Automated individualization of dialysate sodium concentration reduces intradialytic plasma sodium changes in hemodialysis

Michaela Ságová | Ralf Wojke | Andreas Maierhofer | Malte Gross | Bernard Canaud | Adelheid Gauly

1 Fresenius Medical Care-DS, s.r.o, Prague 6, Czech Republic
2 Fresenius Medical Care Deutschland GmbH, Bad Homburg, Germany
3 Faculty of Mechatronics and Medical Engineering, Ulm University of Applied Sciences, Ulm, Germany

Abstract

In standard care, hemodialysis patients are often treated with a center-specific fixed dialysate sodium concentration, potentially resulting in diffusive sodium changes for patients with plasma sodium concentrations below or above this level. While diffusive sodium load may be associated with thirst and higher interdialytic weight gain, excessive diffusive sodium removal may cause intradialytic symptoms. In contrast, the new hemodialysis machine option “Na control” provides automated individualization of dialysate sodium during treatment with the aim to reduce such intradialytic sodium changes without the need to determine the plasma sodium concentration. This proof-of-principle study on sodium control was designed as a monocentric randomized controlled crossover trial: 32 patients with residual diuresis of ≤1000 mL/day were enrolled to be treated by high-volume post-dilution hemodiafiltration (HDF) for 2 weeks each with “Na control” (individually and automatically adjusted dialysate sodium concentration) versus “standard fixed Na” (fixed dialysate sodium 138 mmol/L), in randomized order. Pre- and post-dialytic plasma sodium concentrations were determined at bedside by direct potentiometry. The study hypothesis consisted of 2 components: the mean plasma sodium change between the start and end of the treatment being within ±1.0 mmol/L for sodium-controlled treatments, and a lower variability of the plasma sodium changes for “Na control” than for “standard fixed Na” treatments. Three hundred seventy-two treatments of 31 adult chronic hemodialysis patients (intention-to-treat population) were analyzed. The estimate for the mean plasma sodium change was −0.53 mmol/L (95% confidence interval: [−1.04; −0.02] mmol/L) for “Na control” treatments and −0.95 mmol/L (95% CI: [−1.76; −0.15] mmol/L) for “standard fixed Na” treatments. The standard deviation of the plasma sodium changes was 1.39 mmol/L for “Na control” versus 2.19 mmol/L for “standard fixed Na” treatments (P = 0.0004). Whereas the 95% CI for the estimate for the mean plasma sodium change during “Na control” treatments marginally overlapped the lower border of the predefined margin ±1.0 mmol/L, the variability of intradialytic plasma sodium changes was lower during “Na control” versus “standard
fixed Na⁺ treatments. Thus, automated dialysate sodium individualization by “Na control” approaches isonatremic dialysis in the clinical setting.

**KEYWORDS**
automated sodium adjustment, dialysis fluid, hemodialysis, sodium

# 1 | INTRODUCTION

Chronic sodium and volume overload, leading to hypertension and left ventricular hypertrophy, are major contributing factors to cardiovascular mortality in end-stage kidney disease (ESKD) patients. Several strategies to improve these risk factors have been proposed, including dietary sodium restriction, probing dry weight carefully, tighter fluid volume management guided by bioimpedance, longer and/or more frequent treatment schedules, and individualized dialysate sodium prescription, but uncertainties persist in the management of the fluid status and hemodynamic status of dialysis patients, indicating that more precise and individualized approaches are still needed.

In hemodialysis, sodium mass removal relies on two components: the majority of the sodium being removed by convection via ultrafiltration (≈8 g sodium chloride per liter), and the possibility of an additional fraction being removed by diffusion through the dialysis membrane depending on the dialysate to plasma sodium gradient. Intrapatient fluctuations of pre-dialysis plasma sodium concentrations are usually small, supporting the hypothesis of an individual sodium setpoint of each patient. On the contrary, the interpatient pre-dialysis plasma sodium concentrations vary much more strongly, reflecting genetic diversity, differences in lifestyle, diet, and comorbid states. Despite these large individual differences, most dialysis centers have uniform standard practices, treating most HD patients with a fixed dialysate sodium concentration (eg, 138 mmol/L). This routine clinical practice may induce a diffusive sodium loss for patients with a pre-dialytic plasma sodium concentration higher than the dialysate sodium concentration, and leads to a diffusive sodium gain for those with a pre-dialytic plasma sodium concentration lower than the dialysate sodium concentration.

A negative gradient decreases plasma sodium and may reduce patient thirst and interdialytic weight gain, but tends to be associated with cardiovascular instability and dialysis intolerance due to hypovolemia and osmotic fluid shifting. On the other side, a positive gradient may help to preserve intradialytic cardiovascular stability, but causes a sodium load which may result in thirst and consequently to a high interdialytic fluid uptake and increased interdialytic weight gain. This additional volume must be removed during the subsequent dialysis session and increases the risk of hemodynamic intolerance.

Aligning dialysate sodium to the pre-dialysis patient's individual plasma sodium concentration seems attractive as it has the potential to avoid unnecessary interdialytic sodium load while reducing the risk of interdialytic symptoms related to diffusive sodium removal. As routine online measurements of plasma sodium are not feasible, tools embedded in HD machines have been developed, driving a surrogate parameter, the plasma conductivity normalized to a temperature of 25°C, to a predefined value at the end of the dialysis session. This works because sodium chloride is by far the most important contributor to plasma and dialysate conductivity. Setting the plasma conductivity determined within the first 15 minutes of dialysis as the end dialysis target value has been evaluated as a method of achieving isonatremic dialysis.

Recently, a different approach has been implemented into a dialysis monitor. An automated controller continuously adjusts the dialysate inlet conductivity to that of the spent dialysate in order to keep the plasma conductivity constant. A clinical study has shown that this tool reduces variability in intradialytic plasma sodium changes but at the expense of a slight but significant increase in plasma sodium. Taking into account potassium as the second most abundant cation, a zero diffusive sodium balance could be approached. This shows that the dialysate conductivity-based control algorithm must be extended by additionally taking into account the concentrations of potassium and eventually other ions to achieve a sodium control algorithm. The present study has been devised to confirm that this revised control algorithm adequately works in a clinical setting by managing the sodium balance and reducing the variability of intradialytic plasma sodium changes.

# 2 | PATIENTS AND METHODS

## 2.1 | Sodium control algorithm

The sodium control algorithm investigated in this study has the aim to control the intradialytic plasma sodium change. It uses measurements of dialysate conductivity normalized to 25°C at the dialysate inlet and outlet. While the relationship between dialysate conductivity and sodium content is precisely known for the fresh dialysate because of the known electrolyte composition, this is not the case for the spent dialysate: the clearance of uremic substances and the flux of electrolytes other...
than sodium (eg, potassium and bicarbonate) modify the composition of spent dialysate and alter the relationship between conductivity and the sodium concentration.

Unfortunately, there is no practical way to determine the composition of the spent dialysate continuously during treatment. An alternative is the estimation of the time-dependent concentration of spent dialysate components using a patient kinetic model (cf. Appendix). The kinetic model approximates changes in plasma electrolyte concentrations allowing the estimation of dialyzer outlet concentrations. This method is based on measurements of ionic dialysance, the known fresh dialysate composition, and the typical pre-dialytic patient plasma electrolyte composition. Thus, effects on the spent dialysate conductivity from solutes other than sodium are mitigated.

In this way, the electrolyte balancing algorithm becomes a “sodium-like balancing” algorithm that continuously matches the inlet dialysate sodium concentration to that of the outlet, virtually abolishing the inlet-to-outlet sodium gradient and consequently doing the same to the effective dialysate to plasma gradient.

This new “automated sodium control algorithm” was implemented in the dialysis system 5008 (Fresenius Medical Care, Bad Homburg, Germany) as the option “Na control.” To make the kinetic model applicable for clinical routine where pre-dialytic ion concentrations are not available, this implementation instead uses parameter values derived from a clinical study. All electrolytes other than sodium are summarized in a “pseudo-potassium” parameter because a previous study showed that a predominant part of the deviation in plasma Na kinetics from isonatremia could be explained by potassium kinetics. The pre-dialytic value of pseudo-potassium was fixed at 4.8 mmol/L, and kinetics are calculated using the dialysate potassium concentration prescription.

### 2.2 Study objective

The aim of the study was to demonstrate that “Na control,” through the adjustment of the dialysate sodium concentration to the plasma sodium, may reduce the change of the plasma sodium concentration. The objective was thus to test the study hypothesis, which consisted of 2 components:

A. The mean plasma sodium change, defined as the difference between the individual plasma sodium concentration at the start and end of hemodialysis treatment, staying within ±1.0 mmol/L for treatments with “Na control.”

B. The variability of the plasma sodium change being less for treatments with “Na control” than for treatments with center-standard fixed dialysate Na (“standard fixed Na” treatments).

Moreover, a safety analysis of adverse events, vital signs, and the hydration status was included.

### 2.3 Clinical study design

The clinical study was designed as a prospective open crossover study with a randomized sequence of study phases “Na control” versus “standard fixed Na” (treatments with a fixed dialysate sodium concentration of 138 mmol/L). Each study phase was scheduled to last for 2 weeks, ie, including 6 treatments.

This study was conducted in a single center in Prague, Czech Republic, on 32 adult ESKD patients treated thrice weekly by maintenance double-needle hemodialysis who met the following inclusion criteria: residual diuresis lower than 1000 mL/day, a pre-dialytic plasma sodium concentration at the start of the study between 130 and 150 mmol/L, a predialytic hemoglobin value of at least 9 g/dL at the start of the study, no known problems with vascular access or high access recirculation, and no severe intradialytic blood pressure instabilities.

### 2.4 Study treatment

During the study, all patients received high-volume online HDF treatments in post-dilution mode on 5008 dialysis machines (Fresenius Medical Care) according to their normal treatment schedule, using a FX600 HDF or FX800 HDF dialyzer, and dialysis fluid with the following composition in mmol/L: bicarbonate 32; acetate 3; calcium 1.5; magnesium 0.5; and glucose 5.6. Dialysate potassium was 2 mmol/L (5 patients), 3 mmol/L (25 patients), and 4 mmol/L (1 patient). Dialysate sodium was set to 138 mmol/L in the “standard fixed Na” treatments, while it was adjusted automatically during the “Na control” treatments. Standard dialysate temperature setting was 36°C. Two dialysis machines with conductivity meters thoroughly calibrated immediately before study start by the use of an external reference device were used for all treatments.

Total body water was measured before dialysis once per week by bioimpedance spectroscopy using the Body Composition Monitor (BCM, Fresenius Medical Care).

Pre- and post-dialytic blood samples were taken in all study treatments. Pre-dialytic samples were taken directly from the arterial cannula. Post-dialytic samples were taken at the end of the treatment from the arterial blood line applying the slow-flow method according to the KDOQI guidelines. Plasma sodium concentrations were determined by direct potentiometry using a blood gas analyzer (ABL 815FLEX, Radiometer Medical ApS, Børnshøj, Denmark).

Although food and beverage intake during hemodialysis treatment add to the water and salt load of a patient, all patients were allowed to drink and eat without limitation according to the common practice at the study site. Food and beverage intake was documented qualitatively.
Study data were recorded manually in a study-specific case record form or automatically through the internal data storage in the 5008 dialysis machine to document treatment-related data.

### 2.5 | Statistical analysis

In accordance with the 2 components of the study hypothesis (A and B), the analysis consisted of 2 separate statistical tests. Both were based on the sodium change (SCH) parameter, which is defined as “plasma sodium concentration at end of treatment—plasma sodium concentration at start of treatment.”

Firstly, to examine whether a zero plasma sodium change was reached in “Na control” treatments (component A of the study hypothesis), it was tested whether the mean sodium change across “Na control” treatments $\mu_{NaC}$ deviated from 0 by less than the prespecified margin $\delta = 1 \text{ mmol/L}$. Specifically, based on the 95% confidence interval for the mean sodium change estimate for $\mu_{NaC}$:

- the null hypothesis $H_{0A}: \mu_{NaC} \notin [-\delta; \delta]$ was tested against
- the alternative hypothesis $H_{1A}: \mu_{NaC} \in [-\delta; \delta]$.

Secondly, it was examined whether the variability of SCH values expressed as standard deviation was less for “Na control” (= NaC) treatments compared to “standard fixed Na” (= sfNa) treatments. Hence,

- the null hypothesis $H_{0B}: \text{Var}(SCH_{NaC}) = \text{Var}(SCH_{sfNa})$ was to be tested against
- the two-sided alternative hypothesis $H_{1B}: \text{Var}(SCH_{NaC}) \neq \text{Var}(SCH_{sfNa})$,

with $SCH_{NaC}$ denoting the random variable of SCH under “Na control” treatment and $SCH_{sfNa}$ the random variable of SCH under “standard fixed Na” treatment. Assuming a bivariate normal distribution, the 2 hypotheses can be equivalently reformulated as follows:

\begin{align*}
H_{0B}: \rho\left(SCH_{NaC} + SCH_{sfNa}, SCH_{NaC} - SCH_{sfNa}\right) &= 0 \text{ vs.} \\
H_{1B}: \rho\left(SCH_{NaC} + SCH_{sfNa}, SCH_{NaC} - SCH_{sfNa}\right) &\neq 0,
\end{align*}

with $\rho$ denoting the Pearson correlation coefficient.

The significance level $\alpha$ was set to 0.05. As the objective was to test both null hypotheses of the study hypothesis, $H_{0A}$ and $H_{0B}$, implying that “Na control” leads to a zero sodium change and decreases the variability of the sodium change, no multiplicity adjustment was necessary (intersection–union test). Primary analysis was based on the intention to treat (ITT) population. An additional analysis on the per protocol (PP) population was performed to assess the validity of results (sensitivity analysis).

Safety parameters were analyzed in all 32 enrolled patients.

The assessment of the intra-individual variability of pre-treatment sodium levels is based on the mean of 31 patient-specific standard deviations per study phase, which had been calculated based on all available pretreatment sodium values per patient in the respective study phase.

Accordingly, the assessment of the inter-individual variability of pretreatment sodium levels is based on the mean of 6 treatment-specific standard deviations per study phase, which had been calculated based on all available pretreatment sodium values per treatment (1st to 6th) in the respective study phase.

### 2.6 | Ethics

This clinical trial was conducted in accordance with the Declaration of Helsinki, the European Medical Device Directive and the laws of the Czech Republic. All participating patients were informed orally and by a patient information sheet about the purpose, meaning, and risks of the trial before signing the consent form.

### 3 | RESULTS

In total, 32 patients were enrolled. The most common diseases underlying renal failure were diabetes (25%), hypertensive and large vessel disease (22%), and interstitial nephritis and pyelonephritis (19%). Comorbidities were mostly of a cardiovascular (91%), endocrine (78%), or metabolic (59%) nature. Vascular access was via an arteriovenous fistula (88%), graft (9%), and central venous catheter (3%). Sixteen patients were males (50%). Other patient characteristics such as age, dry weight, body composition, residual renal function and laboratory parameters are given in Table 1.

Although eligible at enrollment, one patient repeatedly presented a pre-dialytic plasma sodium concentration of <130 mmol/L during the study, so sodium control could not be performed due to the limited range of dialysate sodium settings; this patient was excluded from the analysis.
The remaining 31 patients were included in the ITT population. In total 372 treatments were used for the analysis. Fourteen treatments in 11 patients were affected by intradialytic events requiring administration of saline bolus or premature termination of sodium-controlled treatments. These 11 patients were not considered in the PP population (N = 20), in which a sensitivity analysis including 240 treatments was performed. The safety analysis included all 32 enrolled patients.

Treatment characteristics are given in Table 2. The patients received high-volume HDF treatments with convective volumes of >23.0 L. The median treatment duration was 4.7 and 4.6 hour in the “Na control” and “standard fixed Na” phase, respectively. Treatment characteristics were nearly identical in both study phases.

### 3.1 | Pre-dialytic plasma sodium concentration

Patient-specific mean values of pre-dialysis plasma Na were obtained by averaging over all sessions in each study phase. Mean values ± SD of these patient means in the pre-dialytic plasma sodium concentration were 139.1 ± 3.3 mmol/L ("Na control") and 139.2 ± 2.7 mmol/L ("standard fixed Na"). For statistics describing the distribution of treatment-specific pre-dialysis plasma sodium levels, of pre-dialysis concentrations of potassium, bicarbonate and hemoglobin as well as distributions of intradialytic changes of plasma concentrations of all 4 laboratory parameters, see Table 3. The intra-individual variability of pretreatment sodium values, given by the mean of patient-specific standard deviations, was 1.21 ± 0.52 and 1.19 ± 0.51 mmol/L in the “Na control” phase and “standard fixed Na” phase, respectively. The inter-individual variability, given as the mean of the treatment-specific standard deviation, was 3.51 ± 0.15 and 2.95 ± 0.26 mmol/L in the “Na control” phase and “standard fixed Na” phase, respectively.

### 3.2 | Intradialytic change of plasma sodium

In the ITT population, the pre- to post-dialysis mean plasma sodium change was −0.95 ± 2.19 mmol/L for “standard fixed

---

**TABLE 1** Patient characteristics at study start (ITT population, N = 31, if not stated otherwise* )

| Unit          | Mean ± SD/Median [Q1; Q3]* |
|---------------|----------------------------|
| Age           | Years                     | 66 ± 13                      |
| Dry weight    | kg                        | 83 ± 24                      |
|               |                           | 80 [69; 87]                  |
| Body mass index| kg/m²                     | 29 ± 6                       |

### Body composition (N = 29)

| Unit          | Mean ± SD/Median [Q1; Q3]* |
|---------------|----------------------------|
| Total body water | L                         | 35.7 ± 9.5                  |
| Extracellular water | L                        | 17.5 ± 4.9                  |
| Fluid overload | L                         | 1.60 ± 1.01                 |
| Lean tissue index | kg/m²                    | 1.80 [1.0; 2.1]             |

### Residual renal function (mL/day)

| Unit          | Mean ± SD/Median [Q1; Q3]* |
|---------------|----------------------------|
| <100          | 47%                        |
| 100-500       | 22%                        |
| 501-1000      | 31%                        |

**Laboratory parameters**

| Unit          | Mean ± SD/Median [Q1; Q3]* |
|---------------|----------------------------|
| Phosphate     | mmol/L                     | 1.5 ± 0.4                   |
| Total protein | g/L                       | 65 ± 6                      |
| Total cholesterol | mmol/L               | 4.7 ± 1.2                  |
| HDL cholesterol | mmol/L                | 1.1 ± 0.4                  |
| Triglycerides | mmol/L                     | 2.1 ± 1.1                   |

Abbreviations: N, number of patients; ITT, intention to treat.

*Mean ± SD, and additionally median [Q1; Q3] for continuous variables that are not normally distributed.
As the second part of the study objective, the variability of the plasma sodium change, assessed by the standard deviation of sodium change values, was significantly lower in the “Na control” phase than in the “standard fixed Na” phase (Table 5, P = 0.0004).

In the per protocol population, the sensitivity analyses mainly confirm these results: the estimated mean sodium change was −0.44 mmol/L in the “Na control” phase (see Table 4), with the corresponding 95% CI [−1.11, 0.23] again slightly overlapping the predefined range of −1.0 to 1.0 mmol/L. The estimate for the standard deviation of sodium changes was again lower although not significantly in “Na control” treatments versus “standard fixed Na” treatments (1.44 vs. 1.84 mmol/L, Table 5).

### 3.3 Association between intradialytic plasma sodium change and pre-dialytic plasma sodium

Pre- to post-dialysis plasma sodium changes appear to be linearly and negatively associated with the mean pre-dialytic plasma Na in both study phases. However, this association is less strong and the slope of the regression line less steep and closer to zero for treatments with automated sodium control (Figure 1). In “standard fixed Na” treatments, a positive or negative sodium gradient throughout the treatment leads to diffusive sodium uptake or removal, whereas with “Na control” treatments, the sodium gradient is minimized, leading to less pronounced intradialytic plasma sodium changes.

Changes of the plasma sodium concentration of ≥±4 mmol/L were observed in 25 treatments during “standard fixed Na” treatments, but in only 3 during “Na control” treatments. Four patients presented in more than half of their treatments changes in plasma sodium by more than 2 mmol/L during “Na control” treatments for an unknown reason without clinical consequences. All treatments but one of the remaining 27 patients in the “Na control” phase resulted in sodium changes within <+3 mmol/L.

### 3.4 Safety of the sodium control module

Vital signs (systolic and diastolic blood pressure, heart rate) showed no clinically relevant differences between study phases (Table 6).

Thirty adverse events were reported in 18 of 32 patients: 16 adverse events during or after “standard fixed Na” treatments and 14 adverse events during or after “Na control” treatments. The adverse events were mostly cramps (8 cases) and hypotension (5 cases), equally distributed between study phases. No serious adverse events occurred.

Whether “Na control” has an impact on the fluid status has been assessed in the last treatment of each phase. With a

---

### TABLE 2  Distribution of treatment parameters in both study phases (patient means*, ITT population, N = 31**)

|                      | Na control        | Standard fixed Na |
|----------------------|-------------------|-------------------|
| $T_{\text{dial}}$ [h]| 4.9 ± 0.4         | 4.9 ± 0.4         |
| Blood flow rate [mL/min]| 382 ± 62 | 385 ± 63          |
| Dialysate flow rate [mL/min]| 678 ± 97 | 682 ± 96          |
| $Kt/V_{\text{OCM}}$| 2.08 ± 0.35       | 2.08 ± 0.37       |
| UF volume [L]         | 2.60 ± 0.9         | 2.55 ± 0.93       |
| $V_{\text{sub,post}}$[L]| 25.7 ± 6.3 | 26.5 ± 6.1        |

Notes: $T_{\text{dial}} = $ treatment duration; dialysate flow rate: total rate of dialysis fluid produced by the machine, that is, flow rate at the dialyzer plus substitution flow rate; UF = ultrafiltration volume; $V_{\text{sub,post}} = $ substitution volume in post-dilution mode.

*Patient means = averages of 6 treatment-specific values per patient and study phase.

**Mean ± SD, in addition median [Q1; Q3] for not normally distributed continuous variables.

### TABLE 3  Distribution of pre-dialytic blood concentrations and intradialytic changes (patient means*, ITT population, N = 31 patients**)

|                      | Na control        | Standard fixed Na |
|----------------------|-------------------|-------------------|
| Pre-dialytic concentrations |              |                  |
| $Na_{\text{pre}}$ [mmol/L]| 139.1 ± 3.3 | 139.2 ± 2.7       |
| $K_{\text{pre}}$ [mmol/L]| 4.9 ± 0.4       | 4.8 ± 0.4         |
| $Bic_{\text{pre}}$ [mmol/L]| 20.2 ± 1.6 | 20.2 ± 1.6        |
| $Hb_{\text{pre}}$ [mg/dL]| 11.8 ± 0.9 | 11.9 ± 1.0        |

|                      | Na control        | Standard fixed Na |
|----------------------|-------------------|-------------------|
| Intradialytic concentration changes |              |                  |
| $Na_{\text{change}}$ [mmol/L]| −0.5 ± 1.4 | −1.0 ± 2.2        |
| $K_{\text{change}}$ [mmol/L]| −1.1 ± 0.4       | −1.1 ± 0.5        |
| $Bic_{\text{change}}$ [mmol/L]| 6.1 ± 1.4 | 6.2 ± 1.3         |
| $Hb_{\text{change}}$ [mg/dL]| 1.1 ± 0.5 | 1.1 ± 0.5         |

*Patient means = averages of 6 pre-dialytic measurements/6 differences between pre- and post-dialytic values ($\Delta$) per patient and study phase.

**Mean ± SD, in addition median [Q1; Q3] for continuous variables that are not normally distributed.
pre-dialytic fluid overload of 1.7 ± 1 and 1.6 ± 1 L measured at the end of the “Na control” phase and the “standard fixed Na” phase, respectively, no effect on fluid status has been found. There was also no difference on mean pre- and post-dialysis body weight between study phases.

4 | DISCUSSION

This randomized controlled crossover trial was a proof-of-principle study of sodium control, which offers an individual adjustment of the dialysate during treatment in order to reduce the intradialytic change of plasma sodium concentration. The underlying sodium control module and algorithm refined the dialysate side-balancing approach based on conductivity measurements by incorporating a kinetic model correcting for the contribution of non-sodium electrolytes in spent dialysate. As already suggested by Kuhlmann et al., this resulted in a substantial and significant reduction in the scatter of intradialytic plasma sodium changes. While in the previous setting, this was accompanied on average by a small but significant increase in the post-dialytic plasma sodium level, the present revised approach provided a virtually isonatremic dialysis in the population mean.

Nevertheless, for some patients deviations from isonatremia were observed despite receiving a zero diffusive Na transfer according to the controller. There may be specific reasons for this: as it is impossible in clinical routine to determine the pre-dialytic concentration of all electrolytes contributing to conductivity, the kinetic model assumes typical proportions of electrolytes at the start of treatment. While this leads to isonatremia on average as shown in the present study, this may lead to deviations for patients with pre-dialytic electrolyte profiles deviating from the average.

Furthermore, pre- and intradialytic food and fluid intake may alter blood electrolyte concentrations with a substantial delay after gastrointestinal absorption. These compartmental shifting effects may change the blood electrolyte composition without affecting the mass balance across the dialyzer membrane. Intradialytic food and fluid intake was not restricted which might have influenced plasma sodium kinetics. However qualitative assessment of intradialytic food and fluid intake within patients showed quite constant eating and drinking habits. Furthermore, as shown by the small individual variation in pre-dialytic plasma sodium, patients tend to balance salt intake by fluid intake in a relatively constant relation in the interdialytic period. As food and fluid intake was not restricted during dialysis, it is a sound assumption that the same is the case with intradialytic intake, so that plasma sodium concentration will not be influenced much or at least to the same extent in both study phases.

Patients with a residual diuresis of >1000 mL/day have been excluded to limit the impact of residual renal function (RRF) on sodium balance. With a crossover design and total study duration of 4 weeks, an intra-patient comparison is possible at a comparable level of RRF and why the influence of RRF on the outcome in the 2 study phases is assumed to be marginal.

Unlike other methods as indirect potentiometry or flame photometry, direct potentiometry as our reference method measures the sodium concentration in plasma water, therefore, changes in plasma protein concentration per se will not influence the measured plasma sodium concentration. Thus, the unphysiological effect of pseudohyponatremia with increasing plasma protein concentrations is avoided.

As the plasma protein concentration is increased by net ultrafiltration, the Gibbs-Donnan effect between plasma and dialysate tends to slightly increase the plasma sodium as measured by direct potentiometry when comparing pre- to post-dialytic sodium values. However, as the ultrafiltration volume is much smaller than the sodium distribution volume, we expect this effect to be negligible.

Decline in plasma glucose concentration in diabetic patients with poor control of blood glucose, being dialyzed

| Study phase                  | Population | Sodium change | Lower 95% CI | Upper 95% CI |
|------------------------------|------------|---------------|--------------|--------------|
|                              |            | mmol/L        | mmol/L       | mmol/L       |
| Na control                   | ITT        | −0.53         | −1.04        | −0.02        |
|                              | PP         | −0.44         | −1.11        | 0.23         |
| Standard fixed Na            | ITT        | −0.95         | −1.76        | −0.15        |
|                              | PP         | −0.89         | −1.75        | −0.03        |

| Population | Sodium change | Lower 95% CI | Upper 95% CI | P value |
|------------|---------------|--------------|--------------|---------|
| ITT        | 1.39          | 2.19         |              | 0.0004  |
| PP         | 1.44          | 1.84         |              | 0.1023  |
against a fixed dialysate glucose concentration of 1 g/L, might have influenced plasma sodium measurement.\textsuperscript{27,28} Plasma glucose levels were not measured in our study. However, intradialytic plasma sodium changes during “Na control” treatments showed no signs of relative increase in plasma Na in diabetic in comparison to non-diabetic patients. Moreover, glucose shifts are assumed to not influence sodium balancing which is based only on conductivity measurements on the dialysate side. Glucose as an uncharged molecule will not contribute to electric conductivity and will only marginally lower total dialysate conductivity due to its contribution to viscosity. In total this will be negligible for sodium control and will have no impact on the patient’s sodium mass balance.

The balancing approach to intradialytic sodium control provides a paradigm shift compared to the concept of a fixed end dialysis plasma conductivity,\textsuperscript{29–31} turning from considerations valid for the average patient population to the individual physiology of each patient. As shown in several studies, the pre-dialytic plasma sodium of ESKD patients, known as the personal plasma sodium concentration or osmolality “set-point,” is very stable from treatment to treatment,\textsuperscript{8} resulting

**FIGURE 1** Change of plasma sodium concentration during treatment versus plasma sodium concentration at the start of treatment [mmol/L]
The zero diffusive balancing approach tries not to interfere with the complex physiologic equilibration mechanisms of fluid and osmotic status. It only removes sodium dissolved in the excess fluid via net ultrafiltration and does not actively alter the plasma sodium level. In this context, knowledge of the absolute plasma sodium concentration value is not necessary.

In the fixed end dialysis plasma conductivity approach, achieving a predefined plasma sodium concentration becomes easier with longer treatment times and more efficient treatment modalities. In this setting, the effects of non-sodium electrolytes on conductivity are mitigated by a tendency toward an equilibrium with the prescribed dialysate concentrations. In contrast to this, the balancing approach, though not dependent on the knowledge of absolute pre-dialysis sodium concentrations, relies on the precise determination of the integral intradialytic diffusive sodium mass balance in the dialyzer. As the underlying principle—conductivity measurement—is influenced by all electrolytes, kinetic modeling of these electrolyte contributions becomes necessary.

An additional beneficial effect of the automatic adaption of the dialysate composition on the patient’s plasma sodium is the concomitant compensation of deviations in the concentrate supply and mixing system. The zero diffusive sodium concept can easily be extended to a quantifiable amount (in mmol Na or g NaCl) of intradialysis diffusive sodium transfer. This brings the aspects of dialysis treatments related to salt and water balance closer to the functioning principle of the kidney in terms of free water clearance. The zero diffusive sodium balance approach presented in this study corresponds to a “zero free water clearance.” Prescriptions for diffusive sodium gain would correspond to a positive free water clearance, while prescriptions for diffusive sodium removal would correspond to a negative free water clearance. Thus, dialysate sodium prescriptions are no longer fixed concentrations with no relation to the individual patient’s status but are related to the patient’s physiology, allowing for sodium and water to be controlled by medical prescription.

The study has some limitations. Although designed according to the gold standard as a prospective randomized clinical trial, bias could not be totally excluded. Other pathways of electrolyte and water transfer such as oral food and fluid intake, transpiration, exhalation, and residual diuresis could not be quantified. Further studies in larger patient populations and the performance of sodium measurements during treatment are needed for a better understanding of the role of sodium and intracorporeal sodium kinetics during hemodialysis treatments. Also, restrictions concerning food and beverage intake before and during dialysis treatment would reduce confounding.

5 | CONCLUSION

The present sodium control algorithm provides the instrumental basis to better manage intradialytic sodium changes. Clinical benefits in terms of improved long-term fluid overload and blood pressure control are highly plausible based on common medical knowledge but are yet to be proven in dedicated long-term outcome-based clinical studies.

ACKNOWLEDGMENTS

The staff in the study center is gratefully acknowledged for their dedicated work to realize this clinical study.

CONFLICT OF INTEREST

MS, RW, AM, BC, and AG are current, and MG is a former full-time employee of Fresenius Medical Care.

AUTHOR CONTRIBUTIONS

MS included patients, performed study specific treatments, collected data and reviewed manuscript; RW, AM, and AG participated in study design, analysis, and interpretation, manuscript drafting and review; the Na control algorithm was developed by AM and MG; MG participated in study design, manuscript drafting, and review; BC drafted and reviewed the manuscript.

ORCID

Malte Gross https://orcid.org/0000-0002-7269-0077
Adelheid Gauly https://orcid.org/0000-0002-2554-0711
REFERENCES

1. Charra B, Chazot C, Jean G, Hurot JM, Terrat JC, Vanel T, et al. Role of sodium in dialysis. Minerva Urol Nefrol 2004;56:205–13.

2. Hecking M, Karaboyas A, Saran R, Sen A, Inaba M, Rayner H, et al. Dialysate sodium concentration and the association with interdialytic weight gain, hospitalization, and mortality. Clin J Am Soc Nephrol 2012;7:92–100.

3. Zoccali C, Moisll U, Chazot C, Mallamaci F, Tripepi G, Arkossy O, et al. Chronic fluid overload and mortality in ESRD. J Am Soc Nephrol 2017;28:2491–7.

4. Lindley EJ. Reducing sodium intake in hemodialysis patients. Semin Dial 2009;22:260–3.

5. Penne EL, Levin NW, Kotanko P. Improving volume status by comprehensive dietary and dialytic sodium management in chronic hemodialysis patients. Blood Purif 2010;30:71–8.

6. Mann H, Stiller S. Sodium modeling. Kidney Int Suppl 2000;76:S79–88.

7. Basile C, Lomonte C. It is time to individualize the dialysate sodium prescription. Semin Dial 2016;29:24–7.

8. Keen ML, Gotch FA. The association of the sodium “setpoint” to interdialytic weight gain and blood pressure in hemodialysis patients. Int J Artif Organs 2007;30:971–9.

9. Basile C, Libutti P, Lisi P, Vernaglione L, Casucci F, Losurdo N, et al. Sodium setpoint and gradient in bicarbonate hemodialysis. J Nephrol 2013;26:1136–42.

10. Oduvu A, Lambie S, Taal MW, Fluck RJ, McIntyre CW. Use of online conductivity monitoring to study sodium mass balance in chronic haemodialysis patients: prospects for treatment individualisation. Kidney Blood Press Res 2011;34:439–46.

11. Zerbe RL, Miller JZ, Robertson GL. The reproducibility and heritability of individual differences in osmoregulatory function in normal human subjects. J Lab Clin Med 1991;117:51–9.

12. Flanigan MJ. Role of sodium in hemodialysis. Kidney Int Suppl 2000;76:S72–8.

13. Moret K, Hassell D, Kooman JP, et al. Ionic mass balance and blood volume preservation during high, standard, and individualized dialysate sodium concentration. Nephrol Dial Transplant 2002;17:1463–9.

14. Santos SF, Peixoto AJ. Revisiting the dialysate sodium prescription as a tool for better blood pressure and interdialytic weight gain management in hemodialysis patients. Clin J Am Soc Nephrol 2008;3:522–30.

15. Munoz Mendoza J, Sun S, Chertow GM, Moran J, Doss S, Schiller B. Dialysate sodium and sodium gradient in maintenance hemodialysis: a neglected sodium restriction approach? Nephrol Dial Transplant 2011;26:1281–7.

16. Kim DY, Kim B, Moon KH, Lee S, Lee DY. Effect of gradually lowering dialysate sodium concentration on the interdialytic weight gain, blood pressure, and extracellular water in anuric hemodialysis patients. Ren Fail 2014;36:23–7.

17. de Paula FM, Peixoto AJ, Pinto LV, Dorigo D, Patricio PJ, Santos SF. Clinical consequences of an individualized dialysate sodium prescription in hemodialysis patients. Kidney Int 2004;66:1232–8.

18. Munoz Mendoza J, Arranreddy R, Schiller B. Dialysate sodium: choosing the optimal hemodialysis bath. Am J Kidney Dis 2015;66:710–20.

19. Hanafusa N, Tsuchiya K, Nitta K. Dialysate sodium concentration: the forgotten salt shaker. Semin Dial 2018;31:563–8.

20. Flythe JE, Mc Causland FR. Dialysate sodium: rationale for evolution over time. Semin Dial 2017;30:99–111.

21. Bosetto A, Bene B, Petiticlerc T. Sodium management in dialysis by conductivity. Adv Ren Replace Ther 1999;6:243–54.

22. Chevalier L, Tielemans C, Debelle F, Vandervelede D, Fumeron C, Mandart L, et al. Isotonic dialysis biofeedback in hemodialfiltration with online regeneration of ultrafiltrate in hypertensive hemodialysis patients: a randomized controlled study. Blood Purif 2016;41:87–93.

23. Kuhlmann U, Maierhofer A, Canaud B, Hoyer J, Gross M. Zero diffusive sodium balance in hemodialysis provided by an algorithm-based electrolyte balancing controller: a proof of principle clinical study. Artif Organs 2019;43:150–8.

24. KDOQI Clinical Practice Guideline for Hemodialysis Adequacy: 2015 update. Am J Kidney Dis 2015;66:884–930.

25. Bogle W, Hsu YS. Sample size determination in comparing two population variances with paired-data: application to bilirubin tests. Biometrical J 2002;44:594–602.

26. Kim GH. Pseudohyponatremia: does it matter in current clinical practice? Electrolyte Blood Press 2006;4:77–82.

27. Penne EL, Thijssen S, Raimann JG, Levin NW, Kotanko P. Correction of serum sodium for glucose concentration in hemodialysis patients with poor glucose control. Diabetes Care 2010;33:e91.

28. Katz MA. Hyperglycemia-induced hyponatremia–calculation of expected serum sodium depression. N Engl J Med 1973;289:843–4.

29. Locatelli F, Stefoni S, Petiticlerc T, Coli L, Di Filippo S, Andruhilli S, et al. Effect of a plasma sodium biofeedback system applied to HFR on the intradialytic cardiovascular stability. Results from a randomized controlled study. Nephrol Dial Transplant 2012;27:3935–42.

30. Coli L, La Manna G, Comai G, Ursino M, Ricci D, Piccari M, et al. Automatic adaptive system dialysis for hemodialysis-associated hypotension and intolerance: a noncontrolled multicenter trial. Am J Kidney Dis 2011;58:93–100.

31. Petiticlerc T, Gaillard F. The different modalities of isotonic hemodialysis. Nephrol Ther 2019;15:22–8.

32. Funck-Brentano JL. Sodium-free water clearance in hemodialysis. Artif Organs 1981;5:51–3.

33. Gross M, Maierhofer A, Tetta C, Senecal L, Canaud B. Online clearance measurement in high-efficiency hemodiafiltration. Kidney Int 2007;72:1550–3.

How to cite this article: Ságová M, Wojke R, Maierhofer A, Gross M, Canaud B, Gauly A. Automated individualization of dialysate sodium concentration reduces intradialytic plasma sodium changes in hemodialysis. Artif Organs. 2019;43:1002–1013. https://doi.org/10.1111/aor.13463

APPENDIX

Transition from conductivity to concentration balancing

The total electrical conductivity $\sigma$ of an electrolyte solution is influenced by the conductivity contribution $\sigma_j$ of each electrolyte. In general, $\sigma$ is a nonlinear function of the time-dependent concentration $c_j(t)$ of the different electrolytes. Within the narrow range of physiologically acceptable concentrations, the total conductivity can be approximated by a...
linear function of these contributions at physiological ionic strength, with fixed ion-specific conductivities \( \gamma_j \), and an offset \( \sigma_{\text{ofs}} \) due to the linearization:

\[
\sigma(t) = \sum_j \sigma_j(t) = \sum_j \gamma_j c_j(t) + \sigma_{\text{ofs}}
\]  

(1)

By solving for the sodium concentration, \( c_{\text{Na}} \) at time \( t \) can be expressed as:

\[
c_{\text{Na}}(t) = \frac{1}{\gamma_{\text{Na}}} \left( \sigma(t) - \sigma_{\text{ofs}} - \sum_{j \neq \text{Na}} \gamma_j c_j(t) \right)
\]  

(2)

Sodium balancing is done by continuously calculating the dialysate side (index “di” and “do”: dialyzer inlet and outlet, resp.) diffusive mass transfer \( J_{\text{diff}} \):

\[
J_{\text{diff},\text{Na}}(t) = Q_d \left( c_{\text{di},\text{Na}}(t) - c_{\text{do},\text{Na}}(t) \right)
\]  

(3)

Unlike in Kuhlmann et al.\(^{23} \) where sodium concentration was assumed to be strictly proportional to conductivity at the dialyzer inlet and outlet, using (2) for the continuous calculation of \( c_{\text{Na}}(t) \) in principle permits real sodium balancing based on conductivity measurements even in the case of changing contributions of other electrolytes.

While the composition on the dialysate inlet side is precisely known from the dialysate prescription, this is not the case on the outlet side because of the electrolyte transfer between the blood and dialysate. For example, in most dialysis sessions plasma potassium decreases due to diffusive transfer. As the extracorporeal blood circuit can be considered a closed system,\(^{33} \) conservation of mass is maintained, so solvents extracted from the blood side have to appear on the dialysate outlet side, and solvents added to the blood side by transfer from the dialysate will have a lower concentration on the dialysate outlet side compared to the dialysate inlet side. Diffusive mass transfer in the dialyzer is governed by the transmembrane concentration gradient.

\[
J_{\text{diff},j}(t) = D_j \left( \frac{c_{\text{di},j}(t)}{\alpha_j} - c_{\text{bi},j}(t) \right) = Q_d \left( c_{\text{di},j}(t) - c_{\text{do},j}(t) \right)
\]  

(4)

with \( c_{\text{bi},j} \) being the concentration of electrolyte \( j \) on the blood inlet side, \( D_j \) the dialysance of this electrolyte, and \( \alpha_j \) the Gibbs-Donnan factor.

It is assumed that \( D_j \) is proportional to the dialysance \( D \) obtained from intradialytic online clearance measurements.

\[
D_j = f_j D
\]  

(5)

Considering the impact of mass transfer on the body electrolyte concentration in a single pool model under the assumption that electrolytes are uniformly distributed in their respective distribution volume \( V_j \) results in a kinetic model for the blood inlet concentration

\[
dc_{\text{bi},j} = \frac{J_{\text{diff},j}(t)}{V_j} \, dt
\]  

(6)

with the time-dependent solution for constant dialysate inlet concentrations \( c_{\text{di},j} \):

\[
c_{\text{bi},j}(t) = c_{\text{di},j}(0) + \left( c_{\text{bi},j}(0) - c_{\text{di},j}(0) \right) e^{-\frac{J_{\text{diff}}}{V_j} t}
\]  

(7)

The blood side concentration at the start of treatment, \( c_{\text{bi},j}(0) \), can be either measured from blood samples or taken as a population-fixed standard value.

Solving (4) for \( c_{\text{do},j} \) gives:

\[
c_{\text{do},j}(t) = c_{\text{di},j} - \frac{f_j D}{Q_d} \left( \frac{c_{\text{di},j}}{\alpha_j} - c_{\text{bi},j}(t) \right)
\]  

(8)

This can be entered into (2) to deduce the dialysate outlet Na concentration from conductivity measurements and finally calculate the Na balance according to (3).

However, in clinical routine knowledge of all blood electrolytes is neither possible nor required: As shown already\(^{23} \) the implementation of a correction for changes in measured plasma potassium concentration using specific conductivities from literature could reduce the average expected plasma sodium shift nearly to zero.

This approach can be generalized to an arbitrary number of ions

\[
\Delta c_{\text{Na,corr}}^{(k)} = \Delta c_{\text{Na,Lab}}^{(k)} + \sum_{j \neq \text{Na}} \frac{\gamma_j}{\gamma_{\text{Na}}} \Delta c_{j,\text{Lab}}^{(k)}
\]  

(9)

where \( \Delta c_{\text{Na,Lab}}^{(k)} \) and \( \Delta c_{j,\text{Lab}}^{(k)} \) represent the intradialytic change of plasma Na and the other electrolytes measured by the reference method in the \( k \)th “Na control” treatment. \( \Delta c_{\text{Na,corr}}^{(k)} \) is the shift in plasma Na if the influence of other ions had been taken into account. In “Na control” treatments, the algorithm assures that \( \Delta c_{\text{Na,corr}}^{(k)} = 0 \).

In clinical routine electrolyte lab values are not available, so \( \Delta c_{j,\text{Lab}}^{(k)} \) are unknown. Instead, the intradialytic concentration change of ion \( j \) can be estimated by the kinetic model (7):

\[
\Delta c_{j,\text{Lab}}^{(k)} = \Delta c_{j,\text{Mod}}^{(k)} = c_{\text{bi},j}^{(k)}(t) - c_{\text{bi},j}(0) = \left( c_{\text{bi},j}(0) - \frac{c_{\text{di},j}}{\alpha_j} \right) e^{-\frac{J_{\text{diff}}}{V_j} t} - c_{\text{bi},j}(0)
\]  

where \( c_{\text{di},j}^{(k)} \) is taken from the machine dialysate prescription in treatment \( k \), \( c_{\text{bi},j}(0) \) is set to the population average\(^{23} \) of this parameter and \( \frac{J_{\text{diff}}}{V_j} t \) is assumed to be equal to the dialysis
dose $Kt/V$ obtained by the Online Clearance Monitor (OCM).

To obtain the values of the coefficients $\gamma_j$, $\alpha_j$, and $f_j$, all “Na control” treatments from\textsuperscript{23} where zero diffusive conductivity balance was reached were taken to minimize at the same time the values of

$$\left| \sum_k \Delta c^{(k)}_{Na,corr} \right| \text{ and the sum of the variations of } \Delta c^{(k)}_{Na,corr}.$$ \(\gamma_{Na} = 0.10 \text{ (mS/cm)/(mmol/L)}\) was taken from lab experiments, in agreement with the “rule of thumb” for the conversion between dialysate concentration and conductivity.

Models with different sets of ions were examined by allowing the values of $\gamma_j$, $\alpha_j$, and $f_j$ to deviate slightly from their physical default values. Already a model with a single ion species beside Na summarizing the effect of all electrolytes gave reasonable results. In accordance with\textsuperscript{23}, this species is dominated by the potassium concentration and might be named “pseudo potassium” $K^\ast$. As initial value for this parameter, the population average of the real plasma potassium concentration $c_{bi,K^\ast}(0) = c_{bi,K}(0) = 4.8 \text{ mmol/L}$ was taken.

Optimal values were found as $\gamma_{K^\ast} = 0.16 \text{ (mS/cm)/(mmol/L)}, \alpha_{K^\ast} = 0.8, f_{K^\ast} = 1.2$.

Adding more complexity to the model, for example, by taking into account changes in plasma bicarbonate, did not improve the fit. Thus, this least complex model was chosen for the implementation of the controller.