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# Overcoming the Limitations of Post-Dilution On-Line Hemodiafiltration: Mixed Dilution Hemodiafiltration

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**Abstract**

The impact of hemodiafiltration (HDF) on survival is still a topic of under investigation. Most recently, the results of two large prospective trials (the CONTRAST Study and the Turkish HDF Study) did not find any difference in survival between on-line HDF versus low- and high-flux hemodialysis (HD) in the overall dialysis population. However, secondary subgroup analyses of both studies showed a significant reduction in death risk among patients on HDF with high volume exchange, confirming the preliminary observation of the European DOPPS Study. Higher middle molecule removal is definitely attained in high-efficiency HDF compared to high-flux HD, and lower basal $\beta_2$-microglobulin levels may result in reduced death risk, as suggested by an analysis of the HEMO Study.



In this scenario, a new modality of hemodiafiltration (HDF), namely mixed dilution HDF (mixed HDF), was conceived in the first years of the 21st century that aimed at maximizing the efficiency of HDF while reducing the shortcomings and risks associated with the traditional pre- and post-dilution infusion modes. Mixed HDF is assisted by a feedback control system which automatically adjusts the total infusion/ultrafiltration rate and the ratio between pre- and post-dilution infusion rates at the maximal filtration fraction (FF) tolerated by the system. This system takes patient and flow conditions, internal pressures and hydraulic membrane permeability, and their complex interactions and changes during the session into account. The TMP/UF profile prevents the development of dangerous hydrostatic pressures within the dialyzer and helps to better

preserve membrane permeability. This facilitates a significant increase in solute removal during treatment in a wide molecular range as well as minimal protein leakage.

Preliminary clinical results indicate that mixed HDF could be the most powerful convective strategy, easily adapted to every patient, especially those with high hematocrit, excessive hemoconcentration or failure of their refilling capacity to maintain a sustainable ultrafiltration. Such patients typically have a low tolerance for post-dilution HDF.

## Domain of the Mixed HDF Concept

Several prospective studies have provided definite evidence that HDF, as compared to standard and high-flux hemodialysis (HD), promotes enhanced removal of small, middle molecular and some protein-bound compounds and succeeds in reducing their basal levels in the long term [1–6]. The result is a sustained improvement in the uremic toxicity profile, which may help to prevent the progression of (or to ameliorate) some severe uremic complications of chronic dialysis treatment, such as anemia [5, 7], chronic inflammation [8, 9], dyslipidemia [7], hyperphosphatemia and secondary hyperparathyroidism [5, 7, 10], all of which lead to accelerated atherosclerosis in dialysis patients. Significantly lower plasma $\beta_2$-microglobulin ($\beta_2$M) levels, attained with the use of high-flux membranes [1, 3, 4, 11], have been shown to reduce the incidence of dialysis-related amyloidosis and carpal tunnel syndrome [12, 13] and were associated with reduced all-cause and infection-related mortality in dialysis patients [11, 14].

The impact of HDF on hard clinical end-points is still under investigation. However, the available evidence is suggestive of a benefit of convective treatments, at least in some categories of patients and/or treatment modalities. Observational studies on large patient databases with long-term follow-up have shown a reduced mortality risk of around 35% in patients on on-line HDF compared to patients on low- and high-flux HD [9, 15, 16]. A small Italian, randomized study reported a 55% reduced death risk in patients on hemofiltration (HF) compared to low-flux HD over a 3-year period [17]. In a retrospective analysis of the European Dialysis Outcomes and Practice Patterns Study [18], a significant 35% lower mortality risk was only observed in patients on high-efficiency HDF (volume exchange of 15–25 liters/session) compared to low- and high-flux HD, while no difference was observed between low-efficiency HDF and conventional or high-flux HD.

More recently, the results of two large-database, prospective studies comparing survival in patients on on-line HDF versus low-flux HD, the CONTRAST Study [19], and versus high-flux HD, the Turkish HDF Study [20], did not find any difference in survival in the overall dialysis population after a 3- and 2-year follow-

up, respectively. However, secondary subgroup analyses of both studies showed a significant reduction in the risk of death for cardiovascular and overall causes among patients on HDF with high volume exchange of over 20 liters/treatment in the CONTRAST Study and over 17.4 liters/session in the Turkish Study.

Even though secondary analyses of prospective studies entail reduced statistical power, the results obtained with high-efficiency HDF are impressive. Certainly HDF results in higher middle molecule removal than high-flux HD, provided that this technique is performed with high volume exchange. In randomized studies comparing the two strategies, a significant difference in basal $\beta_2$M levels only emerged when HDF was performed with a mean filtration volume of 21 liters/session [6], but not with a relatively low volume of 8–12 liters/session [3]. These experiences of the past may attractively link to the results of the CONTRAST and Turkish studies in the light of the relation between $B_2$-M levels and mortality which was suggested by an analysis of the HEMO Study [11, 14].

## Scope of Mixed HDF and Infusion Modalities

In the first years of the 21st century, a new modality of HDF, namely mixed dilution HDF (mixed HDF), was conceived and continuously refined with the aim to maximize the efficiency of the HDF while reducing the shortcomings and risks associated with the traditional pre- and post-dilution infusion modes [21–23].

HDF is the strategy enabling the high hydraulic and solute permeability of high-flux membranes to be most properly exploited, but the modality of substitution fluid infusion influences its performance to a different extent [24]. In the case of post-dilution HDF, the most efficient infusion mode, hemoconcentration, high blood viscosity and resistance to flow (all of which progressively increase during the treatment session) limit the ultrafiltration flow rate ($Q_{UF}$) and may result in capillaries and dialyzer clotting [25]. Thickening of the secondary protein layer, which is proportional to the filtration pressure, results in a permanent and significant reduction of the membrane permeability. This can compromise the efficiency of the sessions and would require the application of increasingly higher and often unpredictable transmembrane pressure (TMP) gradients to maintain the planned $Q_{UF}$ [22]. However, this is often impossible in the face of the consequences described above, and repeated reduction of the infusion and ultrafiltration rates are necessary to avoid technical and clinical problems – at the price of a decline in convective solute removal.

Pre-dilution HDF ensures better rheological and hydraulic conditions than post-dilution, and the possibility of higher infusion rates, but at the price of reduced efficiency due to dilution of the solute concentrations available for diffusion and convection.

Some years ago, the advent of on-line production of sterile substitution fluid facilitated a broad clinical application of HDF and made the use of large volume

exchanges at low cost feasible. However, control systems implemented on available dialysis machines were of little help in counteracting the events described above (especially in post-dilution HDF) so that it was difficult to plan and carry out a session in which efficient and safe operational conditions could be maintained. Thus the concept of mixed HDF was born, targeting maintenance of a constant, maximum infusion/ultrafiltration flow under optimal TMP conditions over the whole treatment time. This was achieved by shifting small amounts of infusion from the post- to the pre-infusion site according to changes in TMP. It was during the realization of the mixed HDF project that a TMP-reactive feedback mechanism was first developed and applied in a clinical setting [22]. This feedback mechanism was able to optimize $Q_{UF}$ and so achieve the most efficient convective transport while maintaining a safe pressure/flow within the dialyzer through the reactive control of TMP. A schematic representation of the mechanism is depicted in figure 1.

## Optimization of Sustainable Convection

Several observations form the basis of the new technique, which will be explained in the following.

*Maximizing Treatment Efficiency.* At a given blood flow, the maximal efficiency in convective solute removal occurs at the highest achievable FF [21], i.e. the ratio between ultrafiltration rate $Q_{UF}$ and plasma water flow rate $Q_{PW}$. Maximal achievable FF is often unpredictable individually and variable during the treatment due to changing conditions of the membrane permeability, as described above, and to a patient variability, mainly related to the individual refilling capacity as ultrafiltration progresses. At any given blood flow, TMP is exponentially related to the FF, and the slope of the curve is a function of the hydraulic permeability of the dialyzer [21]. Above a certain TMP level, the system enters a critical state and sudden dangerous pressure increases are likely to result from small changes in blood flow or viscosity, venous pressure, or for technical reasons [25]. These events are difficult to prevent or counteract without a feedback system which is able to automatically ensure the highest convective efficiency while maintaining optimal operational conditions in the hemodialyzer. Figure 2 shows how the highest convective removal is achievable theoretically under operational conditions independent of patient and dialyzer parameters.

*Conditioning of the Membrane.* High-flux membranes, generally having a cut-off up to 60 kDa, may be responsible for massive protein leakage, mainly when high filtration pressure is applied to the intact membrane in the early phase of the session. Even large molecules such as albumin may be forced into the intact pores and either cross them and get lost in the dialysate or be entrapped inside, with the effect of a partial obstruction of the pores and a permanent and

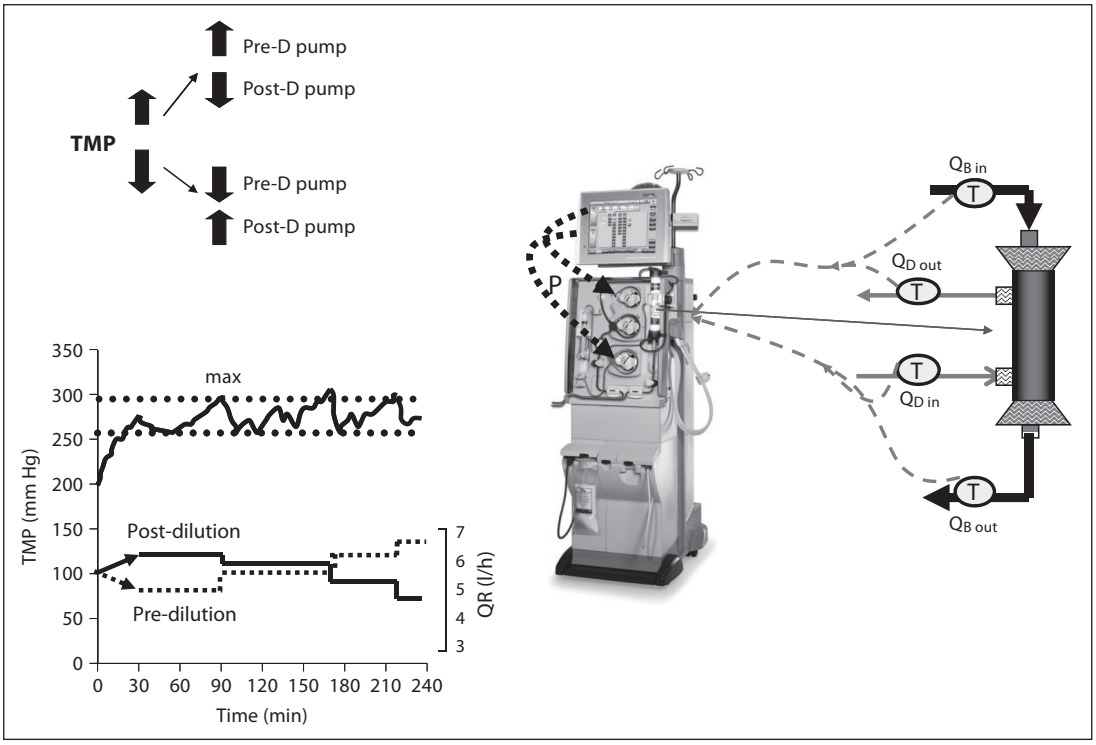


**Fig. 1.** Schematic representation of on-line mixed HDF with the TMP/$Q_{UF}$ feedback control system. TMP is continuously calculated from measures obtained with four pressure transducers (T) placed at inlet and outlet blood and dialysate ports (right side of the figure). Sterile infusion fluid, prepared on-line with double ultrafiltration, is driven to the infusion ports of the dialyzer by means of two peristaltic pumps (P) at relative infusion rates modulated by the TMP/$Q_{UF}$ feedback through changes of the pumps speed. TMP is forced to follow a definite profile during the session by modulating the ratio between pre- and post-dilution in order to optimize the filtration fraction (left side of the figure).

significant reduction of the membrane permeability. If a low $Q_{UF}$ is set at the start of the session, i.e. less transmembrane driving force, only small peptides and proteins are driven to the membrane surface and adhere more regularly to the inner surface of its pores. Compared to the pristine membrane, this secondary membrane layer shows smaller pore sizes, but permeability to middle molecular solutes like $\beta_2$M is not substantially modified, whereas larger plasma molecules, such as albumin, are rejected or integrated into the secondary membrane. Based on these findings, the mixed HDF treatment was designed to start with low filtration pressure at the beginning of the session by setting relatively low FF (0.35–0.40) obtained with a prevailing rate of substitution fluid infused in pre-dilution. Then, with the help of the TMP feedback, TMP is ramped up gradually by means of automatic shifts of small amounts of the infusion fluid

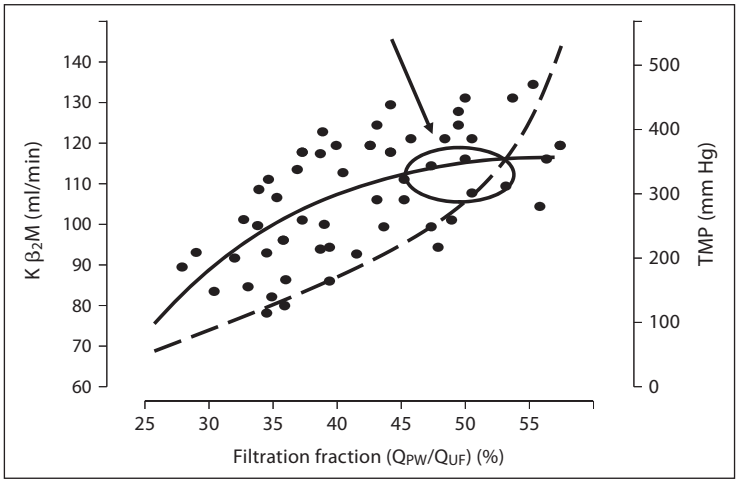


**Fig. 2.** Relationship between filtration fraction (FF, X-axis), $\beta_2$M clearance (K $\beta_2$M, left Y-axis) and transmembrane pressure (TMP, right axis) tested in mixed HDF patients K $\beta_2$M increases with FF increase up to a FF value of about 50%, where the curve reaches its plateau, depending on the applied blood flow rate (here $Q_B$ = 400 ml/min). Beyond these FF values, the exponential TMP curve becomes steeper and it is likely to cause technical and clinical problems. The ellipse in the figure delimits the domain of operational conditions which may ensure maximal efficiency (highest K $\beta_2$M) under safe hydraulic and flow conditions.

from pre- to post-dilution until it achieves the defined TMP range without reducing the total $Q_{UF}$.

## Principles and Parameterization of Mixed Dilution HDF

On-line mixed HDF was originally performed in our center on a 4008 H on-line Fresenius system (Fresenius Medical Care, Germany) modified with the application of a Y-shaped infusion line and an additional pump on one Y branch that diverted part of the total infusion from the post-filter to the pre-filter infusion site. A feedback system for TMP control was used in mixed HDF to modulate the pre-dilution/post-dilution ratio while maintaining the total infusion constant throughout the session (fig. 1). The basic concept is that splitting and varying the infusion between pre- and post-filter in order to treat with an optimal relative filtrate flow rate guarantees the best possible rheological and hydraulic conditions within the dialyzer at the highest fluid exchange rate and with maximal solute removal by convection.

The control variable, i.e. the mean pressure gradient between blood and dialysate compartments along the dialyzer (TMP, mm Hg), was calculated on-

line by means of a dedicated software analyzing signals from pressure transducers located at the inlet and outlet blood and dialysate ports of the dialyzer ($P_{B\,in}$, $P_{B\,out}$, $P_{D\,in}$, $P_{D\,out}$, respectively) using the equation:

$$TMP = 0.5 \bullet [(P_{B\,in} + P_{B\,out}) - (P_{D\,in} + P_{D\,out})] - P_{onc} \quad (1)$$

where $P_{onc}$ (mm Hg) is the mean oncotic pressure exerted by the plasma proteins, set by default to a constant value of 25 mm Hg. TMP was kept in a specified TMP window by both adjusting the overall substitution volume and the momentary distribution of pre- and post-dilution flow rates.

As mentioned above, the FF was defined arbitrarily as the fraction of $Q_{PW\,in}$ filtered during the passage through the dialyzer:

$$FF = (1 - Q_{PW\,out}/Q_{PW\,in}) = Q_{UF}/Q_{PW\,in} \quad (2)$$

where the suffix 'in' and 'out' define flow at the inlet and outlet dialyzer port. $Q_{PW\,in}$ was determined online from the effective blood flow rate ($Q_{B\,eff} = Q_B$ compensated for the arterial pressure in front of the blood pump), from hematocrit (Hct), monitored on-line with an integrated device (blood volume monitor, FMC), and from the water fraction of plasma ($F_p$), according to the classic equation:

$$Q_{PW\,in} = Q_{B\,eff} \bullet (1 - Hct/100) \bullet F_p \quad (3)$$

The initial infusion rate ($Q_S$) was usually set equal to $Q_{PW\,in}$ but, according to the clinical needs of the individual patient and the characteristics of the dialyzer, different values for $Q_S/Q_{PW\,in}$ ratio were chosen between 0.7 and 1. With a lower post-dilution rate at the start of the treatment (FF from 0.3 to 0.5), a slow start with a progressive TMP ramp in the first 30 min could be realized in order to condition the dialyzer membrane.

An optimal patient-specific setting of both initial and treatment FF could be evaluated after 3–6 mixed HDF treatments. Typical values for the overall substitution volume would be up to 50% of the processed blood volume, delivered in close to equal proportions both in pre- and post-dilution. With a new algorithm, the 5008 dialysis machine evaluates and adapts the treatment settings in an automatic way including the data from the last treatment stored for each patient.

## Mixed HDF with Closed Loop Control and Adaption Mode

As discussed above, mixed HDF offers the two principal possibilities of choosing the substitution volume relative to blood or plasma water flow and the split of the substitution volume in pre- and post-dilution volumes to maximize the treatment result with respect to convective clearances.

The mixed HDF treatment setting is controlled in two phases. In the initial phase of approximately 15 min an optimal secondary membrane layer

formation is primed by inducing progressive small increases in TMP from its initial low values (about 100 mm Hg) up to its preselected range (from 260–280 to 300–330 mm Hg). After this initial TMP ramp, the first closed loop control keeps TMP values within the planned range by preventing excessive increase in TMP with infusion shifts from post- to pre-dilution with the effect to reduce the FF or, vice versa, by compensating for drops in TMP with infusion shifts from pre- to post-dilution that increase the FF. Besides that, TMP can also be stabilized by reducing the total infusion rate in small steps to compensate for the progressive hemoconcentration caused by the weight loss and recorded on-line by means of the BVM. In this mode, fewer shifts between post- and pre-dilution are necessary to maintain constant TMP values.

A second closed loop control algorithm aims at a balanced treatment result in terms of both dilution modalities. High FF values would cause the TMP values to repeatedly exceed the upper limit of the target range and, as a consequence, the treatment would develop towards a pre-dilution HDF treatment. Low FF would drive the treatment in the opposite direction, i.e. would eventually result in a post-dilution treatment. The adaption algorithm varies the FF value in order to keep the treatment result balanced in terms of the volume split before and after the dialyzer. In a first version, the objective was set to equally distributed volumes as this showed the best results for middle molecular clearances [22]. Depending on future clinical results, modified versions could aim at different ratios emphasizing either pre- or post-dilution depending on the specific clearance or anticoagulation and clinical needs of the patient concerned.

## Experimental and Clinical Results of Mixed HDF

Continuous improvement of the mixed HDF technique was carried out in the first years of this century following experimental application in selected centers and with a limited number of patients. Since its implementation on the new 5008 Fresenius Dialysis System, several European Dialysis Centers have started to offer this advanced therapy to their patients.

Theoretical validation of the new HDF technique was obtained in an experimental setting [26] by comparing the clearances of different molecular weight dextran fractions measured by means of size exclusion chromatography and obtained during the three HDF infusion modes (mixed, pre- and post-dilution) and during high-flux HD. The curves derived and depicted in figure 3 showed that the clearance in the molecular weight range between 2 and 60 kDa, covered by three different dextran fractions, were always higher for mixed HDF than for the other HDF modalities and HD. The small loss of urea clearance results from the pre-dilution component and corresponding decrease of the diffusion gradient.

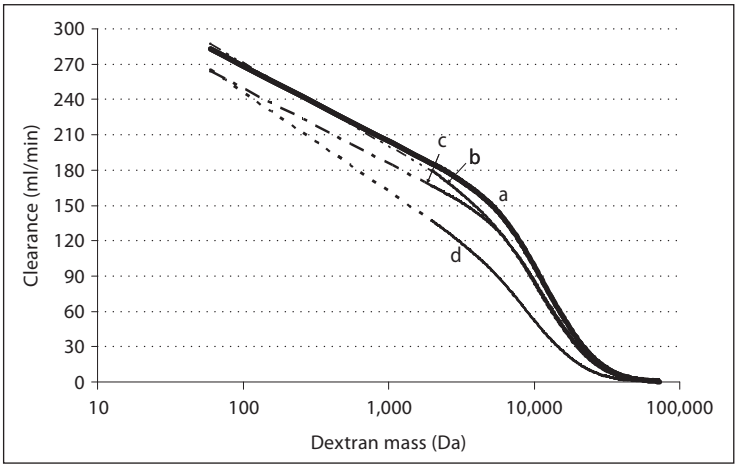


**Fig. 3.** Dextran clearance comparison between various HDF techniques (a, mixed HDF; b, post-dilution HDF; c, pre-dilution HDF) and high-flux HD (d), performed with a 5008 Dialysis Machine (FMC, Bad Homburg, Germany) and a high-flux dialyzer (FX800, FMC). Clearance was measured by means of size exclusion chromatography (Agilent 1200 System) using a mix of three technical grade dextran fractions with 3.5, 15 and 40 kDa (flow rate 300 ml/min). The clearance curves start at 60 Da with the value of the clearances for urea, which was added to the dextran mix. All components were dissolved in a NaCl solution at a concentration of 0.35 mol/l, the same NaCl solution was used as 'dialysis fluid'. Due to the NaCl artifact in the measurements, all values from 60 to 2,000 Da were replaced by a line between the urea value and the first dextran clearance value of 2,000 Da. From this value on, the curves only represent dextran clearances. All treatment settings corresponded to the default settings of the 5008 Dialysis Machine.

Clinical controlled trials published to date showed that mixed HDF performed at the maximal infusion/ultrafiltration rate possible in post-dilution HDF (FF ~50%) achieved similar efficiency in small solute removal while ensuring safe hydraulic conditions similar to pre-dilution HDF [21]. The advantage of mixed HDF clearly appeared with respect to middle molecule removal when higher infusion rates were applied under the feedback control, which allowed the TMP to be set and modulated according to a defined ultrafiltration profile. Convective transport was optimized under these conditions and on-line mixed HDF yielded a significantly higher $\beta_2$M removal than that obtained in pre- and post-dilution [22, 23] (fig. 4) and in mid-dilution HDF [27], a convective technique recently proposed and claimed to be of greater efficiency when compared to the traditional pre- or post-dilution infusion modes in HDF [28]. Different diffusive and convective dialysis modalities were compared in an independent multicenter study recently published [29]. In this study, the highest Kt/V for urea and $\beta_2$M were reported in the patients of the mixed HDF group among a total study population of 407 subjects.

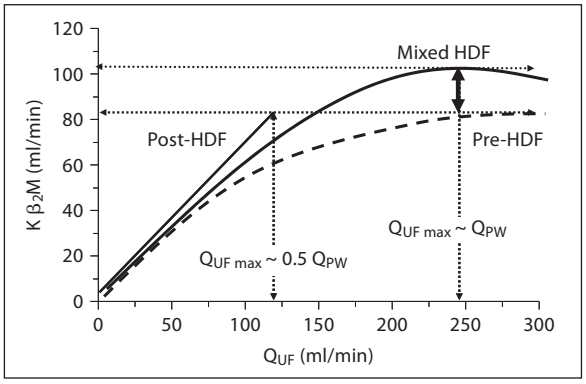


**Fig. 4.** Relations between ultrafiltration rate ($Q_{UF}$, X-axis) and $\beta_2$M clearance (K $\beta_2$M, Y-axis) in on-line HDF with different infusion modalities (blood flow rate, $Q_B$ = 400 ml/min, plasma water flow rate, $Q_{PW}$ = 242 ml/min). The linear relation is limited in post-dilution by the maximal FF achievable with this infusion mode. The exponential curve for K $\beta_2$M in pre-dilution reaches a plateau when the $Q_{UF}$ rate approximates $Q_{PW}$. This trend is similar in mixed HDF but the K $\beta_2$M curve reached its plateau at a higher value. The possible advantage in K $\beta_2$M achievable with mixed HDF is shown by the arrow.

Remarkably, superior results in mixed HDF compared to mid-dilution HDF were obtained with the application of much lower pressure regimen within the dialyzer by means of the TMP/$Q_{UF}$ profile, thus better preserving the permeability of the membrane and minimizing the protein leakage favored by very high hydrostatic pressures.

The feedback automatically adjusts the infusion ratio between pre- and post-dilution at the maximum FF without reducing the total infusion and taking into account flow conditions, internal pressures, membrane permeability and their complex interactions and changes occurring during the sessions. For this reason, mixed HDF may be of special advantage in patients with high pre-dialysis hematocrit and an increased risk of filter clotting with post-dilution HDF due to hemoconcentration [30]. Moreover, this new infusion modality may offer the possibility to keep all those patients on HDF therapy who could hardly be submitted to post-dilution HDF due to failure of their refilling capacity and therefore to a scarce availability of ultrafiltrable plasma water (e.g. patients with diabetes, heart failure, autonomic nervous system diseases). In fact, the feedback mechanism efficiently compensates for the progressive hemoconcentration occurring during the treatment by proportional addition of small amounts of pre-dilution infusion fluid to the blood entering the dialyzer.

## References


1 Lin CL, Yang CW, Chiang CC, Chang CT, Huang CC: Long-term on-line hemodiafiltration reduces predialysis $\beta_2$-microglobulin levels in chronic hemodialysis patients. Blood Purif 2001;19:301–307.

2 Lin CL, Huang CC, Yu CC, Yang HY, Chuang FR, Yang CW: Reduction of advanced glycation end product levels by on-line hemodiafiltration in long-term hemodialysis patients. Am J Kidney Dis 2003;42:524–531.

3 Locatelli F, Mastrangelo F, Redaelli B, Ronco C, Marcelli D, La Greca G, Orlandini G: Effects of different membranes and dialysis technologies on patient treatment tolerance and nutritional parameters. The Italian Cooperative Dialysis Study Group. Kidney Int 1996;50:1293–1302.

4 Pedrini LA, De Cristofaro V, Comelli M, Casino FG, Prencipe M, Baroni A, Campolo G, Manzoni C, Coli L, Ruggiero P, Acquistapace I, Auriemma L: Long-term effects of high-efficiency on-line haemodiafiltration on uraemic toxicity. A multicentre prospective randomized study. Nephrol Dial Transplant 2011;26:2617–2624.

5 Vaslaki L, Major L, Berta K, Karatson A, Misz M, Pethoe F, Ladanyi E, Fodor B, Stein G, Pischetsrieder M, Zima T, Wojke R, Gauly A, Passlick-Deetjen J: On-line haemodiafiltration versus haemodialysis: stable haematocrit with less erythropoietin and improvement of other relevant blood parameters. Blood Purif 2006;24:163–173.

6 Ward RA, Schmidt B, Hullin J, Hillebrand GF, Samtleben W: A comparison of on-line hemodiafiltration and high-flux hemodialysis: a prospective clinical study. J Am Soc Nephrol 2000;11:2344–2350.

7 Pedrini LA, DeCristofaro V, Comelli M, Casino FG, Prencipe M, Baroni A, Campolo G, Manzoni C, Coli L, Ruggiero P, Acquistapace I, Auriemma L: Long-term effects of high-efficiency on-line haemodiafiltration on uraemic toxicity. A multicentre prospective randomized study. Nephrol Dial Transplant 2011;26:2617–2624.

8 Kim HW, Yang HN, Kim MG, Choi HM, Jo SK, Cho WY, Kim HK: Microinflammation in hemodialysis patients is associated with increased CD14CD16+ pro-inflammatory monocytes: possible modification by on-line hemodiafiltration. Blood Purif 2011;31:281–288.

9 Panichi V, Rizza GM, Paoletti S, Bigazzi R, Aloisi M, Barsotti G, Rindi P, Donati G, Antonelli A, Panicucci E, Tripepi G, Tetta C, Palla R: Chronic inflammation and mortality in haemodialysis: effect of different renal replacement therapies. Results from the RISCAVID Study. Nephrol Dial Transplant 2008;23:2337–2343.

10 Minutolo R, Bellizzi V, Cioffi M, Iodice C, Giannattasio P, Andreucci M, Terracciano V, Di Iorio BR, Conte G, De Nicola L: Postdialytic rebound of serum phosphorus: pathogenetic and clinical insights. J Am Soc Nephrol 2002;13:1046–1054.

11 Cheung AK, Rocco MV, Yan G, Leypoldt JK, Levin NW, Greene T, Agodoa L, Bailey J, Beck GJ, Clark W, Levey AS, Ornt DB, Schulman G, Schwab S, Teehan B, Eknoyan G: Serum $\beta_2$-microglobulin levels predict mortality in dialysis patients: results of the HEMO Study. J Am Soc Nephrol 2006;17:546–555.

12 Koda Y, Nishi S, Miyazaki S, Haginoshita S, Sakurabayashi T, Suzuki M, Sakai S, Yuasa Y, Hirasawa Y, Nishi T: Switch from conventional to high-flux membrane reduces the risk of carpal tunnel syndrome and mortality of hemodialysis patients. Kidney Int 1997;52:1096–1101.

13 Locatelli F, Marcelli D, Conte F, Limido A, Malberti F, Spotti D: Comparison of mortality in ESRD patients on convective and diffusive extracorporeal treatments. The Registro Lombardo Dialisi e Trapianto. Kidney Int 1999;55:286–293.

14 Cheung AK, Greene T, Leypoldt JK, Yan G, Allon M, Delmez J, Levey AS, Levin NW, Rocco MV, Schulman G, Eknoyan G: Association between serum $\beta_2$-microglobulin level and infectious mortality in hemodialysis patients. Clin J Am Soc Nephrol 2008;3:69–77.

15 Vilar E, Fry AC, Wellsted D, Tattersall JE, Greenwood RN, Farrington K: Long-term outcomes in online hemodiafiltration and high-flux hemodialysis: a comparative analysis. Clin J Am Soc Nephrol 2009;4:1944–1953.
16 Jirka T, Cesare S, Di Benedetto A, Perera CM, Ponce P, Richards N, Tetta C, Vaslaky L: Mortality risk for patients receiving hemodiafiltration versus hemodialysis. Kidney Int 2006;70:1524–1525.
17 Santoro A, Mancini E, Bolzani R, Boggi R, Cagnoli L, Francioso A, Fusaroli M, Piazza V, Rapana R, Strippoli GF: The effect of on-line high-flux hemofiltration versus low-flux hemodialysis on mortality in chronic kidney failure: a small randomized controlled trial. Am J Kidney Dis 2008;52:507–518.
18 Canaud B, Bragg-Gresham JL, Marshall MR, Desmeules S, Gillespie BW, Depner T, Klassen P, Port FK: Mortality risk for patients receiving hemodiafiltration versus hemodialysis: European results from the DOPPS. Kidney Int 2006;69:2087–2093.
19 Grooteman M, van den Dorpel R, Bots M, Penne L, van der Weerd N, Mazairac A, den Hoedt C, van der Tweel I, Levesque R, Nubé M, ter Wee P, Blankestijn P: Online hemodiafiltration versus low-flux hemodialysis: effects on all-cause mortality and cardiovascular events in a randomized controlled trial. The Convective Transport Study (CONTRAST). 2011 (in press).
20 Ok E, Asci G, Ok ES, Kircelli F, Yilmaz M, Hur E, Demirci MS, Ozdogan O, Demirci C, Sertoz OO, Duman S, Ozkahya M, Kaykcioglu M, Elbi H, Basci A, Toz H: Comparison of postdilution on-line hemodiafiltration and hemodialysis (Turkish HDF Study). 2011 (in press).
21 Pedrini LA, De Cristofaro V, Pagliari B, Sama F: Mixed predilution and postdilution online hemodiafiltration compared with the traditional infusion modes. Kidney Int 2000;58:2155–2165.
22 Pedrini LA, DeCristofaro V: On-line mixed hemodiafiltration with a feedback for ultrafiltration control: effect on middle-molecule removal. Kidney Int 2003;64:1505–1513.
23 Pedrini LA, Cozzi G, Faranna P, Mercieri A, Ruggiero P, Zerbi S, Feliciani A, Riva A: Transmembrane pressure modulation in high-volume mixed hemodiafiltration to optimize efficiency and minimize protein loss. Kidney Int 2006;69:573–579.
24 Pedrini LA: On-line hemodiafiltration: technique and efficiency. J Nephrol 2003;16(suppl 7):S57–S63.
25 Henderson LW: Biophysics of ultrafiltration and hemofiltration; in Maher JF, (ed): Replacement of Renal Function by Dialysis. Dordrecht, Kluwer Academic, 1989, pp 300–326.
26 Sharifi H, Wiesen G, Vienken J, Mottaghy K: Analysis of low- to middle-molecular clearance ratios in haemodialysis and different haemofiltration dilution options using a method based on dextrans and size exclusion chromatography; Master Thesis in Biomedical Engineering, RWTH, Aachen, Germany 2010.
27 Feliciani A, Riva MA, Zerbi S, Ruggiero P, Plati AR, Cozzi G, Pedrini LA: New strategies in haemodiafiltration (HDF): prospective comparative analysis between on-line mixed HDF and mid-dilution HDF. Nephrol Dial Transplant 2007;22:1672–1679.
28 Krieter DH, Collins G, Summerton J, Spence E, Moragues HL, Canaud B: Mid-dilution on-line haemodiafiltration in a standard dialyser configuration. Nephrol Dial Transplant 2005;20:155–160.
29 Casino FG, Pedrini LA, Santoro A, Mandolfo S, David S, De C, V, Teatini U, Lomonte C, Lopez T: A simple approach for assessing equilibrated Kt/V $\beta_2$M on a routine basis. Nephrol Dial Transplant 2010;25:3038–3044.
30 Kuhlmann MK: Phosphate elimination in modalities of hemodialysis and peritoneal dialysis. Blood Purif 2010;29:137–144.

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