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Fluid state and blood pressure control in patients treated with long and short haemodialysis

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Abstract

Background. Patients treated at the haemodialysis (HD) centre in Tassin, France have been reported to have superior survival and blood pressure (BP) control. This control has been ascribed to maintenance of an adequate fluid state, antihypertensive drugs being required in $<5\%$ of the patients, although it could not be excluded that a high dose of HD regarding removal of uraemic toxins might also have been of value.

Methods. The aim of the study was to assess the fluid state and BP in normotensive patients on long HD (8 h) in Tassin (group TN) using bioimpedance to measure extracellular volume (ECV), ultrasound for determining the inferior vena cava diameter (IVCD), and 'on-line' monitoring of the change in blood volume (BV), and to compare them with normotensive (group SN) and hypertensive (group SH) patients on short HD (3–5 h) at centres in Sweden. ECV was normalized (ECVn) by arbitrarily setting the median ECV (in % of body weight) in SN patients at 100% for each gender, recalculating the individual values and combining the results for male and female patients in each group.

Results. The dose of HD (Kt/V urea) was higher for TN patients than for Swedish patients who had a similar Kt/V, whether hypertensive or not. SH patients had significantly higher ECVn and IVCD than TN and SN patients. TN and SN patients did not differ significantly regarding ECVn and IVCD before and after HD. However, in a subgroup of eight TN patients, ECVn was below the range of that in SH and SN patients, due to obesity with a high body mass index. Another subgroup of 14 TN patients had a higher ECVn than most of the SN patients and also higher than the median ECVn in the SH group, without any difference in body mass index, but they were nevertheless normotensive. The fall in BV was greater in SN than in TN patients, presumably due to a higher ultrafiltration rate in SN patients. However, SH patients had a smaller change in BV than SN patients, presumably because their state of overhydration facilitated refilling of BV from the interstitial fluid.

Conclusions. Normotension can be achieved independently of the duration and dose (Kt/V urea) of HD, if the control of post-dialysis ECV is adequate. However, this is more difficult to achieve with short than with more prolonged HD during which the ultrafiltration rate is lower, BV changes are smaller and intradialysis symptoms less frequent. The results in the subgroup of patients with high ECVn at Tassin suggest that normotension may also be achieved in patients with fluid overload provided that the dialysis time is long enough to ensure more efficient removal of one or more vasoactive factors that cause or contribute to hypertension.

Key words: blood volume; chronic renal failure; extracellular volume, fluid state; haemodialysis; hypertension

Introduction

Since the early days of chronic haemodialysis (HD), it has been known that normal blood pressure (BP) can be achieved by maintaining normohydration in patients treated for 12–14 h twice a week [1,2] or for 8 h three times a week [3]. Subsequently, more efficient dialysers were developed and shorter dialysis times became increasingly common. However, sodium retention, hypertension and long-term cardiac complications were reported to be increased with short dialysis time [4,5].

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BP control, mainly induced by antihypertensive drugs (AHD), appears to be far from adequate, although new and more effective agents are now available [6]. On the other hand, results from the dialysis centre in Tassin, France, where long (8 h) HD is still in use, show that excellent BP control can be obtained in 95% of patients without AHD [7]. Charra *et al.* [8] have proposed that these results are due to the maintenance of correct dry weight by removing the extracellular fluid excess more efficiently and restricting dietary salt intake. However, no direct measurements of fluid state were performed, and it can therefore not be excluded that a high dose of HD for removal of uraemic toxins might also have played a role.

In the present study, we assessed the extracellular volume (ECV) by multiple-frequency bioimpedance spectroscopy [9] and recorded the inferior vena cava diameter (IVCD) by ultrasound [10], in normotensive patients treated in Tassin with long HD (8 h) and in normotensive and hypertensive Swedish patients treated with short HD (3–5 h). The aim of the study was to explore whether control of ECV is associated with normotension and whether there was any difference in this respect between Tassin and Swedish patients, who differed markedly regarding HD time. We also recorded changes in blood volume (BV) by continuous monitoring of haematocrit 'on line' [11] during HD with the aim of examining how these changes were related to fluid state and HD time.

Subjects and methods

Patients

One hundred and twelve patients volunteered to participate in this study. The inclusion criteria were age between 18 and 80 years, dialysis therapy for >4 months and absence of active malignant, infectious or psychiatric disease. At the HD centre in Tassin, only patients on long HD were included in the study. For practical reasons, patients treated at night and with home HD were not studied. Six patients with serological evidence of hepatitis were also excluded and, of the remaining 74 patients, 59 (43 male and 16 female) were selected randomly to participate in the study (group TN). All were normotensive and were not being treated with AHD at the time of the study. Fifty two of these patients were treated with AHD before dry weight was achieved with HD treatment, and four were never treated with AHD. Data regarding previous exposure to AHD were not available for three of these patients. The group of TN patients was compared with 53 (34 male and 19 female) Swedish patients recruited from three HD centres where treatment times were considerably shorter. All patients from two HD centres who met the inclusion criteria were included in this group. The remaining patients in this group were recruited from the morning shift in a third centre. The Swedish patients with pre-dialysis mean arterial pressure (MAP) >110 mmHg (mean of last eight HD before the study) and/or needing AHD were considered as hypertensive (group SH). This group consisted of 28 patients (16 male and 12 female); 20 of them were treated with AHD: 11 with one, eight with two and one with three AHD (ACE inhibitors, α-blockers, β-blockers, Ca-channel blockers).

The Swedish normotensive group consisted of 18 males and 7 females (group SN). Eight of them had previously been treated with AHD for high BP and data for four patients were missing. The evaluation of dry weight was based on clinical experience, taking various signs and symptoms such as interdialytic weight gain, oedema, congestion, hypertension, intra- and post-dialysis hypotension and cramps into consideration in the Swedish HD centres. In Tassin, the definition of dry weight was based on the normal pre-dialysis BP with no AHD [8]. Ten patients (17%) in the TN group, 23 patients (92%) in the SN group and 25 patients (89%) in the SH group were treated with erythropoietin (Epo). The median weekly doses were similar in the three groups.

All vasoactive drugs were discontinued 48 h before the study to minimize any effects of these drugs on the measurements of IVCD and BV changes. Although a residual antihypertensive effect could not be excluded, we considered it unethical to withdraw AHD for a longer period.

The study was approved by the Ethics Committee of Karolinska Institute at Huddinge University Hospital.

Haemodialysis

The HD session in Tassin lasted 7–8 h, three times per week. One patient was treated with 12 h HD twice weekly. Blood flow was 200–220 ml/min, dialysate flow was 500 ml/min. The dialysate sodium and acetate concentrations were 138 mmol/l and 35 mmol/l, respectively. Thirty patients were treated with plate dialysers having cuprophan membranes (Kiil-Meltec Ltd, UK, H10-10&Discap, Hospal SA, Lyon, France and Alfa 500, Gambro AB, Lund, Sweden). The other patients were treated with different types of capillary dialysers having cuprophan (Calisto, Fresenius-SMAD, L'Abresle, France and Hospal Discap, Hospal SA, Lyon, France) or haemophan (Fidelio, Fresenius-SMAD, L'Abresle, France) membranes.

The Swedish patients were treated with HD lasting 3–4.5 h, three times per week. In three cases, HD was performed twice weekly (4.5–5 h). Blood flow was 250–300 ml/min, dialysate flow 500 ml/min. The dialysate sodium and bicarbonate concentrations were 140–143 mmol/l and 34 mmol/l, respectively. Several types of dialysers were used: AC 130, 170 (Baxter, Deerfield, Il, USA), F 5, F 8 (Fresenius AG, Oberursel, Germany), GFS+20, GFS+12, GEF15 and GEF18 (Gambro AB, Lund, Sweden). In all HD machines used, ultrafiltration (UF) was controlled volumetrically.

Bioimpedance

ECV was measured in all patients before and 20 min after HD by multiple-frequency bioimpedance [9]. Four electrodes were placed on the wrist and ankle on the non-fistula side, and a multiple-frequency bioimpedance XITRON 4000 B device (XITRON TECH, San Diego, CA, USA) was used. Fifty logarithmic space frequencies (5–500 kHz) were applied. A software program designed by the producer was used to compute the ECV. The ECV data are presented as the percentage of post-dialysis body weight. The measurements were performed by the same investigator and with the same device throughout the whole study. The coefficient of variation of the method for intra-observer error was 2.5%.

Ultrasound of IVCD

IVCD was visualized in expiration in subcostal orthogonal projection by two-D and measured by M-mode

echocardiography as previously described [10]. The IVCD data were normalized by post-dialysis body surface area (BSA). All patients remained supine for 20 min before the pre-dialysis measurements of ECV and IVCD. Post-dialysis IVCD measurements were made 40 min after the end of the procedure. The measurements were performed in 20 patients in group TN, 18 patients in group SN, and 17 patients in group SH. Two different investigators made the measurements, one in Tassin and one in Sweden, following the same protocol.

Monitoring change in BV

The changes in BV (in %) during HD were monitored 'on-line' by spectrophotometry and light scattering, using a CRIT-LINE instrument (In-Line Diagnostic, Riverdale, UT) [11]. The monitoring was performed by the same investigator throughout the whole study.

Kt/V

Blood samples for determination of urea were taken pre- and immediately post-dialysis. Using the second generation formula introduced by Daugirdas [12], Kt/V for urea was calculated and the results were compared between the groups.

Statistics

The results are presented as mean $\pm$ standard deviation and median and quantiles. Significant differences among the groups were determined using ANOVA or the Kruskal–Wallis test. Paired comparison between the groups were made by using the Fisher PLSD test. The relationships between various parameters were evaluated, using analysis of linear regression. Values of $P<0.05$ were considered significant. The calculations were made by use of the StatView 4.5 pack (SAS Institute, USA).

Results

The characteristics of the patients are given in Table 1. TN female patients were on HD significantly longer than SH female patients, but no such difference was found among male patients. TN and SN male patients were significantly older than SH male patients. TN male and female patients and SN female patients were shorter in height than corresponding patients in group SH. TN male patients were also significantly shorter than male patients in group SN. There was no significant difference between the groups in pre- and post-HD body weight and body mass index (BMI). Pre- and post-HD BP (systolic and diastolic, the average BP in the last eight HD) in groups TN and SN were very similar, but significantly lower than those in group SH. The UF rate and reduction in body weight (as a percentage) were significantly lower in group TN than in groups SN and SH (Table 2). No significant difference in haematocrit was found between the groups, but Kt/V was significantly higher in group TN than in groups SN and SH (Table 2). Kt/V in the last two groups was virtually identical (Table 2). As shown in Table 3, the ECV in TN male and female patients did not differ significantly from the corresponding ECV values in SN patients before and after HD, but in both TN and SN patients it was lower than the ECV in SH patients.

Since male and female patients were comparable with regard to differences between the groups, we 'normalized' the data by setting the median post-dialysis ECV (as a percentage of body weight) in SN patients for each gender at 100%, recalculating the individual values as a percentage of the SN post-dialysis value ('normalized' ECV, ECVn) and combining the results in male and female patients in each group. The results are presented in Figure 1. ECVn was significantly higher in the SH group than in the other two groups. However, there was a large inter-individual variation, with considerable overlap between the groups. The largest variation was observed in the TN group, in which there was a subgroup of eight patients with ECVn $<80\%$, i.e. below the range of the other two groups. BMI in this subgroup was much higher than in the rest of the Tassin patients (30.8 ± 3.7

Table 1. Comparison of time on HD, age, height, body weight, body mass index (BMI) and BP (average from the last eight dialyses) in group TN, group SN and group SH patients

	Group TN		Group SN		Group SH	
	Male ($n=43$)	Female ($n=16$)	Male ($n=18$)	Female ($n=7$)	Male ($n=16$)	Female ($n=12$)
Time on HD (months)						
Median	43	58	49	22	27	18
Range	4–321	4–360	4–131	4–72	4–193	4–84
Age (years)	65 ± 11^{b}	64 ± 12	71 ± 8^{b}	65 ± 17	55 ± 13	61 ± 11
Height (cm)	$168\pm8^{a,d}$	157 ± 8^{c}	173 ± 6	158 ± 7^{c}	177 ± 7	164 ± 5
Body weight pre-HD (kg)	75.0 ± 14.5	57.5 ± 14.0	78.5 ± 14.2	60.6 ± 11.7	77.3 ± 10.0	58.8 ± 10.7
Body weight post-HD (kg)	73.3 ± 14.4	56.3 ± 13.8	76.2 ± 14.0	58.3 ± 10.9	75.1 ± 9.4	56.8 ± 10.6
BMI post-HD	25.8 ± 4.0	23.1 ± 6.0	25.4 ± 4.5	23.3 ± 3.4	23.8 ± 2.8	21.2 ± 4.0
Systolic BP (mmHg) pre-HD	137 ± 15^{a}	128 ± 22^{a}	138 ± 19^{a}	127 ± 31^{b}	179 ± 24	171 ± 19
Diastolic BP (mmHg) pre-HD	74 ± 10^{a}	69 ± 13^{a}	72 ± 7^{a}	68 ± 13^{b}	95 ± 18	90 ± 11
Systolic BP (mmHg) post-HD	119 ± 19^{a}	109 ± 26^{a}	123 ± 22^{b}	124 ± 36^{c}	155 ± 32	153 ± 20
Diastolic BP (mmHg) post-HD	67 ± 10^{a}	63 ± 9^{a}	68 ± 10^{a}	67 ± 16^{c}	89 ± 16	84 ± 12

[a]$P<0.0005$ *vs* group SH; [b]$P<0.005$ *vs* group SH; [c]$P<0.05$ *vs* group SH; [d]$P<0.05$ *vs* group SN.

Table 2. Change in body weight (%ΔBW), HD time, UF rate, haematocrit and Kt/V in group TN, group SN and group SH patients

	Group TN ($n=59$)	Group SN ($n=25$)	Group SH ($n=28$)
ΔBW (%)	2.2±1.9	3.2±1.5[a]	3.2±2.0[a]
HD time (h)[c]	7.8±0.9	4.0±0.6[b]	3.9±0.4[b]
UF rate (ml/h/kg)	5.4±2.5	10.3±4.7[b]	10.2±4.4[b]
Haematocrit (before HD)	33.2±5.0	33.8±4.9	35.1±4.0
Kt/V	1.93±0.43	1.55±0.43[b]	1.58±0.34[b]

[a]$P<0.05$ *vs* group TN; [b]$P<0.0005$ *vs* group TN.
[c]HD time refers to patients treated three times weekly.

Table 3. Extracellular volume as a percentage of the post-dialysis body weight (%ECV) in the male and female patients in groups TN, SN and SH before and after HD

	%ECV before HD	%ECV after HD
Males		
Group TN ($n=43$)	27.34±3.17[b]	23.88±2.86[a]
Group SN ($n=18$)	27.48±2.29[d]	24.22±1.54[c]
Group SH ($n=16$)	29.39±2.51	26.03±2.78
Females		
Group TN ($n=16$)	25.36±3.92[c]	22.20±3.52[b]
Group SN ($n=7$)	24.62±2.21[c]	21.48±1.25[c]
Group SH ($n=12$)	28.05±2.86	24.61±2.21

[a]$P<0.01$ *vs* group SH patients; [b]$P<0.025$ *vs* group SH patients; [c]$P<0.05$ *vs* group SH patients; [d]$P=0.056$ (NS) *vs* group SH patients.

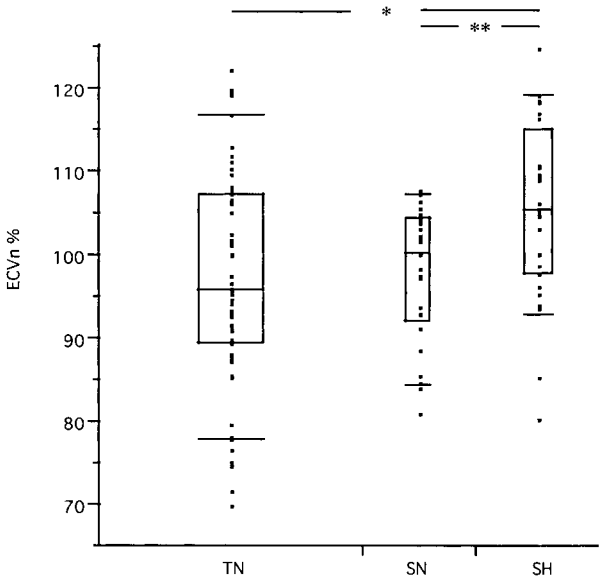

Fig. 1. Normalized extracellular volume (ECVn) as a percentage of post-dialysis median ECV (as a percentage of post-dialysis body weight) in group TN ($n=58$), group SN ($n=25$) and group SH ($n=28$). The individual, median, and 10, 25, 75 and 90% quantile values are given. *$P=0.005$ *vs* groups TN; **$P=0.0005$ *vs* groups SN.

vs 24.1±4.2, $P<0.001$), indicating that these patients were obese. This may explain why their ECVn values were low, considering that actual post-HD body weight was the basis of reference for ECV. On the other hand, the 14 patients in the highest 25% quantile in the TN group had higher ECVn than most of the SN patients and also higher than the median ECVn in the SH group, whereas BP was not higher than in the rest of the patients. However, BMI in these patients (23.4±4.4) did not differ from the average, thus precluding that the difference in relative fat mass might explain why these TN patients had elevated ECVn post-dialysis. Therefore, one may assume that this subgroup of patients was normotensive, in spite of an extracellular fluid overload.

There was no significant difference in ECV and BP between the hypertensive patients who were treated and those not treated with AHD.

IVCD

Both pre- and post-dialysis IVCD (Table 4) in TN patients ($n=20$) were similar to those in SN patients ($n=18$). The pre-dialysis IVCD in the TN and SN groups was within the normal reference range (8.0–11.5 mm/m^2 [10]), but slightly below it after HD. IVCD in group SH ($n=17$) was above the normal reference range before HD and within it after HD.

There was no correlation between the number of months on dialysis and ECV or IVCD in the material or in any of the groups.

BV

The largest reduction in BV (Figure 2) was observed in group SN ($n=23$), who differed significantly from group TN ($n=18$) and group SH ($n=17$). The reductions in BV in groups TN and SH were similar. The reduction in BV correlated significantly with the UF rate ($r=0.59$, $P=0.0001$), change in body weight ($r=0.57$, $P=0.0001$) and change in ECV ($r=0.30$, $P<0.025$) in the entire study population.

Table 4. Inferior vena cava diameter (IVCD) in mm/m^2 post-dialysis body surface area in groups TN, SN and SH before and after HD

	IVCD before HD	IVCD after HD
Group TN ($n=20$)	9.06±2.42[a]	7.22±2.26[c]
Group SN ($n=18$)	10.27±1.78[b]	7.51±1.87[c]
Group SH ($n=17$)	12.31±1.96	9.18±2.90

[a]$P<0.0001$ *vs* group SH; [b]$P<0.005$ *vs* group SH; [c]$P<0.05$ *vs* group SH.

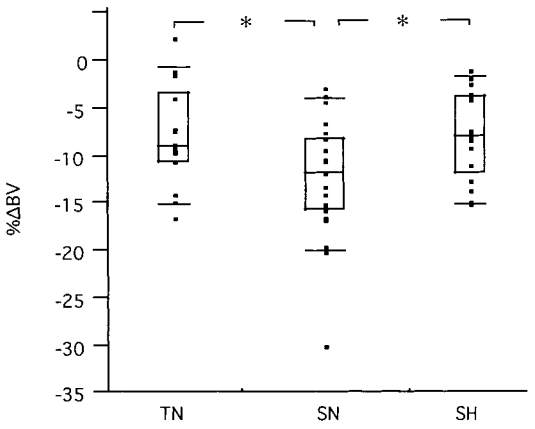

Fig. 2. Percentage changes in blood volume (%ΔBV) in group TN ($n=18$), group SN ($n=23$) and group SH ($n=17$). The individual, median, and 10, 25, 75 and 90% quantile values are given. *$P=0.015$ *vs* groups TN and SH.

Discussion

In the present study, we determined the relationship between fluid state and BP in three different groups of HD patients. ECV was chosen to assess the patient's fluid state because it is considered to be a major determinant of BP in chronic renal failure (CRF) [13] and can be measured non-invasively using multiple-frequency bioimpedance. Previous work has demonstrated the utility of multiple-frequency bioimpedance for measurement of ECV in healthy individuals [9], patients with sepsis [14] and patients on HD [15,16]. In this study, the measurements were made by the same investigator and with the same device in all patients, thus excluding methodological differences between the participating centers.

At the HD centre in Tassin, most patients have been dialysed three times per week for 8 h, using 1 m^2 Kiil dialysers or dialysers with larger surface areas, i.e. a treatment schedule which provides a higher dose of HD for removal of small and middle molecules than is achieved with short HD lasting for 3–5 h. The long HD time also facilitates asymptomatic fluid removal by UF. The Tassin patients are reported to have superior BP control, with only 3–5% of the patients requiring AHD therapy [7] which was, in turn, thought to be due to more adequate control of post-dialysis extracellular fluid volume [8].

In the present study, we compared Swedish normotensive patients without AHD, who had been treated for an average 4 h, with normotensive patients from Tassin who were treated for 8 h, and we found no significant difference in BP and ECV between the groups as a whole. Thus, it appears that short HD *per se* does not preclude achievement of normotension to the same extent as long HD, provided that the fluid state is well controlled. Hypertensive patients, on the other hand, had higher ECV both before and after HD than the normotensive groups, which is in agreement with earlier findings that extracellular overhydration is an important factor in the pathogenesis of dialysis-related hypertension [13]. However, there is a relatively large overlap of ECVn values between the groups and also an overlap of values between the normotensive and hypertensive patients. This variation may be explained to some extent by a variation in fat among the patients, i.e. the same factor that accounts for the difference in the percentage ECV between male and female patients. In fact, a subgroup of eight Tassin patients had extremely low ECVn, which could be explained by these patients being markedly obese, with a mean BMI of 30.1.

Moreover, it is conceivable that individual endocrine, neurogenic and metabolic [18] factors may influence BP independently of ECV. It is noticeable that no less than 25% of the Tassin patients had elevated post-dialysis ECVn in the upper range of that in the Swedish hypertensive patients in the presence of a normal BMI, i.e. they appeared to be fluid-overloaded but nevertheless normotensive. An explanation might be that, in the Tassin patients, there was more efficient removal by long dialysis of one or more vasoactive compounds, which act in concert with fluid overload to maintain hypertension in patients dialysed less efficiently. Preliminary data from a prospective, randomized study comparing long and short HD also suggest that an increase in the dose of dialysis by prolonging the dialysis time can lower BP, independently of changes in body weight [17].

We also measured IVCD, since it has been thought to reflect the fluid state and, particularly, circulating BV in HD patients [10]. The data confirm earlier results demonstrating that IVCD is significantly higher in hypertensive than in normotensive patients [19], thus further supporting the role of hypervolaemia in the development of dialysis-related hypertension. There was no difference between the normotensive Swedish and Tassin patients with regard to IVCD, which corroborates the conclusions drawn from the bioimpedance results that their hydration states were, on average, similar.

When comparing the Tassin and Swedish patients, it should be noted that the composition of the dialysis fluid was different both with regard to sodium concentration and buffer source and that these differences may be relevant to the results reported. The lower sodium concentration at Tassin may be one reason why this group of patients had less marked interdialytic fluid intake (less thirst), as reflected by lower weight loss during HD. Hence, less demand for UF may have facilitated adequate control of ECV at the end of HD. Nevertheless, post-dialysis ECV was not different between the Swedish normotensive and Tassin patients, and BP was similar both before and after HD. The results suggest that achievement of normohydration post-dialysis is required for adequate BP control, and they agree with previous studies [20] showing that an increase in body weight (ECV) in the interdialytical period has little, if any, influence on BP.

The presence of acetate in the dialysis fluid is another confounding factor which might have influenced the results, since acetate is an established peripheral vasod-

ilator [21]. However, it is inconceivable that acetate contributed to better BP control in the Tassin compared with the Swedish patients, considering that acetate is rapidly metabolized post-dialysis and could not have a prolonged effect during the interdialytical period.

The proportion of patients treated with Epo was much higher in the Swedish groups than at Tassin but, despite this difference, the mean haematocrits were similar. Epo treatment is associated with hypertension [22] and it cannot be excluded that Epo may contribute to the higher prevalence of hypertension in Swedish centres than in Tassin. However, the percentages of patients on Epo treatment were similar in the Swedish normotensive and hypertensive groups, implying that Epo cannot explain the difference in BP between these groups.

We observed that the fall in blood volume (BV) was larger in the Swedish normotensive patients than in the Swedish hypertensive patients and the Tassin normotensive patients. The smaller reduction in BV in the Swedish hypertensive patients than in the normotensive patients, despite similar rates of UF and UF volume removed, indicates that the refilling of BV from the interstitial space was more rapid in the hypertensive patients. This was presumably a consequence of fluid overload, which has been demonstrated to facilitate refilling in previous studies [23].

In the Tassin patients, on the other hand, the change in BV was much smaller than in the normotensive Swedish patients, presumably because the UF rate was much slower in the Tassin patients, so that less rapid refilling was required to counteract UF-induced changes in BV.

A previous report [24] has suggested that intradialytic changes in BV reflect the patient's fluid state during HD and, specifically, that intradialytic changes in BV are larger in patients who are closer to normohydration than are overhydrated patients. While a greater BV reduction in the normotensive than in the hypertensive (overhydrated) Swedish patients is consistent with this hypothesis, the smaller intradialytic change in BV in the Tassin than in the Swedish normotensive patients, despite a similar state of hydration, conflicts with it. Therefore, changes in BV during HD cannot be used to evaluate the fluid state, without taking the UF rate into consideration [25,26].

In Swedish centres from which the study population was recruited, the prevalence of hypertension is considerably higher (20–50%) than that reported in Tassin patients (<5%). The main reason for this may be that the removal of fluid by UF is hampered by intradialytic complications, such as hypotension related to an excessive fall in BV and to muscle cramps.

In conclusion, our results suggest that normotension in HD patients may be achieved independently of the duration and dose (Kt/V urea) of HD, if the control of post-dialysis ECV is adequate. However, this is more difficult to achieve with short dialysis than with more prolonged dialysis, during which the UF rate is lower, the BV change smaller and intradialytic symptoms less frequent. The results in the subgroup of patients with high ECVn at Tassin suggest that normotension may also be achieved in patients with fluid overload, provided that the dialysis time is long enough to ensure more efficient removal of one or more vasoactive factors that cause or contribute to hypertension.

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