Chapter 5

High-efficiency Hemodiafiltration

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Additional information is available at the end of the chapter

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Abstract

The high mortality of hemodialysis (HD) patients is partly due to the limited capacity of diffusion-based HD to remove large uremic toxins. Hemodiafiltration (HDF) which combines convection with diffusion could enhance both large and protein-bound uremic toxin removal. Recently, there have been several randomized controlled trials demonstrating that high-efficiency post-dilution online HDF could improve survival. Indeed, high blood flow rate, which is the necessary requirement, could not be achieved in some patients. The alternative HDF techniques that could provide comparative efficacy would be considered. Pre-dilution online HDF could be performed without risk of hemoconcentration. Mid-dilution online HDF could be conducted via either simple way by using two dialyzers with the substitution fluid line in between or using special designed dialyzer. Mixed-dilution online HDF requires additional substitution pump for both pre- and post-dilution. There are interesting HDF techniques that could be performed with the conventional HD machine and these include HD with double high-flux, enhanced internal filtration, or super high-flux dialyzers. These modalities enhance the convective clearance in combination with internal backfiltration within the dialyzer in HD platform. All of these alternative high-efficiency HDF modalities are available and can potentially provide quite equivalent benefits with the high-efficiency post-dilution online HDF.

Keywords: hemodialysis, high-efficiency, online hemodiafiltration, survival, double high-flux, super high-flux, enhanced internal filtration

1. Introduction

The long-term mortality of either conventional or high-flux hemodialysis (HD) patients has been persistently high despite an achievement of adequate diffusive small solute removal in terms of Kt/V urea. Increasing urea clearance does not yield survival improvement [1]. One of the important explanations is the limited capacity of these diffusion-based HD to remove larger molecular weight uremic toxins and protein-bound toxins. There is an increasing evidence that these compounds are associated with increased overall and cardiovascular mortalities [2]. Enhanced removal of these uremic toxins by hemodiafiltration (HDF) may offer a feasible approach to improve long-term dialysis patient outcome.

2. What is hemodiafiltration (HDF)

Hemodiafiltration (HDF) is defined by the European Dialysis Working Group (EUDIAL) group as a blood purification therapy combining diffusive and convective solute transport achieved by an effective convection volume of at least 20% of the total blood volume, using a high-flux membrane characterized by an ultrafiltration coefficient (KUF) greater than 20 mL/h/mmHg/m^2, and a sieving coefficient (S) for β_2-microglobulin (β_2M) of greater than 0.6 [3]. HDF could enhance both large molecular and protein-bound uremic toxin removals. Various HDF techniques have been innovated and can be divided into two categories.

2.1. HDF with external fluid substitution

HDF with external fluid substitution such as classical HDF (substitution fluid in bag) and online HDF (online preparation of substitution fluid).

2.2. HDF with internal fluid substitution

HDF with internal fluid substitution such as enhanced internal filtration high-flux HD, double high-flux HD, push-pull HDF.

Among various HDF techniques, post-dilution online HDF in external fluid substitution category has been widely used and studied, and is the standard reference to demonstrate the beneficial clinical effects of HDF.

3. Benefits of high-efficiency HDF

3.1. Survival benefit

Recently, there have been several large prospective randomized controlled trials (RCTs) comparing survival outcomes in patients receiving HD with post-dilution online HDF. In the Convective Transport Study (CONTRAST) [4], post-dilution online HDF was compared with low-flux HD in 714 prevalent HD patients. The primary outcome of all-cause mortality was not different after a mean follow-up of 3.0 years. However, subgroup analysis suggested a benefit on all-cause mortality (hazard ratio 0.57; $p < 0.016$) among those patients treated with high convection volume (>21.95 L/treatment). The second RCT was the Turkish Online HDF Study [5], which compared post-dilution online HDF with high-flux HD in 782 patients. The primary outcome of the composite of death from any causes and nonfatal cardiovascular events was comparable after 2 years follow-up period. In a post-hoc analysis, treatment with online HDF achieving a substitution volume >17.4 L was associated with a 46% reduction ratio for overall mortality (p = 0.02) and a 71% reduction ratio for cardiovascular mortality (p = 0.003). Finally, in Catalonia (Spain), the Estudio de Supervivencia de Hemodiafiltración Online (ESHOL) study [6], randomized 906 patients to either continuing HD or switching to high-efficiency post-dilution online HDF. ESHOL is the first RCT demonstrating a significant advantage of online HDF in reducing all-cause mortality by 30% (primary outcome, p = 0.01), infection-related mortality by 55% (secondary outcome, p = 0.03), and cardiovascular mortality by 33% (secondary outcome, p = 0.06). The mean convective volumes were 23.7 L/session.

Individual participant data sets of all the above 3 RCTs [4–6] and another French study aggregating 2793 patients were pooled and used to compare online HDF with HD in European HDF pooled project. The first analysis on the relationship between convection volume with or without standardizing to patient anthropometrics and patient outcomes demonstrated that all-cause mortality was reduced when the convective dose was unstandardized or standardized to body surface area (BSA) or total body water for those receiving higher convective doses. Standardization by body weight or body mass index was not associated with significant survival advantages [7]. The second analysis investigated the effects of convective volume standardized to BSA on patient outcomes across different clinical subgroups. Online HDF reduced the risk of all-cause mortality by 14% and cardiovascular mortality by 23%. There was no evidence of a differential effect in the subgroups. The greatest survival benefit was for patients receiving the highest delivered convection volume (>23 L/1.73 m^2 BSA/session) [8]. This pooled individual participant analysis indicates that online HDF reduces the risk of mortality in dialysis patients. This effect holds across a variety of important clinical subgroups of patients and is most pronounced for those receiving a higher convection volume either crude or standardized to BSA.

In a meta-analysis of six RCTs including 2402 patients compared HDF achieving a significant convective volume with HD, all-cause mortality, and cardiovascular mortality were reduced with HDF compared to HD (RR = 0.8 and 0.73, respectively) [9].

A recent retrospective dose-finding study in 2293 incident HDF patients also found the relative survival rate positive correlation between convective dose and survival rate. The survival benefit was found to significantly increase at convective volume about 55 L/week and to stay increasingly up to about 75 L/week. Pre-dialysis β_2M concentration was decreased as the convective volume was increased from 40 to 75 L/week [10].

These studies support the conclusion that high volume or high-efficiency post-dilution online HDF, the convective volume of which above 20 L/session (60 L/week), is associated with improved overall survival when compared with HD. However, the optimal volume is suggested above 23 L/session (66 L/week) [11]. This advantage was mainly the result from lower cardiovascular and infectious mortalities. Other additional benefits also had contributory roles.

3.2. Enhanced removal of both large and protein-bound uremic toxins

The convective transport in HDF could effectively remove middle molecule solutes such as β_2M (12 kDa) [12, 13], leptin (16 kDa) [14, 15], and various cytokines when compared with high-flux HD. HDF is accompanied by a significant decline of circulating β_2M concentrations over a mid-term period [13]. Pre-dialysis β_2M was reduced to less than 27.5 mg/L, which was the cut-point that showed survival benefit [16]. β_2M amyloidosis, a major concern in long-term HD therapy has nearly disappeared with HDF therapies and ultrapure dialysis fluid. Leptin is a middle molecule uremic toxin that accumulates in dialysis patients and is implicated in malnutrition and anorexia [15]. Free leptin is effectively removed by HDF as reflected by reduced circulating concentrations in HDF-treated patients [14].

Regarding protein-bound uremic toxins, indoxyl sulfate and p-cresylsulfate have been most extensively studied [17]. Many studies demonstrated that p-cresylsulfate was related with negative outcomes including infectious disease, uremic symptoms, vascular calcification, coronary artery disease, cardiovascular disease, and overall mortality [17, 18]. Indoxyl sulfate was also associated with IL-6 concentration, coronary artery disease, vascular damage, progression of chronic kidney disease, and mortality [17, 19]. Removal of protein-bound solutes by dialysis strategies is less efficient than that of non-protein-bound solutes of similar molecular weight. HDF increases reduction rate as well as clearance [20], resulting in a longitudinal decrease in pre-dialysis concentrations [20].

3.3. Improved intra-dialytic clinical tolerance and blood pressure stability

Improvement of clinical tolerance was reported and the incidence of hypotensive episodes was reduced in HDF [21, 22]. Maltolerance symptoms including nausea, vomiting, cramps, headache, and post-dialysis fatigue were also reduced with HDF. Better blood pressure control with a reduced occurrence of cardiac events has been reported [13, 23].

3.4. Reduced pro-inflammatory stage

A low-grade inflammation is commonly observed in dialysis patients. Both dialysis-related factors such as microbiological quality of the dialysate or membrane bioincompatibility and non-dialysis-related factors such as retention of uremic toxins, infection, and comorbidity may contribute to this persistent inflammation, which plays a major role in the pathogenesis of atherosclerosis and cardiovascular disease. HDF might provide a beneficial effect by convective removal of cytokines and pro-inflammatory factors as well as reducing the pro-inflammatory production from using good quality of dialysis fluid and good biocompatibility membrane. Anti-inflammatory effects of HDF have been shown in several studies [24].

This benefit might lead to facilitate anemia correction that was demonstrated by better hemoglobin level or reduced weekly erythropoietin dose requirement [25].

3.5. Reduced infectious complication

Improvement in immune response is another beneficial aspect of HDF. Uremic dialysis patients have a significant risk of infectious complication. Several identified middle molecule uremic toxins, such as degranulation-inhibiting protein I, II, and factor D, play adverse impact to immune response. All these uremic toxins are better removed with HDF [26]. Lower infection-related mortality was found in HDF compared with HD patients [6], and this benefit was obviously demonstrated in dialysis patients who had lower middle molecular weight uremic toxin surrogate (β_2M) [27].

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3.6. Improved nourishment

Enhancing convective clearances of anorexic substance such as leptin also enhance appetite and improve nourishment [14, 15]. Anti-inflammatory effect of HDF is associated in the situation of inflammatory cachexia with an improvement of nutritional parameters such as dry weight and albumin [13, 28]. The muscular volume was either preserved or increased in long-term HDF compared with decrease in HD [29]. Taken together, the quality of life observably improved in HDF [24].

3.7. Preserved residual renal function

Recent studies have shown that HDF modality contributed to a better preservation of the residual renal function over time than conventional HD [30].

4. High-efficiency post-dilution online HDF

The basic requirements to provide online HDF consist of the good quality of dialysis water treatment system that could deliver ultrapure dialysis fluid and sterile substitution fluid to the patients as well as the online HDF machine integrated with two endotoxin-retention filters. Two standard methods of fluid substitution in online HDF comprise post-dilution and pre-dilution modes (**Figures 1** and **2**). Post-dilution online HDF is the more efficient mode in molecular clearance of uremic toxins. It could maintain small solute removal compared with high-flux HD along with enhanced larger molecule clearance correlated with its convective volume (equal to substitution plus net ultrafiltration volume). Nevertheless, such efficiency is limited by hemoconcentration and high blood viscosity as well as excessive secondary concentrated protein layer at the mem-

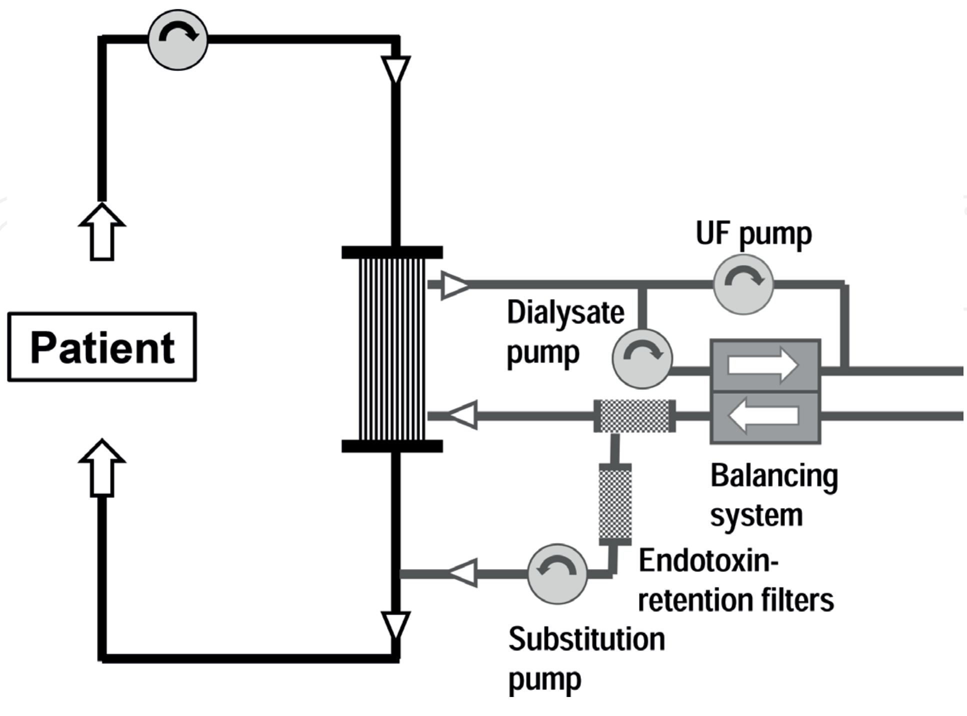

Figure 1. Post-dilution online HDF.

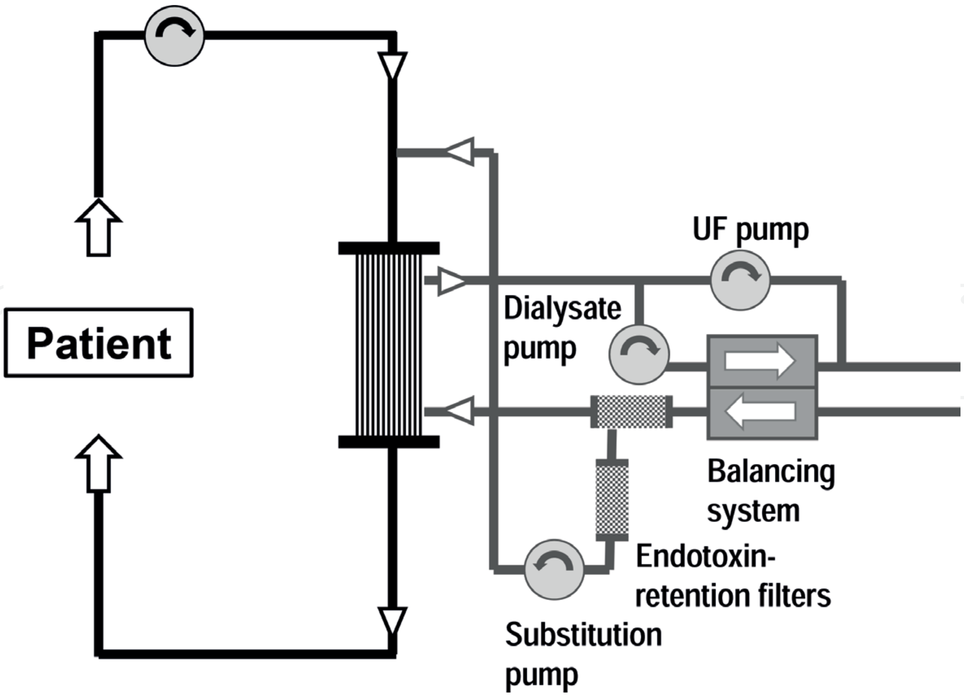

Figure 2. Pre-dilution online HDF.

brane interface, which lead to declining membrane permeability with requirements of increasing TMPs to maintain scheduled filtration rates as plasma water is continually ultrafiltered along the length of the hollow dialyzer fibers. The hemoconcentration may also induce high transmembrane pressure which can induce red blood cell damage, protein denaturation, and clotting of the dialyzer fibers. The convective rate should not be prescribed above 30% of blood flow rate (BFR) or filtration fraction, which would increase hematocrit, for example from 35 to 50%.

Taken together, the above studies support the conclusion that the adequate dose of convection is important to provide survival benefit in HDF. To achieve high volume or high-efficiency post-dilution online HDF of more than 23-L convective volume per session, the high BFR at least 400 mL/min is the necessary requirement as demonstrated in **Table 1** [31].

	Prescription	Recommendations
Blood flow rate (Qb)	350–500 mL/min	The maximum possible
Dialysis fluid flow rate	400–500 mL/min + substitution flow rate	No influence on convective dose
Substitution flow rate	25–33% of Qb (90–160 mL/min)	The maximum possible
Session duration	4.0–5.0 h/session	The maximum possible
Convective volume (substitution volume + net ultrafiltration volume	>23 L/session	The maximum possible
Filtration fraction (convective volume/ blood volume processed)	25–30%	The maximum possible
Dialyzer	High-flux	Ultrafiltration coefficient >20 mL/h/ mmHg/m^2 and sieving coefficient for β_2-microglobulin >0.6

Table 1. Recommended prescription to obtain the high-efficiency post-dilution online HDF.

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Indeed, this high blood flow could not be achieved in some patients because of the vascular access problem or cardiovascular instability. The alternative HDF techniques that could provide comparative efficacy would be considered.

5. High-efficiency pre-dilution online HDF

Pre-dilution online HDF (**Figure 2**) could be performed without the risk of hemoconcentration. Therefore, convective volume could be augmented at a lower BFR. The convective volume in pre-dilution technique would be double of post-dilution technique in order to get the equivalent large molecule clearance [32]. A study from Japan demonstrated the additional benefit of enhanced removal of larger low-molecular-weight proteins (LMWPs), which are larger than β_2M (12 kDa), when using "super high-flux" or "protein permeable" dialyzer in pre-dilution online HDF. Post-dilution online HDF could actually remove these molecules with this type of membrane but causes adverse massive albumin leakage [33]. A recent study demonstrated that pre-dilution technique in low BFR when using super high-flux or protein permeable dialyzer, which was widely used in Japan, could provide comparable large molecule and protein-bound molecule removal with high-efficiency post-dilution technique. The only drawback of pre-dilution technique is the slightly lesser small solute clearance than post-dilution technique. This is because of lower diffusive clearance from the diluted blood [34]. Biocompatibility is another postulated beneficial effect of pre-dilution online HDF [33]. In post-dilution OL-HDF, the blood is concentrated inside the filter, and leukocytes and platelets can be activated by shear stress [35]. In pre-dilution online HDF, the blood is diluted before reaching the filter, thereby avoiding the shear stress.

6. High-efficiency mid- or mixed-dilution online HDF

The other two dilution techniques that have been introduced in the clinical practice and could avoid the technical problem of post-dilution technique as well as reduced small solute clearance from hemodilution of pre-dilution technique are mid- and mixed-dilution online HDF.

Mid-dilution technique could be performed by either simple way by using two dialyzers in a serial alignment with the substitution fluid line in between (**Figure 3**) or using special designed dialyzer called "Nephros OLpur™" that the substitution fluid is infused in the middle of the dialyzer fiber pathway (**Figure 4**), resulting post-dilution HDF stage in either first dialyzer (simple method) or first fiber pathway (Nephros OLpur™) followed by a pre-dilution HDF phase. By this configuration, a high concentration gradient is created in the first stage for efficient removal of small molecules by diffusion while maximal ultrafiltration of plasma water occurs in both stages for efficient clearances of larger molecules by convection. Previous studies including ours demonstrated that both mid-dilution techniques provided middle molecule clearance better than pre-dilution online HDF and either equivalent or superior to the high-efficiency post-dilution online HDF [36–38].

Mixed-dilution technique requires additional substitution pump to deliver the substitution fluid in both pre- and post-dilution at the same time (**Figure 5**). The convective dose could be increased in pre-dilution fashion on top of the limited post-dilution convection because of

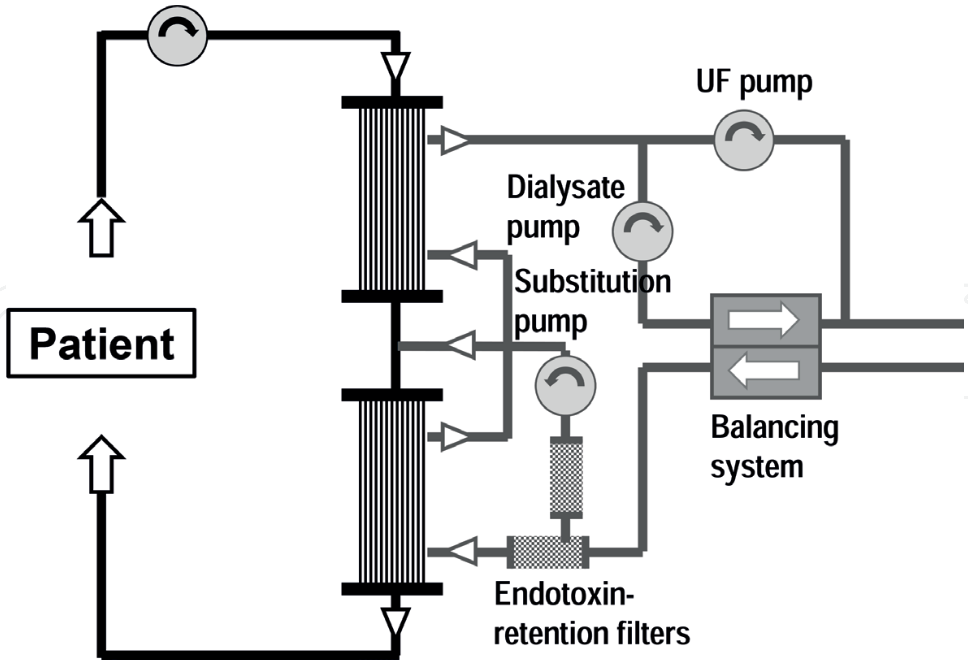

Figure 3. Simple mid-dilution online HDF.

hemoconcentration and high transmembrane pressure (TMP) [39]. The advancement in this technique moves from simple fixed pre-dilution/post-dilution substitution flow rate ratio to feedback system for TMP control to modulate the pre-dilution/post-dilution ratio while maintaining the total infusion constant throughout the session. Splitting the infusion between the

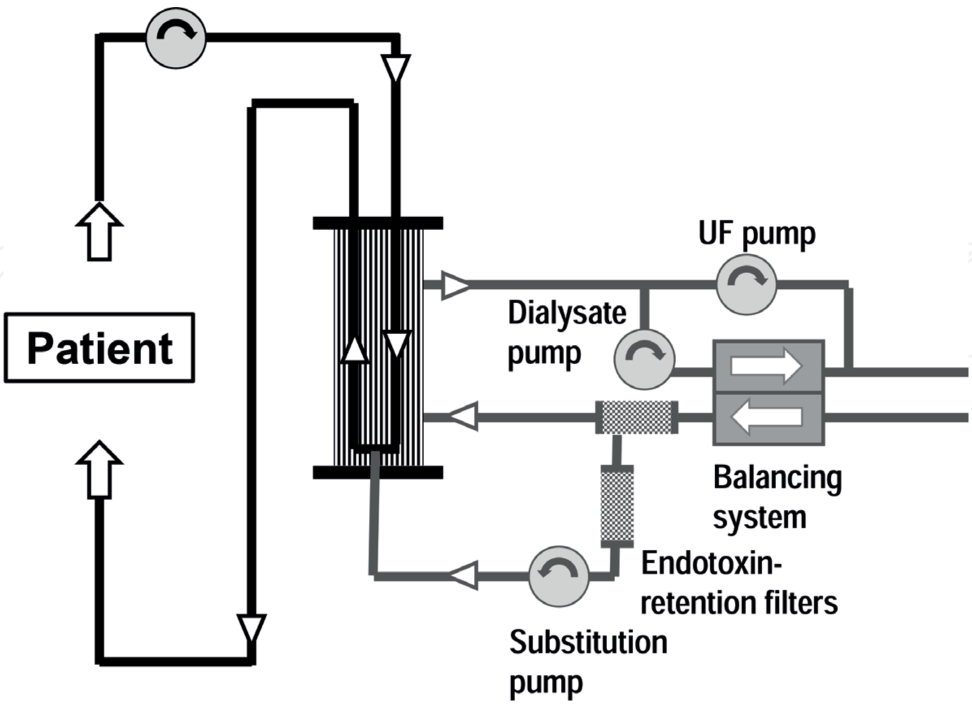

Figure 4. Mid-dilution online HDF with Nephros OLpur™ dialyzer.

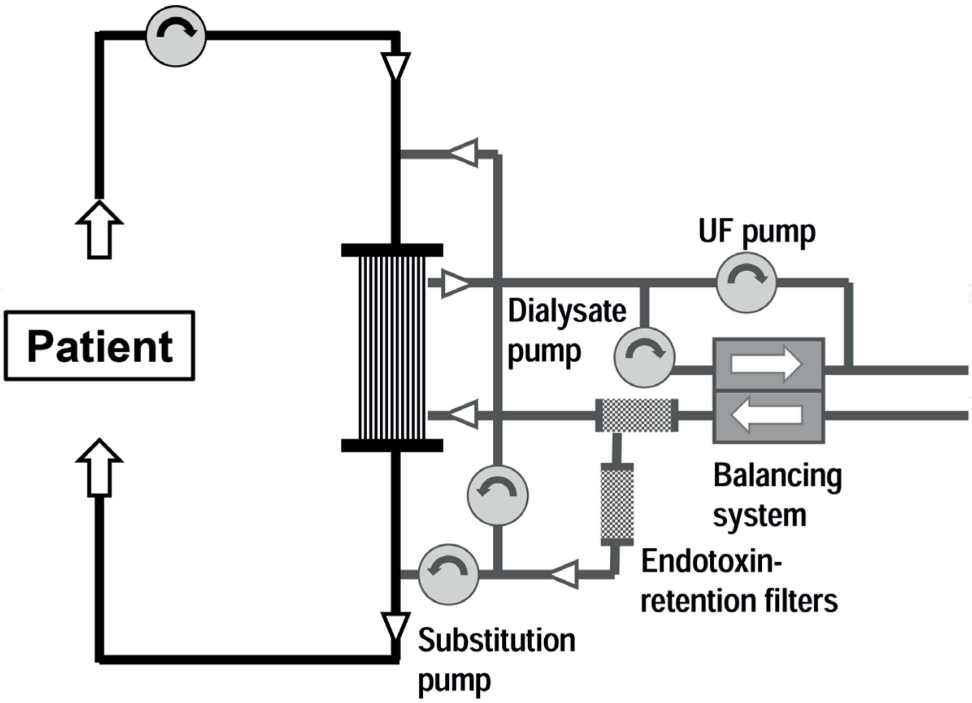

Figure 5. Mixed-dilution online HDF.

pre- and post-dialyzer could optimize filtration fraction for the best possible rheological and hydraulic conditions within the dialyzer at the highest fluid exchange rate and with the most solute removal by convection. Some new HDF machine could operate mixed-dilution technique with TMP feedback control. This TMP feedback control acts by modulating the ratio between pre- and post-dilution in order to gradually achieve and then maintain an optimal and safe TMP value for the entire session (250–300 mmHg). If TMP falls, a small amount of fluid (5–10 mL/min) is diverted from pre- to post-dilution, increasing filtration fraction, and thus TMP as a result. Vice versa, the same amount of fluid is diverted from post- to pre-dilution, thus reducing filtration fraction, whenever TMP rises [40]. Previous studies including ours showed the very good efficacy without high TMP [39, 41].

7. High-efficiency internal filtration HDF

There are interesting HDF techniques that could be performed with the conventional HD machine. These modalities enhanced the convective transport at the proximal part of the device in combination with internal backfiltration within the dialyzer in standard HD platform. In the countercurrent setting, backfiltration of fresh dialysate acts as a “spontaneous substitution,” in which the exact volume is controlled by the dialysis fluid balancing system of HD machine. Exploiting backfiltration implies a need for good dialysis fluid quality. Usual high-flux HD also provides this phenomenon within the dialyzer but the convective volume could not reach the high-volume level. Therefore, the special design of circuit or dialyzers is required to catch up the high-efficiency HDF.

7.1. Double high-flux HD

Double high-flux HD is set-up using two high-flux dialyzers in the serial alignment [42]. The restrictor is applied in the countercurrent dialysate pathway between the two dialyzers (**Figures 6** and **7**). The convection occurred in the first while the fluid substitution from fresh dialysis fluid took place in the second dialyzer. During treatment, a hydrostatic pressure gradient exists between blood and dialysate compartments of the first dialyzer, resulting in high ultrafiltration to dialysate, and thus increasing the blood oncotic pressure in the second dialyzer. Combination of lower blood compartment hydrostatic pressure and higher dialysate hydrostatic pressure results in a reverse TMP toward the end of the second dialyzer and transfer of fluid from dialysate to blood. This backfiltration is facilitated by oncotic pressure. The magnitude of these fluxes is evident from the diminished representative blood flow during passage of the first filter, due to ultrafiltration. Conversely, countercurrent dialysate flow decreases in the second filter, due to backfiltration and increases again in the first filter, due to addition of ultrafiltration.

The original restrictor design in double high-flux HD leads to unadjustability of the convective rate resulted by the fixed intermediary dialysate diameter (**Figure 6**). To improve this system, convective-controlled double high-flux hemodiafiltration (CC-HDF) has been introduced. The convection can be set on the real-time basis by applying adjustable C-clamp restrictor on the intermediary line (**Figure 7**). A previous study demonstrated that this technique was safe and provided comparable efficacy with the high-efficiency post-dilution online HDF [43]. The better survival when compared with HD was reported in an observational study [44].

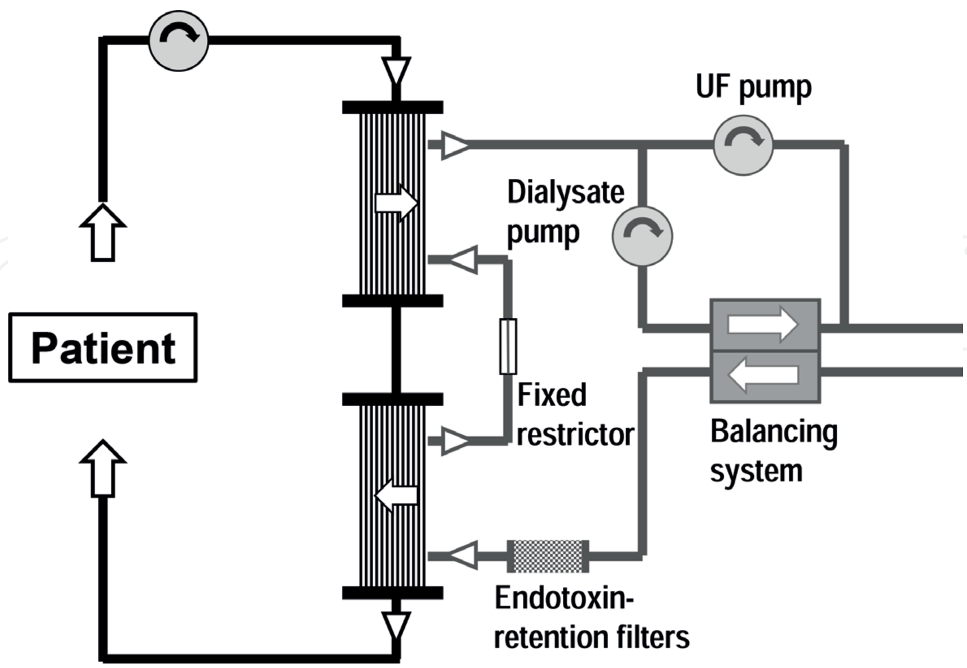

Figure 6. Original double high-flux HD.

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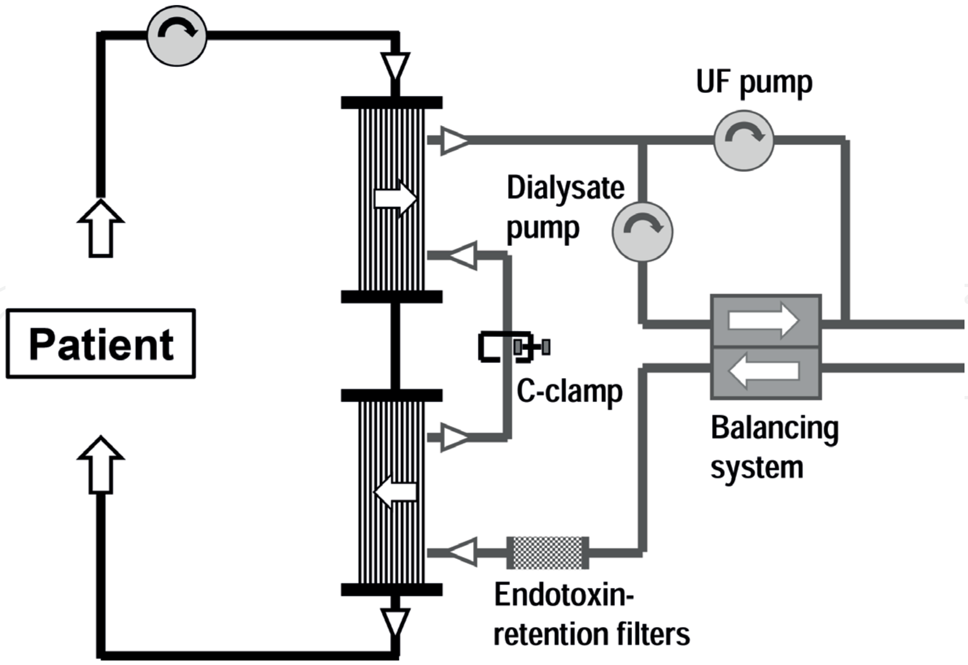

Figure 7. Convective-controlled double high-flux hemodiafiltration (CC-HDF).

7.2. HD with enhanced internal filtration dialyzer

This modality is a high-flux HD method performed with the dialyzer designed to enhance internal filtration [45]. This approach is currently achieved by reducing the internal diameter of dialyzer fiber lumen and elongating the fiber length (**Figure 8**). In the usual countercurrent setting, significant amount of internal ultrafiltrate occurs in the proximal part of the dialyzer, which has high TMP and provides for convective solute removal since ultrafiltrate is discharged with the exhausted dialysate. Distal backfiltration of fresh dialysate because of the negative TMP acts as a "spontaneous substitution" ensuring fluid balance. Utilizing backfiltration needs good water quality. Dialyzer's membrane itself acts as an additional final screen for the substitution fluid without the need for substitution fluid or additional technology. Internal filtration and backfiltration are governed by hydraulic and oncotic pressures as well as TMP, as sketched in **Figure 8**. Locally, the amount of membrane filtration depends on local TMP and on the membrane's water permeability.

HD using this kind of dialyzer has been named internal hemodiafiltration (iHDF). Previous studies showed that iHDF has an intra-dialytic removal ability of uremic toxins higher than low-flux HD and similar to online HDF, but with technical complexities lower than online HDF and similar to HD [46, 47].

7.3. HD with medium to high cut-off or super high-flux dialyzer

Another method to enhance the large molecule clearance by either convection and diffusion is using high pore size dialyzer, which has effective molecular weight cut-offs closer to that of the glomerulus (65 kDa) with limited albumin (62 kDa) loss. This class of the membrane

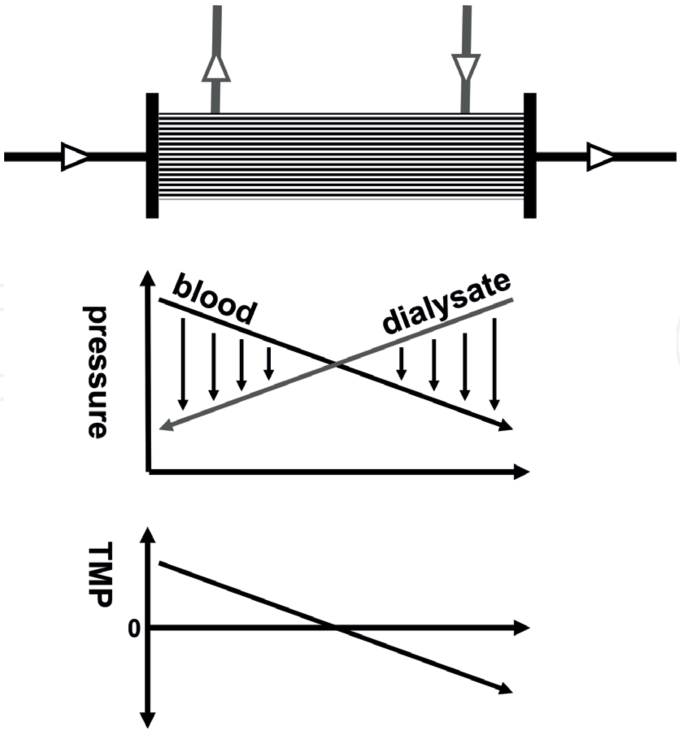

Figure 8. Enhanced internal filtration dialyzer and graphs demonstrated the blood dialysate and transmembrane pressure (TMP) values along with the dialyzer length.

has various nomenclature. The membranes that have larger pore-sizes than ordinary high-flux membrane (KUF ≥ 20 mL/h/mmHg/m^2 and $β_2$M clearance ≥ 20 mL/min) is called super high-flux or high-performance membrane (Japanese type IV and V dialyzer categories [$β_2$M clearance (12 kDa) ≥ 50 mL/min]) [48]. Sub-set of these kinds of membrane might be divided into significant albumin loss membrane in HD modality, called protein permeable or high cut-off dialyzer (HCO; $β_2$M > 80 mL/min, S of $β_2$M 0.9–1.0, and albumin 0.01–0.03) [49] or type V dialyzer (Japanese type V dialyzer category [$β_2$M clearance (12 kDa) ≥ 70 mL/min]) and not significant albumin loss called medium cut-off dialyzer (MCO) [50] or Japanese type IV dialyzer [48]. These new classes of dialyzers enable the elimination of middle molecule uremic toxins, including various toxins larger than $β_2$M, with both diffusion from these large membrane pores and convective internal filtration/backfiltration of its high ultrafiltration coefficiency. Similar to other HDF technique, these dialyzers are used with ultrapure dialysis fluid. The removal of large molecule of this modality especially was effectively comparable with online HDF [51]. A recent study also demonstrated that MCO HD removes a wide range of middle molecules more effectively than high-flux HD and even exceeds the performance of high-volume HDF for large solutes, particularly 45 kDa lambda immunoglobulin light chains (FLCs) [50]. One concern of this treatment is the albumin loss, which is greater than with high-flux HD and HDF. In general, a small amount of albumin loss no more than 3 g/session is safe and would beneficially induce an acceleration of turnover of albumin [48].

Considering the comparable performance of the above three high-efficiency internal filtration techniques operated with conventional HD machine, these modalities might be a cost-effective alternative to the standard post-dilution online HDF.

8. Conclusion

High-efficiency post-dilution online HDF has provided the survival advantage among HD patients. Some patients could not achieve this reference online HDF modality because of either limited blood flow or unavailable HDF machine. Fortunately, alternative high-efficiency HDF modalities are available for all patients and can potentially provide quite equivalent benefits of high-efficiency post-dilution online HDF.

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