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Original Article

Predilution haemofiltration—the Second Sardinian Multicentre Study: comparisons between haemofiltration and haemodialysis during identical Kt/V and session times in a long-term cross-over study

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Abstract

Background. The potential superiority of various renal replacement treatment modalities consisting largely of convective mass transfer as opposed to primarily diffusive mass transfer, is still a matter of debate. The objective of the present study was to evaluate acute and long-term clinical effects of varying degrees of convection and diffusion in a group of 24 clinically stable patients with end-stage renal disease.

Methods. The patients were prospectively assigned to three consecutive treatment schedules of 6 months each: phase I (HF1) (on-line predilution haemofiltration)→ phase II (HD) (high-flux haemodialysis)→ phase III (HF2; as phase I). We used the AK100/200 ULTRA monitor (Gambro), which prepares ultrapure dialysis fluid for HD and sterile, pyrogen-free substitution solution for HF. The membrane (polyamide), fluid composition, and treatment time were the same on HF and HD. The targeted equilibrated Kt/V was 1.2 for both treatment modes, creating a similar urea clearance.

Results. Fifteen patients, mean age 62.8 ± 8.4 years, completed the study according to the above conditions. Urea kinetics, nutritional parameters, and dry weight were similar in the three periods. The frequency of intra-treatment episodes of hypotension/patient/month was significantly lower on HF1 (1.24) and HF2 (1.27) than on HD (1.80) ($P < 0.04$). It decreased progressively on HF1, then increased on HD, and decreased again during HF2. Patients had fewer muscular cramps on HF than on HD ($P < 0.03$) and required significantly less saline and plasma expander during HF than HD sessions. The prevalence of inter-treatment symptoms, including fatigue and hypotension, was lower on HF than on HD (score difference $P = 0.04$). Quality of life, determined by the Laupacis method in all three periods, showed a tendency towards improvement during the study, reaching the best values during HF2.

Conclusions. HF has a progressive stabilizing haemodynamic effect, producing a more physiological cardiovascular profile than HD. This long-term effect, observed in stable patients treated under strictly identical conditions, is probably due to the mechanism of convection, and is different from the acute effect observed mainly in unstable patients.

Keywords: convective treatments; haemofiltration adequacy; on-line haemofiltration; pre-dilution haemofiltration.

Introduction

The benefits of haemofiltration over haemodialysis (HD), which include better cardiovascular stability [1], lower morbidity [2], and higher survival rate in high-risk patients [3] have been well documented in the literature. In a previous prospective collaborative study [4] we described the results of treatment in 23 stable patients who received high-flux HD followed by pre-dilution haemofiltration (HF). In both treatment modes we used the same membrane (high-flux polyamide), electrolyte composition, and quality of fluid.

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The treatment dose in terms of urea clearance was targeted at $Kt/V = 1.4$ for the HD and $Kt/V = 1.0$ for the HF treatment. Although the Kt/V was lower on HF, metabolic control was equally good in both treatments, with generation of similar normalized protein catabolic rate (nPCR). During the HF period, the patients showed fewer hypotensive episodes and fewer symptoms during the intra- as well as the inter-dialytic periods. The main limitation to our conclusion was the difference in treatment time and Kt/V between HD and HF that could have influenced the generation of symptoms shown by the patients. We therefore designed a new study to test whether differences in symptoms between HD and HF would persist under conditions of constant time and urea clearance.

The present prospective cross-over study compared the clinical outcome of 24 stable patients, treated for three subsequent periods of 6 months each on HF—HD—HF, using the same type of membrane and the same on-line fluid preparation system, while eliminating any differences in small-solute clearance by keeping the treatment time and the Kt/V-values similar.

Patients and methods

Patients

Twenty-four end-stage renal disease patients from nine Sardinian dialysis units were randomly selected to be included in the study. The mean age of the patients was 61.9 ± 8.7 years and they had been on dialysis for at least 6 months (74.5 ± 59.2 months). The patients' body weight at the start of the study was 55.8 ± 7.2 kg. All patients were in a stable clinical condition. Reasons for exclusion included a daily diuresis of more than 300 ml, the presence of acute or chronic infection, malignancy, diabetes, systemic disease, liver insufficiency or active liver illness, malnutrition, clinically evident cardiac dysfunction, serious endocrine dysfunction, vasculopathies, malfunction of vascular access, and body weight exceeding 75 kg.

Patients showing a difference in $Kt/V > 0.1$ between the different treatment periods were excluded from the final analysis.

Study design and treatments

The study was divided into three phases, each lasting 6 months: the first phase (HF1) consisted of treatment with pre-dilution HF with on-line prepared bicarbonate substitution fluid; second phase (HD) involved treatment with HD with ultrapure bicarbonate dialysis fluid; and the third phase (HF2) comprised pre-dilution HF with the same conditions as in HF1.

In all three phases, the same dialysis machine, an AK 100/200 ULTRA (Gambro AB), was used. When used for HD, the machine prepares ultrapure dialysis fluid by stepwise ultrafiltration of water and bicarbonate-containing dialysis fluid (BiCart)using polyamide ultrafilters (U 8000S). When used for HF, sterile pyrogen-free substitution solution is prepared on-line from the ultrapure dialysis fluid by an additional step of ultrafiltration using a sterile polyamide ultrafilter (U2000).

The hygiene of the fluid pathway, including the U 8000S ultrafilters, was assured by chemical disinfection after each treatment. The monitor and the filters were treated with peracetic acid disinfectant overnight and over week-ends.

The U 8000S ultrafilters were changed monthly and microbiological surveillance was performed according to the manufacturer's instructions. The final ultrafilter (U2000) was employed on a single-use basis to guarantee the sterility of the infusion solution.

The same fluid electrolyte concentration was used for both HD and HF: sodium 138–140, potassium 1–2, chloride 108.0–109.5, calcium 1.50–1.75, magnesium 0.5, bicarbonate 30–34, acetate 3, and glucose 0–5.55 mmol/l.

The temperature setting on the machine, normally 37°C, was unchanged during the study.

The hemofilter used for HF was a 2.0 m^2 polyamide filter (Hemofilter 20, Gambro AB). Q_B was 350–400 ml/min and the filtrate volume was aimed at 1.25 times the dry body weight.

The dialyser used for HD was a 1.4-m^2 polyamide filter (Polyflux 14, Gambro AB). The blood flow was approximately 300 ml/min, and the dialysis fluid flow was 500 ml/min.

Both HF and HD were targeted to achieve $Kt/V = 1.2$ with similar treatment time (aimed at 4 h).

During the first month of each treatment phase small adjustments in blood flow rate and treatment time were made to achieve $Kt/V = 1.2$ with similar treatment time.

Study parameters

Treatment parameters. During each treatment session the following treatment parameters were recorded: blood flow (Q_b), infusion flow (Q_{inf}), weight loss rate, infusion volume, treatment time and composition of the dialysis and substitution fluids.

Definition of a hypotensive episode. A hypotensive episode was defined as a symptomatic fall of systolic blood pressure (BP) by 20 mmHg or more, requiring saline or plasma expander infusion during the HD or HF session, or a change in prescription of antihypertensive drugs.

Definition of a hypertensive episode. A hypertensive episode was defined as a symptomatic rise in systolic BP above 160 mmHg, with an increase of 20 mmHg or more above the basal values and change in prescription of antihypertensive drugs.

Clinical parameters

Body weight, BP, heart rate, and body temperature were monitored before and after each treatment.

Intra-treatment symptoms. The number of episodes of symptomatic hypotension and hypertension, cardiac arrhythmia, dyspnoea, fever, muscular cramps, headache, pruritus, nausea, and vomiting were recorded during each treatment.

Inter-treatment symptoms. The patients were asked to record the presence of the following symptoms during the inter-treatment period: hypotension, hypertension, arrhythmia, respiratory distress, pruritus, muscular cramps, arthralgia, headache, insomnia, fatigue, abnormal thirst, diarrhoea and constipation.

Urea kinetics analysis

The urea kinetics were determined at the beginning of each treatment phase and subsequently every 2 weeks during the midweek session. Pre-session urea and post-session urea were determined in blood samples taken in the arm contralateral to the fistula. Post-session urea samples were taken 30 min after the end of the treatment and thus represent the equilibrated urea concentration. Kt/V was calculated using the natural logarithm formula according to Daugirdas [5]. The nPCR was calculated from this equilibrated Kt/V value and the pre-session urea concentration using another formula by Daugirdas [5]. Because this nPCR value can be considered an equilibrated value, it should only be used for comparison within the study.

Blood analysis

A full blood analysis was made every 2nd week from samples taken before the first treatment of the week.

Infusion therapy and drugs

Intravenous dextran and hypertonic saline administration per session were recorded. The use of antihypertensive, anti-arrhythmic and cardiokinetic drugs, anti-aggregant–anticoagulant, anti-H_2 receptor, phosphate binders, calcitriol and derivatives, tranquillizers, iron, and erythropoietin during the inter-treatment period was registered.

Ambulatory blood-pressure monitoring (ABPM)

All 24 patients were fitted for ABPM with a Space-Lab device [6] and were monitored for 48 h midweek. The continuous 48-h monitoring was begun at the end of the first treatment of the week. This procedure was carried out in the middle of the 6th month of both treatment modes and under the same climatic conditions.

Bioelectrical impedance

Resistance (Rx) and Reactance (Xc) parameters were measured in the three periods of the study 30 min after the end of the midweek session. Body composition was evaluated by a single-frequency instrument (50 KHz, BIA-101 Akern/RJL, Firenze) [7].

Quality of life

All patients were submitted to a quality of life test described by Laupacis [8] in the middle of the HF1, HD, and HF2 phases. Two interviews with an interval of 2 weeks were carried out in all three treatments periods, and the average values were calculated.

Statistical analysis

All data are expressed as means $\pm$ SD. The Student *t*-test was used for paired data. Significance was determined at the $P < 0.05$ level.

Results

Twenty of 24 patients completed all three phases of the study. Four patients dropped out for the following reasons: successful renal transplantation in two patients, death after myocardial infiltration in one patient, and non-compliance in one patient. Additionally, five patients were excluded from the final analysis because their Kt/V values in HF and HD differed by >0.1 unit. The 15 patients who completed the study had a mean age of 62.8 ± 8.4 years, their previous treatment duration was 85.1 ± 57.6 months and the dry body weight at the start of the study was $55.0 +$ 9.16 kg. Their previous treatment was pre-dilution HF for eight patients, bicarbonate HD for six patients, and bicarbonate haemodiafiltration for one patient.

Treatment and clinical parameters

Treatment parameters. The main differences between HF and HD treatment parameters was the larger membrane area in HF (2 *vs* 1.4 m^2) and the higher Qb (HF1 421 ± 47, HD 307 ± 38, HF2 421 ± 46 ml/min; $P < 0.001$). The treatment times during the HF1, HD, and HF2 periods were similar (222 ± 27.8, $221 + 21.7$, 218 ± 18.5 min). Weight loss rate, calculated as percentage of body weight/hour was also similar (1.43 ± 0.5, 1.49 ± 0.4, and $1.42 \pm 0.4\%$). The average ultrafiltrate volume (infusion volume plus weight loss) during the two HF periods corresponded to the patient's dry body weight times 1.31 ± 0.09. The dry body weight of patients was also similar during the HF1, HD, and HF2 phases (55.1 ± 9.3, 54.6 ± 10.5, and 55.8 ± 9.8 kg).

Urea kinetics. The main aim of the study, which was to maintain constant treatment time and urea clearance during the different phases, was achieved for the 15 patients included in the final analysis. The pre-session urea concentration was similar during the HF1, HD, and HF2 treatments (76.6 ± 20.5, 72.1 ± 17.5, 73.5 ± 17.3 mg/dl) as was Kt/V (1.25 ± 0.09, 1.28 ± 0.08, 1.26 ± 0.06), nPCR (1.16 ± 0.32, 1.10 ± 0.26, 1.12 ± 0.26), and urea reduction ratio (64.7 ± 2.4, 65 ± 2.5, $64.9 \pm 2\%$).

Blood chemistry. The results of the analyses performed before the first treatment of the week were similar on HF1, HD and HF2 for haemoglobin, urea, creatinine, uric acid, sodium, potassium, phosphate, ionized calcium, magnesium, alkaline phosphatase, cholesterol, triglycerides, albumin, pre-session blood pH, and intact PTH. The only significant differences were a higher leukocyte count on HF (HF1 6453 ± 2129, HD 5969 ± 2009, HF2 $6005 \pm 1883/mm^3$, $P < 0.03$) and a higher plasma bicarbonate concentration during HF periods (HF1 22.8 ± 2.4, HD 21.9 ± 2.4, HF2 22.3 ± 1.8 mmol/l, $P < 0.04$.)

Blood pressure. BP measurements during the three periods of the study showed significant differences between the two treatment modes (Table 1). The pre-session BP, systolic and diastolic, was significantly higher during the HF periods than during the HD period, while the inter-session weight gain was higher on HD. Post-session BP, systolic and diastolic,

Table 1. Blood pressure parameters in HF and HD. Six-month averages of all sessions

	HF1	HD	HF2
Before session			
Inter-treatment weight gain (kg)	2.4 ± 0.7	2.6 ± 0.8[1]	2.4 ± 0.7[1]
Systolic BP (mmHg)	135.8 ± 18[2]	128.2 ± 20.6[2]	130.1 ± 22.8
Diastolic BP (mmHg)	77.2 ± 8[3]	72.7 ± 8.9[3]	74.1 ± 11.1
MAP (mmHg)	96.8 ± 10.7[4]	91.2 ± 12.3[4]	92.8 ± 14.3
After session			
Systolic BP (mmHg)	125.9 ± 16.9[5]	117.8 ± 18.9[5]	122.2 ± 20.1
Diastolic BP (mmHg)	73.8 ± 7.8[6]	69.9 ± 8.5[6]	72 ± 8.8
MAP (mmHg)	91.2 ± 10.3[7]	85.8 ± 11.6[7]	88.8 ± 11.6
Delta MAP before/after session (mmHg)	−5.6 ± 7.2	−5.3 ± 7.2	−4.0 ± 7.9
Average ambulatory BP	HD	HF2	*P*
Systolic 48-h BP (mmHg)	113.9 ± 17.1	118.5 ± 22.7	0.24
Diastolic 48-h BP (mmHg)	67.6 ± 9.7	68.3 ± 12.6	0.585
First 24-h systolic BP (mmHg)	110.8 ± 11.2	117.3 ± 10.6	0.17
First 24-h diastolic BP (mmHg)	66.7 ± 8.3	68.7 ± 5.4	0.42
Second 24-h systolic BP (mmHg)	110.8 ± 11.3	120.7 ± 11.8	< 0.04
Second 24-h diastolic BP (mmHg)	68.3 ± 8.3	68.1 ± 8.2	0.96

[1]HD *vs* HF2, $P = 0.01$; [2]HD *vs* HF1, $P = 0.02$; [3]HD *vs* HF1, $P = 0.001$; [4]HD *vs* HF1, $P = 0.003$; [5]HD *vs* HF1, $P = 0.02$; [6]HD *vs* HF1, $P = 0.01$; [7]HD *vs* HF1, $P = 0.008$.

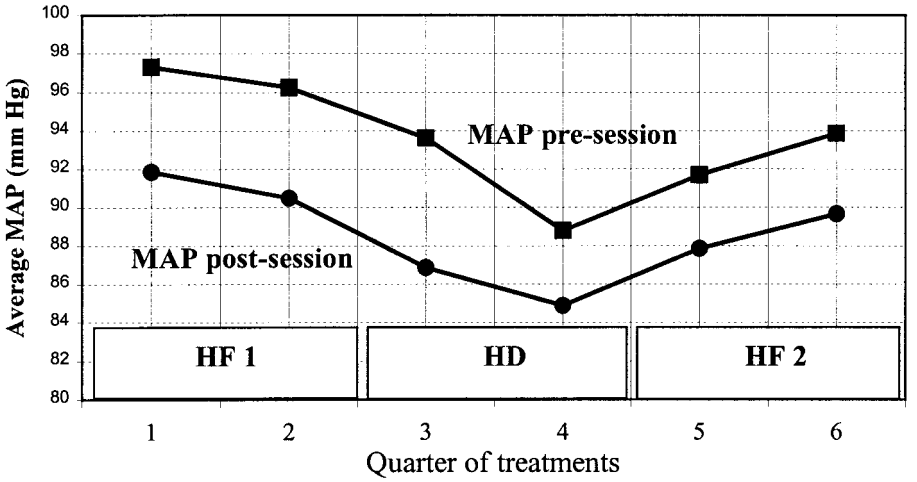

Fig. 1. Average MAP, subdivision in quarters.

were significantly higher after HF than after HD. The change in mean arterial pressure (MAP) was similar for both modes.

During the 6 months of HD, both systolic and diastolic mean BP fell progressively and then increased during the following 6 months of HF treatment (Figure 1).

ABPM during HD and HF2 showed a low prevalence of hypertension: one of 15 patients in the HD and none of 15 patients in the HF2 periods. During the entire inter-treatment mid-week period, BP showed a slight but non-significant increase during HF (Table 1); the only significant difference was noted in the second 24 h systolic BP measurement. The number of nocturnal dippers, defined as patients with a fall in BP > 10% of 24 values, was low in both treatment phases: one of 15 in HD, two of 15 in HF2.

Symptoms. The percentage of patients with at least one incidence of intra-treatment symptoms was significantly higher on HD than on HF for hypotensive episodes and muscular cramps (Table 2). The pre-valence of other symptoms commonly related to dialysis, such as hypertensive episodes, arrhythmia, dyspnoea, pruritus, fever, nausea, and vomiting was low but similar during the different periods. The score obtained from the sum of the prevalence of all the above mentioned symptoms was progressively but not significantly reduced during the two HF phases of treatment (HF1 96.7, HD 106.7, HF2 46.7).

During HF, patients also experienced significantly fewer symptoms in the inter-treatment period, having fewer hypotensive episodes and less fatigue (Table 2). However, the prevalence of hypertensive episodes, arrhythmia, dyspnoea, insomnia, thirst, and vomiting

Table 2. The most relevant findings of the study

Treatment parameters	HF1	HD	HF2	*P*
Equilibrated Kt/V	1.25 ± 0.09	1.28 ± 0.09	1.26 ± 0.07	n.s.
nPCR	1.16 ± 0.32	1.10 ± 0.26	1.12 ± 0.26	n.s.
Intra-session features				
Prevalence of hypotension (%)	46.7	66.7	23.3	< 0.01
Prevalence of muscular cramps (%)	6.7	26.7	6.7	< 0.035
Episodes of hypotension (*n*/pt/month)	1.25 ± 2.2	1.80 ± 2.26	1.28 ± 2.4	< 0.045
Plasma-expander (ml/pt/month)	122.6 ± 273	209.4 ± 433	156.4 ± 389	< 0.038
Inter-session features				
Prevalence of hypotension (%)	10	30	10	0.016
Prevalence of fatigue (%)	10	26.7	10	0.04
Inter-treatment weight gain (kg)	2.4 ± 0.7	2.6 ± 0.8	2.4 ± 0.7	0.01
MAP pre-session (mmHg)	96.8 ± 10.7	91.2 ± 12.3	92.8 ± 14.3	0.003
MAP post-session (mmHg)	91.2 ± 10.3	85.8 ± 11.6	88.8 ± 11.6	0.008
First 24-h systolic BP (mmHg)	–	110.8 ± 11.2	117.3 ± 10.6	n.s.
Second 24-h systolic BP (mmHg)	–	110.8 ± 11.3	120.7 ± 11.8	0.04
Patients on anti-hypertensive drugs (%)	23.3	33.3	26.6	n.s.

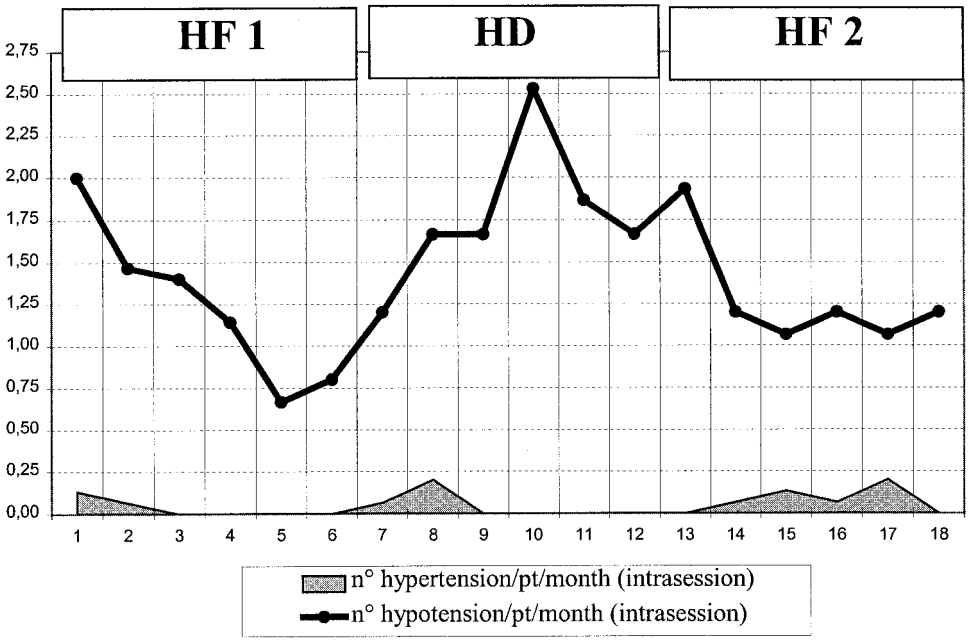

Fig. 2. Hypotensive and hypertensive episodes; monthly outcomes.

was not significantly different. The total score obtained from the sum of the prevalence of all the above-mentioned inter-dialytic symptoms was significantly higher during HD (HF1 123.3, HD 203.3, HF2 133.3; $P < 0.03$).

During the 18 months of the study, there was a progressive decrease in intra-treatment hypotensive episodes during HF1, a subsequent progressive rise during the HD period, and a new fall during HF2 (Figure 2). The inter-session episodes of hypotension were also more frequent on HD than on HF.

Medication. The average dose of plasma expander administered during treatment was significantly higher during HD (HF1 122.6 + 273, HD 209.4 + 433, HF2 156.4 + 389 ml/patient/month; $P < 0.04$). A similar but non-significant trend was observed for saline dose.

Bioelectrical impedance. The body reactance values were significantly lower during the HF periods (HF1 38 ± 15, HD 46 ± 12, HF2 38 ± 12 ohm/m, $P < 0.01$), whereas dry weight was similar in the three phases. The normalized resistance values rose in the HD period but this increase was not significant (HF1 418.9 + 72.9, HD 446.1 + 67.4, HF2 413.7 + 81.8 ohm/m).

Quality of life study (QoL). There were no significant differences in the QoL scores between the treatments (Figure 3). However, during HF2 the scores pertaining to clinical and physical symptoms, fatigue, and

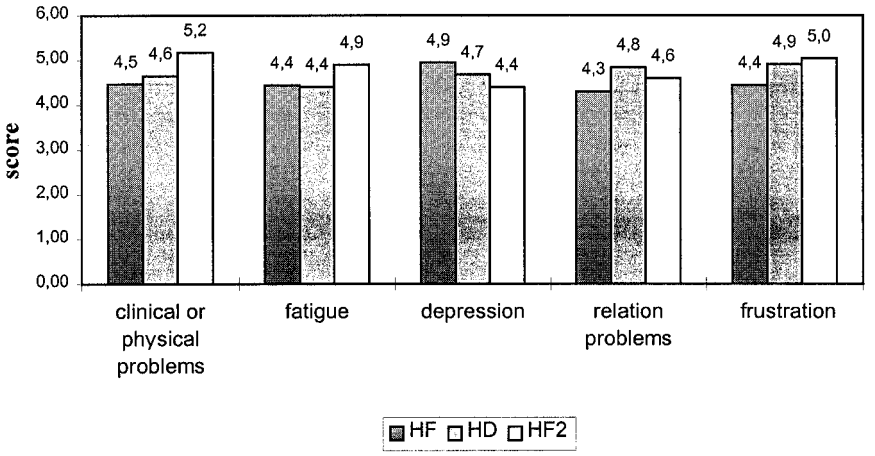

Fig. 3. Quality of life; Laupacis score evaluation (0 points, the worst scenario; 7 points, the best scenario).

frustration reached the highest values, indicating a tendency for improvement of QoL during the final HF phase.

Discussion

The present study shows that stable patients experience fewer BP-related symptoms both during and between treatments when treated with predilution HF rather than HD under otherwise identical conditions. This finding confirms the main results of our first study [4]. Specifically, the lower incidence of hypotensive episodes and muscular cramps is impressive and leads to fewer intra-treatment interventions. During the inter-treatment period the HF treatment also caused fewer symptoms and provided better BP stability.

These findings are particularly note-worthy since HD and HF were conducted using the same membrane, the same fluid composition, the same urea clearance, and the same treatment time. Thus, patients were exposed to similar clearance and fluid removal rates. The main difference was that in HD the blood was separated from the fluid and purified by diffusive transport, while in HF the blood was mixed with the fluid and purified by convection across a larger membrane area and at a higher flow rate.

The number of episodes of symptomatic hypotension progressively decreased during the first phase of HF, then increased during HD, and finally fell during the second phase of HF (Figure 2). The reverse pattern of change was seen for BP (Figure 1).

These changes indicate that in the absence of relevant changes in body weight, the stabilizing effect of the HF treatment was progressive and long-term rather than acute, as has previously been suggested.

This is in apparent contrast to the acute effect, which was attributed to greater lowering of the body temperature by HF compared with HD, as has been described by different authors [9–11].

The difference in BP profile between HD and HF indicates that HF could induce a more physiological response from the cardiovascular system in response to the stress caused by fluid removal with less haemodynamic change. This response may include, in part, a better refilling during HF than during HD [12].

This hypothesis is also supported by the trend towards a larger systolic and diastolic dipping (although not significant) in HF, the reduction in the inter-treatment weight gain, and the finding that HF caused less intra- and inter-treatment hypotension and less inter-treatment fatigue.

The different pattern of bioelectrical impedance indices during HF and HD, in the absence of significant changes in dry weight, deserves further comments. The hypothesis that HF leads to sodium and water retention, caused by a reduced sieving coefficient for sodium due to convective transport, could be compatible with our bioimpedance findings [13].

However, it does not explain the more physiological BP profile (better dipping, less use of antihypertensive drugs and less inter-dialytic weight gain) observed during HF. The higher reactance and resistance after HD could be caused by a greater fluid removal during HD, due a higher interdialytic weight gain, which leads to a similar 'dry weight' after HF and HD sessions [14]. Arguing against this hypothesis is the narrow but significant difference in inter-treatment weight gain during two treatments (2.4 kg during HF and 2.6 kg during HD), a finding that is not consistent with the changes of bioimpedance indexes in HF and HD. The available data indicate that it is inaccurate to attribute the difference in response to HF and HD to a unique, simple phenomenon, such as temperature difference or sodium retention, since the two treatment modalities have a different spectrum of solute removal and are carried out under substantially different technical conditions.

The stabilizing effect of HF in unstable patients has been described previously [1]. Our study provides the only prospective demonstration of a haemodynamically stabilizing effect of HF in a relatively stable group of patients that had a basal low prevalence of hypertension and hypotension.

At present it is not possible to establish which factors are responsible for the better cardiovascular

stability of HF. The present study excludes the possibility that the better tolerance provided by HF treatment is due to its being more biocompatible, since membrane, fluid composition, and fluid quality were the same in both treatments.

HF treatments are usually targeted to a Kt/V that is lower than in HD. In our previous study, the nPCR remained unchanged when patients were switched from HD treatment targeted to a Kt/V of 1.4 to HF treatment targeted to a Kt/V of 1.0.

In the present study the urea removal indices were similar in the two treatment modes, with a target Kt/V of 1.2 in both. The urea clearance was obtained by diffusion in HD and by convection in HF. Larger membrane-permeable solutes were cleared at the same rate as urea in HF, while their removal in HD was at a considerably lower rate.

Since medium- and large-molecular-weight solutes were not evaluated in the present study, we cannot hypothesize that a difference in solute removal between the two therapies could explain the better BP stability during HF. However, this remains a major difference between the therapies [15–17].

Many studies have documented a decreased morbidity and mortality in HD patients when they were dialysed with a high Kt/V and a URR $>60\%$. Retrospective studies indicate that there might be a survival advantage for convective therapies irrespective of the dose administered [18,19].

Since HF is used mainly in unstable patients with potential for high mortality and because there is a lack of prospective studies examining a sufficient number of patients, it is difficult to establish a dose of HF that may protect against the excessive morbidity and mortality that is considered adequate during HD [19].

The present study confirms and advances evidence that on-line convective therapies [20] are capable of obtaining urea removal rates and treatment times that are comparable to HD.

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