the high solutes clearances across a wide spectrum of molecular weights, which are the results of the unique features of this method. In particular, the unique control of hydraulic pressures possibly gives this unit the ability to regulate convective dose. However, the widespread implementation of this technique may require the identification of patients capable of tolerating treatment and the overcoming of the above-mentioned underlying concerns.

2.3 Paired filtration dialysis with endogenous reinfusion (HFR)

Another two-chamber technique for obtaining short and efficient HDF treatment is the so-called paired filtration dialysis (PFD). Like double HDF, PFD is also a strategy of simultaneous HD and HF treatment aimed at increasing both diffusive and convective clearances, but its design principles separate convection from diffusion (Ghezzi et al., 1989, 1987, Ronco et al., 1990). A hemofilter with a relatively small surface area is combined with a hemodialyzer in this sequence (Fig. 3). Ultrafiltration purely occurs at the hemofilter and then blood is dialyzed continually through the hemodialyzer.

The convection, which is not connected with diffusion, can minimize interactions between diffusion and convection, and enable the precise quantification of convective clearance (Ghezzi et al., 1987). Total resulting clearances during HDF are always lower than the sum of convective and diffusive clearances, which is attributed to the reciprocal interactions of these two processes (Gupta & Jaffrin, 1984, Sprenger et al., 1985). As diffusion and convection occur within the same membranes, the contribution made by convection to total clearances is diminished by the presence of diffusion, particularly for highly diffusive

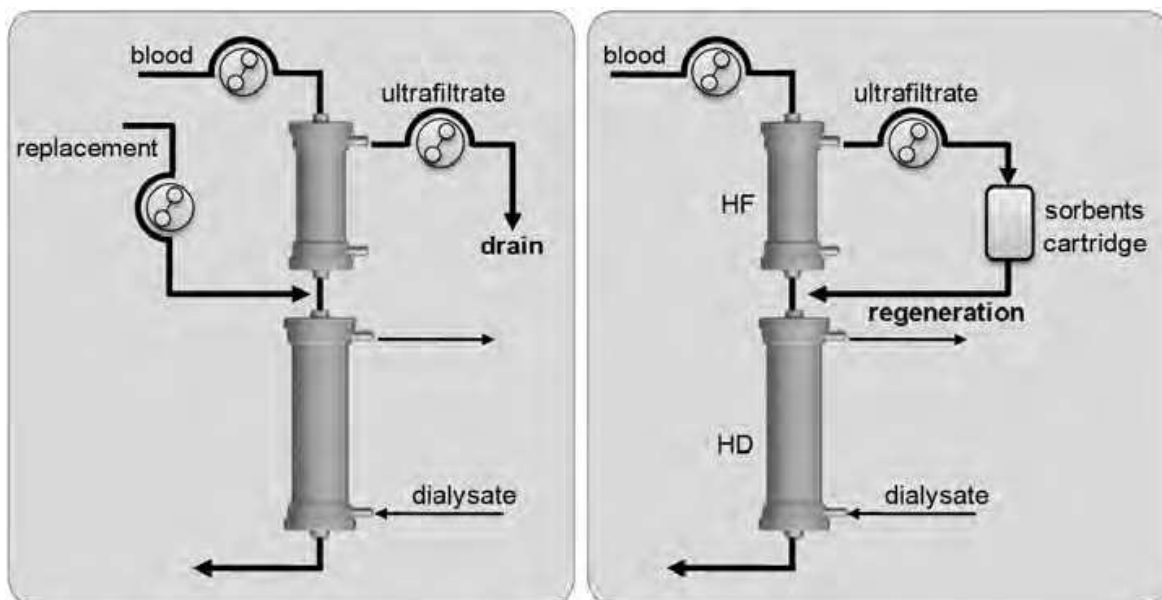


Fig. 3. PFD (left) and HFR (right)

molecules. This is because the concentrations of these molecules promptly decreases along the dialyzer length due to diffusion, and in this situation, solute concentrations in ultrafiltrate are reduced. Likewise, diffusive mass transfer is also disrupted by the presence of convection. High filtration rates throughout the entire membrane causes the formation of protein gel layer, which acts as secondary resistance; that is, the membrane fouling decreases membrane permeability and filtration rates, and consequently, convective clearances are substantially diminished. Furthermore, molecular sieving coefficients are also reduced because of protein binding, which eventually reduces membrane diffusivity (Morti & Zydny, 1998). In the PFD technique, however, convection occurs in a separate region from diffusion and theoretically, no interference between diffusion and convection occurs.

In addition, independent convection allows ultrafiltrate volume to be regulated. The total amount of ultrafiltration surpasses desired volume removal, and sterile replacement fluid is administered at the mid-point between the hemofilter and hemodialyzer shown in the Fig. 3. In addition, desired net-volume removal by PFD can be achieved either by balancing ultrafiltration and reinfusion through the hemofilter, or by balancing internal filtration in the hemodialyzer.

Likewise, as for other convective treatments, simultaneous but separate convection of PFD permitted higher depurative outcomes than standard HD mode, and even allowed treatment times to be reduced (Vanholder et al., 1991). Dialysis times could be reduced to as little as 150 minutes per session in patients with a body weight of < 61 kg, but normally 3 hours was required for larger patients, without compromising dialytic tolerance and efficiency (Botella et al., 1991). PFD also achieves dialytic efficiencies comparable with HDF despite significantly lower filtration rates (40 versus 75 ml/min, respectively) (Bufano et al., 1991), which is primarily due to minimal interference between diffusion and convection. However, β_2 M removal is smaller than in HF mode (Marangoni et al., 1992). Other benefits of PFD may include the minimal use of backfiltration in the hemodialyzer and superior biocompatibility (Panichi et al., 1998). Since convection is achieved at the hemofilter, dialysis can be accomplished with minimal internal filtration and pressure gradients.

However, PFD obviously requires the exogenous substitution infusion because of larger amounts of ultrafiltrate than required volume removal. One unique feature of PDF is that the ultrafiltrate is not mixed with the dialysate. In addition, the ultrafiltrate has a similar composition of plasma. On the other hand, the replacement fluid must possess a physiologic balance of electrolytes after taking into account preexisting deficits or excesses, and also should be sterile and free of pyrogenic substances. These features of ultrafiltrate and infusate enables the regeneration of ultrafiltrate to replace exogenous infusate, and ultrafiltrate for replacement purposes was successfully regenerated using an uncoated charcoal column (Ghezzi et al., 1991, 1992) (Fig. 3). As ultrafiltrate passes through the adsorbent column, solutes with a wide spectrum of molecular weights are adsorbed with the exception of some small molecules (e.g., urea and phosphate), but electrolytes and bicarbonate freely pass through the column. In addition, since small molecules that are not captured by the adsorbent can be removed by diffusion at the hemodialyzer, the regenerated ultrafiltrate is successfully applied as replacement fluid (Sanz-Moreno & Botella, 1995). Trace elements, such as manganese, selenium, arsenic, cadmium, mercury, lead, chromium, and zinc, also remain unaltered after passing through the adsorbent column, whereas copper is completely retained by the charcoal (de Francisco et al., 1997). Adsorption capacities were further increased by combining hydrophobic styrenic resin along with uncoated charcoal, because the resin has a high binding affinity for several mid molecular weight species, such as, β 2M (Marinez de Francisco et al., 2000) and homocysteine (Splendiani et al., 2004), or free immunoglobulin light chains (Testa et al., 2010).

The other benefits of this regenerated ultrafiltrate include a better acid-base balance due to the reinfusion of endogenous bicarbonate (de Francisco et al., 1997), and also the not inconsiderable advantage of combining high convection without compromising physiologic molecule loss. Ultrafiltrate has a composition similar to that of plasma and contains huge numbers of polypeptides and other beneficial substances, such as, hormones, amino acids, and vitamins (Weissinger et al., 2004), and ultrafiltrate regeneration allows these beneficial nutrients to be reinfused (La Greca et al., 1998). In terms of plasma amino acid levels, no significant changes in their intradialytic levels occur during HFR, whereas a ~25% reduction occur during acetate-free biofiltration (Borrelli et al., 2010).

A number of clinical studies on ESRD patients have revealed that HFR remarkably improve dialytic efficiencies and solute removal over a wide molecular weight ranges, such as, the removal of uremic marker molecules (β 2M, leptin and free immunoglobulin light chains) (Bolasco et al., 2006, S. Kim et al., 2009, Testa et al., 2006), cardiovascular risk factors (homocysteine) (Splendiani et al., 2004), inflammatory cytokines (CRP, IL-1, IL-6), and biomarkers of oxidative stress (ox-LDL, IL-1 β) (Calo et al., 2011, Testa et al., 2006). In a comparison between HFR and on-line HDF, both were found to be highly biocompatible and to considerably reduce inflammatory markers, such as, CRP and IL-6 (Panichi et al., 2006). One technical variance of HFR is the repositioning of convection and diffusion. The change of sequence during HFR significantly enhanced reductions in urea and β 2M, possibly due to the less saturated use of adsorbents, and also reduced cytokine levels, e.g., IL6 and TNF α , more than conventional HFR (Meloni et al., 2004, 2005).

In addition, HFR appears to be more beneficial at reducing oxidative stress and the risk of atherosclerotic cardiovascular disease than standard HD mode. A comparative study of HFR and low-flux bicarbonate HD revealed that HFR reduced not only the plasma level of oxidized low-density lipoprotein (LDL), but also the mRNA production of p22phox and PAI-1 (palsminogen activator inhibitor 1), whose protein expressions are known to be

closely related to inflammation and oxidative stress (Calo et al., 2007). Furthermore, plasma total antioxidant capacity (TAC) and antioxidant enzymes activities were found to be lower for HFR than high-flux HD (Gonzalez-Diez et al., 2008).

However, contrary results have also been presented. For ESRD patients who undertook bicarbonate HD and then were switched to HFR, nutritional and inflammatory parameters remained unchanged over a year. Neither serum β 2M nor PTH levels varied over the course of time, which led to the conclusion that although the change to HFR from bicarbonate HD is safe and tolerated, it is not associated with an improvement in nutritional or inflammatory parameters, or a reduction in β 2M levels (Bossola et al., 2005). Prolonged, larger-scale clinical studies for HFR are warranted.

More recently, a significant decrease was observed in cardiac troponin (cTnT) levels, a marker of myocardial damage and cardiac hypertrophy, throughout HFR sessions when using acetate-free dialysate, but cTnT increased after HFR using dialysate containing acetate. These results show that further explanation is required for the correlation between cTnT and acetate (Bolasco et al., 2011). However, both hemoglobin (Hb) levels and erythropoietic-stimulating agent (ESA) doses were not related to the presence of acetate. Hb levels increased, but ESA requirements tended to reduce continually during the 9-month study period (Bolasco et al., 2011).

In summary, PFD is a HDF technique whereby ultrafiltrate is isolated from dialysate. Renal replacement therapies, facilitated by convection and diffusion, are still unsatisfactory for removing uremic toxins, and thus, adsorption as a third mechanism has been employed in HFR units. Adsorption during HFR allows convective treatments to be performed by the endogenous reinfusion of ultrafiltrate. Even if the loss of beneficial substances during HDF is inevitable, ultrafiltrate reinfusion reduces these losses to a minimum, like low-flux HD. Another feature of ultrafiltrate regeneration is the guaranteed purity of substitution fluid. Substitution is continuously obtained from ultrafiltrate, but the ultrafiltration, adsorption, and reinfusion system is totally closed during HFR, and therefore, excludes any possibility of contamination and ensures superior biocompatibility. However, despite these outstanding features, this unit has complications and associated costs. Furthermore, technical improvements in the preparation of ultrapure dialysate are expected to further cut the cost of preparing sterile, ultrapure replacement fluid, and this could increase the cost gap between HFR and on-line HDF.

2.4 Push/Pull Hemodiafiltration

A similar but simpler HDF strategy has been also introduced. This system relies on alternate repetitions of forward and backward filtration during dialysis treatment, and thus, it was named push/pull HDF. When the infusion-free HDF technique using a serial arrangement of two hemodiafilters was described in the early 1980's, the push/pull concept was devised to eliminate the need for two hemodiafilters. It is obvious that repetitive ultrafiltration can increase total filtration volume, but such a system also requires a means of repeating backfiltration (Usuda et al., 1982). Thus, a redundant dialysate bag is integrated downstream of the hemodialyzer, which is connected to the dialysate stream by a bidirectional peristaltic pump. The push/pull action that is accomplished by this bidirectional pump is responsible for alternating the evacuation and replenishment of the bag. During normal operation, inlet and outlet dialysate flow rates are equally maintained and the desired volume removal is achieved by a separate ultrafiltration pump. In this situation, when the bidirectional pump pulls a portion of dialysate into the bag (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 level as dialysate removal from the dialysate compartment. Soon after the ultrafiltration completes, the pump operates in reverse and pushes the dialysate in the bag into the dialysate stream, which causes a volume overload in the dialysate compartment. The surplus dialysate in the closed dialysate compartment is then moved to the blood compartment (backfiltration). In the same manner, 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 plasma. This repetitive ultrafiltration obviously contributes to convective mass transfer and increases the reductions of small-sized (urea) or mid-sized (β_2M) molecules as compared with HF or HD, respectively (Shinzato et al., 1989). On the other hand, repetitive backfiltration during push/pull HDF prevents volume depletion. In addition, the repetitive backflushing of dialysate also helps prevent membrane binding (Usuda et al., 1982).

However, disposable bags and separate bidirectional peristaltic pumps make this unit complicated and increase treatment costs. Instead, a double-chamber cylinder pump was devised with two independent chambers and a reciprocal piston; that is, each chamber is connected to either dialysate or the blood stream (Tsuruta et al., 1994), as seen in Fig. 4. 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 double-chambered pump. Since the blood volume that returns to the blood-side 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 becomes depressurized, which leads 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.

Furthermore, the reciprocating movement of the piston is regulated by pressure differences between the two chambers of the cylinder pump (i.e., $P_b - P_d$). The rotation torque of the driving motor attached to the piston can be expressed in accord with TMP (i.e., torque = $TMP \times S \times L \times \sin\theta$). Voltage applied to the motor is adjusted so that the TMP is set at 400 mmHg during forward filtration, but at -400 mmHg during the backward filtration phase, that is, pressure-controlled push/pull HDF can maintain transmembrane pressures at the maximum permissible level throughout treatment (Shinzato et al., 1994). 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 in 1.5~1.7 seconds.

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 (Shinzato et al.,

1994). Push/pull HDF tends to relieve symptoms like arthralgia (joint pain), irritability, pruritus, and insomnia more rapidly than conventional HD (Maeda et al., 1990, Maeda & Shinzato, 1995, Shinzato et al., 1995). Furthermore, the optimal maintenance of membrane permeabilities by prompt backfiltration has the added benefit of considerably inhibiting albumin loss in addition to increasing convection and diffusion (Shinzato et al., 1996). Albumin loss is inevitable when using membranes with high water permeabilities and sieving characteristics (Combarrous et al., 2002). 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 (Ahrenholz et al., 2004). In addition, filtration-induced elevated albumin concentration at the inner membrane wall also aggravates the albumin loss (Miwa & Shinzato, 1999). 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 (Shinzato et al., 1996).

However, this modality still requires the use of a separate device so that dialysate pressures are regulated instantaneously. In addition, no clinical observation has been conducted to examine the long-term clinical effect of pressure-controlled push/pull HDF versus on-line HDF, which is now regarded as a convective therapy in dialysis practice. Push/pull HDF is based on repetitive dilution at a rate of approximate 15 ml per 1.7s cycle, which exceeds blood flow rates (3.3~5 ml/s). Hence, push/pull HDF is assumed to be close to pre-dilution mode HDF (Shinzato & Maeda, 2007). 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.

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 forward filtration and backfiltration instead of dividing ultrafiltration and backfiltration regions. Pressure-controlled push/pull HDF using a double-chambered cylinder pump 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, which further inhibits albumin loss. However, given the advances represented by membranes with high β_{2M} sieving coefficients (>0.8), but very small albumin sieving coefficients (<0.01) (Ronco et al., 2002), the differences between push/pull HDF and high-flux HD with respect to β_{2M} removal may be reduced, and albumin leakage less problematic. To an extent in modern dialysis practice, albumin permeable membranes are even considered to remove non-soluble and/or much larger molecules (De Smet et al., 2007, Samtleben et al., 2003). 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.

3. Pulse Push/Pull Hemodialysis (PPPHD)

Flow patterns, that is, pulsatile versus non-pulsatile, remain topics of research for treatments requiring extracorporeal blood circulation. Despite controversy, blood pulsation has been

accepted to have a benefit during cardiopulmonary bypass, because it achieves greater perfusion to peripheral vessels and end-organs (Dapper et al., 1992, Orime et al., 1999). Furthermore, blood pulsation in a pediatric CRRT¹ animal model was found to deliver adequate performance over a 2-hour period in terms of ultrafiltration rates and cross-filter blood pressure drops (Lopez-Herce et al., 2006, Ruperez et al., 2003). In addition, it was also found that the pulsatile flow tends to enhance ultrafiltration rates versus non-pulsatile flow (Lim et al., 2009, Runge et al., 1993), which attributed to an increased rheological power of pulsatile flow. However, little clinical or experimental evidence is available that explains the efficacy of pulsatile flow during dialysis. Pulse push/pull HD is a convection enhanced dialysis treatment, based on the use of pulsatile flows to achieve a cyclic repetition of forward and backward filtration. As explained in the previous section, the repetitive manner of ultrafiltration and backfiltration contributes substantially to total volume exchange and convective mass transfer.

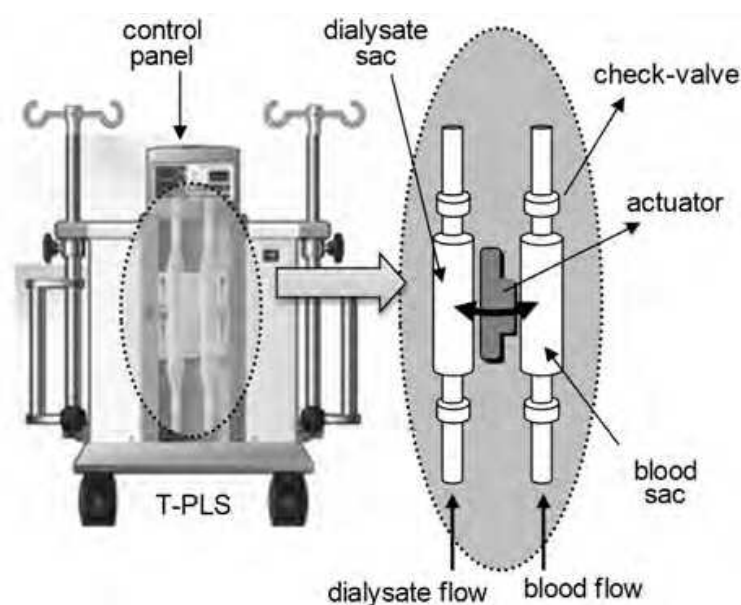


Fig. 5. T-PLS pump for the original PPPHD

3.1 Pulse push/pull HD

Repetitive procedures of ultrafiltration and backfiltration during PPPHD are achieved by replacing conventional roller pumps with pulsatile pumps for both blood and dialysate. During an early trial, a T-PLS pump (Twin Pulse Life Supporter, AnC Bio Inc., Seoul, Korea) was used as pulsatile pumps for blood and dialysate (K. Lee et al., 2008). The T-PLS consists of blood and dialysate sacs, a reciprocating actuator, and a motor-cam assembly (J. J. Lee et al., 2005). The actuator is located between blood and dialysate sacs (Fig. 5). When the actuator squeezes the blood sac, blood in the sac can move only in the forward direction due to the presence of 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 these reciprocating movements create pulsatile flow. By setting their phase difference at 180° degrees, the respective pushing phases of blood and dialysate pumps

¹Continuous Renal Replacement Therapy

alternate, and TMPs cycle between positive and negative, which drive consecutive periods of ultrafiltration and backfiltration.

The hemodialytic efficiencies of PPPHD have been demonstrated *in vitro* and also *in vivo*, and these studies have shown that PPPHD substantially improves the clearances of uremic marker molecules, particularly for mid-sized molecules (Table 1) (K. Lee et al., 2008), which is believed to be due to a higher level of total filtration. Pressure profiles also showed obvious oscillations of TMPs throughout treatment, and their magnitudes were significantly larger than those observed in conventional hemodialysis (CHD) mode.

Group	BPM	QB	QD	Clearance (ml/min)			
				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)

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 (K. Lee et al., 2008). 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 1.68±0.02 and 1.31±0.03 seconds, respectively. Since protein concentration polarization on the blood-side membrane develops during the forward filtration phase and it is reduced by backfiltration, membrane convective capacity might be better maintained during PPPHD than during CHD, showing smaller reductions in post-dialysis hydraulic permeabilities (K. Lee et al., 2008). Furthermore, PPPHD-treated animals were tolerably sustained and their physiologic parameters were stable.

Pulse push/pull HD is conceptually similar to push/pull HDF. Both modalities were devised to increase total filtration level by alternating forward and backward filtration. However, the underlying design of PPPHD differs from push/pull HDF, and thus, the supplementary component required to switch from ultrafiltration to backfiltration phases or vice versa used in push/pull HDF was eliminated for PPPHD and the entire system was remarkably simplified.

3.2 Modification of PPPHD

Repetitive ultrafiltration and backfiltration offers a simple and efficient HDF strategy. However, the pulsatile circulation of blood during extracorporeal renal replacement treatment appears to be potentially problematic. In particular, instant suction generated by a pulse pump through a narrow needle or 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 risk of circuit aeration, but also lead to a failure to maintain predetermined blood flow rates (Depner et al., 1990, Teruel et

al., 2000). Furthermore, the quantification of accurate filtration rates throughout treatment remains implausible.

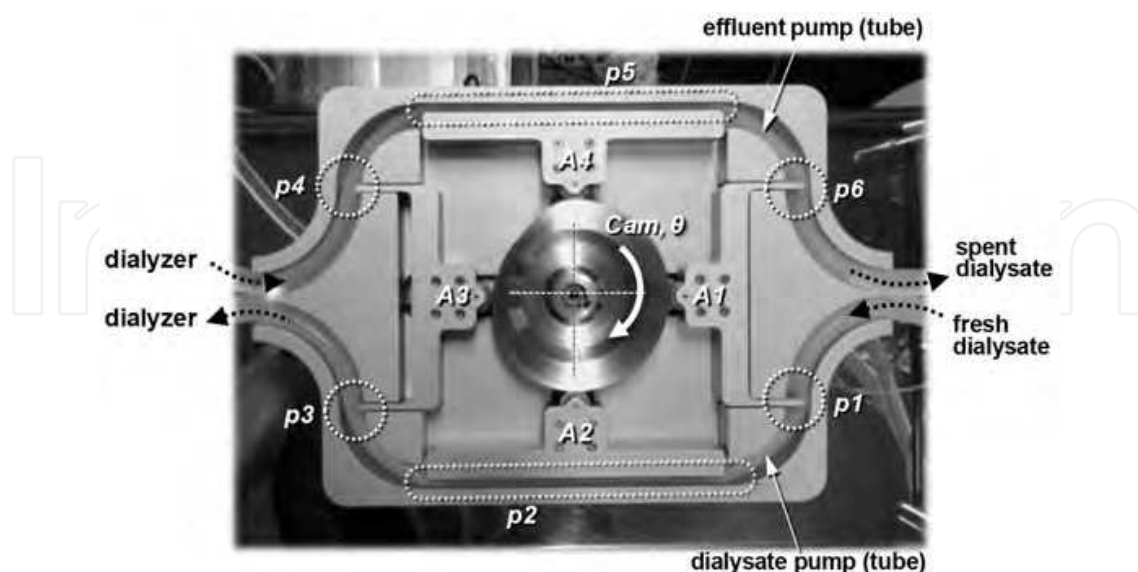


Fig. 6. Dual Pulse Pump (DPP). Its body is made of an aluminum alloy, and comprises a base plate, a unidirectional electric motor (not seen), a cam, and four actuators. It can also contain two separate silicone tubes. Pulsatile flow is generated by squeezing each dialysate and effluent tubing segments. (A1~A4, actuators 1 to 4; p1~p6, silicone tubing segments at positions 1 to 6, respectively)

Hence, we revised PPPHD and many aspects of the original PPPHD were retained in the revised version, including an alternating water flux across the membrane, but blood pulsation was excluded. This was achieved by employing dual pulsation in the dialysate stream, that is, pulsatile devices in the dialysate stream both upstream (a dialysate pump) and downstream (an effluent pump) of the dialyzer. 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, the dialysate pressure is the only variable that regulates TMP in the revised unit. Therefore, an assumption was made; (1) dialysate compartment pressures must be far higher than blood-side pressures when pure dialysate is forced into the dialyzer (that is, when the dialysate sac is squeezed), but (2) dialysate pressures drop to lower than blood pressures during effluent pump expansion. For this purpose, the dialysate and effluent pumps are replaced with a dual pulse pump (K. Lee et al., 2008).

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 (Fig. 6). 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 the Fig. 6. Actuator 1 pushes 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

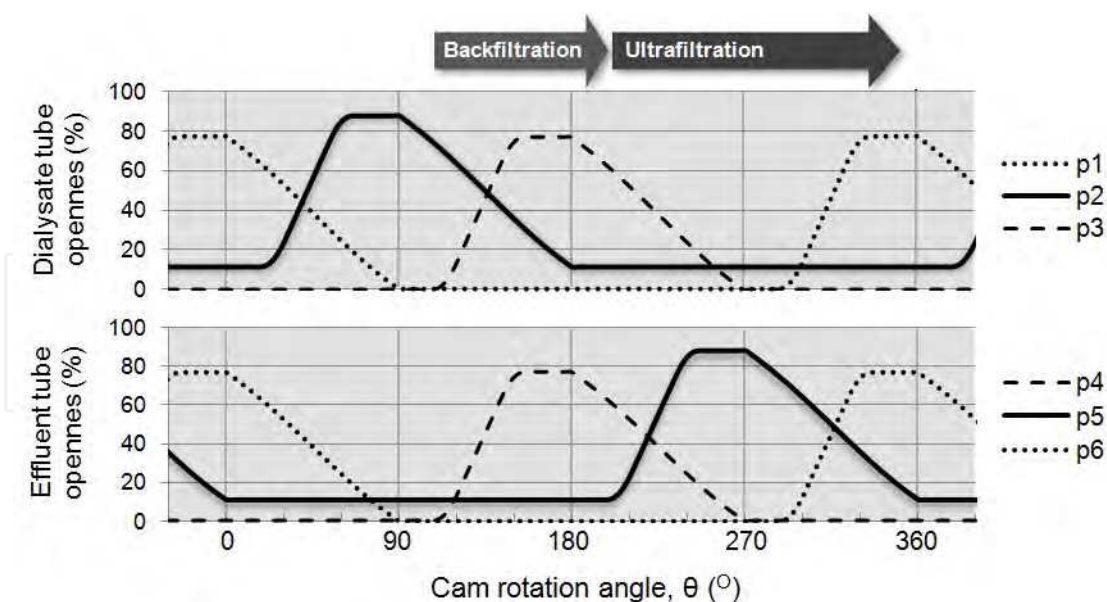


Fig. 7. Tube Openness Diagram for Dialysate (upper) and Effluent Pump (below) of DPP.

2 and 4 squeeze tubing segments at p 2 and p5, respectively, and caused the dialysate in the tube to move in the required direction. The first phase was defined as a cam rotation angle (θ) between 0 and 90°. Likewise, the 2nd and 3rd phases were defined as cam rotation angles between 90°~180° and 180°~270°, respectively. 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 also depicted in the tube openness diagram in Fig. 7. Tube openness is defined as the ratio of compressed tube diameter to the original internal diameter, as described elsewhere (K. Lee et al., 2008). During the first phase, with p3 closed, p2 tube openness increases whereas p1 tube openness decreases. During the 2nd phase ($\theta=90^\circ\sim 180^\circ$), 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. During the 3rd phase ($\theta=180^\circ\sim 270^\circ$), p3 is closed, while p1 and p2 remain closed and in the final phase ($\theta=270^\circ\sim 360^\circ$), 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.

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 should move 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), 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 animal experiments using the PPPHD, in which we used an acute canine renal failure model (achieved by ligating renal arteries and veins), the animals remained stable without any procedurally related complications. Molecular removals were satisfactory, and total protein levels, albumin concentrations, and glucose levels were preserved uniformly throughout PPPHD sessions (Table 2). Furthermore, TMPs clearly cycled positive and negative due to huge fluctuations in hydraulic dialysate pressures (Fig. 8). In addition, 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 for conventional HD, which provides evidence of dialysate flux to the blood stream or vice versa (Fig. 8).

In addition, as stated before, the DPP is 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. Furthermore, with the exception of small tubing sections at p1, p3, p4, and p5, most of the tubing is operated non-occlusively, which reduces the probabilities of tubing rupture and spallation (W. G. Kim & Yoon, 1998, Leong et al., 1982).

PPPHD

(h)	PCV	TP	ALB	Glu	Ca2+	Na+	K+	BUN	Crea
0	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	90.3±12.7	6.5±0.9
2	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	63.7±5.7	4.6±0.7
4	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	47±7.2	3.8±0.4

Table 2. Animal Experiment Results. PCV, packed cell volume (%); TP, total protein (g/dl); ALB, albumin (g/dl) ; Glu, glucose (mg/dl); BUN, blood urea nitrogen (mg/dl); Crea, creatinine (mg/dl)

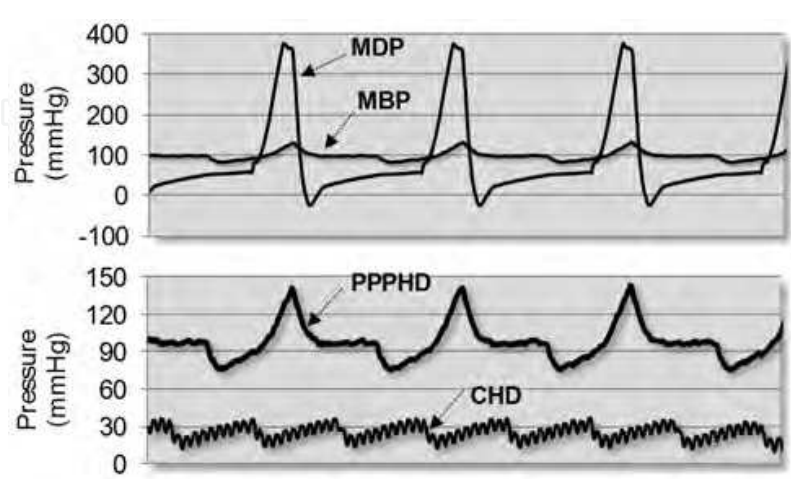


Fig. 8. Pressure Profiles during PPPHD treatment (upper), and Changes in Blood Pressures for PPPHD and CHD (below). (MDP, mean dialysate pressure; MBP, mean blood pressure; CHD, conventional HD)

3.3 Fluid management in PPPHD

Recently, the dual pulsatile pump integrated into the dialysate stream has been remarkably ameliorated to achieve a substantial increase in the accuracy of volume control. 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. Therefore, the dual pulsation system acting on the PPPHD dialysate compartment was replaced with a dual piston pump, as shown in Fig. 9. This modification allows pulse generation and push/pull to be achieved, not only by the novel design of the piston pump, but also by the unique control of piston movements offered (Fig. 10). 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, and thus, dialysate compartment pressures increase rapidly and backfiltration occurs (Phase 1). The effluent piston then begins to expand and dialysate moves into the effluent cylinder, while the dialysate supply line is still closed at the dialysate pump. Because of effluent suction, dialysate compartment pressures fall sharply and water flux from blood lumen to dialysate occurs (Phase 2). During the final step, pure dialysate fills the dialysate cylinder, and simultaneously used dialysate is drained (Phase 3).

In an *in vitro* test of PPPHD with the dual piston pump, in which bovine blood was circulated through the blood lumen of the hemodialyzer at 200 ml/min and isotonic saline solution was used as dialysate at the rate of 400 ml/min, the phenomena of push (backfiltration) and pull (ultrafiltration) were well sustained throughout sessions, and their levels perfectly matched those of stroke volumes of the dialysate and effluent pumps, respectively. In addition, as was expected, dialysate and effluent piston pumps served as a flow equalizer, and controlled isovolumetric dialysate flow rates upstream and downstream of the dialyzer. Hydrostatic dialysate pressures were maintained at 520~700 mmHg during the backfiltration phase (Phase 1) and at -400~-540 mmHg during the ultrafiltration phase (Phase 2).

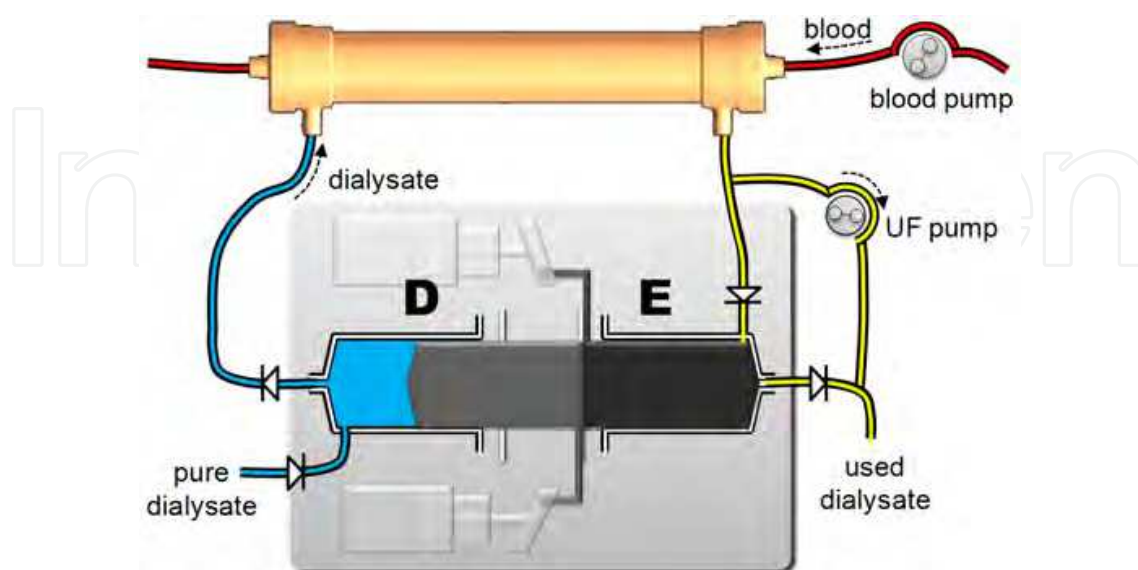


Fig. 9. Schematic Diagram of PPPHD with Dual Piston Pump. (D, dialysate pump; E, effluent pump)

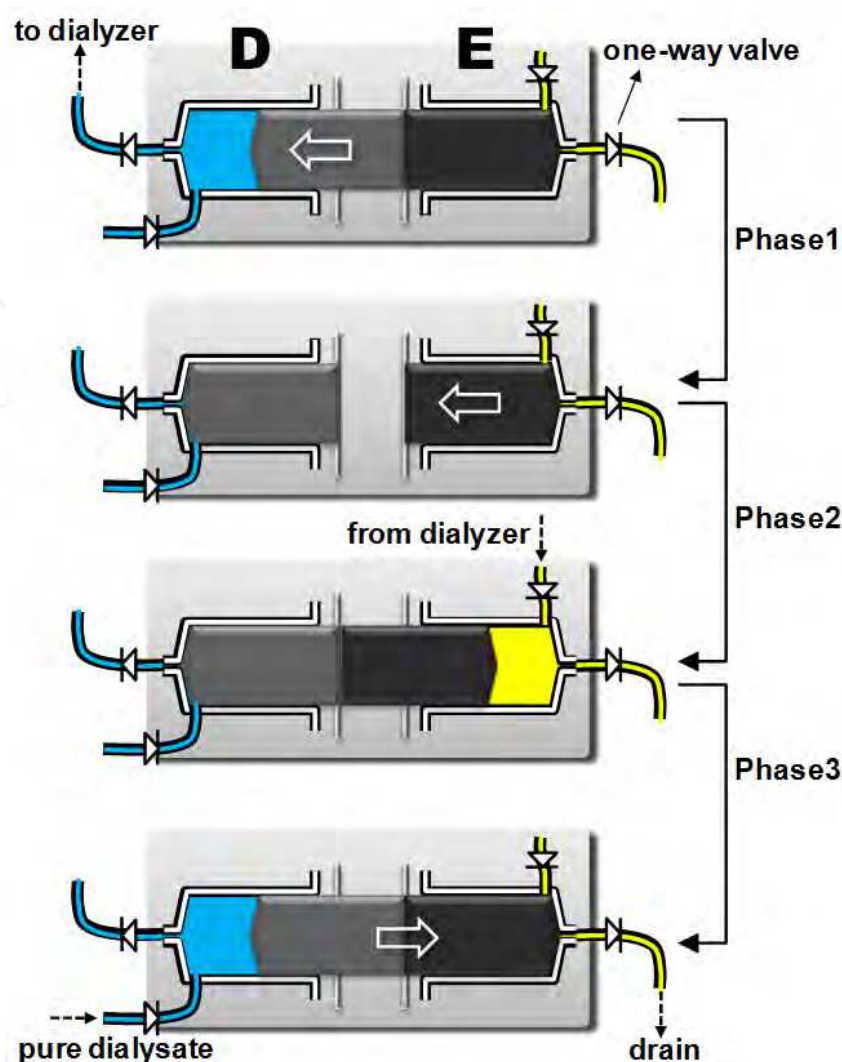


Fig. 10. Pulse Generation and Push/Pull during PPPHD with Dual Piston Pump. (D, dialysate pump; E, effluent pump)

In addition, PPPHD is also versatile and can be easily converted to conventional high-flux HD. 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 flow into blood lumen. In this situation, the two piston pumps serve as a flow equalizer and dialysis is largely achieved by diffusive mass transfer.

The PPPHD unit presented was developed recently, and thus, it requires further investigation. Convective volume attained during PPPHD was equal to the accumulated total dialysate volume, and consequently, this unit delivered the maximally permissible level of total volume exchange. This encourages us to speculate on the capability of this unit in terms of removing mid-sized uremic toxins. Another issue regarding the enormous fluid exchange is the quantification of the contribution made by convection to dialytic efficiency. Backfiltration and ultrafiltration repeat in a relatively short time, and despite a large amount of filtration, the probability that some ultrafiltrate comes directly from dialysate backfiltered during a previous phase cannot be excluded, because that portion of ultrafiltrate does not

contribute to depurative efficiency. In addition, forward filtration and backfiltration rates exceed the blood flow rate, which implies a reduction in solute concentrations due to dilution. As is the case for pre-dilution HDF, this repeated dilution may be expressed by an efficiency drop. Finally, although convection commonly inhibits diffusion during HDF, this inhibition is expected to be small for PPPHD due to repetitive backfiltration. Although an *in vitro* or *in vivo* setup revealed that alternate backfiltration has a positive influence on inhibiting concentration polarization and permeability reduction, it is believed that optimizations, in terms of pulse frequencies and stroke volumes, will further benefit the optimal use of membrane convective capacities throughout PPPHD treatments.

4. Conclusion

Much evidence shows that HDF delivers better dialysis outcomes than high-flux HD; for example, HDF has been shown to improve middle-to-large size molecular removal, allow better EPO control, reduce oxidative stress and inflammation (Lornoy et al., 2000, Vaslaki et al., 2006, Ward et al., 2000), and even to positively influence patient mortality (Canaud et al., 2006, Jirka et al., 2006). These benefits have been attributed to the higher convective doses permitted during HDF. Furthermore, ultrapure dialysate, required due to the large amount of substitution infusion, further inhibits the inflammation risk (Lonnemann, 2000). In this chapter, we review HDF techniques that do not require exogenous substitution infusion. These techniques must be accompanied by spontaneous fluid restoration, such as, backfiltration or ultrafiltrate regeneration (Table 3). A simpler way might be to increase forward and backward filtration rates during HD sessions, although this can only be done to a limited extent. Much higher efficiencies can be achieved by the two-chamber techniques, that is, double high-flux HDF and HFR, which were developed in an effort to increase solute removal and shorten treatment times, by separating ultrafiltration and backfiltration, or convection and diffusion domains. However, these modalities appear to unavoidably increase overall system complexity. Push/pull HDF, which uses a single hemodialyzer, was derived by considering phases, rather than physical regions, for forward and backward filtration. The pulse push/pull HD described here is also based on the phase-separated use

Modality	Filter(s)	Additional components	TFV §	Filtration	Reinfusion
Internal HDF	1	-	+	proximal part of dialyzer	BF
Double HDF	2	flow restrictor	++	hemodialyzer (upstream)	BF
HFR	2	adsorbent column, filtrate pump	+	hemofilter (upstream)	FR
PP HDF	1	double-chamber pump	+++	whole membrane	BF
Pulse PP HD	1	-	+++	whole membrane	BF

§ Total filtration volume per session (4 hours, L); +, low (<20L); ++, moderate (20-40L); +++ high (>60L)

Table 3. Infusion-free HDF modalities. (HFR, hemofiltrate reinfusion; TFV, total filtration volume; PP, push/pull; FR, filtrate regeneration; BF, backfiltration)

of forward filtration and backfiltration using a single high-flux dialyzer. This strategy was devised as a result of efforts to modulate flow patterns for extracorporeal dialysis treatment, and thus, a unique design for managing dual pulsation through the dialysate compartment allows the whole unit to be as simple as the conventional HD unit.

As these novel HDF strategies evolved, remarkable improvements have been achieved in dialysis technologies. Modern dialysis machines offer HDF and HD as default therapies, and are also equipped with outstanding monitoring facilities not only for patients (BTM, BVM, OCM²), but also for treatments (fail-safe design and high-precision balancing) (Polaschegg, 2010). In particular, advances in water treatment allow ultrapure replacement fluid to be prepared in real time. These technical advancements are certainly lowering the barriers to higher convective HDF therapies.

Therefore, in addition to convective clearances, we believe the PPPHD system should be equipped by features that simplify overall treatment and enable dialysis to be performed in outside clinics, because this unit allows simple and efficient operation. Future development targets designed to accomplish these features include; greater user friendliness (that is, intuitive control and operation, fail-safe operations and treatment automation), readily available sterile dialysate, accessible maintenance, and a miniaturized unit that is both light and portable (without compromising depurative efficiency). A dialysis unit equipped with these features may also provide treatment alternatives beyond the current thrice weekly 4-h practice, and perhaps allow even daily dialysis for ESRD patients.

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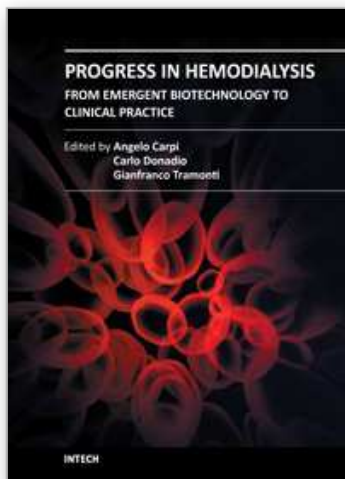
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