Chapter 2

Principles of Haemodiafiltration: Rationale for Improved Patients' Survival

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Additional information is available at the end of the chapter

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Abstract

Haemodiafiltration (HDF) is a renal replacement modality that combines diffusion and enhanced convection in order to remove small- and middle-molecular-weight compounds, respectively. They are removed along solvent drag effect of ultrafiltration through increased transmembrane pressure (TMP), whereas the replacement solution is infused intravenously at equal amount minus the desired fluid volume removal for achieving dry weight. Limiting factors for high-volume on-line haemodiafiltration (HV oHDF) are blood flow and viscosity (haematocrit, protocrit), filter performance and technical features of HDF monitor. Most recent advanced technology of dynamic analysis of pressure pulses along the blood flow pathway in the dialyser has enabled optimal ultrafiltration flow performances. HV oHDF offers today the best compromise of cardioprotective option by reducing cardiovascular risk factors in end-stage kidney disease patients. Recent randomised controlled trials (RCTs), individual participant data meta-analyses and a number of observational studies have shown the evidence of survival advantage of HDF over conventional haemodialysis (HD). The convective volume has become the key quantifier for HV oHDF as the measure of dialysis dose. Its cut-off values for better survival have been recognised, but the research is still needed in the years to come to set the required optimal volumes tailored to individual patients' needs.

Keywords: haemodialysis, haemodiafiltration, convection, ultrafiltration, mortality

1. Introduction

The uremic syndrome is characterised by an accumulation of uremic toxins due to inadequate kidney function. There have been more than 90 compounds considered to be uremic toxins listed

by the European Uremic Toxin Work Group. Sixty-eight have a molecular weight less than 500 Da, 10 have a molecular weight between 500 and 12,000 Da and 12 exceed 12,000 Da. Twenty-five solutes (28%) are protein bound [1]. These figures are further increasing with the adoption of new knowledge and technology of uremic toxins detection.

The clearance of solutes during conventional haemodialysis (HD) depends on their size and the concentration gradient across the dialysis membrane. Solutes weighing less than 500 Da are considered low-molecular-weight solutes and they are removed by passive diffusion down a favourable concentration gradient. Urea is considered a marker of such toxins. Its clearance, as measured by Kt/Vurea, correlates with patient morbidity [2] showing the evidence that such toxins contribute to the uremic syndrome.

However, despite improvements in technology and patient care, the mortality rate of patients on maintenance dialysis remains high, at approximately 15–20% per year [3]. As specified in the United States Renal Data System report, the expected remaining life span after the initiation of renal replacement therapy was eight years for dialysis patients aged 40–44 and 4.5 years for those 60–64 years of age. In general population the ranges of the expected remaining life span at specified ages are 30–40 years and 17–22 years, respectively. The values in older dialysis patients are only slightly better than those in patients with lung cancer [4]. Therefore, there is an obvious need to change the practices and to attempt to approach the problem differently.

2. Historic background

In an attempt to reduce mortality, it was postulated in 1983 that a higher Kt/V than commonly prescribed during conventional short dialysis may increase survival among patients undergoing renal replacement therapies [5]. However, the hemodialysis (HEMO) study failed to show a positive effect on patient survival when dialysis dose per haemodialysis session was increased above the current K/DOQI recommendations [6]. Possible explanation for this unfavourable outcome could be in the kinetics of urea removal which is representative of small solutes, but not of larger sized molecules such as middle molecules, large-molecular-weight proteins or protein-bound solutes, thereby making Kt/V misleading. Clearance of urea accounts for only one-sixth of physiological clearance [1]. In addition, several shortcomings are associated with short dialysis schedules that are not captured by Kt/V index such as extracellular fluid volume control, phosphate control and adequate removal of middle and larger uremic molecules compounds.

Beta-2 microglobulin levels are associated with the development of dialysis-related amyloidosis and possibly reduced survival [7]. It seems likely that beta-2 microglobulin is a marker for overall middle-molecule clearance, including more toxic and as yet unidentified uremic compounds [8–11]. Those solutes are better removed by high-flux membranes compared to low-flux membranes due to their more porous characteristics with increased permeability.

Whether survival differs upon exposure to randomly assigned high- or low-flux membranes was also evaluated in the HEMO study [6]. No difference was observed. The same result was

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obtained in the Membrane Permeability Outcome study, in which patients were also randomly assigned to high- or low-flux dialysis membranes [12].

In an attempt to improve patients' outcomes, alternative renal replacement therapies have been developed, since removal by diffusion becomes less efficient as the molecular weight of a solute increases. Therefore, the need to mimic the kidney function seems to become mandatory in order to enhance middle-molecule removal because the diffusion in the tubules and loop of Henle follows filtration in glomerulus, which is the principle of convection (**Figure 1**).

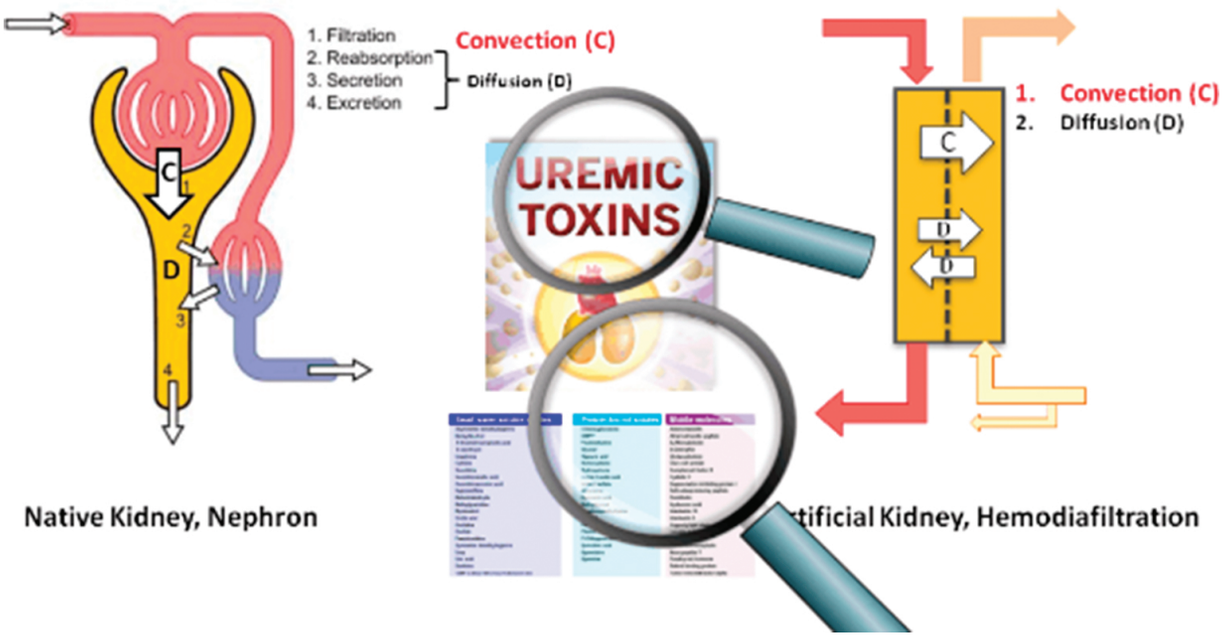

Figure 1. Mimicking native kidney function to enhance middle-molecule removal.

Haemofiltration (HF) is the treatment modality that employs convection in order to facilitate removal of larger molecular weight solutes while using high-flux dialysers only. In convection the small- and large-molecular-weight solutes are removed in the ultrafiltrate by solvent drag. Although HF is effective in the removal of the larger molecular weight solutes, it is less effective in the removal of small molecules as it is restricted by the magnitude of the ultrafiltration volume achievable. Haemodiafiltration (HDF) is the treatment modality that combines diffusion and enhanced convection in order to facilitate removal of small-molecular-weight solutes. Moreover, small-molecule removal is further increased with the use of high-volume on-line HDF (HV oHDF) (see section "Towards more cardioprotective renal replacement therapy") and can be higher than haemodialysis, depending upon the volume of the replacement solution [13].

The ratio between treatment techniques, processes and molecular weights of the solutes is shown in **Figure 2**.

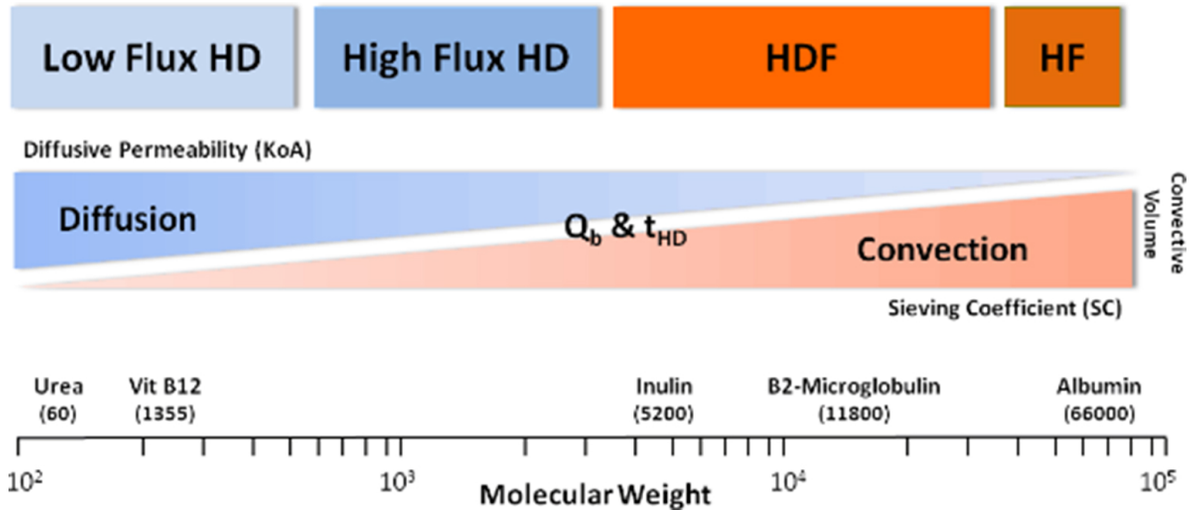

Figure 2. The ratio between treatment techniques, processes and molecular weights of solutes. HD, haemodialysis; HDF, haemodiafiltration; HF, haemofiltration; KoA, mass transfer area coefficient; Q_B, blood flow; t_{HD}, duration of HD session; SC, sieving coefficient (the proportion of a substance to be removed for a particular filter).

The utilization of convective therapies has been variable. Between 1998 and 2001, about 12% of patients were on HDF in the European countries participating in the Dialysis Outcome and Practice Patterns Study (DOPPS) study [14].

There have not been too many studies to compare the patients' survival between convective modalities and high-flux HD. One of them was Italian MAMHEBI study, which was a randomised controlled trial (RCT). Significantly higher three-year survival was noted with HF (68% versus 52%) [15]. Dialysis Outcome and Practice Patterns Study (DOPPS) was prospective observational study which showed better survival with HDF, but it compared high-efficiency HDF with composite predictor of high- and low-flux haemodialysis [14]. Vilar et al. conducted retrospective cohort study and showed better survival with on-line HDF than with high-flux haemodialysis [16], as well as Imamović et al. in incident patients' population [17], but the latter three were epidemiological studies and RCT to show survival benefit of HDF over conventional HD was still missing.

3. Technological principles of haemodiafiltration

Ultrafiltrate volume, derived from Q_{UF} times treatment time (**Figure 3**), is removed by the dialysis machine through increased transmembrane pressure (TMP), whereas the replacement solution is infused intravenously at equal volume minus the desired fluid volume removal to preserve extracellular fluid balance and isovolemic state. The replaced solution represents *substitution volume*, whereas convective volume represents the sum of substitution volume and desired fluid volume removal during the dialysis session.

Filtration fraction (FF) (proportion of ultrafiltration volume obtained compared with total blood volume processed during the HD session) was traditionally supposed to be 25% (**Figure 3**).

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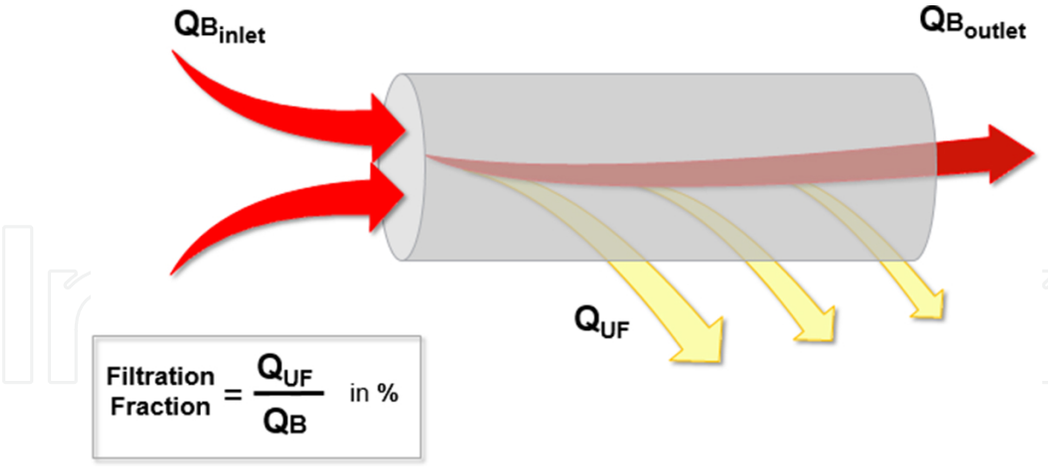

Figure 3. Filtration fraction. Q_B, blood flow rate; Q_{UF}, ultrafiltration flow rate.

3.1. Dilution modes

The fluid can be substituted either after the dialyser as the reference mode (post-dilution mode) or before the dialyser (pre-dilution mode) (**Figure 4**), or both (mixed dilution mode).

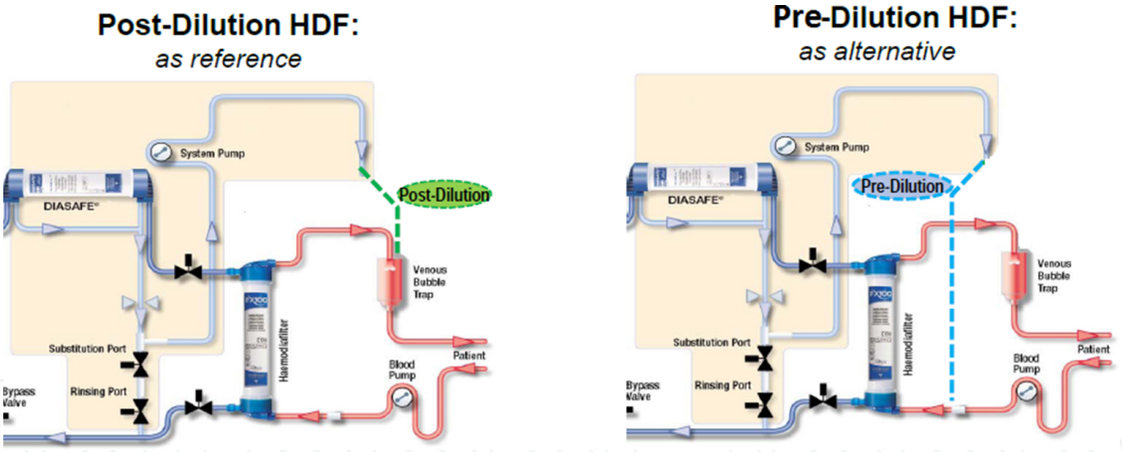

Figure 4. Dilution modes in haemodiafiltration; HDF, haemodiafiltration.

Choice on which dilution mode to apply depends on patient haemorheology and clinical performance (**Table 1**).

Post-dilution HDF	Pre-dilution HDF	Mixed-dilution HDF
Pros	**Pros**	**Pros**
High solute clearance and removal	Haemodilution	Avoids the drawbacks of post- and pre-modes
Reduced consumption of substitution volume	Decreased viscosity and oncotic pressure	**Cons**

Post-dilution HDF	Pre-dilution HDF	Mixed-dilution HDF
Cons	Reduced fibres and membrane fouling	Requires specific hardware equipment and software
Haemoconcentration	Preserved hydraulic and solute membrane permeability	
Increased viscosity and oncotic pressure	Reduced membrane stress	
Fibres and membrane fouling	**Cons**	
Reduced hydraulic and solute membrane permeability	Reduced solute clearance and removal	
Increased transmembrane pressure	Increased consumption of substitution volume	
Reduced sieving coefficient		
Fibre clotting		
Potential alarms		
Increasing membrane stress		
Potential albumin leakage		

HDF – Haemodiafiltration

Table 1. Pros and cons of dilution modes.

4. Water for dialysis

Possible pyrogenic reactions were considerable threat to patients on HDF since the risk of microbiological contamination with high substitution volumes was increased. Besides, costs were greater with increased substitution volumes used as well as with storage bags for them. Therefore, the need for the production of high purity substitution fluid at lower cost was a challenge, not only because of threatening pyrogenic reactions and financial constraints but also because of higher risk of accelerated atherosclerosis and malnutrition due to ongoing low-grade inflammation [18]. Therefore, the American Association for the Advancement of Medical Instrumentation set the microbiological standards for water for dialysis at <200 colony-forming units (CFU) and <0.5 endotoxin units (EU)/ml. The European Pharmacopoeia was more stringent with <100 CFU and <0.25 EU/ml. Eventually, <0.1 CFU and <0.03 EU/ml were adopted for a solution to be considered "ultra-pure" and it is now widely used even for conventional haemodialysis [19].

"On-line" fluid production has enabled the concept of on-line HDF (oHDF). It facilitates the provision of an unlimited volume of sterile, non-pyrogenic substitution fluid not requiring storage, which is an efficient approach to prevent bacterial contamination and growth at a cost close to that of dialysate for conventional haemodialysis [20, 21]. The first step of the process

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includes the filtration of the water after it is produced using the reverse osmosis technique. The water is then used for the production of dialysate. This step has also been adopted in several haemodialysis machines to produce dialysate of improved purity. The second step includes further filtration of the dialysate. Finally, a third filtration by a disposable microfilter completes the creation of the substitution solution. The disposable microfilter is replaced at the end of the dialysis session. The dialysate prior to the last filtration is used for the diffusive element of HDF. The purity achieved using this approach has been repeatedly confirmed [21, 22] (**Figure 5**).

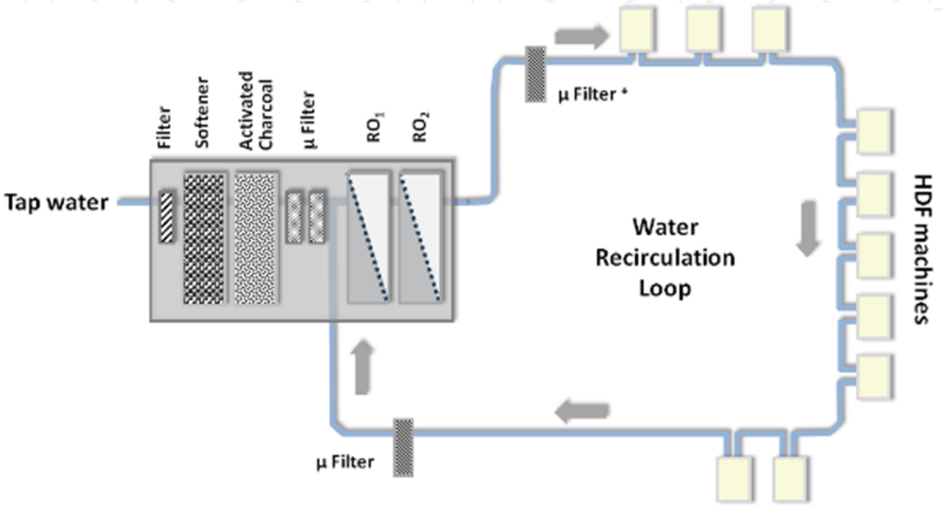

Figure 5. One of the examples of water treatment system in the dialysis centre in Hemodialysis Unit of Lapeyronie Hospital in Montpellier (France) with microfilters depicted plus two microfilters within HDF machines (not depicted) showing the water for dialysis passing through HDF machines. The amount used ends up in the sewage; RO, reverse osmosis; HDF, haemodiafiltration.

So, an additional step to ensure full safety of dialysis and substitution fluids is to implement two sterilising ultrafilters built in within HDF machines on the path after the dialysate was prepared. They are disinfected regularly with the HDF machine and are replaced after a certain time of use as defined by manufacturer.

From an economic perspective, the added cost of the ultrafilters used to prepare the substitution solution has been nullified because of growing tendency of using ultra-pure dialysate even in conventional haemodialysis, thereby leaving the only difference in cost in the amount of water consumed per treatment. Above all, the remaining cost has been balanced by the biochemical and clinical benefits of HDF [20].

5. Rational for improved patients' survival on high-volume haemodiafiltration

The European Dialysis Working Group (EUDIAL) performed a systematic review and meta-analysis of randomised controlled trials on haemodiafiltration in 2014 and found the beneficial

effect of post-dilution oHDF over HD in reducing all-cause and cardiovascular mortality (pooled RR-0.84; 95% CI, 0.73–0.96) and recommended wide acceptance of this treatment modality [23]. EUDIAL recommends the adoption of effective convective volume as a key quantifier for HDF. Providing time is constant and anticoagulation is adequate, limiting factors for high-volume haemodiafiltration (i.e. the amount of substitution fluid produced) are blood viscosity, filter performance and blood flow rate.

5.1. Limiting factors for high-volume on-line haemodiafiltration

5.1.1. Blood viscosity as a limiting factor for high-volume on-line haemodiafiltration

It is not only that FF from **Figure 3** accounts for the proportion of UF volume in the blood volume, but in reality, FF is even higher, because UF volume comes from plasma water, not from the whole blood. **Figure 6** shows the example of a patient with FF of 0.30 (UF rate 120 ml/min and blood flow rate 400 ml/min). However, if the haematocrit of this patient is 30%, it means that his/her plasma water flow is only 280 ml/min, which increases FF to 0.43 (**Figure 6**).

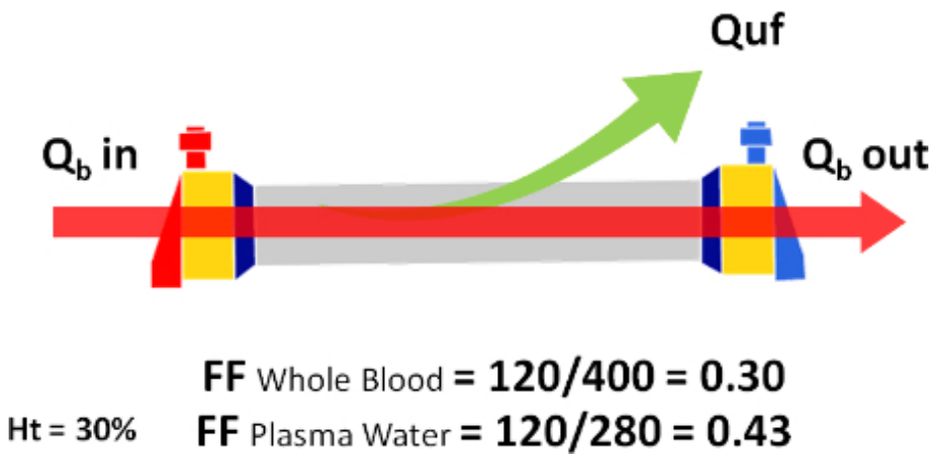

Figure 6. Increased filtration fraction in plasma water.

Consequently, too much convective volume increases the risk of haemoconcentration, thereby compromising the fine balance between the two by interfering with membrane permeability both on hydraulic and solute fluxes.

5.1.2. Filter performance as a limiting factor for high-volume on-line haemodiafiltration

The efficiency of HDF might be improved by increasing the size of the surface area of the membranes (provided optimal blood flow was achieved), so that high efficiency might be achieved with a surface area of 2.2 m^2, as opposed to the standard surface of 1.4 m^2, thereby allowing much more substitution fluid to be replaced at a rate of 120 ml/min in post-dilution mode, in contrast to 60 ml/min which was achieved with standard surface [24].

The size of a membrane pore dictates the sieving coefficient (SC) of a substance to be removed. The higher the sc, the higher the UF and clearance of a particular solute. The reduction ratios

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of beta-2 microglobulin with low-flux, high-flux haemodialysis and HDF are 20, 60 and 75% per session, respectively [25]. The EUDIAL group, nominated by the European Renal Association – European Dialysis and Transplant Association (ERA–EDTA), set the SC for beta-2 microglobulin at minimum of 0.6 [26] in high-flux filters (which are mandatory with HDF). However, in order to achieve the optimal outcome for the patients, filters are nowadays designed with even higher SC for beta-2 microglobulin of 0.8 for efficient elimination, but still retention of albumin (**Figure 7**).

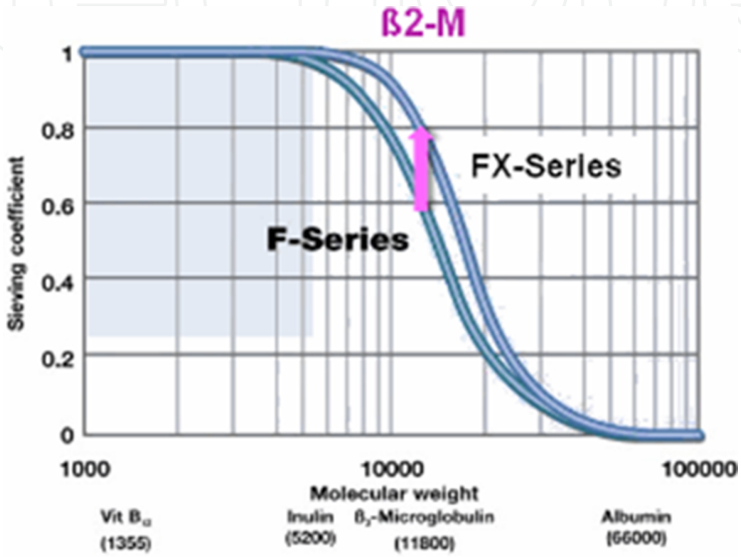

Figure 7. Solute membrane permeability: higher sieving coefficient for beta-2 microglobulin.

Correlation between ultrafiltered volume and beta-2 microglobulin elimination is linear, as specified by Lornoy et al. (**Figure 8**) [27].

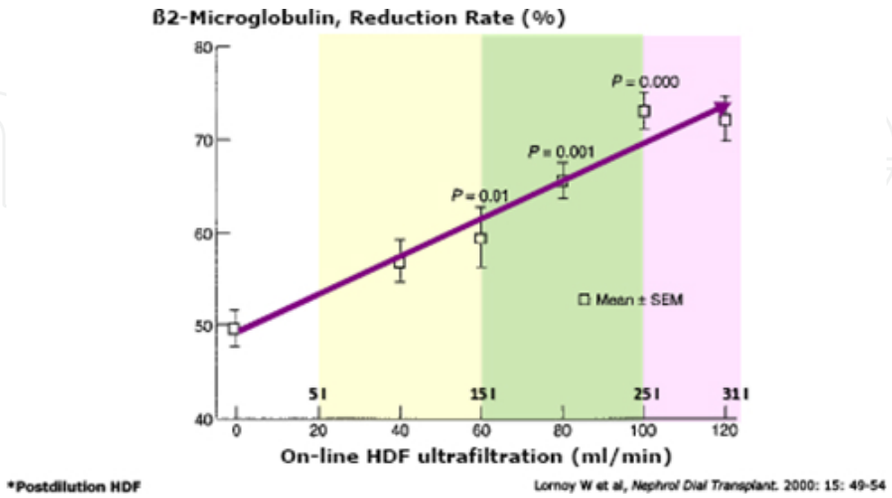

Figure 8. A linear function of ultrafiltered volume and beta-2 microglobulin elimination. HDF, haemodiafiltration (with permission of authors).

Enhanced clearances of middle molecules such as beta-2 microglobulin [28] and phosphate [29] and other small molecules, such as homocysteine and complement D factor [30] are the main biochemical benefits of convective-based treatment over conventional HD.

5.1.3. Blood flow as a limiting factor for high-volume haemodiafiltration

On-line monitoring of blood parameters allows adjustment of ultrafiltration rate to identify the patient-specific exchange rate possible at any given point in time while enabling haemodynamic stability. The substitution rate is adjusted to blood flow rate, thereby controlling haemoconcentration, whereas blood flow rate is adjusted to dialysis flow rate to control diffusion [31] (as for the diffusion component on-line clearance monitoring is used and the goal is to achieve spKt/V of 1.4). Therefore, if the blood flow rate drops from 100 L to 70 L per session, and the total UF volume remains at 25 L, the filtration fraction rises from 25% to 37% (**Figure 9**), which may generate a lot of difficulty during the session, lot of alarms and lot of critical TMP notifications, and the session may not end with a volume that was targeted.

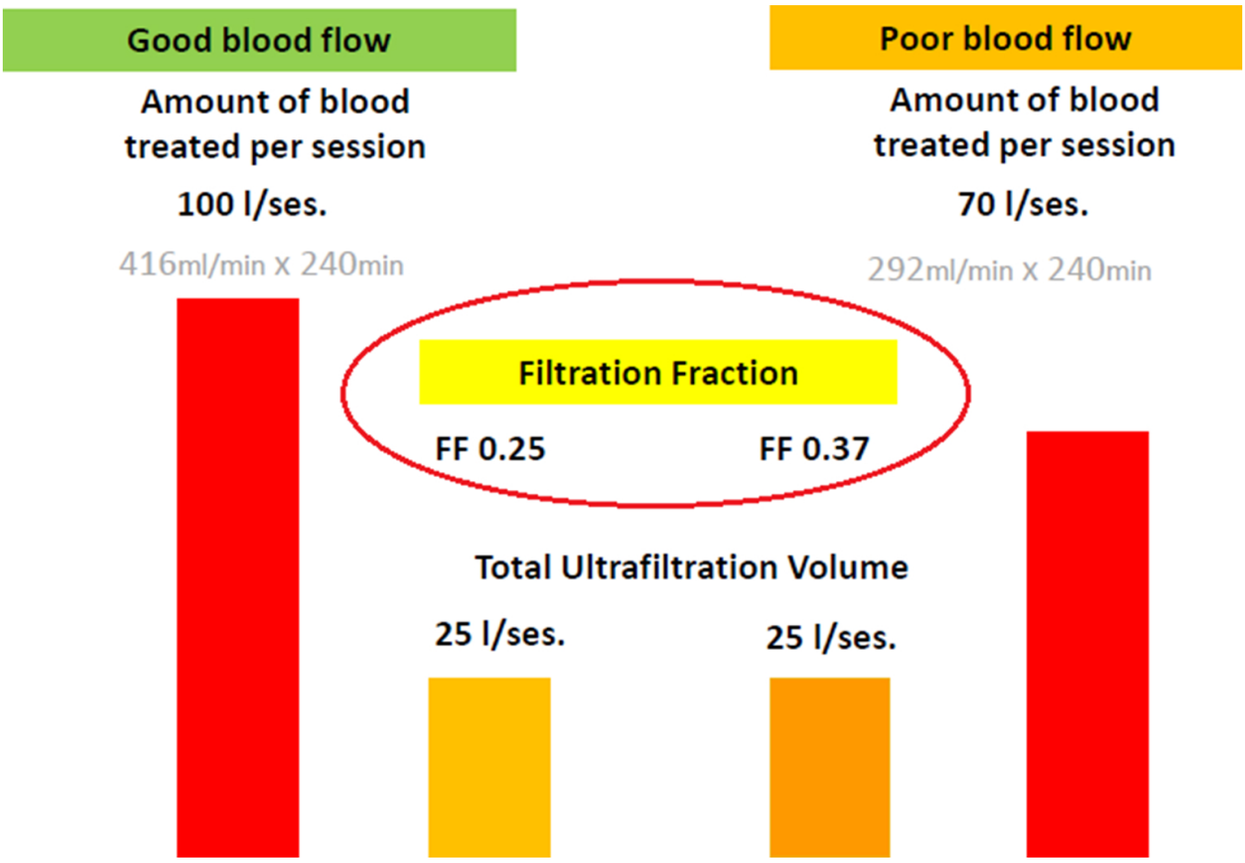

Figure 9. The impact of blood flow on filtration fraction.

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6. Towards more cardioprotective renal replacement therapy

In the very beginning of oHDF era, both the physician and the nurse in charge were supposed to do manual interventions in an attempt to prescribe and to keep the desired convective volume for each individual patient, respectively. The physician was able to do manual calculation based on the formula that included optimal blood flow rate, desired ultrafiltration rate to compensate for interdialytic weight gain, haematocrit, total proteins and filter performance, which was frequently producing alarms indicating threatening haemoconcentration and possible membrane fouling due to an excessive ultrafiltration rate. Therefore, the nurse had to carefully monitor the TMP (indicator of threatening problems) and react during the session in three possible ways in order to prevent TMP from reaching critical level: (a) rinse the dialyser with substitution fluid or normal saline, (b) decrease the UF rate or (c) switch to conventional haemodialysis. The latter two interventions were reducing the anticipated convective volume in the dialysis prescription, whereas the former intervention was only temporarily fixing the problem.

The advanced technology of automatic adaptation by the built-in software AutoSub®, Fresenius Medical Care or Ultracontrol®, Baxter, was later developed in order to achieve alarm-free setting and to avoid the related problems, so that no manual calculation was needed any more by the physician in charge, but yet not all parameters with impact on flow conditions and blood viscosity were considered in formula. Therefore a nurse still had to do manual interventions because warning notification used to be received by the built-in software in order to opt for (a) ignoring the warning; (b) accepting the warning and letting the software reduce the UF at a new recommended rate in order to be within a safe range and prevent TMP from reaching critical level, albeit reducing the expected convective volume defined at the beginning of the session; or (c) turning off software monitoring. Besides, the nurse can always turn off the substitution pump and switch to HD.

Finally, with the development of the new technology for automatic ultrafiltration control in the dialyser, alarm-free maximisation of substitution volumes has been achieved, which is based not only on information about conditions across the membrane but also along the blood flow pathway in the dialyser, so that calculation of substitution volume based on the parameters specified above has become obsolete [32]. This was shown in a crossover study of patients treated during 240-min sessions on the same day with three different blood flow rates (Q_B300, Q_B350 and Q_B380) and switched after two consecutive weeks from conventional HDF to this new technology. The convective volumes were 24.8 ± 3.1, 27.8 ± 3.0, 28.8 ± 2.4 and 23.9 ± 1.2, 27.2 ± 1.9, 28.5 ± 2.1, respectively ($p > 0.05$), to provide the evidence that the biological markers specified above are not needed for each and every haemodialysis session in order to achieve optimisation of the procedure [33].

This innovative technology is known as AutoSub plus mode [32] (**Figure 10**).

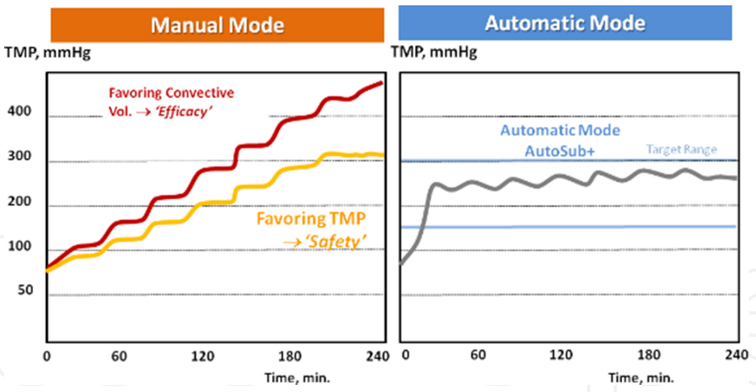

Figure 10. Switch from manual to automatic mode. TMP, transmembrane pressure.

Figure 10 shows the red line in manual mode favouring increasing convective volume and efficacy, whereas yellow line represents safety and favours TMP limitations, which means that TMP increases over time during the dialysis session as convective volume increases. However, in automatic mode on the right side of **Figure 10**, the optimisation of substitution volume has been achieved by setting the safety target range so that the machine itself sets the safe TMP target range and continuously regulates the optimal UF rate at an optimal time throughout the session in order to keep the TMP in optimal range to prevent haemoconcentration and membrane complications specified above (**Table 1**). However, the nurse can still switch to manual mode or even to conventional HD should extraordinary conditions prevent high-volume oHDF (such as special rheologic properties of a patient's blood) [32]. Owing to continuous analysis of haemorheological conditions throughout the dialysis session, continuous adaptation of UF flow takes place (**Figure 11**).

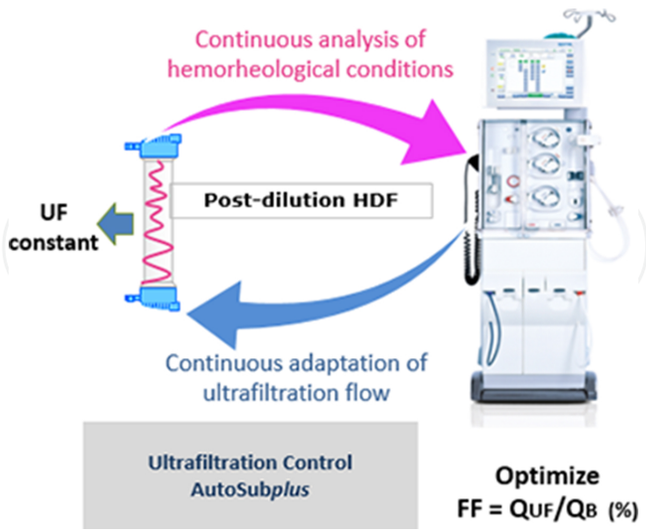

Figure 11. Continuous adaptation of ultrafiltration flow in AutoSub plus mode while keeping UF loss constant; red line within the dialyser illustrates dynamic analysis of pressure pulses along the blood flow pathway; UF, ultrafiltrate to be lost during the dialysis session; HDF, haemodiafiltration; FF, filtration fraction; Q_{UF}, ultrafiltrate flow; Q_B, blood flow.

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For this improvement sieving coefficient for beta-2 microglobulin was further increased to 0.9 in a new series of Cordiax© dialysers (**Figure 12**).

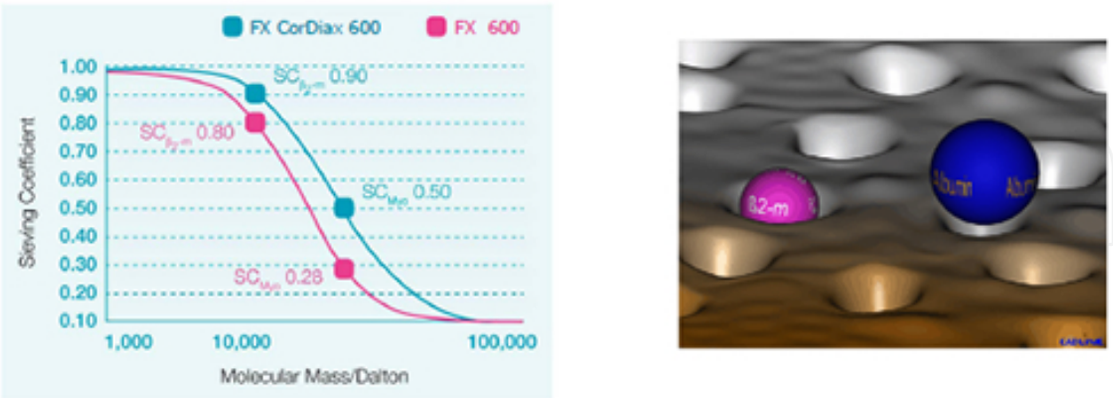

Figure 12. New series of Cordiax© dialysers with sieving coefficient for beta-2 microglobulin of 0.9 achieved by widened pore diameter which permits better molecule removal, but still retention of albumin (simplified graph based on manufacturer's internal data).

The result is the improved removal of middle molecules (while ensuring the retention of albumin) due to increased filtration fraction, thereby generating increased substitution fluid volumes, with no need to even keep the high blood flow rate, so that equally adequate dialysis can also be delivered to patients with suboptimal blood flow rates (such as inpatients with poor vascular access or inadequate needle size). This technology introduced the concept of high-volume oHDF with substitution volumes >20 L as well as the related concept of cardioprotective haemodialysis due to its beneficial effects of cardiovascular system. It introduced the new era of high-volume cardioprotective renal replacement therapy as the major clinical effect of high-volume oHDF.

7. Clinical effects of high-volume oHDF

The main clinical effects of high-volume oHDF include haemodynamic stability [34, 35], possibly improved quality of life [30], a delay in the development of dialysis-related amyloidosis [36], improvement in anaemia management [17], plasma lipid profiles [37] and inflammation [37].

Haemodynamic stability is maintained by salt loading via substitution fluid administration [38]. A higher predialysis plasma sodium concentration in patients with higher frequency of oHDF was reported, thus suggesting reduced sodium removal [39]. Haemodynamic stability is maintained by decreasing core body temperature as a result of the infusion of large amounts of fluid at a lower temperature, leading to vasoconstriction [34]. Imamović et al. demonstrated reduction in both erythropoietin (EPO) consumption and EPO resistance index in patients on HV oHDF compared to high-flux HD [17], which reveals the evidence of an increased haemodynamic stability due to improved anaemia management [40].

8. The impact of substitution volume in haemodiafiltration on patients' survival

In the era of convective treatment modalities employed in oHDF, the substitution volume appears to be critical for patient survival in prevalent patients [14, 41–43]. The Dialysis Outcomes and Practice Patterns Study (DOPPS) showed better survival of prevalent patients with high-volume HDF defined as having a substitution fluid volume of >15 L compared to low-flux HD (RR 0.65) [14]. The Turkish RCT and the CONTRAST RCT revealed survival benefits of oHDF over conventional HD in prevalent patients with 17.4 L (RR 0.54) and 21.95 L (RR 0.61) of substitution and convective volumes, respectively, but only in post hoc analyses [41, 42]. The first positive RCT in favour of improved survival of oHDF over conventional HD was the ESHOL study which showed convective volumes cut-offs of 23.1–25.4 L (RR 0.60) and >25.4 L (RR 0.55) in the intermediate and upper tertiles, respectively, also in post hoc analysis of prevalent patients' data [43]. Eventually, the observational Balkan study in incident HD patients conducted in Bosnia and Herzegovina, Serbia and Slovenia, while using European Clinical Database (EuCliD®), [17] showed the lowest RR for mortality of 0.29 on high-volume oHDF compared to high-flux conventional HD. The substitution volume cut-off of 20.4 L was discriminating between low- and high-volume oHDF, which makes the convective volume at least in the range of the one achieved in ESHOL study. Consequently, overall negative correlation may be observed between increasing ultrafiltration volumes and mortality risks in patients on convective-based treatments in comparison with conventional HD. **Figure 13** shows descriptive hazard ratios for mortality based on literature data (not on forest-plot analysis).

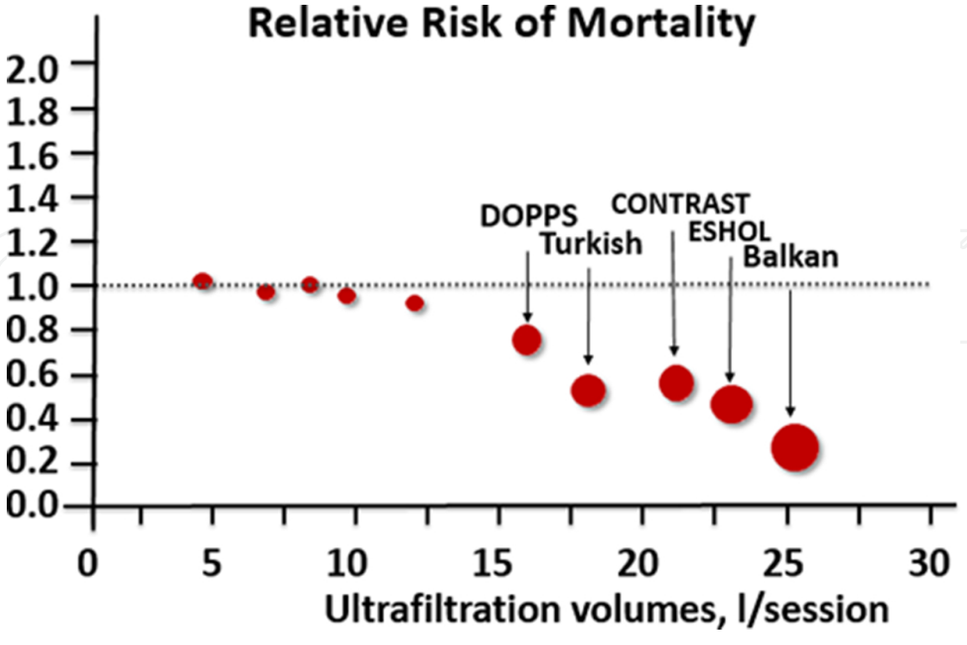

Figure 13. Negative correlation between increasing ultrafiltration volumes and decreasing relative risk of mortality in patients on haemodiafiltration.

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Recently, Canaud et al. aimed at determining optimal convection volume in 2293 international incident dialysis patients treated for 4 h with oHDF in post-dilution mode. Two-year survival rate was found to increase at about 55 L of convection volume per week and to stay increased up to about 75 L/week [44].

9. Conclusions

HV oHDF is a renal replacement treatment modality that is becoming increasingly employed in haemodialysis units worldwide because of a strong body of evidence of its survival benefit over conventional haemodialysis. Optimal substitution volume has become the measure of convective dose, reflecting mainly middle- and large-molecular-weight solutes, and it completed former Kt/V that was mainly dedicated to small-molecular-weight solutes. Both dialysis dose components are intent to act synergistically and provide more precise tools for assessing dialysis adequacy. More specifically, convective dose should be tailored to individual patients' needs depending on optimal blood flow rate, rheological blood conditions and the condition of vascular access. Studies in this field are still needed to set the cut-offs of substitution volumes to be adjusted based on the residual renal function. An alternative proposal for dialysis dose is serum beta-2 microglobulin clearance or plasma level determination, but those measurements are relatively expensive and confounded by calibration differences and variations in the generation rate. The convective volume must be set for each individual patient and should be normalised to a body size-related factor as a surrogate for the convective dialysis dose [26], but given that they varied a lot between the studies, research is still needed to set the required cut-off values in the years to come [23].

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