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Effect of a plasma sodium biofeedback system applied to HFR on the intradialytic cardiovascular stability. Results from a randomized controlled study

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Abstract

Background. Intradialytic hypotension (IDH) is still a major clinical problem for haemodialysis (HD) patients. Haemodiafiltration (HDF) has been shown to be able to reduce the incidence of IDH.

Methods. Fifty patients were enrolled in a prospective, randomized, crossover international study focussed on a variant of traditional HDF, haemofiltration with endogenous reinfusion (HFR). After a 1-month run-in period on HFR, the patients were randomized to two treatments of 2

months duration: HFR (Period A) or HFR-Aequilibrium (Period B), followed by a 1-month HFR wash-out period and then switched to the other treatment. HFR-Aequilibrium (HFR-Aeq) is an evolution of the haemofiltration with endogenous reinfusion (HFR) dialysis therapy, with dialysate sodium concentration and ultrafiltration rate profiles elaborated by an automated procedure. The primary end point was the frequency of IDH.

Results. Symptomatic hypotension episodes were significantly lower on HFR-Aeq versus HFR (23 ± 3 versus 31 ± 4% of sessions, respectively, P l= l0.03), as was the per cent of clinical interventions (17 ± 3% of sessions with almost one intervention on HFR-Aeq versus 22 ± 2% on HFR, P <0.01). In a post-hoc analysis, the effect of HFR-Aeq was greater on more unstable patients (35 ± 3% of sessions with hypotension on HFR-Aeq versus 71 ± 3% on HFR, P <0.001). No clinical or biochemical signs of Na/water overload were registered during the treatment with HFR-Aeq.

Conclusions. HFR-Aeq, a profiled dialysis supported by the Natrium sensor for the pre-dialysis Na^+ measure, can significantly reduce the burden of IDH. This could have an important impact in every day dialysis practice.

Keywords: biofeedback; intradialytic hypotension; sodium online measure

Introduction

In the last decades, the chronic kidney disease population has changed widely and the median age of the incident dialysis patients is >70 years, with diabetes and hypertension being the major underlying diseases; moreover, a great percentage of the patients starts dialysis with a burden of at least one to two comorbidities [1].

Despite this epidemiological scenario, haemodialysis (HD) sessions usually last no more than 3:30–4:30 h and that further exacerbates the patient's cardiovascular instability.

Thus, although during the last years the technological aspects of dialysis have remarkably improved [2], intradialytic hypotension (IDH) still represents the most frequent and important HD complication [3, 4]. IDH not only interferes with the delivery of an adequate dialysis dose but also causes a critical hypoperfusion of the cerebral, cardiovascular and mesenteric districts [5–7]. Therefore, reducing the frequency of IDH is of paramount importance to improve patients' quality of life and possibly general outcomes.

It has recently been demonstrated in a randomized control trial [8] that online haemodiafiltration (HDF) and, to a lesser extent, online haemofiltration significantly reduced the frequency of IDH in comparison with standard low-flux HD. The adjusted relative risk reduction of IDH was 54% in patients randomized to HDF in comparison with low-flux dialysis.

The commonest cause of IDH is an ultrafiltration rate that exceeds an adequate plasma refilling rate, thus reducing plasma volume to a critical level. During the first 2 h of treatment, there is a marked fall in plasma osmolality mainly due to the reduction of urea and to a lesser extent of sodium and other small electrolytes. Thus, it is not surprising that sodium profiling represents one of the most investigated approaches to the IDH [9]. Tailored approaches, based on the biofeedback core concept, have been also developed to further counteract the frequency of IDH.

The difficulties in the realization of a correct intradialytic sodium mass balances have led to a decline in everyday clinical practice the use of sodium profiling. Colì *et al.* developed a new mathematical model of sodium profiling, named 'Profiler', in order to predict the intradialytic sodium removal [10–13]. The model takes into account blood flow, pre-dialysis plasma sodium (Na^+) and urea concentration, creating coupled ultrafiltration and sodium conductivity profiles in order to achieve the planned weight loss (WL) and reach the desired target post-dialysis plasma sodium concentration. This approach was implemented in clinical practice by coupling the Profiler kinetic model with the haemodiafiltration with endogenous reinfusion (HFR) extracorporeal technique [14] realizing the so-called HFR-Aequilibrium (HFR Aeq). Colì *et al.* found a significant reduction of the number of sessions complicated by hypotension by applying this kinetic model to HD in an open-loop system named automated adaptive system dialysis (AASD) [15]. The incidence of other disequilibrium syndrome symptoms was also lower on AASD.

The aim of the present randomized controlled multinational trial was to evaluate the impact of HFR-Aeq (sodium profiling) in comparison with the standard (no sodium profiling) HFR technique on the overall and cardiovascular intradialytic stability.

Materials and methods

Study design

Aequilibrium International Multicentric Study (AIMS) is a prospective, multicentric multinational randomized crossover study. Thirteen dialysis centres around Europe, Italy (five), Germany (one), France (four), Belgium (one), Spain (one), UK (one) participated in this study. After a run-in period of 1 month on HFR, the patients were randomized either to HFR (Period A, control treatment) or to HFR-Aeq (Period B, intervention treatment), 2 months duration each, followed by a wash-out period of 1 month on HFR and then switched to the other treatment (BA design). The randomization was centrally carried out according to a balanced block randomization list (Figure 1).

Study end points

The primary end point was the assessment of HFR-Aeq impact on cardiovascular tolerance by using as response variable the number of sessions complicated by hypotension.

Secondary end points were the frequencies of other intradialytic symptoms, nurse interventions and the intradialytic variations for systolic blood pressure (SBP), diastolic blood pressure (DBP) and mean arterial pressure (MAP).

Inclusion and exclusion criteria

The patients enrolled should have met the following inclusion criteria: hypotension prone patients (>30% of dialysis sessions complicated by hypotension in the last month before the study enrolment), age between 18 and 85 years, dialysis vintage of >6 months, residual creatinine clearance of <2 mL/min/1.73m^2, native fistula or central venous catheter with a blood flow rate Q_b ≥250 mL/min.

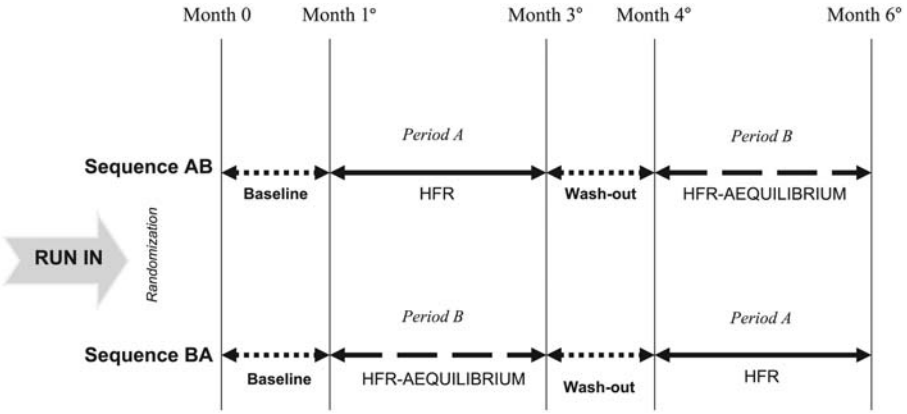

Fig. 1. Study design.

Exclusion criteria were life expectancy <1 year, important clinical events during the last 3 months (as ictus, myocardial infarction, cachexia, pregnancy), solid neoplasm, dysfunction of the vascular access and no IDH during the last month of dialysis.

Control treatment (HFR)

HFR is based on the use of a double chamber filter coupled with a resin cartridge (HFR and Selecta; Bellco, Mirandola, Italy). The first one is a convective chamber (high-flux high permeability polyphenylene membrane) in which the ultrafiltration of patient's plasma water (the ultrafiltrate) is regenerated through a resin cartridge inserted into the ultrafiltration circuit. This regenerated ultrafiltrate is reinfused into the bloodstream before the second diffusive chamber (low-flux low permeability polyphenylene membrane), in which standard HD process takes place [16].

Intervention treatment (HFR-Aequilibrium)

The patient's plasma sodium concentration was estimated on the available pre-resin ultrafiltrate by means of a conductivity cell sensor as a surrogate for sodium cell sensor (Natrium sensor). The Natrium sensor measures the pre-dialysis ultrafiltrate conductivity and by means of a correlation equation ($[Na^+]$ l= 113.95 × C_{uf} − 53.48) is able to calculate the plasma sodium to be given to the kinetic model, which adapts the profiles to the daily sodium and water overloads [14].

HFR coupled to the Profiler kinetic model was named HFR-Aequilibrium (Figure 2). The Natrium sensor also allows the intradialytic online control of the achievement of prescribed targets (intradialytic plasma sodium concentration curves and sodium balance of the session). The plasma sodium concentration was measured with direct potentiometry.

Run-in period

A 1-month HFR run-in period was foreseen to get all the patients used to HFR treatment. Ultrafiltration was set according to the patient's interdialytic weight gain and kept constant during the whole treatment duration. Bicarbonate dialysate concentration and total conductivity were set according to the attending physician's usual prescription and kept constant during the study follow-up.

Baseline period

One further month period with standard HFR (baseline period) after, the run-in period was foreseen as a reference period for comparisons.

Period A

During the 2 months of Period A with HFR treatment, the dialysis prescription was set in accordance to the run-in period. Ultrafiltration, bicarbonate and dialysate conductivity were kept constant during the whole treatment, as well as the temperature and the session duration. The arterial blood pressure was measured every 30 min. The symptoms and the medical interventions were reported on the CRF. All the treatments were delivered with Formula Therapy Bellco dialysis monitor (Bellco).

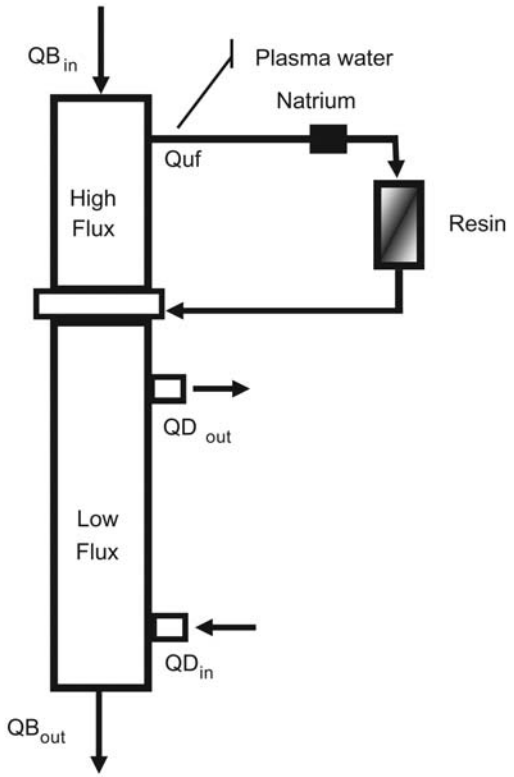

Fig. 2. HFR-Aequilibrium outline.

Period B

During the 2 months of Period B with HFR-Aeq, the treatment usual prescription was modified in consequence of the kinetic model required settings. Mainly, two new parameters needed to be daily defined at the beginning of every treatment: the 'target Na^+' and the maximum value (UF_{max}) of ultrafiltration. The Profiler mathematical model creates coupled curves for ultrafiltration and total dialysate conductivity characterized by a parabolic shape. The maximum value is reached for both curves after 1 h of treatment. The target sodium value was set according to the mean value of post-dialytic plasma sodium concentrations observed during the run-in period. UF_{max} varies in a predefined range, defined in accordance with the treatment duration and the total ultrafiltration volume.

The average ultrafiltration peak was set between 50 and 70% of the given range. Bicarbonate dialysate conductivity prescription was kept constant, as well as the temperature and the duration.

All the treatments were delivered with Formula Therapy Bellco dialysis monitor (Bellco).

Primary and secondary response variables

The primary response variable was the proportion of dialysis sessions complicated by hypotension during each period. IDH was defined as follows:

- in the case of patients with a pre-dialysis SBP value >100 mmHg. An SBP value ≤90 mmHg even if not accompanied by symptoms and therapeutic interventions (standard saline or hypernatric solutions infusions, plasma expander, Trendelenburg or other manoeuvres, reduction in blood flow, stop of ultrafiltration);
- any SBP reduction ≥25 mmHg compared to the pre-dialysis value, in the presence of symptoms and therapeutic manoeuvres;
- in the case of patients with a pre-dialysis SBP value <90 mmHg, an SBP reduction of at least 10% accompanied by the characteristic symptoms (nausea, vomiting, headache, dizziness, etc.).

Secondary response variables were SBP, DBP, MAP and heart rate (HR) measured at the beginning of each treatment and every 30 min till the end of dialysis in clinostatism; intradialytic symptoms (nausea, vomiting, hypotension, headache, cramps) and related clinical interventions.

Blood pressure measures were performed by the on-board oscillometric sphygmomanometer dialysis monitor Formula 2000 sphygmomanometer (Formula Therapy; Bellco).

Sample size

The sample size was calculated assuming the percentage of sessions complicated by IDH as the main response variable. A significant level of 0.05 (α error) and a test power of at least 0.8 (β error of 0.2) were assumed. Furthermore, the average incidence of IDH for the study population was assumed to be at least 30%. An average percentage difference of −30% between the two groups was considered clinically relevant. A two-tailed *T*-test was used to estimate the sample size and a 10% increase was applied to account for possible dropouts. By employing these assumptions, a total number of 50 patients was found per crossover design.

Statistics

Each parameter considered for analysis was expressed as mean ± standard error. A significant level of 0.05 (α error) was considered for all the tests.

Preliminarily, the skewness and the curtosis tests were performed for all the sampled variables to assess the normality of their distribution.

Analysis of variance test for repeated measures was performed to compare the blood pressure trends during the treatment; both time, type of treatment (HFR or HFR-Aeq) and their combined interaction were considered as independent factors.

For the normally distributed variables, the *t*-test was used, while for the non-normally distributed variables, the Wilcoxon signed-rank test for matched pairs was performed to compare the incidence of IDH, symptoms, therapeutic manoeuvres and hydration status between the two different periods (Period A and Period B) of the study.

Regulatory considerations

The study was conducted according to the Helsinki declaration. The Ethics Committees of each participating centre approved the study. All the patients gave their informed consent before entering the study.

Results

Patient and dialysis session characteristics

Forty-three of 50 examined patients, from 13 dialysis units, were admitted to the study according to the inclusion and exclusion criteria.

Seven dropouts occurred due to vascular access problems (three patients), intolerance to HFR (two patients), consensus withdrawn (one patient) and death (one patient, unknown cause) (Figure 3). Patient demographic data are shown in Table 1, together with the main dialysis prescription parameters, which did not vary along the whole study period.

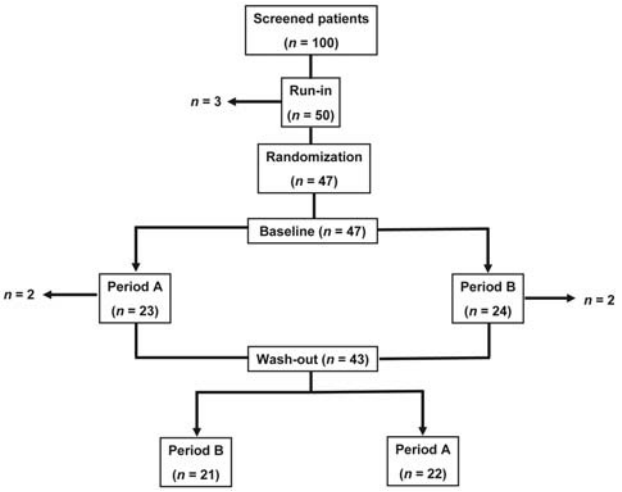

Fig. 3. Patients disposition scheme.

Delivered treatments

Blood flow (Q_b, mL/min), reinfusion flow (Q_{inf}, mL/min), dialysate temperature (T, °C) did not vary throughout the whole study period. Data are shown in Table 1.

Table 1. Patients and dialysis session characteristics (mean ± SEM)

Characteristic	Value
No. patients	43
Men/women	20/23
Age, years[a]	72 ± 9
Dialysis vintage, months[a]	72 ± 77
Origin of kidney disease	
Hypertension (%)	22
Glomerulonephritis (%)	17
Interstitial nephritis (%)	13
Diabetes (%)	13
Congenital disorders (%)	4
Renal tumour (%)	4
Unknown (%)	27
Comorbidities	
Hypertension (%)	21
IHD (%)	21
Vasculopathy (%)	16
Diabetes (%)	13
Stroke (%)	10
Neoplasia (%)	5

	HFR	HFR-Aequilibrium	P
No. sessions studied	923	988	
Q_b, mL/min	325 ± 2	323 ± 2	0.67
Q_{inf}, L/h	2.7 ± 0.1	2.7 ± 0.1	0.88
T,°C	36.2 ± 0.1	36.3 ± 0.1	0.68
Time, min	236 ± 2	234 ± 2	0.90
Total conductivity, ms/cm	14.2 ± 0.1	profiled	

[a]Indicates SD calculation instead of SEM.

Treatment tolerance

IDH resulted to be non-normally distributed (skewness l= l0.84, curtosis l= l−0.26); in this case, the Wilcoxon non-parametric signed-rank test for matched pairs was used. The number of patients considered for analysis was 43 and the total number of sessions was 1911 (923 sessions HFR + 988 sessions HFR-Aeq, respectively).

IDH incidence statistically decreased from 31 ± 4% in HFR (Period A) to 23 ± 3% in HFR-Aeq (Period B), with a relative risk reduction of dialysis complicated by hypotension of −26% (P l= l0.03). During both the run-in and the baseline periods, the incidence of IDH was 35 ± 5 and 35 ± 3%, respectively, with no statistical difference in comparison to Period B. Table 2 shows the number of sessions complicated by IDH (symptomatic is highlighted as a subcategory) and the number of related interventions of any type necessary to recover from the acute event (UF stop, the Trendelenburg manoeuvre, infusion of plasma expanders, saline solution or sodium chloride 4%). The other dialysis-related symptoms (nausea, vomiting, etc.) are shown as well.

It is worth noting that there was a wide difference for overall (31% in HFR versus 23% in HFR-Aeq, respectively) and symptomatic hypotension (5% in HFR and 3% in HFR-Aeq) while the incidence of other intradialytic complications was two times the incidence of IDH. The relative risk reduction was −38 and −33%, respectively, for symptomatic IDH and other symptoms favouring HFR-Aeq.

Intradialytic blood pressure time course

Figure 4 shows the SBP behaviour. The values registered during HFR significantly differed from the HFR-Aeq ones after the first hour of treatment. In Figure 5, the overall data are divided according to the sequence of treatment administered to the patients: the arm AB was treated with HFR first and the arm BA was treated the opposite. Figure 5 confirms that when HFR-Aeq followed HFR (sequence AB, dashed black line), SBP was kept higher throughout the treatment and the difference increased significantly in the last hour. However, during the HFR-Aeq period, blood pressure values were slightly higher at any time measure than correspondent of HFR values and

Table 2. Results about overall and cardiovascular tolerance[a]

All patients (N = l43)	HFR (%)	HFR-Aequilibrium (%)	Wilcoxon, P
Primary end point			
Dialysis complicated by hypotension	31 ± 4	23 ± 3	0.03
Secondary end points			
Symptomatic hypotensions	5 ± 1	3 ± 1	0.04
Intradialytic symptoms	9 ± 1	6 ± 2	0.01
Nurse interventions	22 ± 2	17 ± 3	<0.01

[a]Data are expressed as mean ± SEM.

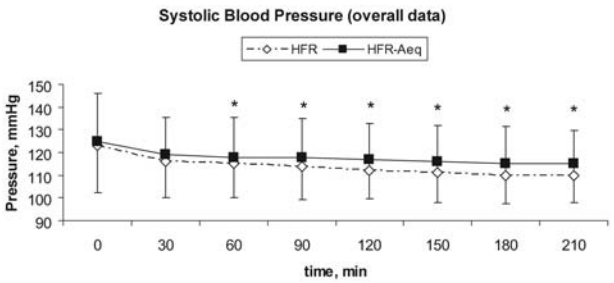

Fig. 4. SBP: overall treatments trends. *P <0.05 HFR-Aeq versus HFR.

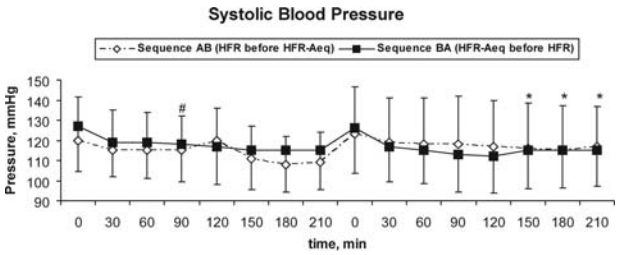

Fig. 5. SBP: longitudinal data divided by sequences (AB, BA). *P <0.05 HFR-Aeq versus HFR (AB) and #P <0.05 HFR-Aeq versus HFR (BA).

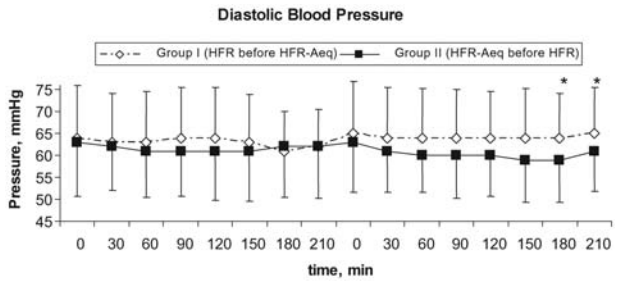

Fig. 6. DBP: longitudinal data divided by sequences (AB, BA). *P <0.05 HFR-Aeq versus HFR (AB).

reached a significant difference after 90 min of treatment (P <0.05). The SBP increase was numerically modest and within the range of normally accepted values.

As for the SBP, the HFR-Aeq was associated with more stable DBP values; the difference between HFR-Aeq and HFR was significant after 2 h and the significant difference was maintained until the end of the treatment. Figure 6 shows the values for the two arms according to dashed and solid black lines, respectively. Differently from the SBP behaviour, the DBP values seemed not to be markedly influenced by the sequence of treatments. When standard HFR was performed first, HFR-Aeq showed significantly higher values only after 3-h treatment, while in the opposite sequence, the difference with HFR was significant after 2-h treatment. In this sequence, the possible carry-over effect seemed to be less evident for the DBP values. Figure 7 shows the MAP behaviour. Consistent to the SBP behaviour, when HFR was performed first, MAP values during HFR-Aeq were

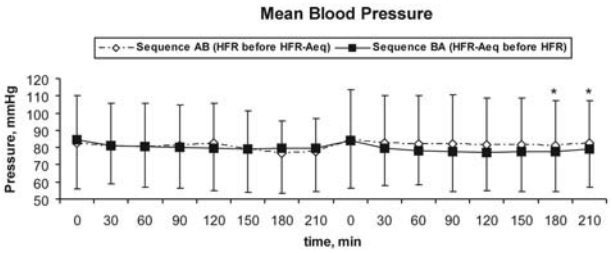

Fig. 7. MAP: longitudinal data divided by sequences (AB, BA). *P <0.05 HFR-Aeq versus HFR (AB) and *P <0.05 HFR-Aeq versus. HFR (BA).

significantly higher in the last part of the treatment. HR during HFR-Aeq did not vary significantly.

Sodium and BW assessment

Table 3 shows the variation of the hydration status during the study. Both the pre- and post-dialysis plasma sodium concentrations did not vary significantly between HFR and HFR-Aeq; the amount of sodium removed during the two treatments was also similar, although numerically slightly higher during HFR-Aeq treatments. The sorbent cartridge, peculiarity of the HFR treatment, does not adsorb sodium, potassium, calcium, bicarbonate and urea [17].

Both the intradialytic WL and the dry body weight (BW) did not vary significantly during the whole trial follow-up.

The Profiler kinetic model showed to be effectively able to drive the patient's post-dialysis natraemia significantly close to the physician's initial set.

The dialysis dose was adequate and stable during the whole study, as confirmed by the equilibrated *kt/V* calculation.

As far as the anti-hypertensive therapy is concerned, most of the patients were on a multiple drugs treatment. The most prescribed drugs were the adrenergic receptors antagonists (25%), followed by diuretics (22%), angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists (19% each). Less frequent were the use of calcium channel blockers (12%) and alpha-2 antagonists (4%). None of the above-mentioned drug changed significantly during the study follow-up.

Table 3. Hydration status evaluation (mean ± SEM)[a]

	HFR	HFR-Aequilibrium	Wilcoxon, P
Sodium balance			
Serum pre-D Na^+, mmol/L	138.6 ± 0.5	139.4 ± 0.5	0.55
Serum post-D Na^+, mmol/L	139.2 ± 0.2	139.7 ± 0.2	0.26
Post-D Na^+ set, mmol/L	not set	139.0 ± 0.1	
ΔNa, mmol	319 ± 19	347 ± 19	0.24
Dialysis dose			
e_*kt/V*	1.27 ± 0.02	1.31 ± 0.03	0.27
Fluid balance			
BW, kg	68.0 ± 2.0	68.5 ± 2.0	0.86
WL, kg	2.4 ± 0.1	2.5 ± 0.1	0.78
Blood crasia			
Hb, g/dL	10.9 ± 0.3	11.0 ± 0.3	0.96
ESA, IU/week	6866 ± 1040	6500 ± 1045	0.81
Albumin, g/dL	3.7 ± 0.06	3.8 ± 0.05	0.96

[a]Pre-D stands for pre-dialysis and post-D stands for post-dialysis.

Post-hoc analysis on treatment tolerance

Given the wide SD of the number of dialysis complicated by hypotensions, we investigated the hypothesis of an association of HFR-Aeq benefit and the severity of haemodynamic derangement. According to the distribution of sessions complicated by IDH, patients were grouped by quartiles (calculated on the HFR period) and the same analysis on overall IDH incidence was performed.

The cumulative distribution data show a lack of difference for stable patients (Quartiles I and II). The better cardiovascular stability of HFR-Aeq was seen in the VI quartile, which includes highly critical patients (see Table 4).

Discussion

Most of the patients nowadays on a maintenance dialysis programme are characterized by left ventricular hypertrophy and other cardiovascular abnormalities; critical patients are prone to a higher degree of sensitivity towards the blood volume changes during the treatment. They seem to be unable to both increase the peripheral vascular resistance and to vary the venous unstressed volume in case of hypotension [17–23].

Avoiding IDH is of paramount importance because repeated episodes of cardiac hypoperfusion may lead to increased cardiac fibrosis and stiffness [4]. Hung *et al.* [5] demonstrated that patients with symptomatic hypotension have significantly higher serum levels for creatine kinase isoenzyme MB and cardiac troponin I even 44 h after the end of the treatment. Shoji *et al.* [6] found a 2-year mortality rate ∼8% higher for the patients showing intradialytic blood pressure values <110/59 mmHg and Tislér *et al.* [7] observed that patients undergoing frequent IDH have a 25% reduction in life expectancy in comparison with hypotension-resistant patients.

The primary analysis of this study on the population as a whole showed a −40% highly significant relative risk reduction of IDH during HFR-Aeq in comparison with standard HFR. Furthermore, when the patients were grouped by quartiles of IDH incidence, HFR-Aeq showed its maximum effect on the most critical patients (IV quartile, 12 patients), on which a 50% significant decrease of sessions complicated by IDH (P <0.01) was observed.

The effect of reducing IDH is much more relevant when standard HFR was performed first; Figure 6 suggests a carry-over effect driven by the HFR-Aequilibrium treatment.

As far as the safety is concerned, in clinically stable patients, the amount of sodium and water to be removed during dialysis has to be equal to the amount of sodium and water accumulated during the interdialytic period to ensure a zero net balance, in order to avoid the risk of IDH on one side and of overhydration with hypertension and pulmonary oedema on the other. However, in order to

Table 4. Comparison of treatment tolerance in the two treatments according to the patients severity identified by quartiles of the distribution of dialysis complicated by hypotension in HFR (mean ± SEM)

	0–25%		25–50%		50–75%		75–100%	
	HFR	HFR-Aeq	HFR	HFR-Aeq	HFR	HFR-Aeq	HFR	HFR-Aeq
No.	11		11		10		11	
IDH%	4 ± 1	5 ± 1	14 ± 1	22 ± 3	36 ± 2	24 ± 3	71 ± 3	35 ± 3
Wilcoxon, P	0.80		0.75		0.06		<0.001	

avoid the hypotension occurrence, the patients with IDH are treated in everyday clinical practice with standard HD on higher and constant dialysate sodium concentration [24]. The major drawback of this approach is the possible lower than needed sodium removal, which can lead to hypertension and pulmonary oedema, because the intradialytic sodium balance is not taken into consideration [25, 26].

In the last 20 years, the mathematical modelling of sodium kinetics has been developed and validated in many studies [10–14]. Even if nowadays there are technological premises to simplify the daily use of profiling, their routine application is still scarce.

Over the years, the complexity of mathematical model has been progressively tuned down and the setting requires just a few minutes at the beginning of every treatment. The core concept was to start the treatment with a high dialysate sodium concentration to curb the drop in plasma osmolarity and then to reduce it towards the end to avoid thirst, the consequent large interdialytic BW increase and the risk of acute and/or chronic congestive heart failure [27] by achieving a zero sodium mass balance.

During HFR-Aeq period for both arms AB and BA, SBP and DBP were more stable on significantly higher values, during the last treatment hour, but clinically modest and still in the acceptable range of values. Apparently, no additional stress on the cardiovascular system was observed during HFR-Aeq, as suggested by the fact that the HR did not vary significantly.

Moreover, pre- and post-dialysis plasma sodium concentrations were continuously monitored during the entire experimental sessions by using the conductivity as a surrogate. From the run-in to the wash-out period to the end of the trial for both A and B periods, a non-significant increase of plasma sodium concentration from 138.2 ± 0.5 to 139.4 ± 0.5 mmol/L was registered.

As reported above, the peculiar sorbent cartridge of the HFR treatment does not adsorb sodium, potassium, calcium, bicarbonate and urea [16]. This suggests that only convection and diffusion are fully accounted for the electrolytes mass balances, as in standard HD. There were neither statistical nor clinical significant variations of both BW and WL and, consequently, the better cardiovascular stability in HFR-Aeq seemed not to be due to a dialysis-induced hypervolaemia. The anti-hypertensive therapy did not show any significant variation during the study follow-up further, supporting this hypothesis.

In addition to the water and sodium balance, HFR-Aeq has shown to be effective in the reduction of intradialytic symptoms.

The better effect on the cardiovascular tolerance was further supported by the number of interventions made by the nurses during the sessions. A marked reduction of saline infusions, stop UF and premature interruption of the treatment due to IDH was obtained during the profiled period. These data were confirmed by the contingency tables analysis: during HFR-Aeq periods, a more than −30% relative risk reduction of any intervention due to hypotension occurrence was observed. Adding up these positive confirmations, the better clinical tolerance was noted during the standard HFR period for the arm BA patients.

This study has both weaknesses and strengths. One of its strengths is that it is a primary analysis of a randomized control multicentric multinational study, thus the general applicability of the result is very high. Another strength is the crossover study design and the prospective 2-month run-in period before the experimental phase, heavily reducing the interpatient variability. Moreover, the enrolled patients were well dialysed, treated with HFR and with a low level of inflammation. The difficulty of demonstrating the positive effect of any kind of experimental treatment under optimal conditions of the control group is well known. As far as the weaknesses of the study are concerned, we would like to underline that, despite the relative small number of the enrolled patients, the power of this study is mainly dependant on its crossover design, thus as underlined above, dramatically reducing interpatients variability. As far as selecting online HDF as an option for the control treatment, the prominent presence of infusion flow with online HDF would have largely altered the electrolytes and thermal balances. On the other hand, the clinical efficacy of the 'Profiler' in HD had already been demonstrated [15]. Unfortunately, the blood pressure behaviour during 24 h and bioimpedentiometry measures were not collected as well as the evaluation of patient's quality of life.

In conclusion, the application of HFR-Aeq further improved the intradialytic tolerance in comparison with standard HFR and did not induce any risk of sodium and water overload during the whole study follow-up. These positive findings may have an important clinical impact, considering the relevance of hypotension for both patient well-being and life expectancy and for the related increase in workload of the nurses in the daily management of dialysis patients.

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