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# Sodium balance-neutral sodium profiling does not improve dialysis tolerance

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## Summary

*Background:* Modern haemodialysis monitors offer computerised ultrafiltration and sodium concentration profiles which promise better dialysis tolerance. This presumption was tested in chronic haemodialysis patients.

*Methods:* Using Fresenius MC 4008S monitors a group of nine patients were dialysed with a given ultrafiltration profile comparing sessions with decreasing sodium concentration (145 to 133 mmol/L) to sessions with constant sodium concentration (138 mmol/L) in random order. The built-in blood volume monitor recorded changes in haematocrit and blood volume during each dialysis. The analyses included dialytic weight loss, interdialytic weight gain and adverse symptoms (hypotensive episodes and muscle cramps).

*Results:* 321 dialysis sessions, 160 with and 161 without sodium profile, were available for analysis. No significant differences could be detected regarding changes in haematocrit, blood volume and weight in relation to sodium profiling. No significant difference in the incidence of hypotension or muscle cramping was observed with 55 symptomatic dialyses of 160 with sodium profile, compared to 52 symptomatic dialyses of 161 without sodium profile. Interdialytic weight gain and consequent weight loss during dialysis was higher in symptomatic dialyses both with sodium profile or without sodium profile. The same was true of increase in haematocrit and decrease in blood volume, which were greater for symptomatic versus symptom-free dialyses irrespective of sodium profiling.

*Conclusions:* Sodium balance-neutral sodium profiling failed to improve dialysis tolerance in a group of stable chronic haemodialysis patients. This may be explained by the fact that vascular refilling as deduced from changes in haematocrit was uninfluenced by sodium profiling.

*Key words: blood volume monitoring; dialysis hypotension; dialysis tolerance; muscle cramps; sodium balance neutral Na concentration profile; ultrafiltration profile*

## Introduction

Dialysis tolerance is adversely affected by episodes of hypotension, muscle cramps and other symptoms, which vary in frequency between patients and also between dialysis sessions in the same individuum. The main cause of dialysis hypotension and muscle cramps is rapid ultrafiltration with inadequate vascular refilling from the interstitial space, leading to cardiovascular instability [1–4]. Another factor predisposing to hypotension and muscle cramps is decreasing plasma osmolality, due either to removal of urea or more probably to low sodium concentration in the dialysis solution [5]. Increasing the dialysis sodium concentration has long been known to decrease adverse symptoms during dialysis [6]. However, regular use of a high sodium dialysate stimulates thirst and leads to overhydration and hypertension [7–10]. Since high ultrafiltration rates and decreasing osmolality appear to be the two main factors responsible for hypotension and muscle cramps, it seemed reasonable to combine a high ultrafiltration rate with a high dialysate sodium concentration early in the dialysis session, followed by low ultrafiltration rates with a lower dialysate sodium concentration late in the dialysis session, thus counteracting the adverse effects of a high ultrafiltration rate with a high dialysate sodium concentration and vice versa [6, 7, 9]. Further, it was expected that a decreasing sodium concentration profile would improve vascular refilling by smoothing the decreasing plasma osmolality curve resulting from urea removal during dialysis. In a cross-over study of 10 patients, Movilli et al. [11] were in fact able to show a smaller decrease in blood volume for a haemodialysis session with a decreasing sodium concentration profile compared to a session with constant dialysate

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sodium, but ensuring an equal ultrafiltration volume and sodium removal for both types of session. In a similar study Coli et al. [12] reported better cardiovascular stability with an individually computed sodium concentration profile in 12 relatively hypotensive patients.

The aim of the present study was to test the hypothesis that combining a continuously or stepwise decreasing ultrafiltration rate with a similarly decreasing sodium concentration profile would improve vascular refilling and thereby dialysis tolerance. Fresenius haemodialysis machines with built-in blood volume monitor, which according to the manufacturer were programmed to perform sodium balance neutral dialysis sessions with or without sodium profiling [13], were used in 9 stable patients during a study period of three months. Each dialysis session was randomised to be applied with the appropriate sodium concentration profile as compared to constant sodium, to allow patients to serve as their own control regarding symptoms such as hypotension, muscle cramps and changes in blood volume.

## Methods

Fresenius MC 4008S haemodialysis monitors with volume-controlled ultrafiltration were used. These monitors make it possible to apply automatically controlled ultrafiltration and sodium concentration profiles that have been suggested as improving dialysis tolerance [13]. As an additional feature, they have a blood volume monitor which continuously determines the haematocrit by measuring the blood density ultrasonographically in a cuvette within the arterial line. Assuming a constant red blood cell volume, changes in haematocrit will reflect inversely proportional changes in blood volume expressed digitally as percent changes from initial blood volume at the start of a dialysis session. The three different profiles applied are shown schematically in figure 1. In contrast to standard ultrafiltration, which denotes a constant ultrafiltration rate to achieve the desired dry weight at the end of the dialysis session, profiles 1–3 apply decreasing ultrafiltration rates which may or may not be combined with their respective sodium concentration profile.

Profile 1 denotes a linearly decreasing ultrafiltration rate which starts at 1.3 times the rate that would be needed at constant ultrafiltration, and which may be combined with a linearly decreasing sodium concentration. Profile 2 combines a stepwise reduction of the ultrafiltration rate by half in the middle of the dialysis session with or without a stepwise reduction in the sodium concentration. Profile 3 applies a 60% higher than standard ultrafiltration rate during the first third and a 60% lower than standard ultrafiltration rate during the last third of the dialysis session.

For all studies, a standard sodium concentration of 138 mmol/L was chosen. For dialyses with sodium profile, the initial sodium concentration was always set at 145 mmol/L (Fresenius suggests not exceeding 150 mmol/L), which results in the sodium concentration falling to 133 mmol/L at the end of dialysis. It should be stressed that the sodium profile allows sodium balance-neutral ultrafiltration. In other words, the total amounts of water and of sodium removed do not differ when comparing dialysis with equal ultrafiltration volume with or without sodium profile.

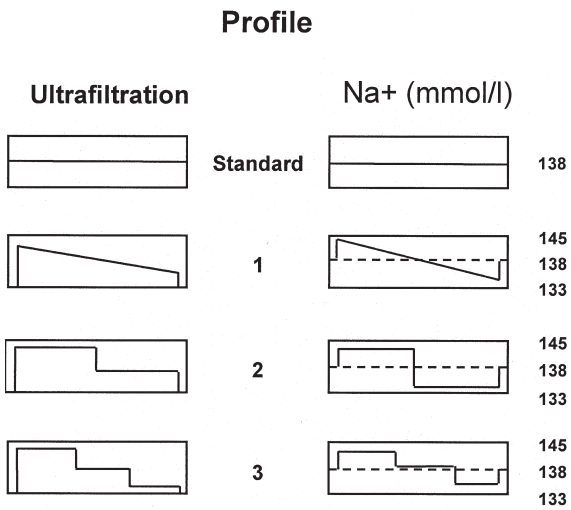



**Figure 1**

The ultrafiltration and Na concentration profiles applied: profile 1 with linearly decreasing ultrafiltration rate and Na concentration, Profiles 2 and 3 with decreasing ultrafiltration rate and Na concentration in 2 or 3 steps respectively.

Dialysate for all patients contained sodium at 138 mmol/L (or varying depending on the profile chosen), potassium 1–3 mmol/L as needed for hyperkalaemia, calcium 1.5 mmol/L, magnesium 0.5 mmol/L, bicarbonate 32 mmol/L, acetate 3 mmol/L and glucose 11 mmol/L. Dialysate flow was set at 500 ml/min.

Informed consent was obtained from the 9 patients chosen for the study, who frequently exhibited symptoms of dialysis intolerance such as hypotension and muscle cramps. Otherwise, they were stable patients who had been established on maintenance dialysis 0.5 to 5.5 years earlier. The cause of end-stage renal disease was analgesic nephropathy in an 80-year-old male and a 67-year-old female, glomerulonephritis in a 55-year-old female and a 33-year-old male, undetermined nephropathy also in a 33-year-old male and diabetic nephropathy in 4 patients. The latter were all obese type II diabetics of whom only the 57-year-old female required insulin, whereas 2 males aged 73 and 65 were on oral sulfonylurea and a third male aged 54 had ceased to need antidiabetic drugs after starting haemodialysis. At dry weight, all the diabetic patients had normal blood pressure without antihypertensive drugs and did not suffer from orthostatic hypotension off dialysis. Only 2 patients were receiving cardiovascular medication: the 80-year-old male with analgesic nephropathy had been started on verapamil 240 mg daily 5 months before the study because of episodes of atrial fibrillation which never recurred thereafter. The 33-year-old male with undetermined nephropathy was on atenolol 50 mg after each dialysis for mild hypertension. All had well-functioning AV fistulae, allowing two-needle single pass dialysis with blood flows of 250 to 300 ml/min.

Ultrafiltration profile 1 was applied to 7 patients and profiles 2 and 3 to one each. Over a three-month study period each patient was always dialysed with the same ultrafiltration profile, which was combined in randomised order either with or without the respective sodium profile by drawing a lot before each dialysis session. Thus, each patient served as his or her own control. Dialysis time was 3 or 3½ hours per 3 times weekly session. Dialysers were either Hiflux Fresenius F 80 polysulfone or Hospal Filtral 16 polyacrilonitrile with Renatron re-use. $^{KT}/_{V}$ exceeded 3.3 per week (including residual renal function) in all patients [14].

The patients were weighed before and after each dialysis on an electronic scale (Seca). Blood pressure was measured with a mercury sphygmomanometer before and after each dialysis and whenever symptoms occurred during dialysis. Dialysis hypotension was defined as a decrease in blood pressure which necessitated intervention by administering 200 ml saline. Muscle cramps were defined as a symptomatic event for which the nurse administered an i.v. bolus of 10 ml 5 molar NaCl. Weight loss during each dialysis session was correlated with symptoms and with changes in blood volume and haematocrit during dialysis. The study was approved by the ethical committee of the Kantonsspital Basel.

The programme Statistica for Windows [15] was used for statistical evaluation using Student's t-test, Mann-Whitney's U-test or Fisher's exact test as appropriate. To estimate the relative risk for adverse effects, we used logistic regression taking into account the within subject clustering effect with a robust variance estimate (STATA 5.0).

## Results

All patients had been free of intercurrent complications or illness for at least 5 months preceding inclusion and continued to be so during and up to the end of the 3 months' study period. Dry weight was set and varied if necessary by the attending physician according to the usual clinical criteria [16, 17]. In 6 patients dry weight increased by 1–2 kg; in 2 patients it decreased stepwise by a total of 3 kg; in one patient it remained unchanged.

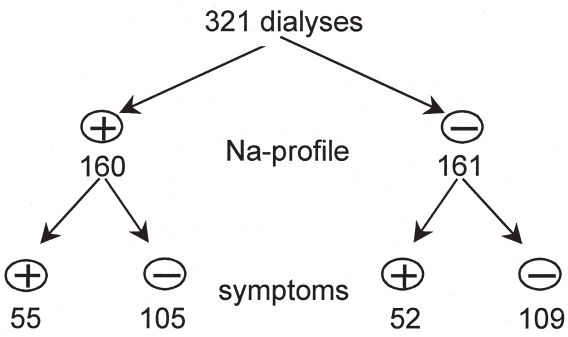



**Figure 2**

Number of symptomatic (+) and symptom-free (–) dialysis sessions with (+) and without (–) Na profile.

**Table 1**

Symptoms occurring during dialysis with versus without Na-profile (all symptoms not significantly different by Fisher's exact test).

| Dialysis sessions | Na-profile | |
|---|---|---|
| | with (n) | without (n) |
| Hypotension | 42 | 37 |
| Muscle cramps | 23 | 26 |
| Dizziness | 2 | – |
| Nausea | 2 | – |
| Discomfort | 1 | 1 |
| Headache | 1 | – |

**Table 2**

Changes in weight, hematocrit and blood-volume with and without Na-profile (mean ± SD, Student's t-test).

| | with Na-profile | without Na-profile | p |
|---|---|---|---|
| Weight gain before dialysis (kg) | 2.40 ± 0.81 | 2.49 ± 0.79 | 0.32 |
| Weight loss during dialysis (kg) | 2.42 ± 0.65 | 2.47 ± 0.63 | 0.48 |
| hematocrit before dialysis (%) | 31.6 ± 2.9 | 31.5 ± 3.1 | 0.87 |
| hematocrit after dialysis (%) | 37.1 ± 4.8 | 36.5 ± 4.8 | 0.24 |
| Decrease of bloodvolume (%) | 10.1 ± 5.0 | 9.3 ± 5.0 | 0.12 |
| Weight gain after dialysis (kg) | 2.46 ± 0.72 | 2.40 ± 0.82 | 0.53 |

Although a group of frequently symptomatic patients had been selected, there was a relatively high rate of asymptomatic dialysis sessions (67%) during the study (figure 2). As shown in table 1, the most frequent symptom was a fall in blood pressure necessitating nurse intervention with i.v. normal saline followed by muscle cramps which were treated with i.v. bolus of 10 ml 5molar (29%) saline. Other symptoms such as dizziness, nausea, general discomfort and headache were rarely complained of. Symptoms were almost equally distributed between dialysis sessions with and without sodium profile both in individual patients (data not shown) and in the group as a whole. Sodium profiling certainly did not decrease the rate of symptoms in our patients during dialysis. To have a symptomatic dialysis with a hypotensive episode with sodium profile as compared to without sodium profile, the odds ratio was OR = 1.09 (95% CI 0.76–1.56), p = 0.65.

The changes in weight during the interval between dialysis sessions and during dialysis, the mean haematocrit before and after dialysis and the percent change in blood volume are shown in table 2 separately for dialyses with and without sodium profile. It is obvious that weight gain before dialysis did not differ between sessions with or without sodium profile and thus weight loss with ultrafiltration was identical for the two types of treatment. The same was true of mean haematocrits before dialysis, and mean haematocrits after dialysis did not differ appreciably. Thus, there was no statistically significant difference with regard to the decrease in blood volume due to ultrafiltration. Finally, mean weight gain after dialysis did not differ between sessions with and without sodium profile.

However, there were differences of weight gain in symptomatic compared to symptom-free dialysis sessions. Weight gain before dialysis and subsequent weight loss due to ultrafiltration were significantly greater for symptomatic than for asymptomatic sessions (figure 3). The higher ultrafiltration rates during symptomatic sessions were associated with a greater increase in haematocrit and thus a greater relative fall in blood volume, which was unaffected by applying a sodium profile (figure 4).

**Figure 3**

Weight gain before dialysis and weight loss during symptomatic vs. symptom-free dialyses (mean ± SD) in relation to Na profiling (Student's t-test).

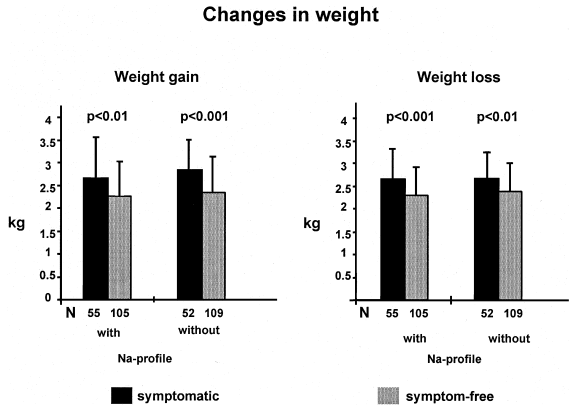
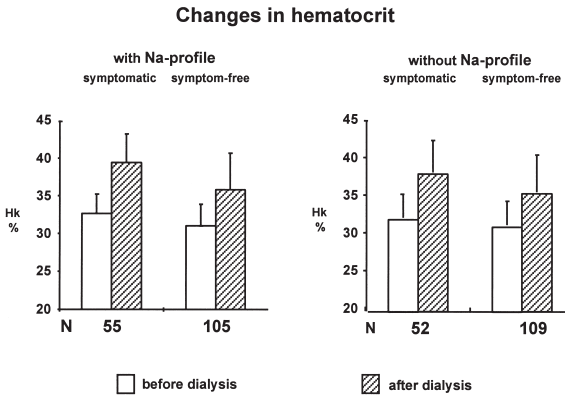



**Figure 4**

The increase in haematocrit during dialysis (difference between the pairs of columns) was significantly higher during symptomatic versus symptom-free dialyses (with Na-profile p <0.001, without Na-profile p <0.001, Student's t-test).




## Discussion

The most frequent and undesirable symptoms during high efficiency haemodialysis are hypotension and muscle cramps. It is well known that cardiovascular stability during dialysis depends on an equilibrium between fluid moving outside the body by ultrafiltration and vascular refilling from the interstitial space. Any imbalance between these two flows leads to changes in blood volume and in the event of inadequate refilling may cause hypovolaemia and hypotension [1, 2, 4]. Ultrafiltration and refilling are thought to be governed in principle by Starling forces. However, osmotic effects also appear to play a role in vascular stability and muscle cramps respond best to small boluses of hypertonic saline. The absence of osmolar changes, and in particular the absence of urea removal, appeared to explain why isolated ultrafiltration is better tolerated than combined ultrafiltration with dialysis [17]. It seemed logical, therefore, as had been tried many years earlier [6], to increase dialysate sodium at the beginning of dialysis when the blood urea concentration and thus urea removal is high, followed by lower dialysate sodium during the remainder of the dialysis session. This did indeed result in a lower incidence of hypotensive episodes and muscle cramping [6, 7, 19]. However, the amount of sodium removed was lower and interdialytic weight gain higher [10, 20], which would eventually lead to chronic sodium overload and hypertension [9].

The effect of dialysate sodium concentration on plasma volume and vascular reactivity was studied by van Kuijk et al. [21]. At an equal ultrafiltration rate, plasma volume decreased less during a 2-hour dialysis with a sodium concentration of 144 mmol/L than with one of 134 mmol/L. However, despite slower refilling, blood pressure was unaffected by lowering the dialysate sodium concentration. No effect on blood pressure but better preservation of blood volume with a decreasing sodium concentration profile vs. constant dialysate sodium was also found in ten patients comparing single dialysis sessions with an equally negative sodium balance [11]. In contrast to Movilli et al [11], Coli et al. [12] reported a lesser reduction in blood pressure with astoundingly better preservation of blood volume using a sophisticated individually computed sodium profile that reportedly ensured an equally negative computed – though not directly measured – sodium balance at constant ultrafiltration. From data presented in an earlier paper, however, the individually computed sodium profiles with dialysate Na concentrations above 148 mmol/L during the better part of the dialysis sessions resulted in increasing plasma Na concentrations attaining end dialysis values between 141 and 151 mmol/L [22]. This casts some doubt on the assumption that the real sodium mass removal was in fact the same as in standard haemodialysis against an Na concentration of 141 mmol/L with an equal ultrafiltration volume. Thus, better blood volume preservation in these studies was presumably due to extra sodium with a higher plasma Na concentration during the entire sodium profiled dialysis sessions.

The studies cited above nevertheless offered a rationale for increasing the dialysate sodium concentration during periods of high ultrafiltration rate and decreasing dialysate sodium when refilling appeared less critical during periods of slow ultrafiltration. With the new technology offered by Fresenius dialysis monitor MC 4008S, any relative gain in sodium during the high sodium concentration phase would be balanced automatically by an additional diffusional loss of sodium during the low sodium concentration phase. With an equal total ultrafiltration volume and sodium removal, postdialytic body weight and plasma sodium concentration would become identical irrespective of the profiles chosen.

To test the hypothesis that a sodium profile logically adapted to an ultrafiltration profile should improve dialysis tolerance, we chose nine stable patients on three-times-weekly high flux haemodialysis (from our population of some 60 patients) who had been suffering from relatively frequent episodes of hypotension or muscle cramps. Each patient, while being dialysed with a fixed ultrafiltration profile, was randomly assigned for every dialysis session either to the respective sodium profile (figure 1) or to a constant dialysate sodium concentration of 138 mmol/L during the three months' study period. This study design, with every patient serving as his or her own control, appeared the best way of ensuring comparability of the two dialysis regimes. With no difference in weight and haematocrit before dialysis (table 2), comparability was almost perfectly achieved. The fact that weight gain after dialysis with sodium profile did not differ from that without sodium profile shows that thirst and fluid intake were comparable after the two types of dialysis session, probably as a result of the equally negative sodium and water balance effected by the computerised profiles.

The results regarding symptoms and preservation of blood volume are simple and straightforward. Altering the dialysate sodium concentration during dialysis, to give an elevated sodium concentration and a high ultrafiltration rate at the beginning of the session and a decreased sodium concentration during low ultrafiltration at the end, neither improved nor worsened dialysis tolerance of any of the nine patients studied. The number of hypotensive episodes or muscle cramps remained unchanged and the relative decrease in blood volume per dialysis session was unaffected.

Analysis of symptomatic versus asymptomatic dialysis sessions both with and without sodium profile confirmed that excessive ultrafiltration subsequent to excessive interdialytic weight gain increased the frequency of symptoms due to imbalance between ultrafiltration and refilling with a more marked reduction in plasma volume. The net imbalance between ultrafiltration and refilling per entire dialysis session was unaffected by applying a decreasing sodium concentration profile in combination with a decreasing ultrafiltration profile.

The expectations aroused by the dialysis equipment manufacturers, that a sodium profile-adapted ultrafiltration profile would improve dialysis tolerance, could not be substantiated. Further studies with rigorous randomisation are needed to find out whether more sophisticated "biofeedback kinetic sodium modelling" [23, 24] will be more successful in the future.

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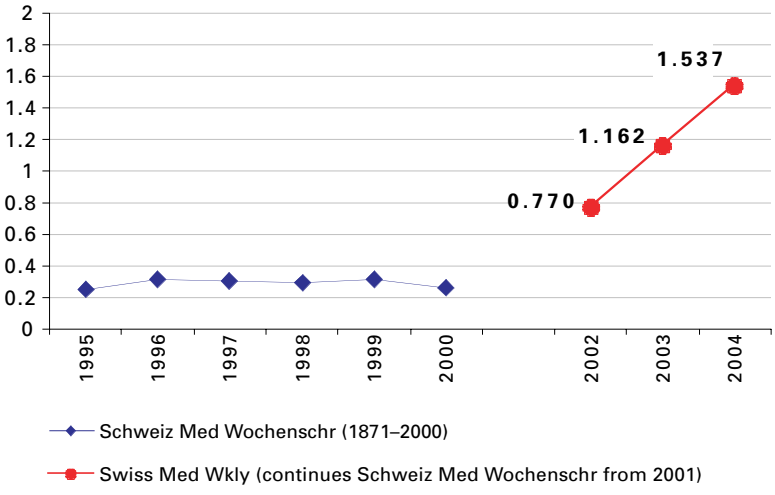


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