The life-sustaining technology of maintenance hemodialysis attempts to accomplish in a dozen or so hours a week what the kidneys labor to do 24 hours per day: maintain the optimal composition and volume of body fluids. Claude Bernard’s insight in the 1800s about the \textit{milieu intérieur} (‘‘all of the vital mechanisms, however varied they may be, have always one goal, to maintain the uniformity of the conditions of life in the internal environment’’) (1) are not easily achieved by an intermittent therapy, particularly for sodium and fluid balance, which normal kidneys regulate constantly. As reviewed by Flanigan, in the early days of hemodialysis, patients were mostly dialyzed twice per week for >8 hours per session with very high glucose dialysate solutions to remove excess water via the creation of an osmotic gradient (2). A lower dialysate sodium (DNa) concentration was used, typically in the range of 125–130 mEq/L (3), to facilitate sodium removal by diffusion.

The advent of hydrostatic-driven ultrafiltration allowed dialysis times to be shortened while maintaining satisfactory clearance, as measured by urea kinetic modeling. However, these shorter dialysis sessions came at the price of increased dialysis-related complaints, including nausea, headaches, abdominal pain, muscle cramps, dizziness, fainting, seizures, and hypotension (2). This constellation of symptoms was referred to as the disequilibrium syndrome and was felt to be related to rapid changes in the chemical composition of the extracellular and intracellular compartments. Many early theories centered on the role of osmolarity shifts, and anecdotal evidence suggested that the administration of hypertonic fluids ameliorated many of these unwanted side effects.

Consequently, the “standard” DNa increased to the more recent range of 138–140 mEq/L (3). The concept of improved hemodynamic stability with higher DNa also accounts for the development of sodium modeling as a treatment option, where the DNa concentration at the start of dialysis is high and subsequently declines during the course of the procedure. Previous studies have reported improved hemodynamic stability with these measures (4–6), but they came with downsides—as an association with increased thirst (6), interdialytic weight gain (IDWG) (7), and BP (8). Individualization of the DNa has been investigated as one of many attempts to offset these presumed detrimental effects. Indeed, alignment of the DNa with the predialysis serum sodium concentration (SNa) has been shown to associate with reduced thirst and less IDWG compared with the use of fixed DNa concentrations greater than SNa (9). Based on these important observations, several thoughtful commentators have argued that the DNa should be lowered or tailored to the SNa (isotonic) to lessen diffusive sodium gain and thereby lower BP, minimize IDWG, and improve clinical outcomes (10–12).

In this month’s \textit{CJASN}, Hecking et al. (13) present the results of an observational study of SNa and DNa in Dialysis Outcomes and Practice Patterns Study (DOQI), a large international database of dialysis patients that has provided important insights into worldwide treatment patterns in hemodialysis. Their findings run counter to what many may have predicted: higher DNa appeared to be associated with lower risk of hospitalization despite being associated with higher IDWG. The associations with mortality and systolic BP (SBP) were not as straightforward. In the overall dataset, there appeared to be no association between DNa and mortality and 0.88 mmHg lower SBP for every 2 mEq/L higher DNa. Because of the variability in treatment patterns—55% of patients were from facilities using largely a single DNa, whereas 44% were from facilities that had variable DNa—the investigators performed subgroup analyses in those centers that did and did not individualize the DNa. Among those centers with “nonindividualized” DNa, higher DNa was associated with lower mortality (hazard ratio [HR] of 0.88 per 2 mEq/L higher DNa) and higher SBP. Among those centers with “individualized” DNa, higher DNa was associated with higher mortality (HR, 1.04; 95% confidence interval, 1.00–1.08 per 2 mEq/L higher DNa) and lower SBP. The authors argue that the “nonindividualized” analyses represent the findings of a pseudo-randomized experiment, suggesting that because DNa was not adjusted according to patient characteristics, there is little possibility for confounding by indication. Indeed, their findings on SBP support this notion: SBP was lower with higher DNa in the individualized analyses, possibly because higher DNa may be used in those prone to intradialytic hypotension, whereas SBP was higher in the nonindividualized analyses, possibly from increased salt loading. However, the nonindividualized analyses are not comparable to a balanced randomized trial, in which differences across groups are expected to be minimal if sufficiently large. In the nonindividualized analyses, there were several significant imbalances: those with higher DNa were younger, less likely to be diabetic, and had lower serum albumin.

\textit{Milieu Intérieur}

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Multivariable modeling attempts to account for measured differences, but unmeasured confounding from differences in case-mix, physician practices, geographical imbalances, and other variables may have been missed or incompletely assessed and led to biased results. Indeed, analyses from DOPPS have previously demonstrated significant geographic variability in hemodialysis practice patterns and outcomes (14,15), and one is left wondering if statistical adjustment for facility clustering and stratification by region—as done in the hospitalization and mortality analyses by Hecking et al.—adequately captures such variability and their confounding effects on analyses examining outcomes among a select subcohort (i.e., those from facilities with nonindividualized dialysate sodium). Selection bias should also be considered in these analyses, because nearly 7000 individuals (13% of the eligible cohort) were excluded because of the use of sodium modeling. Because the time-average dialysate sodium concentration in sodium modeling algorithms is typically >140 mEq/L, these patients could have been included in the higher dialysate groups and shed additional light on this common and relatively untested prescription pattern.

The implications of the study by Hecking et al. need to be considered in the context of recent studies conducted on dialysate and serum sodium. In a separate publication by Hecking et al. involving some of the same patients (31%), the association between dialysate sodium and mortality differed according to the SNa: dialysate sodium >140 mEq/L was associated with a trend toward higher mortality among those with serum sodium ≥140 mEq/L (HR, 1.26; P=0.10), whereas higher DNa was associated with lower mortality among those with serum sodium <137 mEq/L (HR, 0.77; P=0.04) (16). We found similar results from analyses of a medium-sized dialysis organization in the United States (n=2272): those treated with higher DNa (≥140 mEq/L, including sodium modeling) had higher mortality only in the setting of higher SNa, with a trend toward lower mortality among those with lower SNa (17). In both our study and the CJASN study by Hecking et al., the effect of higher dialysate sodium on IDWG was clinically small, although statistically significant: an increase of 0.17% of postdialysis blood volume for every 2 mEq/L higher DNa (Hecking et al.) or 0.14% increase in DNa >140 mEq/L compared with DNa ≤140 mEq/L (Mc Causland et al.). We found no association between DNa and BP, a finding also noted by Munoz Mendoza et al., who examined the sodium gradient (i.e., dialysate − serum sodium concentration) (18).

Overall, taken in the context of other studies, it appears that higher DNa may be beneficial in certain patients and detrimental in others. Higher DNa may be associated with a lower risk of hospitalization, despite a modest increase in IDWG and variable effect on SBP. The association between DNa and mortality is complex and may depend on SNa. Patients with lower SNa may experience better outcomes with higher, rather than lower, DNa; conversely, those with higher SNa may experience worse outcomes with higher DNa. Higher DNa may lead to improved intradialytic cardiovascular stability by promoting entry of fluid from the intracellular to the extracellular compartment and possibly by facilitating vasopressin release (19). In certain patients, the potential beneficial effect of improved cardiovascular stability with higher DNa may outweigh adverse effects from diffusive sodium gain.

Net sodium balance during hemodialysis results from both diffusion and convection. Although one might assume that the difference between the dialysate and plasma sodium concentration is the simple factor governing diffusive clearance (or gain) of sodium and hence postdialysis SNa, the reality is likely more complicated, as evidenced by the fact that postdialysis SNa is variable and difficult to predict accurately; part of this results from unintended differences between prescribed and delivered (i.e., measured) DNa concentrations (20). The plasma water sodium concentration is determined by the total body exchangeable sodium, total body exchangeable potassium, and total body water (21,22)—all three of which are in flux during hemodialysis. Physiochemical factors governing electrolyte flux across the dialysis membrane additionally include ionic activities of sodium, potassium, chloride, and bicarbonate; the Gibbs-Donnan effect near the membrane (which will vary among patients); and aggregation of proteins during dialysis that may lead to effective spatial variations of electric potential along the dominant flow direction. A fundamental approach by mathematically modeling these processes is needed to determine the physical mechanisms responsible for net sodium transport.

Clinicians are faced with a number of options for dialysate sodium prescriptions: fixed sodium concentrations at various levels; tailoring the dialysate to the serum sodium concentration; sodium modeling strategies; and, where available, online monitoring of plasma conductivity with automatic adjustment of dialysate conductivity. The manuscript by Hecking et al. provides important insights on the variability of clinical practice and hypothesis-generating results on associations between DNa and morbidity and mortality. Testing different dialysate prescriptions in randomized trials will be difficult, although important. Surrogate endpoints such as IDWG and BP may be misleading based on the intriguing results provided by Hecking et al. Differences in the response to DNa according to SNa (or other associated characteristics) further complicate any planned trial examining mortality as a primary endpoint. Lowering DNa or tailoring it to the SNa may be beneficial for some, but harmful for those with lower SNa, suggesting that randomization should be stratified according to the baseline SNa or that separate interventional trials should be considered for those with lower SNa. Our dialysis patients have entrusted us with their milieu intérieur—we owe it to them to continuously strive to optimize the safe, effective, and evidence-based delivery of this life-sustaining therapy.

Disclosures
None.

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