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Optimization of mid-dilution haemodiafiltration: technique and performance

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Abstract

Background. Mid-dilution haemodiafiltration (MD-HDF), reported as a highly efficient convective-mixed technique, has demonstrated serious drawbacks in relation to the high pressure originating inside the blood compartment of the filter during clinical application. This randomized crossover design study was planned to optimize the efficiency of the MD-HDF technique while reducing its inherent risks.

Methods. Fifteen patients on RRT were submitted in random sequence to standard and reverse MD-HDF under similar operating conditions. Efficiency in solute removal was evaluated by measuring urea (U), phosphate (P) and beta2-microglobulin (β2-m), mean dialysate clearances (K_{DQ}) and eKt/V. Blood and dialysate compartment pressures were monitored on-line during the sessions, and instantaneous hydraulic and membrane permeability indexes were calculated.

Results. During standard MD-HDF sessions, unlike with reverse MD-HDF, excessive blood inlet and transmembrane pressure prevented the planned infusion from being maintained. Resistance index and membrane permeability to

water and middle molecules substantially improved with reverse MD-HDF. This resulted in higher β2-m removal (221.3 ± 81.3 versus 185.1 ± 65.5 mg/session, $P = 0.007$). Phosphate removal was comparable, while U removal was greater with standard MD-HDF (K_{DQ} 272 ± 35 versus 252 ± 29 ml/min, $P = 0.002$; eKt/V 1.63 ± 0.23 versus 1.49 ± 0.17, $P = 0.005$).

Conclusions. This study demonstrated the ability of MD-HDF to remove significant amounts of medium-sized uraemic compounds and phosphate, but safe rheologic and hydraulic conditions were only maintained by carrying out treatments with the dialyser used in reverse configuration. For this purpose, the larger MD-220 dialyser ensured better tolerance together with higher middle molecules clearance, even though small molecule removal was slightly worsened. The results of this study may provide some insight into the complex interactions between pressures and flux within the original structure of MD-dialysers and help optimize the clinical application of the technique and reduce its risks.

Keywords: beta2-microglobulin; convective treatments; haemodiafiltration; mid-dilution HDF; transmembrane pressure

Introduction

Convective dialysis strategies with synthetic high-flux membranes may induce substantial improvement in the uraemic toxicity profile by reducing the level of small and middle molecular compounds, some of which are recognized as pathogenic factors of the more common long-term uraemic complications [1–6]. A link between enhanced solute removal and survival on dialysis, even if not definitely established, was suggested by the Euro DOPPS Study [7], which reported a significant 35% lower mortality risk in patients on high-efficiency haemodiafiltration (HDF, volume exchange 15–25 l), compared to low- and high-flux haemodialysis (HD).

Among the recently proposed techniques aimed at increasing convective solute transport, mid-dilution HDF (MD-HDF) has been claimed to be of greater efficiency when compared to traditional pre- or post-dilution infusion modes in HDF [8,9]. However, when applied as proposed in the original study, MD-HDF often carries with it serious risks. Indeed, a considerably high transmembrane pressure (TMP) of ∼1000 mmHg in the post-dilution section of the filter was necessary to achieve the planned ultrafiltration of about 10 l/h [10]. This finding was confirmed by other authors [11], who succeeded in reducing the internal dialyser pressure regimen by reversing the configuration of the blood tubing (reverse MD-HDF), i.e. connecting the arterial line to the venous port of the MD-190 dialyser and vice versa, but at the cost of a substantial reduction in the infusion rate from 10 to 6 l/h and less efficient small molecule removal. Subsequently, the possibility of using higher volume exchange under safer hydraulic conditions in MD-HDF was preliminarily shown in a few patients with the use of a filter with a larger overall surface area (OLpur™ MD-220, 2.2 m^2) in standard MD-HDF configuration [12]. Even if not yet confirmed by a systematic study, this finding suggests that the risk of high TMP in standard MD-HDF with the MD-190 dialyser may be reduced with the use of the larger MD-220 filter. On the other hand, more substantial advantages in safety have been obtained by reversing the configuration of both MD-190 and MD-220 dialysers [11,12]. This might be rather surprising, as the surface of the capillaries of the post-dilution section, where the highest resistance to flux is generated, is smaller in reverse than in standard MD-HDF, and as a consequence, higher hydraulic pressure should be found in reverse configuration. The available experience is sufficient neither to fully understand the complex relationship between pressure and flux in this technique nor to distinguish the respective roles of dialyser configuration and its surface area in influencing the performance of reverse MD-HDF in terms of solute removal, rheology and hydraulics. Thus, while planning this crossover comparison study between standard and reverse MD-HDF, we selected two dialysers of different overall membrane surfaces (MD-190 for standard and MD-220 for reverse MD-HDF), but with a very similar area of capillaries devoted to post-dilution (see Figure 1), in order to match the size of the filter section where post-dilution occurs and the most critical pressures are generated. Possibly, by minimizing the effect of this variable, the differences between the configurations could be more clearly revealed, with the final aim of defining a correct procedure for the clinical application of MD-HDF and of evaluating its true capacity to safely remove small- and middle-sized uraemic solutes.

Subjects and methods

Study design

In this prospective crossover study, reverse MD-HDF with the larger MD-220 haemodiafilter was evaluated by comparing it with standard MD-HDF performed with the MD-190 dialyser, as originally proposed [8,9]. This comparison was between dialysers with the same membrane and with a similar surface area of the capillaries devoted to post-dilution (see Figure 1), so ensuring that the difference in the surface would have no significant impact on the evaluation of the effects of the dialyser configuration. Patients were submitted randomly to a mid-week session of both treatments. Defined end-points of the comparison were the extent of overall solute removal and the efficiency and safety of both technique configurations in terms of hydraulic and solute membrane permeability, rheological conditions and hydrostatic pressures within the system. The study was approved by the local Ethics Committee. Written informed consent was obtained from all participants.

Patients

Fifteen patients (12 males, 3 females) who were stable on three times weekly renal replacement therapy in our centre for at least 6 months were included in the study. The mean age was 67.3 ± 8.7 years, mean dialysis duration was 44.1 ± 20.8 months (range 8.2 – 77) and mean dry body weight was 76.9 ± 14 kg. All patients had a permanent native or prosthetic vascular access capable of delivering an effective blood flow rate ($Q_{B\,eff}$, blood flow corrected for the effect of the negative arterial pressure) of at least 300 ml/min, without significant access recirculation (<10%).

System and treatments

All experimental sessions were performed with a Fresenius 4008 dialysis system (Fresenius Medical Care, Bad Homburg, Germany), equipped with five pressure transducers that continuously measured the hydraulic pressure in mmHg at the inlet and outlet blood and dialysate ports of the dialysers ($P_{B\,in}$, $P_{B\,out}$, $P_{D\,in}$ and $P_{D\,out}$, respectively) and at the mid-dilution infusion port (P_{inf}). About 600 signals/min were transmitted from each probe to an external computer that filtered, buffered and

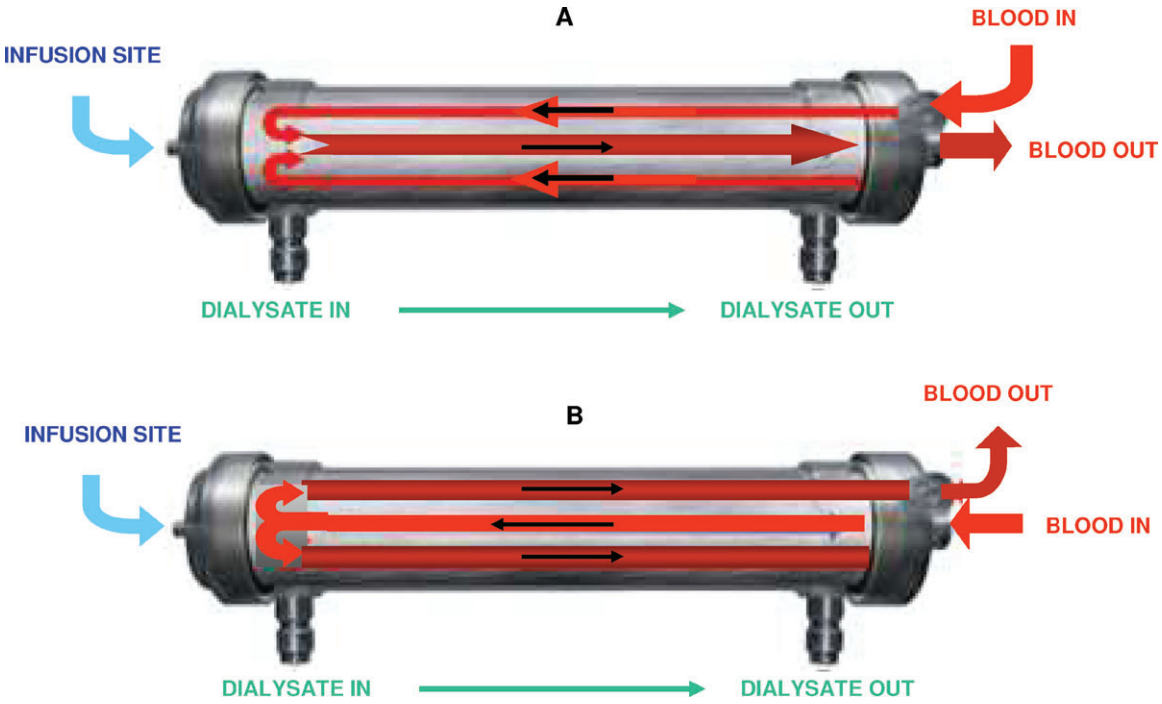

Fig. 1. OLpur^{TM} dialysers for MD-HDF. Panel **A**: standard configuration with MD-190. Blood flows counter-currently with dialysate in the annular region of the fibre bundle (1.1 m^2), where post-dilution occurs, reverses its direction at the infusion site where it mixes with substitution fluid, then flows co-currently with dialysate through the core region of the fibre bundle (0.8 m^2). Panel **B**: reverse MD-HDF with the MD-220 dialyser. Post-dilution occurs in the core region of the fibre bundle (1.0 m^2) through which blood first flows, then pre-dilution is performed in the annular region (1.2 m^2) with co-current dialysate flow.

averaged measured pressure values for each minute of the session by means of a dedicated software program. This produced a series of Excel files at the end of each experimental session that contained the minute-by-minute values of all pressures and fluxes (blood, dialysate, infusate and ultrafiltrate) occurring within the dialyser compartments during the session. More detailed explanation of the system was reported in a previous work [10]. The hollow-fibre filters employed were the OLpur^{TM} MD-190 and MD-220 (Nephros, NeY, USA) in the original (standard) and in reverse configurations, respectively. Both dialysers include a capillary bundle with two blood compartments in series in a U configuration and an infusion port for substitution fluid in between, where blood flow reverses its direction. In the common dialysate compartment, flow is counter-current for one of the serial blood compartments and co-current for the other (see Figure 1).

Treatment sessions to be compared were carried out on each patient using similar blood and dialysate flow (Q_B and Q_D, respectively), ultrafiltration rate (Q_{UF}), session duration and dialysate/infusate composition (see Table 1). The initial infusion rate (Q_{inf}), which was adapted individually to the patient's blood flow rate, was also the same for both techniques. According to the indications of the haemodiafilter manufacturer, Q_{inf} had to be manually and progressively reduced on reaching an infusion pressure (P_{inf}) of 650 mmHg. The anticoagulation protocol was adapted individually in preliminary sessions in order to achieve a mean activated clotting time between 210% of the basal value after the initial unfractionated heparin bolus and 150% under continuous heparin administration.

'Ultrapure' dialysate was produced on-line, as per routine use, using a double reverse osmosis system for water treatment and a polysulfone ultrafilter (Diasafe plus, FMC) for subsequent filtration of the dialysate. A further stage of dialysate filtration was required for production of the infusion fluid. Both dialysate and infusion fluid were free of endotoxins (negative LAL test) and met the standards of microbial purity recommended by the European Best Practice Guidelines [13].

Data collection and laboratory analysis

Pre-treatment blood samples were drawn immediately after needle insertion, and post-treatment blood samples were taken from the arterial port using the slow-flux technique. Separate blood samples from the arterial

Table 1. Patient and treatment characteristics

	Standard MD-HDF (MD-190) ($n = 15$)	Reverse MD-HDF (MD-220) ($n = 15$)	P-value*
Dialysers			
Membrane	Polyethersulfone	Polyethersulfone	
Surface (m^2)	1.9	2.2	
Annular/core region (m^2)	1.1/0.8	1.2/1.0	
Wall thickness (μm)	30		
Inner diameter (μm)	200		
Nominal K_{UF} (ml/h/mmHg/m^2)	47.4		
Flux (ml/min)			
$Q_{B\ eff}$	375 ± 26	382 ± 30	n.s.
$Q_{Inf\ start}$	166 ± 14	169 ± 2	n.s.
$Q_{UF\ start}$	175 ± 13	179 ± 5	n.s.
$Q_{D\ in}$	593 ± 8	606 ± 5	n.s.
Body weight, start session (kg)	76.6 ± 13.3	77.1 ± 15.0	n.s.
Body weight loss (kg)	2.0 ± 1.0	1.9 ± 0.9	n.s.
Treatment time (min)	224 ± 22	222 ± 22	n.s.

Abbreviations and definition of the parameters are in the text (see the 'Subjects and methods' section).
Data are presented as means ± SD.
*Student's t-test for paired data. A probability value of <0.05 was considered significant.

and vein ports were drawn 5 min after the beginning and 5 min before the end of the session. During each session, the effluent dialysate was collected with a proportional pump at a constant rate of 10 ml/h, following the partial dialysate quantification (DQ) method [14]. The blood and dialysate samples were analysed for urea, phosphate and beta2-microglobulin (β2-m) using conductimetric, colorimetric and immunonephelometric methods, respectively. Haematocrit (Hct) and total plasma protein (TP) concentrations in arterial blood were measured at the beginning and end of the session.

The mass of solute removed during each session (MT_{DQ}) was calculated from the effluent dialysate sample (∼40 ml), which was representative of the entire effective volume of spent dialysate (V_d), as given in

$$MT_{DQ} = C_d \times V_d \quad (1)$$

where C_d is the dialysate concentration of the examined solute. The mean dialysate clearances of the session (K_{DQ}) were calculated with the following equation of the DQ method [14]:

$$K_{DQ} = [MT_{DQ} \times \ln(C_f/C_i)]/[t \times (C_f - C_i)] \quad (2)$$

where C_i and C_f are the initial and end-session plasma water concentrations of the examined solute and t is the session duration in minutes.

The equilibrated Kt/V (eKt/V) for urea was estimated according to the Daugirdas second-generation equations [15]. Dialyser performance in middle molecule removal at different times of the session was evaluated by calculating β2-m instantaneous plasma water clearances (K_i) at the start and the end of the session. The classic equations [16] were used to calculate plasma water flow (Q_{PW}) and K_i:

$$Q_{PW} = Q_{B\,eff}(1 - H_{ct}/100)F_p \quad (3)$$

where F_p is the water fraction of plasma;

$$K_i = Q_{PW}(C_{art} - C_{ven})/C_{art} + Q_{UF}C_{ven}/C_{art} \quad (4)$$

where C_{art} and C_{ven} are the solute concentrations at the arterial and venous port, respectively, and Q_{UF} is the ultrafiltration rate (ml/min).

On-line recording of pressures and fluxes obtained as explained above enabled the calculation of instantaneous values for the TMP proximally to the entry and exit of both blood compartments as the difference between blood and dialysate pressure according to the general equation:

$$P_B - P_D - P_{onc} \quad (5)$$

where P_B and P_D are the hydraulic pressures (mmHg) in the blood and dialysate compartments at the measurement point and P_{onc} (mmHg) is the mean oncotic pressure exerted by the plasma proteins, which was set by default at a constant value of 25 mmHg because it was impossible to obtain blood samples from the mid-dilution port of the MD dialysers during treatment. Moreover, the particular construction of these dialysers with a unique dialysate and two blood compartments prevented us from ascertaining the exact rate of ultrafiltration that occurred in each blood path and thus from deriving a value for protein concentration from changes in plasma flow rate due to ultrafiltration.

The same recorded data were used to calculate the instantaneous pressure drop within the two blood compartments ($P_{B\,in} - P_{B\,out}$), the resistance index (R_I, mmHg/ml/min) was used to evaluate the pressure/flow conditions of the blood compartments and the *in vivo* ultrafiltration coefficients of the dialyser membrane (K_{UF}, ml/h/mmHg of TMP/m^2) were used as a proxy for changes in the hydraulic permeability of the dialyser during the sessions. The following equations were applied:

$$R_I = (P_{B\,in} - P_{B\,out})/Q_{B\,in} \quad (6)$$

where Q_B in is the flow (ml/min) at the inlet blood port;

$$K_{UF} = Q_{UF}/\text{mean TMP/m}^2. \quad (7)$$

Instantaneous values of each of the above-measured and -calculated parameters were stored in the Excel data files and used for statistical analysis and to describe their trend during each session.

Statistical analysis

The descriptive analysis was based on the mean ± SD values of continuous normally distributed variables. The effects of the two procedures on parameters of treatment efficiency (K_I, K_{DQ}, urea Kt/V, and MT_{DQ}) were compared with Student's *t*-test for paired data. A probability value of <0.05 was considered significant.

Results

All patients completed the experimental sessions of both treatments with no technical problems. In particular, there were no occurrences of blood circuit clotting and the regularity of the sessions was not compromised by hypotensive episodes or other clinical problems.

Hydraulic patterns

The mean trend of the hydraulic pressure in the blood compartment at the infusion (P_{inf}) and the blood inlet port ($P_{B\,in}$) during the sessions of standard MD-HDF with the MD-190 dialyser and reverse MD-HDF with the MD-220 dialyser is shown in Figure 2A and C, respectively, and the corresponding trends of the TMP in Figure 2B and D. TMP in the first post-dilution section of the blood compartment progressively increased during the standard MD-HDF sessions from a mean initial value of 500 mmHg, stabilizing at ∼700 mmHg in the last hour and rising to a very high mean value of 722 ± 160 mmHg at the end of the sessions. Mean values at the start and the end of the session and the mean of minute-by-minute values are reported in Table 2. In standard MD-HDF, an increase in P_{inf} beyond the established maximum value (650 mmHg) and associated with very high $P_{B\,in}$ of up to 1000 mmHg was recorded in 8 out of 15 patients in the second half of their experimental sessions (Figure 3), and the control system of the device emitted repeated alarms requesting the infusion rate to be reduced manually. As a consequence, the mean infusion rate in those eight patients decreased from 155 ± 11 to 114 ± 12 ml/min in steps of ∼10 ml/min. As a mean of the 15 patients, the infusion rate had to be progressively reduced from 166 ± 14 to 144 ± 34 ml/min to avoid technical and clinical problems. In contrast, all treatments with the MD-220 dialyser used in reverse configuration were carried out without any intervention to reduce the initial infusion rate (mean 169 ± 2 ml/min) since P_{inf} remained under the prescribed limit in all patients. The mean total volume exchange was 37.5 l/session (10.1 l/h) in reverse MD-HDF and 35.1 l/session (9.4 l/h) in standard MD-HDF ($P = 0.047$). Lower TMP was necessary to maintain the planned ultrafiltration rate, even if in the last half hour of the session TMP values at the inlet blood port of the MD-220 dialyser rose beyond the upper limit of 600 mmHg suggested by the membrane manufacturer, up to a mean end-session value of 623 ± 130 mmHg (see Figure 2D and Table 2). The considerable difference in the pressure regimen originating in the two dialysers tested under similar operating conditions is substantiated by the relative resistance to blood entering the filter (Figure 4A and Table 2), which is significantly higher in standard than in reverse MD-HDF, and also appears from the inspection of Figure 5, where blood and dialysate pressures, filtration pressure and pressure drop in the two different section of the dialysers are depicted schematically. Comparison of the two panels in Figure 5 clearly shows the great difference in hydraulic pressure acting along the first post-dilution section of the two dialysers.

The trend of the *in vivo* ultrafiltration coefficient during the experimental treatments is shown in Figure 4B, and

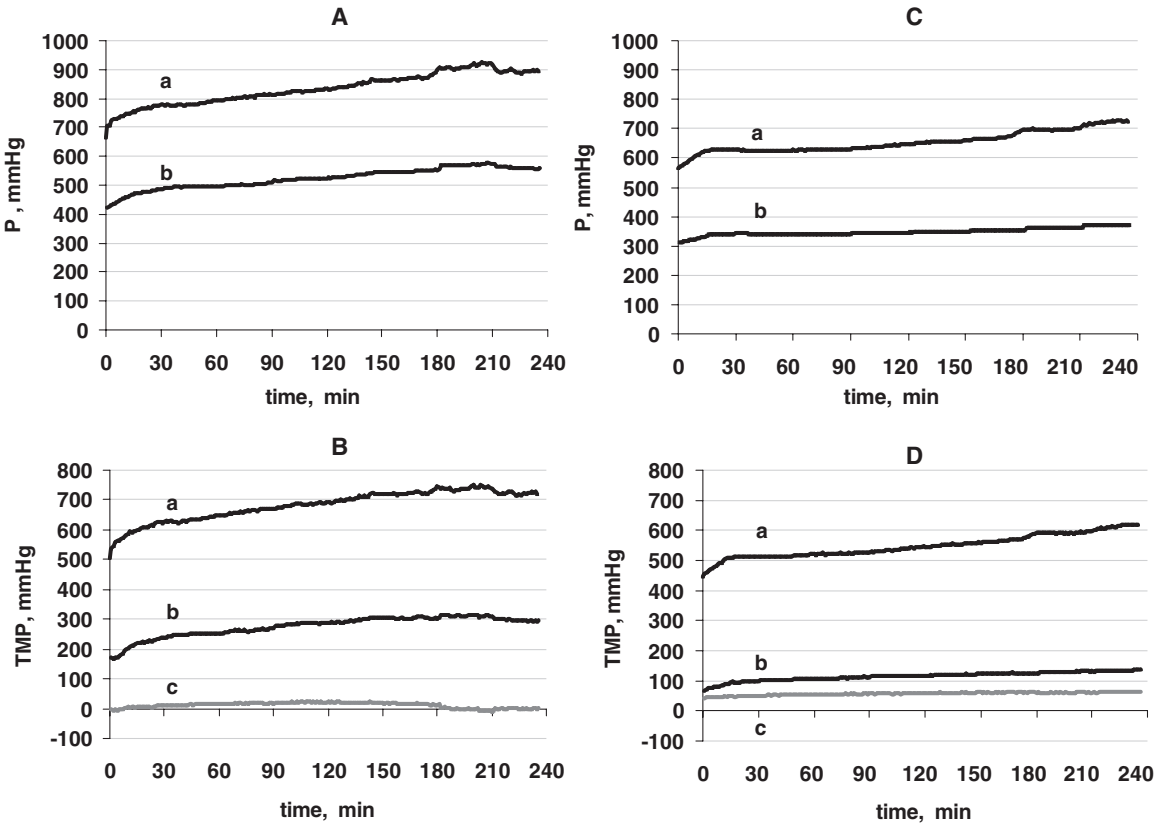

Fig. 2. Panel **A**: mean hydraulic pressure profile of all experiments at the inlet blood port ($P_{B\,in}$, line a) and at the infusion port (P_{inf}, line b) of the OLpur^{TM} MD-190 dialyser during standard MD-HDF. Panel **B**: mean filtration pressure (TMP) profile of all experiments, as calculated from equation (5), at the inlet blood port (line a), at the infusion port (line b) and at the outlet blood port (line c) during standard MD-HDF. In panels **C** and **D**, the same mean pressure profiles recorded during reverse MD-HDF with the OLpur^{TM} MD-220 dialyser are shown. Numerical values and statistics are reported in Table 2.

the mean values at the start and the end of the sessions are reported in Table 2. K_I is an index of the *in vivo* permeability to water of the membrane, which may be affected by an enhancement of the protein polarization phenomenon with thickening of the secondary protein layer due to excessive pressure exerted on the membrane, as possibly occurred in this study to a greater extent during the sessions with the MD-190 dialyser.

Efficiency of dialysers and procedures

The concentrations of the examined parameters at the start and the end of the experimental sessions are reported in Table 3. Only urea end-session values exhibited significant differences between the two procedures. Instantaneous β2-m clearance at the start of the session (Table 4) was similar to the two compared treatments. However, the tendency to decline during the session was less pronounced during reverse MD-HDF with the MD-220 dialyser (21% versus 32%), with the result that end-session β2-m K_I values were significantly higher than those calculated during standard MD-HDF with the MD-190 dialyser. This resulted in overall β2-m removal that was significantly greater with the reverse MD-220 HDF treatments. In addition, the mean β2-m K_{DQ} of the sessions was higher in absolute values during reverse MD-HDF and the difference between the two treatments was very close to statistical significance.

Phosphate removal was similar in terms of mass recovered in the dialysate and mean K_{DQ} while, surprisingly, standard MD-HDF with the MD-190 dialyser showed a greater ability to remove small molecules, as demonstrated by the significantly higher mean urea K_{DQ} and eKt/V values compared with those obtained during reverse MD-220 HDF.

Inversion of both blood and dialysate lines, tested in the same patients of the study in supplementary sessions of reverse MD-HDF, did not produce significant effects on the efficiency of the technique in removing urea (K_{DQ} 252 ± 29 versus 254 ± 33 ml/min, eKt/V 1.49 ± 0.17 versus 1.52 ± 0.21, in reverse versus 'double reverse' MD-HDF, respectively). Phosphate and β2-m removal were not compared in reverse versus double reverse configurations.

Discussion

Mid-dilution HDF was originally proposed as a technique that was able to warrant large ultrafiltration volumes and consequently the maximal middle molecular solute removal by convection. Indeed, reported β2-m (11.8 kD), cystatin

Table 2. Hydraulic pressure and indexes during the experimental procedures

	Standard MD-HDF (MD-190) ($n = 15$)	Reverse MD-HDF –(MD-220) ($n = 15$)	P-value*
$P_{B\ inlet}$ (mmHg)			
Start session	665 ± 142	567 ± 93	0.006
End session	896 ± 211	730 ± 149	0.0008
Mean of the session	835 ± 56	656 ± 132	<0.0001
P inf. (mmHg)			
Start session	424 ± 71	312 ± 45	<0.0001
End session	559 ± 103	371 ± 52	<0.0001
Mean of the session	524 ± 99	348 ± 53	<0.0001
$P_{B\ outlet}$ (mmHg)			
Start session	153 ± 23	158 ± 23	n.s
End session	172 ± 24	172 ± 27	n.s.
Mean of the session	164 ± 24	163 ± 26	n.s.
TMP inlet (mmHg)			
Start session	508 ± 129	448 ± 74	n.s
End session	722 ± 160	623 ± 130	0.005
Mean of the session	683 ± 144	550 ± 113	0.0003
TMP inf. (mmHg)			
Start session	170 ± 62	68 ± 25	<0.0001
End session	295 ± 63	137 ± 38	<0.0001
Mean of the session	270 ± 89	109 ± 34	<0.0001
TMP outlet (mmHg)			
Start session	−4 ± 28	40 ± 9	<0.0001
End session	−3 ± 47	64 ± 17	0.0013
Mean of the session	16 ± 38	61 ± 12	0.0009
Resistance index (mmHg/ml/min)			
Start session	1.78 ± 0.36	1.48 ± 0.20	0.0045
End session	2.37 ± 0.54	1.88 ± 0.33	0.0004
K_{UF} (ml/h/mmHg/m^2)			
Start session	32.7 ± 7.8	41.6 ± 7.5	<0.0001
End session	19.9 ± 9.5	28.0 ± 6.0	<0.0001

Abbreviations and definition of the parameters are in the text (see the 'Subjects and methods' section). Data are presented as means ± SD.
*Student's t-test for paired data. A probability value of <0.05 was considered significant.

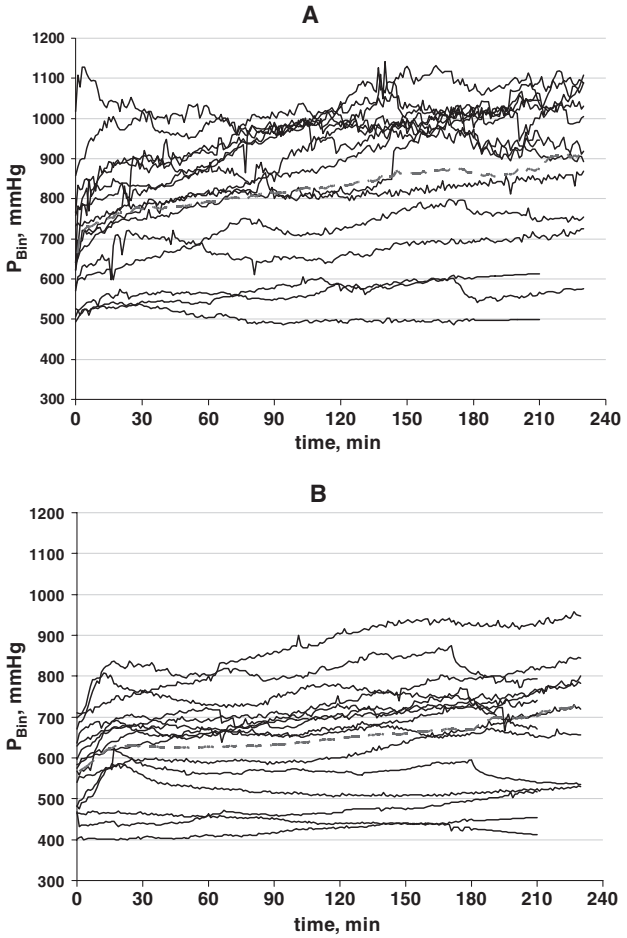

Fig. 3. Hydraulic pressure profile of individual experiments at the inlet blood port ($P_{B\ in}$) of the OLpur^{TM} MD-190 dialyser during standard MD-HDF (panel **A**) and of the OLpur^{TM} MD-220 during reverse MD-HDF (panel **B**). The dotted line is the mean of all experiments.

C (13.4 kD) and retinol-binding protein (21.2 kD) clearances were significantly higher than those obtained in post-dilution HDF [8]. However, after its initial clinical application it was shown that during MD-HDF, considerably high hydraulic pressures may arise in the annular section of the blood compartment of the MD-190 dialyser, where post-dilution takes place [10]. These critical events and the inherent risk, which had not been addressed in the original validation study of the technique [8], have been confirmed by the results of the present study in a larger sub-set of patients and have also been reported by other authors [11], who recorded a mean TMP of up to 1000 mmHg in the first post-dilution section of the MD-190 dialysers, even in sessions performed with substantially lower infusion rates than ours (6 versus 10 l/h). A hypothetical explanation of these high pressures [10] was the high resistance to blood entering the post-dilution section of the dialyser, where the overall surface area of the capillaries is relatively small (1.1 m^2). As also shown in the present study (Figures 2 and 3), resistance further increased during the session as a consequence of the progressive haemoconcentration along the fibres that increased blood viscosity and required proportionally increasing pressure to achieve and maintain the set blood flow. In these conditions, the planned filtration could not be fully maintained even with the very high TMP values progressively set by the machine's volumetric ultrafiltration control.

The preliminary results obtained in a few patients, with a dialyser of larger surface area (the MD-220 filter, 2.2 m^2) used in standard configuration [12], seemed to support the above hypothesis: less resistance to blood and lower pressure were recorded in the larger blood compartment section of this dialyser where post-dilution occurred, even at high blood and infusion rates of 400 and 200 ml/min, respectively. However, a definite improvement in hydraulics was only described when both dialysers were used in reverse configuration [11,12]. Since in this case the post-dilution process occurs in the core region of the fibre bundle of the dialysers rather than in the annular external section, these last observations seem to contradict the former hypothesis, the overall surface of the core capillaries being smaller than that of the annular region in both dialysers.

Our present study confirmed that reverse MD-HDF with the MD-220 dialyser ensures a substantially higher level of safety than standard MD-HDF with the MD-190 dialyser, requiring a lower pressure regimen to obtain high

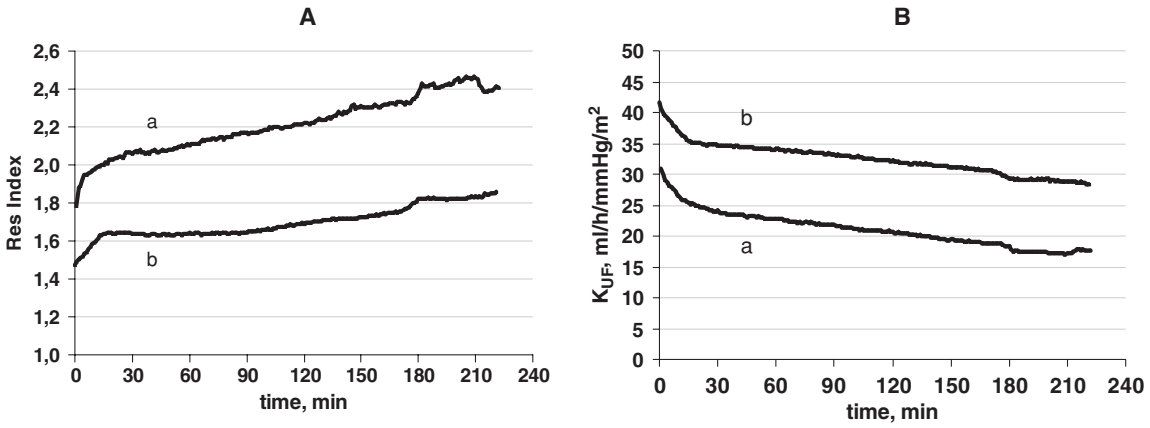

Fig. 4. Mean behaviour of all experiments of the resistance index R_I (panel **A**) and the *in vivo* ultrafiltration coefficient of the dialyser membrane K_{UF} (panel **B**), as calculated from equations (6) and (7), respectively and recorded on-line during standard MD-HDF (line a) and reverse MD-HDF (line b). Numerical values and statistics are reported in Table 2.

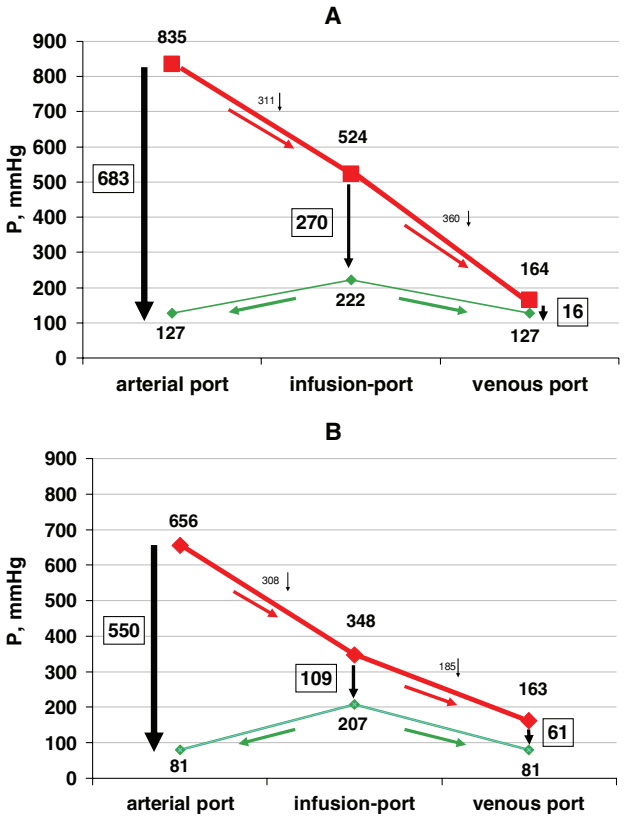

Fig. 5. Schematic representation of the mean filtration pressure (TMP) acting at different points along the length of the capillaries (from the arterial port to the venous port), expressed as a mean value of the standard MD-HDF sessions (panel **A**) and reverse MD-HDF (panel **B**). Values of the mean filtration pressures, calculated from equation (5), are enclosed in the black squares beside the thick vertical black arrows that represent the direction of the transmembrane pressure gradient. Thick lines and arrows (in red, upper part) represent blood flux and its direction in the two blood compartments, while thin lines and arrows (green, lower part) represent the dialysate flux. Mean pressure values at the inlet, mid and outlet blood and dialysate ports of the filter are also reported (see also Table 2). Values in small characters along the blood lines are the pressure drop in the two blood compartments of the dialyser.

Table 3. Baseline and end-session patient parameters

	Standard MD-HDF (MD-190) ($n = 15$)	Reverse MD-HDF (MD-220) ($n = 15$)	P-value*
Urea (mg/dl)			
Start	128.3 ± 24.7	139.7 ± 30.0	n.s.
End	25.7 ± 8.4 (11–37)	31.1 ± 9.3 (21–48)	0.028
Phosphate (mg/dl)			
Start	4.5 ± 1.1	4.5 ± 1.4	n.s.
End	1.9 ± 0.6	1.9 ± 0.7	n.s.
β2-microglobulin (mg/l)			
Start	19.2 ± 5.3	21.3 ± 4.7	n.s.
End	6.5 ± 2.7	6.2 ± 2.4	n.s.
Haematocrit (%)			
Start	34.7 ± 2.4	34.0 ± 2.8	n.s.
End	37.5 ± 3.8	36.8 ± 3.7	n.s.
Total protein (g/dl)			
Start	6.3 ± 0.5	6.3 ± 0.5	n.s.
End	6.6 ± 0.6	6.6 ± 0.5	n.s.

Data are presented as means ± SD.
*Student's *t*-test for paired data. A probability value of <0.05 was considered significant.

ultrafiltration rates. In fact, during reverse MD-HDF $P_{B\,in}$ and P_{inf} remained generally within the safe range, thus allowing the planned ultrafiltration rate to be maintained throughout all sessions, even if hazardous mean TMP values >600 mmHg were also recorded in the reverse MD-HDF technique in the initial post-dilution section of the dialyser in the last half hour of the sessions. However, the level of risk was definitely lower in reverse MD-HDF than in the case of standard MD-HDF with the smaller dialyser.

Our comparison was carried out between dialysers with the same membrane and of similar surface area devoted to post-dilution (annular region 1.1 m^2 in MD-190 and core region 1.0 m^2 in MD-220) and the pressure drop within the relative post-dilution sections was comparable under similar operating conditions (see Figure 5). Thus, it seems likely that the high hydraulic pressures are needed to achieve the set blood flow through the relatively low cross-sectional

Table 4. Efficiency of the experimental procedures

	Standard MD-HDF (MD-190) ($n = 15$)	Reverse MD-HDF (MD-220) ($n = 15$)	P-value*
Urea			
Mass transfer (DQ) (g/session)	38.97 ± 12.36	40.48 ± 11.50	n.s.
K_{DQ} (ml/min)	272 ± 35	252 ± 29	0.002
eKt/V	1.63 ± 0.23	1.49 ± 0.17	0.005
Phosphate			
Mass removal (mg)	839 ± 334	893 ± 272	n.s.
K_{DQ} (ml/min)	128 ± 40	137 ± 26	n.s.
β2-microglobulin			
K_I start session (ml/min)	116 ± 13	123 ± 15	n.s.
K_I end session (ml/min)	79 ± 32	102 ± 25	0.033
Mass removal (mg)	185.1 ± 65.5	221.3 ± 81.3	0.007
K_{DQ} (ml/min)	66.6 ± 10.2	75 ± 15.1	0.055

Abbreviations and definition of the parameters are in the text (see the 'Subjects and methods' section).
Data are presented as means ± SD.
*Student's t-test for paired data. A probability value of <0.05 was considered significant.

area of the fibre lumens, particularly in their sections where post-dilution occurs, but the differences in pressure between the two treatment configurations cannot be explained with differences in surfaces. Instead, it may be reasonably assumed that the higher pressure inside the post-dilution section of the MD-190 is a consequence of the reduction of the overall surface area of the capillaries from 1.1 to 0.8 m^2 at the point where blood flow reverses its direction (infusion port) and its path is constricted. This phenomenon, known as 'the Venturi effect' or hydrodynamic paradox, is a well-known consequence of the Bernoulli's principle of fluid dynamics. In contrast, during treatment with the MD-220 dialyser (as well as with the MD-190) when used in reverse configuration, the overall surface of the capillaries increases at the passage from the post- to the pre-dilution section and lower pressure is required to counteract the resistance created by a larger capillary surface. It is unlikely that a major part of the high resistance to blood entering the MD-190 dialyser in the standard configuration can be attributed to the geometry of the spiral blood path within the dual port header cap of the dialyser, but the role of this factor remains indefinite. In addition, the original structure of MD-dialysers, coupled with the impossibility of obtaining blood samples from the mid-dilution port during treatment, prevented us from fully understanding the reciprocal relationships between their post- and pre-dilution sections as regards the dynamics of transmembrane fluid and solute exchanges and precisely estimating their rates in the different sections.

In the clinical application of MD-HDF, it would be advisable to tailor the infusion rate according to the dialyser and blood characteristics of the patients (blood flow rate, haematocrit, total proteins, coagulation and refilling properties), in order to prevent untoward events related to high pressures and a loss in efficiency due to deterioration of the permeability characteristics of the membrane. Thus, an efficient pressure control system with on-line feedback modulation of the infusion rate, as realized in mixed HDF [17], would be beneficial in improving safety and performance in routine application of the mid-dilution HDF technique. It is important to be aware that the TMP value displayed on the monitor of the machines commonly used in clinical practice, being generally calculated as the difference between $P_{B\,out}$ and $P_{D\,out}$, underestimates the actual filtration pressure at various points along the dialyser and may be misleading when taken as a reference parameter.

The differences in efficiency between the two MD-HDF configurations found in our study arose mainly, in our opinion, from the different hydraulic conditions established in the post-dilution section of the two filters. It is well known that extremely high filtration pressures, particularly in the initial phase of the session, may cause significant deterioration of membrane permeability to water and larger solutes [18,19], probably due to the progressive depositing and thickening of the protein layer on its surface. The effects of these events were also observed in our study and they appeared to be proportional to the set filtration pressure. In fact, the *in vivo* ultrafiltration coefficient of the dialyser, as an index of hydraulic permeability, decreased to a greater extent during standard MD-HDF sessions with the MD-190 dialyser than during reverse MD-HDF with the larger dialyser. Similarly, the trend of instantaneous β2-m clearance, taken as a surrogate index of changes in membrane permeability to middle molecular solutes, showed a greater and more significant decline towards the end of standard MD-HDF sessions compared to the reverse treatment (32% versus 17%). These events may explain why reverse MD-HDF yielded significantly greater β2-m removal than standard MD-HDF in the same patients tested under matched operating flux conditions. The relative contribution to the overall solute transport of the post- and pre-dilution sections of the dialyser could not be defined exactly, even if a contribution of the pre-dilution mechanism to the increased β2-m removal in reverse MD-HDF may be reasonably presumed, due to the higher relative surface area of the dialyser (1.2 m^2 in MD-220 versus 0.8 m^2 in MD-190) and the higher overall replacement volume.

Phosphate removal was in the high range with no statistical difference between the two techniques. In contrast, removal of small soluble molecules (urea) in our study was higher in standard MD-HDF than in the reverse technique, as already reported, but not explained, by other authors [11]. We can hypothesize that this could be a result of the partial compartmentalization of the dialysate flux, which might permeate the external annular capillaries better than the core bundle as a consequence of the dialyser structure. In the annular region, which has a similar surface area in both dialysers (1.1 and 1.2 m^2 in MD-190 and in MD-220 respectively), the gradient for urea diffusion was much higher during standard than reverse MD-HDF, where urea extraction occurred from a highly diluted blood. On the other hand, the higher filtration pressure acting in the MD-190 dialyser could also promote greater removal of a small solute like urea which, unlike β2-m, was not retained by the membrane even when its permeability had deteriorated. Small solutes are mainly removed by diffusion, but evidence exists that high-volume exchange HDF may provide a non-insignificant contribution to urea removal by

convection [17]. As shown by comparing reverse versus 'double reverse' MD-HDF, the direction of the dialysate flux did not have any significant effects on solute transport. Thus, its preferential compartmentalization in the annular region of the dialyser could explain at least partially why urea removal was less effective in reverse compared to standard MD-HDF.

In conclusion, our study demonstrated the ability of MD-HDF to remove significant amounts of medium-sized uraemic compounds and phosphate. Urea removal was sufficient to accomplish current adequacy criteria for small solutes. Safe operational conditions in terms of hydraulic pressure were more reliably maintained by carrying out treatments with the dialyser used in reverse configuration, as a consequence of a stated principle of hydrodynamics. For this purpose, the larger MD-220 dialyser ensures better tolerance together with higher middle molecules clearance. An efficient pressure control system with on-line feedback modulation of the infusion rate according to the patient and the dialyser characteristics and the operational conditions of the treatments would be beneficial to improve safety and performance in the routine clinical application of the mid-dilution HDF technique.

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