

# On-line mixed hemodiafiltration with a feedback for ultrafiltration control: Effect on middle-molecule removal

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## On-line mixed hemodiafiltration with a feedback for ultrafiltration control: Effect on middle-molecule removal.

**Background.** Increased middle-molecular uremic toxin removal seems to favorably influence survival in dialysis patients. The aim of this study was to verify if, in on-line mixed hemodiafiltration, solute removal by convection may be enhanced by forcing the ultrafiltration rate ( $Q_{UF}$ ) and optimizing the infusion technique in order to achieve the highest possible filtration fraction (FF).

**Methods.** Removal of  $\beta_2$ -microglobulin ( $\beta_2$ -m), urea, creatinine, and phosphate were compared in 20 patients randomly submitted to one dialysis session (A), one postdilution hemodiafiltration session (B), and three sessions of mixed hemodiafiltration (C, D, and E) at different infusion rates ( $Q_S$ ). In mixed hemodiafiltration, a newly developed feedback system automatically maintained the transmembrane pressure (TMP) within its highest range of safety (250 to 300 mm Hg) at constant  $Q_{UF}$ , while ensuring the maximum FF by splitting infusion between pre- and postdilution.

**Results.** A mean  $Q_S$  of  $134 \pm 20$  mL/min (mean FF = 0.65) was attained in post-HDF, and up to  $307 \pm 41$  mL/min (mean FF = 0.69) in mixed hemodiafiltration. The mean dialysate clearances ( $K_{DO}$ ) for all tested solutes and urea  $eKt/V$  were significantly higher in all hemodiafiltration sessions than in dialysis. Only in the case of urea did the infusion mode have no significant effect.  $K_{DO}$  for  $\beta_2$ -m was maximal in session D and significantly higher than in session B ( $90.2 \pm 11$  mL/min vs.  $77.5 \pm 11$  mL/min;  $P = 0.02$ ).  $K_{DO}$  for  $\beta_2$ -m significantly correlated with  $Q_S$  and the plasma water flow rate ( $Q_{PW}$ ). The highest  $K_{DO}$  for  $\beta_2$ -m was found at values of  $Q_S \sim Q_{PW}$ . Beyond this value  $K_{DO}$  decreased.

**Conclusion.** The mixed infusion mode in hemodiafiltration, controlled by the TMP-ultrafiltration feedback, seems to improve the efficiency of hemodiafiltration by fully exploiting the convective mechanism of solute removal. The feedback automatically adjusted the infusion rate and site to the maximum FF taking into account flow conditions, internal pressures, and hydraulic permeability of the dialyzer and their complex interactions.

**Key words:** hemodiafiltration,  $\beta_2$ -microglobulin, transmembrane pressure, ultrafiltration, feedback, middle molecule.

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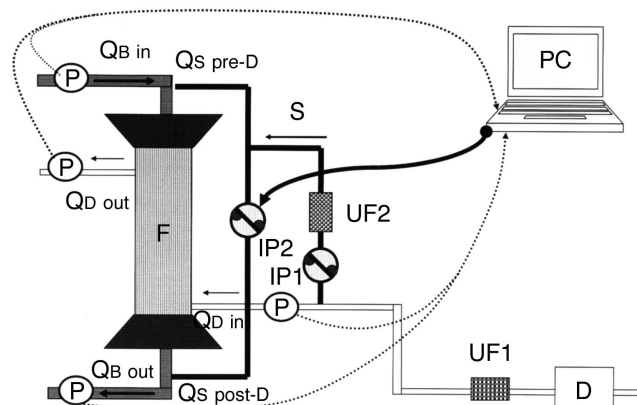
In the last decade several observational studies have reported a reduced death risk in patients undergoing hemodialysis with high-flux membranes [1–5]. In some studies, such an effect has been associated with the increased removal of middle-molecular uremic toxins promoted by these membranes [3–5], independently from the effects related to their high biocompatibility. On the other hand, overall survival was not influenced significantly by high-flux membranes in an Italian registry study [6] and in the HEMO Study [7]. In the latter study, however, a reduced rate of cardiac death in patients of the high-flux group was reported, as well as longer survival in the subgroup undergoing hemodialysis for more than 3.7 years. The relatively low mean  $\beta_2$ -microglobulin ( $\beta_2$ -m) clearance ( $K$ ) in the high-flux group ( $34 \pm 11$  mL/min) possibly prevented the achievement of a clearer difference in the overall outcome between groups. Indeed, solute transport obtained by “internal filtration” in high-flux hemodialysis is definitely lower than that attainable by convection in hemodiafiltration, provided that high rates of fluid exchange are applied. A prospective randomized study comparing high-flux hemodialysis with hemodiafiltration at a relatively low infusion volume (8 to 12 L/session) found similar basal  $\beta_2$ -m levels over a period of 24 months [8], but significant differences in basal  $\beta_2$ -m levels emerged from a long-term prospective study in which a mean filtration volume of 21 L was applied [9]. Compared to high-flux hemodialysis, an increase in convective removal was shown in hemodiafiltration for  $\beta_2$ -m [9–15], for asymmetric dimethyl-arginine (ADMA) [16], for complement fractions, such as factor D [9, 17], fraction Ba [17], C3a, C5a [18], and, with a variable contribution of absorption, for proinflammatory cytokines, such as tumor-necrosis factor- $\alpha$  (TNF- $\alpha$ ) and interleukin-1 (IL-1), IL-6, and IL-8 [19, 20]. These middle-molecular compounds have a pathogenic role or are markers of the most frequent long-term complications and causes of death in hemodialysis patients, such as dialysis-related amyloidosis, cardiovascular disease, inflammation, and malnutrition. Thus, even in the absence of definite evidence, there are strong indications to ad-

vises the use of dialytic strategies, which can ensure increased removal of middle-molecular uremic toxins [21]. Among these, hemodiafiltration is undoubtedly the foremost choice, provided that the high potential of hydraulic and solute permeability of synthetic membranes is properly exploited. However, this is generally not the case in clinical hemodiafiltration practice. During postdilution hemodiafiltration, hemoconcentration, and high transmembrane pressure (TMP) can cause frequent clinical and technical problems. As a precautionary measure, low ultrafiltration rate ( $Q_{UF}$ ) is often set, thus limiting the efficiency of the technique. The predilution infusion mode (prehemodiafiltration) partially prevents these drawbacks, although at the expense of the cumulative solute transfer as a consequence of the diluted solute concentration available for diffusion and convection [10, 14, 22]. Recently, we demonstrated that the mixed pre- and postdilution infusion mode (mixed hemodiafiltration) ensured safer rheological and operating conditions by better preserving the characteristics of water and solute transport of the membrane, and achieved a removal of small and large size solutes which was similar to posthemodiafiltration when  $Q_{UF}$  was matched for the two infusion modes [14].

The present study was designed to verify if, in on-line mixed hemodiafiltration, a greater solute removal than in posthemodiafiltration may be obtained by further increasing the total infusion rate ( $Q_s$ ) and forcing the  $Q_{UF}$  to achieve the most efficient convective transport. The present level of technology of hemodiafiltration machines does not help to automatically plan a session, in order to accomplish this task safely and easily, nor does it allow the precise calculation of the infusion volume best able to maximize solute removal by convection. Consequently, in this study we developed and applied a new feedback system which was able to automatically maintain TMP within the highest range of safety during the session, while at the same time ensuring a constant  $Q_{UF}$  and the highest possible filtration fraction (FF) by optimizing the ratio between prefilter and postfilter infusion.

## METHODS

Twenty uremic patients (7 female and 13 male, aged  $63 \pm 17$  years), who were on three times weekly renal replacement therapy for  $9.7 \pm 7.2$  years (9 with standard hemodialysis, 11 with posthemodiafiltration or mixed hemodiafiltration), gave their informed consent to the study. The mean body weight was  $60.3 \pm 12.8$  kg, and the mean urea distribution volume ( $V_u$ ), kinetically estimated, was  $32.7 \pm 6.3$  L. All the patients underwent a randomized sequence of five procedures (the midweek session of five consecutive weeks): one session of standard



**Fig. 1. Schematic representation of the on-line system for mixed hemodiafiltration with the transmembrane pressure (TMP) feedback control device.** Substitution fluid is diverted from the dialysate circuit (D) by a peristaltic pump (IP1) placed on the common Y branch of the infusion path (S). This divides the solution to the prefilter ( $Q_{Spre-D}$ ) and postfilter ( $Q_{Spost-D}$ ) infusion site. The rate of postdilution infusion is controlled by an additional pump (IP2). Four pressure transducers (P), placed at the inlet and outlet blood and dialysate ports of the filter (F), record and send continuous signals (dotted lines) to a personal computer (PC). The efferent signals (arrow) from the PC regulate the speed of IP2 in mixed hemodiafiltration. The system also works in posthemodiafiltration, where the Y branch of the infusion line connected to the prefilter site is clamped. More detailed explanations are in the text. UF1 and UF2 are the ultrafilters placed on the dialysate and substitute lines, respectively.

hemodialysis (procedure A), one of on-line postdilution hemodiafiltration (procedure B), and three sessions of on-line mixed pre- and postdilution hemodiafiltration with variable substitution fluid volume (procedures C, D, and E). The dialyzers used were a low-flux  $1.8$  m<sup>2</sup>, and a high-flux  $2.1$  m<sup>2</sup> polysulfone membrane (F8 HPS and HDF 100s) (Fresenius, FMC, Bad Homburg, Germany). The length of the session (time,  $227 \pm 18$  minutes) and blood flow ( $Q_B$ ),  $403 \pm 57$  mL/min, were set as constant for each patient for each session in the study. Dialysate flow ( $Q_D$ ) was 500 mL/min in hemodialysis. In hemodiafiltration, the effective  $Q_D$  entering the dialyzer compartment resulted after subtraction of the amount diverted for infusion from the set value of 800 mL/min.

## The TMP feedback control

On-line mixed hemodiafiltration was performed with a 4008 H on-line Fresenius system modified with the application of a Y-shaped infusion line and an additional peristaltic pump on one Y branch, which diverted part of the total infusion directed to the postfilter port to the prefilter infusion site, as detailed elsewhere [14] and schematically shown in Figure 1. Inlet and outlet blood and dialysate pressures were continuously recorded by means of four pressure transducers connected to an external computer and the mean pressure gradient between blood and dialysate compartments along the dialyzer fibers (TMPm, mm Hg) was calculated instantaneously

using the following equation:

$$\text{TMPm} = 0.5 * [(P_{\text{Bin}} + P_{\text{Bout}}) - (P_{\text{Din}} + P_{\text{Dout}})] - \pi_o \quad (\text{Eq. 1})$$

where  $\pi_o$  (mm Hg), the mean oncotic pressure exerted by the plasma proteins, was calculated with the Van't Hoff equation.

Six hundred TMPm values were recorded per minute and were filtered, buffered, and averaged for each minute. Inlet plasma water flow rate ( $Q_{\text{PWin}}$ ) (mL/min) was calculated on-line from the effective blood flow ( $Q_{\text{Be}} = Q_{\text{B}}$  compensated by means of the arterial pressure), from hematocrit, which was monitored on-line with an integrated device (Blood Volume Monitor, Fresenius, FMC, Bad Homburg, Germany) and from a default value for total protein concentration [23]. The FF (i.e., the fraction of  $Q_{\text{PWin}}$  ultrafiltered during the passage through the dialyzer) was defined, in analogy with a more strict definition [24], as:

$$\text{FF} = (1 - Q_{\text{PWout}}/Q_{\text{PWin}}) = Q_{\text{UF}}/Q_{\text{PWin}} \quad (\text{Eq. 2})$$

where  $Q_{\text{PWout}}$  equals the outlet plasma water flow rate (mL/min).

The total infusion rate in posthemodiafiltration (treatment B) was set by the device in order to obtain an initial FF of 0.5 (i.e.,  $Q_{\text{UF}} = 0.5 * Q_{\text{PWin}}$ ). Because one of the purposes of the study was the assessment of the optimal amount of total infusion in mixed hemodiafiltration, three different  $Q_{\text{S}}$  were planned for the three experimental sessions on an individual basis:  $Q_{\text{S}} \sim 0.75 * Q_{\text{PWin}}$  (treatment C),  $Q_{\text{S}} \sim Q_{\text{PWin}}$  (treatment D), and  $Q_{\text{S}} \sim 1.25 * Q_{\text{PWin}}$  (treatment E).  $Q_{\text{S}}$  was split into pre- and postinfusion ( $Q_{\text{Spre-D}}$ ,  $Q_{\text{Spost-D}}$ ) at relative infusion rates allowing a ratio  $Q_{\text{Spost-D}}/Q_{\text{PWin}}$  of 0.5 to be obtained.

Subsequently, the system self-regulated the ratio of pre- to postinfusion in order to maintain the TMPm within its established safe range of variation (250 to 300 mm Hg), without affecting the total  $Q_{\text{S}}$ , nor the planned  $Q_{\text{UF}}$ . If TMPm fell below the lowest value of the range, a small amount of fluid (5 to 10 mL/min) was diverted from pre- to postinfusion at intervals of 2 minutes by increasing the postinfusion pump speed, increasing FF (and thus TMPm) as a result. Vice versa, the same amount of fluid was diverted from post- to predilution, thus reducing FF, whenever TMPm rose beyond its maximum tolerated value. In short, the feedback was aimed at ensuring throughout the sessions the highest FF compatible with the progressive hemoconcentration and loss of hydraulic membrane permeability. The TMP feedback control also worked effectively in posthemodiafiltration, during which the infusion pump speed was increased or decreased by signals generated from the TMPm reading.

Values for the in vivo dialyzer ultrafiltration coefficient ( $K_{\text{UF}}D$ ), calculated on-line as the ratio  $Q_{\text{UF}}/\text{TMPm}$ ,

were used as a proxy to evaluate instantaneous changes in the hydraulic permeability of the dialyzer during the sessions.

### Solute removal

Blood samples were drawn from the arterial port at the start and at the end (slow-flux technique) of each experimental session and plasma concentrations ( $C_i$ ,  $C_f$ ) were measured for urea (60 D), creatinine (113 D), and phosphate (96 D) as markers of the low-molecular-weight toxins, and for  $\beta_2$ -m (11.8 kD) as a medium-high-molecular toxin. The effluent dialysate was collected with a proportional pump connected to the outlet line and withdrawing fluid at a constant rate over the session. The mass of solutes removed ( $MT_{\text{DQ}}$ ) during each session was calculated from the effluent dialysate sample (~50 mL), representative of the whole spent dialysate. Total  $\beta_2$ -m removal was also calculated using the mass balance from the blood side ( $MT_{\text{B}}$ ), being the difference of the products of initial and final extracellular volume ( $V_{\text{ex}}$ ) and C, assuming a value for the final  $V_{\text{ex}}$  equal to one third of the  $V_u$ . Albumin removed by convection was measured by colorimetry in the spent dialysate. The mean efficiency of each session was evaluated by calculating the mean dialysate clearances of the session ( $K_{\text{DQ}}$ ) for urea, creatinine, phosphate, and  $\beta_2$ -m with a modified equation of the direct quantification method (DQ) [25]:

$$K_{\text{DQ}} = [MT_{\text{DQ}} \times \ln (C_f/C_i)]/[t \times (C_f - C_i)] \quad (\text{Eq. 3})$$

Calculated as above,  $K_{\text{DQ}}$  underestimates the actual dialyzer clearance [26]. However, this error is systematic and constant and it is unlikely to affect the results of a comparison between the different procedures in the same patient. Single-pool Kt/V (spKt/V) and equilibrated Kt/V (eKt/V) for urea were estimated with the Daugirdas equations [27].

### Statistical analysis

The descriptive analysis was based on the mean  $\pm$  SD values of continuous normally distributed variables (concentration, flux, clearance, etc.). The effects of the procedures on parameters of treatment efficiency ( $K_{\text{DQ}}$ , urea Kt/V,  $MT_{\text{B}}$ , and  $MT_{\text{DQ}}$ ) were tested with the univariate analysis of variance (ANOVA), and the five group means were compared with the pairwise multiple comparison test of Tukey (post hoc test). A probability value of less than 0.05 was considered significant. Multiple linear regression (MLR) with several sets of explanatory variables and nonlinear analysis was used to study the dependence of  $K_{\text{DQ}}$   $\beta_2$ -m changes during the procedures and curve fitting. The value  $R^2$  was a measure of goodness of fit, and the  $P$  value of the runs tests was used to elicit systematic data deviations from the model (significant deviation if  $P < 0.05$ ). The program SPSS for Windows, Release 11, was used for statistical analysis.

**Table 1.** Flow rates (mL/min) during the experimental procedures

		Hemodialysis	Post-hemodiafiltration	Mixed hemodiafiltration		
		Procedure A (N = 20)	Procedure B (N = 20)	Procedure C (N = 20)	Procedure D (N = 20)	Procedure E (N = 20)
Q <sub>PW<sub>in</sub></sub>	Start	227 ± 35	231 ± 34	230 ± 35	227 ± 36	229 ± 36
	End	210 ± 32	212 ± 31	212 ± 33	209 ± 35	210 ± 35
Q <sub>Spre-D</sub>	Start	—	—	65 ± 28	135 ± 41	201 ± 29
	End	—	—	98 ± 41	174 ± 57	260 ± 60
Q <sub>Spost-D</sub>	Start	—	145 ± 20	122 ± 18	114 ± 17	108 ± 15
	End	—	124 ± 22	90 ± 20	78 ± 28	48 ± 35
FF	Start	—	0.67 ± 0.05	0.67 ± 0.06	0.71 ± 0.04	0.74 ± 0.02
	End	—	0.64 ± 0.07	0.64 ± 0.05	0.67 ± 0.05	0.68 ± 0.05

Abbreviations are: Q<sub>PW<sub>in</sub></sub>, plasma water flowrate in; Q<sub>Spre-D</sub>, prefilter infusion rate; Q<sub>Spost-D</sub>, postfilter infusion rate; FF, filtration fraction. Data are mean ± SD. Values at the start refer to stabilized conditions (see text) achieved about 10 minutes after the start of the sessions. The FF was calculated with equation 2.

## RESULTS

### The TMP feedback control

The mean plasma water flow (Q<sub>PW</sub>) and infusion rates (and their changes during the procedures are reported in Table 1. A total of 30.5 ± 5.6 L per session were infused in posthemodiafiltration. The total amount of fluid infused in mixed hemodiafiltration averaged 42.5 ± 8.7 L, 56.8 ± 10.2 L, and 70 ± 11.6 L in sessions C, D, and E, respectively. In mixed hemodiafiltration procedures, the ratio at which Q<sub>S</sub> was initially split between pre- and postdilution resulted in TMPm values that were generally below the lower established limit for the study. Therefore, the device algorithm caused repeated shifts of replacement fluid from pre- to postinfusion in steps of 5 mL every 2 minutes until TMPm stabilized within the planned range (approximately within the first 10 minutes of the procedure). Subsequently, whenever TMPm rose to its upper level as an effect of the increasing FF, opposite shifts occurred, diluting the incoming blood and preserving the planned ultrafiltration. The mean Q<sub>Spost-D</sub> decreased from a maximum of 65% of the total Q<sub>S</sub> to a minimum of 48% at the end of session C, from 46% to 31% in session D, and from 35% to 16% in session E. In posthemodiafiltration (procedure B), the feedback increased the initial Q<sub>S</sub> until TMPm established within the planned range, then maintained TMPm stable by progressively decreasing Q<sub>S</sub>. Figure 2 shows a graphic representation of one patient file record as an example of the feedback mechanism. The behavior of the apparent K<sub>UF,D</sub>, recorded on-line, is shown in Figure 3. This reveals a significant decrease, which occurred during the post-hemodiafiltration sessions, mostly in the first half hour (from 59.1 to 29.7 mL/hour/mm Hg TMP), indicating a significant deterioration of the hydraulic membrane permeability due to rapid protein layer formation and its progressive thickening. On the other hand, predilution in mixed hemodiafiltration ensured better preservation of the hydraulic membrane characteristics, as shown by the higher and stable recorded K<sub>UF,D</sub> values (mean, 57.5

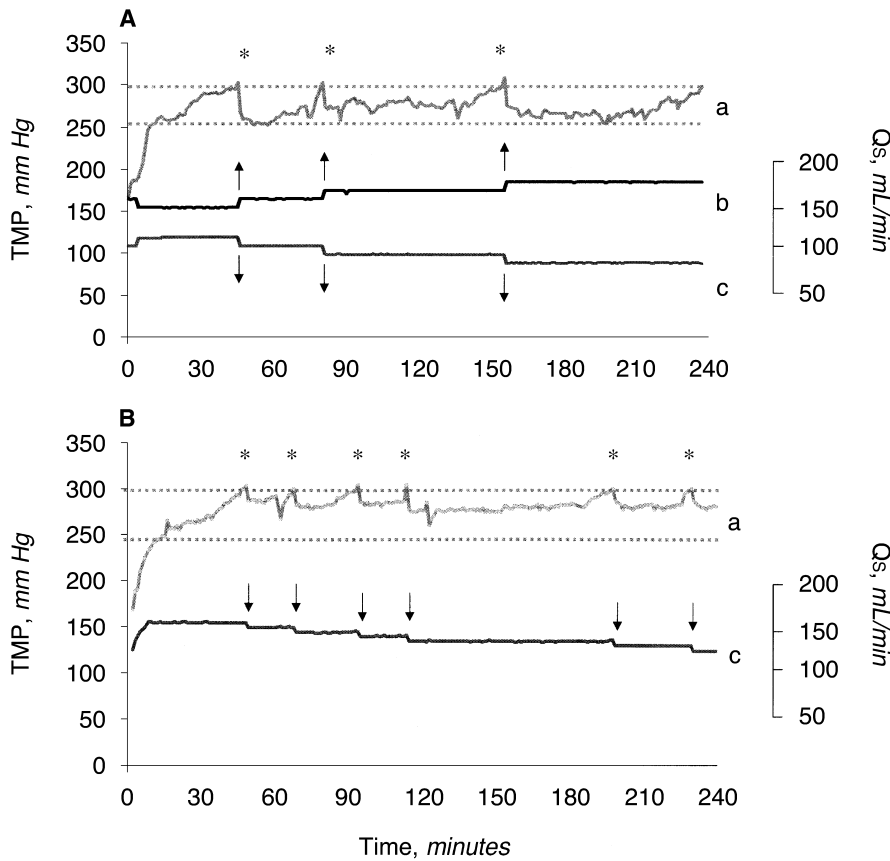
mL/hour/mm Hg). Hemoconcentration with progressive reduction of Q<sub>PW</sub> was presumably the prevailing factor inducing increases in TMPm during this procedure.

### Efficiency of the procedures

Mean initial and final solute concentrations of the five procedures are reported in Table 2. The efficiency of the procedures, as evaluated with urea K<sub>DO</sub> and eKt/V, was significantly higher in on-line hemodiafiltration than in hemodialysis, irrespective of the infusion mode (Table 3). Similar results were found for the other tested small solutes, but a statistically significant difference in creatinine and phosphate K<sub>DO</sub> versus hemodialysis (post hoc tests) was found only in procedures D and B, although limited to phosphate K<sub>DO</sub> in the latter.

Total β<sub>2</sub>-m removal (Fig. 4), estimated with mass balance from the blood side, was minimal in hemodialysis, as expected, and maximal in treatment D (24 ± 20 mg/session and 293 ± 105 mg/session, respectively). Similar differences were found in the amount of β<sub>2</sub>-m recovered in the total spent dialysate (MT<sub>DO</sub>). A difference in removal of about 40 mg/session, clinically relevant but not statistically significant, was shown between posthemodiafiltration and mixed hemodiafiltration (197 ± 62 mg/session vs. 237 ± 83 mg/session). The difference between MT<sub>B</sub> and MT<sub>DO</sub> arises mostly from the use of nonequibrated end-session concentrations in calculations, resulting in an overestimate of MT<sub>B</sub>, and only in part from the amount of β<sub>2</sub>-m absorbed by the membrane during the procedures, which is negligible with polysulfone membranes. The post hoc ANOVA tests elicited a significant difference in the mean K<sub>DO</sub> for β<sub>2</sub>-m (Fig. 5) between procedures B and D (posthemodiafiltration, 77.5 ± 11.2 mL/min; mixed hemodiafiltration with Q<sub>S</sub> ~ Q<sub>PW</sub>, 90.2 ± 10.9 mL/min, P = 0.015), and between procedures D and E (80.9 ± 10.9 mL/min, P = 0.039). During session C, the mean value for β<sub>2</sub>-m K<sub>DO</sub> was lower than in D but higher than in B (83.9 ± 12.2 mL/min, P = NS).

Albumin was not detected in the spent dialysate of hemodialysis sessions, while a negligible loss (from 4.4

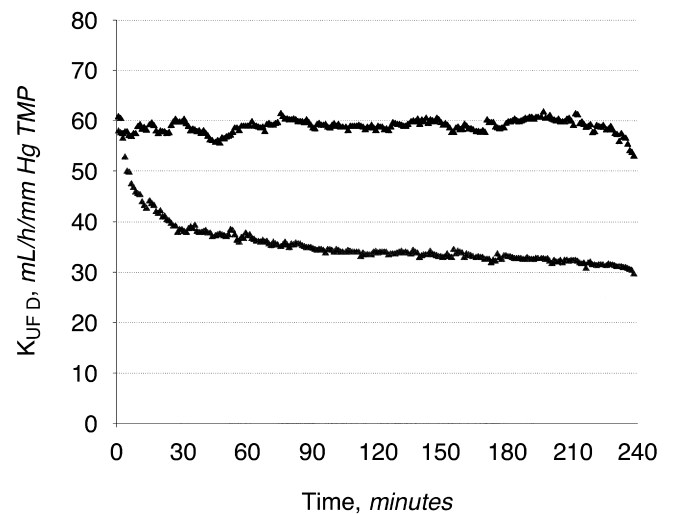


**Fig. 2. Graphic representation of one patient file record.** (A) Mixed hemodiafiltration. At the start of the session, small shifts of infusion fluid from predilution (line b) to postdilution (line c) increase filtration fraction (FF) and stabilize mean transmembrane pressure (TMPm) (line a) within its planned operational range (250 to 300 mm Hg). Subsequently, during the session, TMPm values exceeding the upper limit (\*) are restored by opposite shifts of infusion fluid. (B) Posthemodiafiltration. TMPm control (line a) occurs through changes in the speed of the pump regulating the total infusion rate (line c).

to 5.8 g/session) was found during hemodiafiltration sessions, with no significant differences between the infusion modes.

**Factors influencing  $\beta_2$ -m clearance**

Stepwise regression analysis of the pooled data of the five procedures revealed that among several sets of explanatory variables,  $Q_s$  and  $Q_{Pwin}$  and their interaction are the best predictors of the maximum  $\beta_2$ -m  $K_{DQ}$  likely to be achieved during each session. According to the statistical model which best fits the experimental data, a family of quadratic regression curves may be constructed to represent the dependence of  $\beta_2$ -m  $K_{DQ}$  on  $Q_s$  at a defined value of  $Q_{Pwin}$  (Fig. 6). From the Y intercept (hemodialysis treatment, absence of infusion),  $K_{DQ}$  curves increase quasilinearly when  $Q_s$  increases up to a value depending on  $Q_{Pwin}$ . This is observed within the range of infusion rates applied during postdilution hemodiafiltration or during mixed hemodiafiltration when the amount infused in postdilution is prevailing (session C). After this point, within the typical range of  $Q_s$  applied in mixed hemodiafiltration, the increase in  $K_{DQ}$  per unit increase in  $Q_s$  tends to diminish the more fluid is infused in predilution (decreasing ratio  $Q_{Spost-D}/Q_s$ ). The regression curves tend to flatten and  $K_{DQ}$  clearances achieve their maximum (the vertex of the parabola in Fig. 6) at



**Fig. 3. Behavior of the apparent ultrafiltration coefficient of the dialyzer [ $K_{UF D} = Q_{UF}/\text{mean transmembrane pressure (TMPm)}$ ] as recorded on-line during post-hemodiafiltration (lower curve) and mixed hemodiafiltration (procedure D) (upper curve).**

a  $Q_s$  value that is close to the  $Q_{Pwin}$  value (ratio  $Q_s/Q_{Pwin} = 1 \pm 0.1$ ). From this point on, further increase in  $Q_s$  induces a significant decline in  $K_{DQ}$ , as a result of the combined negative effect of the excessive shift of infusion to the

**Table 2.** Direct quantification: Baseline and end-session solute concentrations

		Hemodialysis	Post-hemodiafiltration	Mixed hemodiafiltration			One-way ANOVA ( <i>P</i> value)
		Procedure A	Procedure B	Procedure C	Procedure D	Procedure E	
Urea <i>mmol/L</i>	Start	24.4 ± 6.3	23.6 ± 5.4	24.1 ± 7.1	23.4 ± 6.7	23.4 ± 6.4	NS
	End	5.2 ± 2.0 <sup>a</sup>	3.9 ± 1.5	3.9 ± 1.6	4.0 ± 1.7	3.9 ± 1.5	0.047
Creatinine <i>μmol/L</i>	Start	769 ± 221	778 ± 230	787 ± 221	769 ± 194	795 ± 239	NS
	End	239 ± 80	195 ± 62	203 ± 62	212 ± 71	212 ± 79	NS
Phosphate <i>mmol/L</i>	Start	1.55 ± 0.52	1.58 ± 0.45	1.56 ± 0.39	1.61 ± 0.44	1.52 ± 0.39	NS
	End	0.68 ± 0.19	0.59 ± 0.13	0.58 ± 0.13	0.57 ± 0.16	0.58 ± 0.16	NS
β <sub>2</sub> -m <i>mg/L</i>	Start	24.2 ± 6.7	23.5 ± 5.8	24.5 ± 6.6	25.4 ± 7.2	24.4 ± 5.9	NS
	End	27.3 ± 8.0 <sup>a</sup>	4.2 ± 1.6	3.7 ± 1.4	3.9 ± 1.2	4.1 ± 1.5	0.0001

Data are mean ± SD.

<sup>a</sup>Procedure A vs. procedure B, C, D, and E; post hoc tests (Tukey HSD)

**Table 3.** Efficiency in small solute removal during the experimental procedures

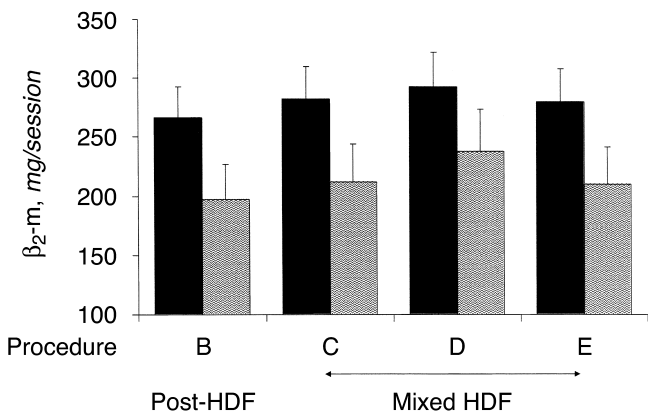
	Hemodialysis	Post-hemodiafiltration	Mixed hemodiafiltration			One-way ANOVA <i>P</i> value
	Procedure A	Procedure B	Procedure C	Procedure D	Procedure E	
K <sub>DO</sub> <i>mL/min</i>						
Urea	222 ± 19 <sup>a</sup>	259 ± 22	263 ± 27	262 ± 24	255 ± 29	<0.0001
Creatinine	189 ± 27 <sup>c</sup>	210 ± 33	213 ± 33	216 ± 24	213 ± 23	0.021
Phosphate	154 ± 28 <sup>b,c</sup>	182 ± 33	175 ± 31	184 ± 38	173 ± 29	0.031
Urea eKt/V	1.59 ± 0.19 <sup>a</sup>	1.86 ± 0.24	1.89 ± 0.24	1.84 ± 0.21	1.84 ± 0.21	<0.0001

Data are mean ± SD; post hoc tests (Tukey HSD).

<sup>a</sup>Procedure A vs. B, C, D, and E

<sup>b</sup>Procedure A vs. B

<sup>c</sup>Procedure A vs. D



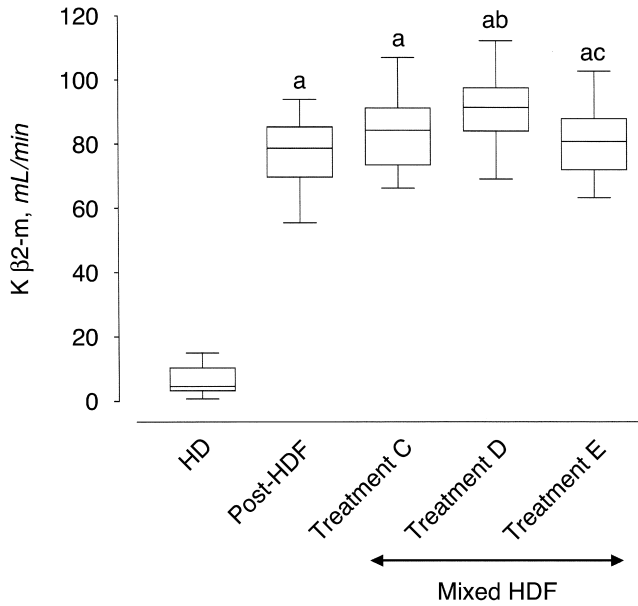
**Fig. 4.** β<sub>2</sub>-microglobulin (β<sub>2</sub>-m) removal in the four on-line hemodiafiltration (HDF) procedures, evaluated from the blood side (■), and by direct quantification in dialysate (▨). One-way analysis of variance (ANOVA); *P* = NS.

predilution site, which is necessary to keep TMPm under control, and of a reduction in the β<sub>2</sub>-m S<sub>C</sub>, elsewhere described as occurring at high Q<sub>UF</sub> [28].

**DISCUSSION**

Postdilution has been commonly held as the most efficient infusion mode in hemodiafiltration. The present study seems to demonstrate that the limits of this method may be overcome with a mixed pre- and postfilter infu-

sion mode. On-line mixed hemodiafiltration, applied in 20 patients, yielded a significant increase in β<sub>2</sub>-m removal compared to that obtained in posthemodiafiltration. The premise for these results is that the total infusion was increased to force convective removal beyond the operational limits placed in posthemodiafiltration. This increased amount of infusion was added in predilution and balanced with that in postdilution in order to ensure the highest possible FF, while simultaneously avoiding excessive dilution of the inlet solute concentrations and dangerous hydrostatic pressures within the dialyzer. This was only feasible by using the feedback device developed in our unit. Indeed, setting Q<sub>S</sub> and Q<sub>UF</sub> purely on the basis of the in vitro ultrafiltration coefficient of the dialyzer may be misleading for several reasons. Basal blood flow, hematocrit, and protein concentration vary widely between patients. During the session, hemoconcentration increases blood viscosity and resistance to flow and progressive protein concentration contributes to a thickening of the secondary membrane layer so limiting its hydraulic permeability. Proteins exert an increasing oncotic pressure that resists ultrafiltration [29]. High Q<sub>UF</sub> exacerbates this phenomenon by increasing the polarization on the blood side of the membrane [30], while low Q<sub>B</sub> acts in the same way, by reducing the shear rate that stirs the protein layer. Consequently, as the session progresses, increasingly higher and unpredictable TPM gradients are often reached in the attempt to maintain the planned

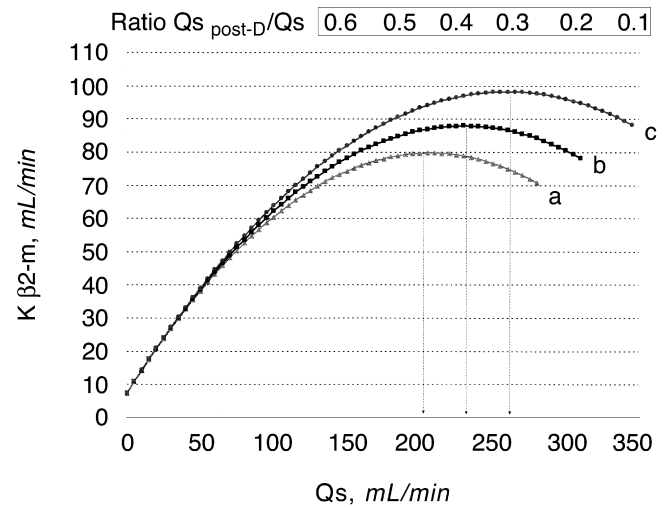


**Fig. 5.** Mean dialysate clearances for  $\beta_2$ -microglobulin ( $\beta_2$ -m) of the five experimental procedures. One-way analysis of variance (ANOVA);  $P < 0.0001$ . Post hoc tests (significance at  $P < 0.05$ ). Treatment effect: a, hemodialysis (HD) vs. posthemodiafiltration (post-HDF) and mixed hemodiafiltration; b, mixed hemodiafiltration (treatment D) vs. post-HDF; c, treatment E vs. treatment D.

$Q_{UF}$  in the face of a deterioration in the permeability of the dialyzer membrane.

Some observations formed the basis of the new feedback mechanism developed for the automatic control of  $Q_{UF}$  through TMPm. First, at a given blood flow, the maximal efficiency in convective removal of small- and medium-molecular weight solutes occurs at the highest FFs [13, 14]. Second, the highest achievable FF is often unpredictable, due to the events described above and to an individual variability, presumably related to the capacity to recruit fluid from the interstitial space (refilling) as ultrafiltration progresses. Third, at any given  $Q_B$ , TMPm is exponentially related to FF, and the slope of the curve is a function of the hydraulic permeability of the dialyzer [14]. Fourth, above a certain level of TMPm, the system becomes unstable and sudden dangerous pressure peaks are likely to result from small changes in blood flow or viscosity, venous pressure, or for technical reasons. In a preliminary experimental setting, similar to that applied in the study, we observed that peaks frequently occurred around TMPm values of 350 mm Hg. In such circumstances, residual irreversible reduction in the performance of the dialyzer was observed, even after restoring safer pressure conditions.

These events are difficult to prevent or counteract by the ultrafiltration control systems presently implemented on hemodiafiltration machines, which are of little help in planning and carrying out a session in which convection at the maximal FF is sought. An increase in ultrafil-



**Fig. 6.** Best fitting curves (polynomial 2nd order) relating  $\beta_2$ -microglobulin ( $\beta_2$ -m)  $K_{D0}$  with  $Q_s$  at three defined values for  $Q_{Pwin}$  (a, 180 mL/min; b, 220 mL/min; c, 260 mL/min). Analysis was performed on the pooled data of the five procedures (explanation in the text). The equation of the model is  $\beta_2\text{-m } K_{D0} = 7.35 + 0.7 * Q_s - 0.0023 * Q_s^2 + 0.000034 * Q_s^2 * Q_{Pwin}$ ;  $R^2 = 0.924$ ,  $P < 0.0001$ . Algebraic solution of the equations for the coordinates of the vertex of each parabola [ $X = b/2a$ ;  $Y = (b^2 - 4ac)/4a$ ], provided the exact value for  $Q_s$  at which  $\beta_2$ -m  $K_{D0}$  is maximal. a,  $K_{D0}$  79.7 mL/min at  $Q_s = 205$  mL/min, ratio  $Q_s/Q_{PW} = 1.1$ ; b,  $K_{D0}$  87.9 mL/min at  $Q_s = 230$  mL/min, ratio  $Q_s/Q_{PW} = 1.05$ ; c,  $K_{D0}$  98.1 mL/min at  $Q_s = 255$  mL/min, ratio  $Q_s/Q_{PW} = 0.98$ .

tration flux through a high-flux polysulfone membrane was observed in an experimental setting with intravenous infusion of hypertonic glucose during postdilution hemodiafiltration [31]. In our study this task was efficiently accomplished automatically and with no technical problems using the TMP feedback control. In mixed hemodiafiltration, the device was able to maintain the TMPm within its highest safe range by means of small shifts (5 to 10 mL) of substitution fluid from the postdilution to the predilution infusion site or vice versa, without reducing the planned  $Q_{UF}$ . In posthemodiafiltration,  $Q_{UF}$  had to be reset to a lower level as the sessions progressed, but the FFs that were maintained safely throughout the treatment were always far beyond the empirical limit of 0.5 taken as a historical reference [32] and yielded a high removal of  $\beta_2$ -m per session. Compared to posthemodiafiltration, a progressive gain in  $\beta_2$ -m clearance was experienced in mixed hemodiafiltration with increasing infusion rates. The difference in  $K_{D0}$  for  $\beta_2$ -m between the two infusion modes was statistically significant at an infusion rate close to the  $Q_{PW}$  of the patient. In mixed hemodiafiltration, the characteristics of water and solute transport of the membrane are better preserved than in postdilution hemodiafiltration [14], as also demonstrated by the comparative behavior of the apparent  $K_{UF}D$  during the sessions. Therefore, higher  $Q_{UF}$  are achievable under safe operating conditions and eventually result in increased solute removal.

The optimal rate of infusion fluid found in this study ( $Q_s \sim Q_{Pwin}$ ) is related to the dialyzer employed in the experimental sessions and was dependent on its hydraulic permeability and size and on its geometric properties (capillary diameter, arterial blood port, housing, etc.), all of which determine the internal resistance to flow. It is likely that other high-flux dialyzers used in hemodiafiltration with different geometry and membrane performance will show variable, but probably limited, deviation from this value. However, regardless of the dialyzer characteristics, the TMP-ultrafiltration feedback is able to establish the optimal ratio between pre- and postdilution in order to optimize the FF.

The four hemodiafiltration procedures showed a high degree of efficiency in removing small-size solutes.  $eKt/V$  was significantly higher in hemodiafiltration compared to hemodialysis sessions. The infusion mode did not apparently influence the results. However, the highest absolute values for creatinine and phosphate  $K_{DO}$  were observed in session D, in which the highest  $\beta_2$ -m removal was also shown.

The high infusion and  $Q_{UF}$  were well tolerated by the patients. Sessions were not complicated by any clinical incident (infections, hypersensitivity reactions, cardiovascular complications). The desired electrolyte and acid-base balance was easily achieved by small modulations of the dialysate composition when requested [33, 34]. No signs of hemolysis were recorded. Loss of albumin was negligible despite the high  $Q_{UF}$ , probably because the careful control conducted by the feedback avoided those critical TMPm values at which albumin leakage is more likely to occur. The system operated automatically, without any intervention by the operators after the initial setting. No technical problems occurred in any experimental session.

## CONCLUSION

The mixed infusion mode in hemodiafiltration, controlled by the TMP feedback, seems to improve the depurative capacity of the technique by fully exploiting the convective mechanism of solute removal. The feedback allowed the TMP to be set and profiled from parameters recorded on-line by the machine. It automatically adjusted the infusion rate at the maximum FF taking into account flow conditions, internal pressures, and hydraulic permeability of the dialyzer, and their complex interactions. The high biocompatibility resulting from the use of synthetic membranes and ultrapure dialysate/substitute prepared on-line with double ultrafiltration, combined with the enhanced removal of small- and middle-molecular uremic toxins, seem to indicate mixed hemodiafiltration as an effective strategy to prevent or delay the occurrence of long-term complications and to promote the improved survival of dialysis patients.

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