Seminars in Dialysis

Editorial

Are Dialysate Sodium Levels Too High?

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ABSTRACT

Universal lower dialysate [Na+] is often advocated as a means of improving the dire cardiovascular plight of our dialysis patients. However, there is evidence associating lower dialysate [Na+] and increased morbidity and mortality especially in frailer patients, probably as a result of more frequent intradialytic hypotension. In this editorial, we summarize arguments for and against lower dialysate [Na+], and provide recommendations around selecting the most appropriate dialysate [Na+] for specific clinical subsets that may benefit from manipulation of salt and water balance. The lack of overall clarity on relative benefits and risks of lower dialysate [Na+] does not support the case for empirical "across the board" change, and experimental testing in clinical trials is required to determine safe and effective use.

The excess cardiovascular (CV) risk in end-stage kidney failure (ESKF) is well established, with 5-year survival statistics that are worse than many cancers (1–3). Previously, this excess risk was thought to be mainly due to atherosclerotic coronary artery disease. However, clinical trials designed to ameliorate atherosclerotic complications in kidney disease have been disappointing: reducing levels of LDL-cholesterol does not reduce CV mortality in the setting of ESKF (4–6). Furthermore, a minority of CV deaths in studies such as 4D and AURORA were actually due to identified myocardial ischemia; more were due to sudden cardiac death. These findings indicate that CV death in ESKF populations may be largely due to lethal arrhythmia (7,8).

The key condition associating sudden cardiac death and ESKF is left ventricular (LV) hypertrophy (8,9). LV hypertrophy activates pathways that lead to intermyocardial cell fibrosis, leading in turn to progressive impairment in contractility and stiffening of the myocardial wall, culminating in dilated cardiomyopathy and congestive heart failure (10–15). Myocardial fibrosis is the substrate for ventricular arrhythmogenesis by superimposing high-resistance conduction pathways, thereby increasing electrical instability and encouraging reentry arrhythmia (9,16,17).

With this in mind, salt balance seems to be a prime target for intervention to reduce CV risk in ESKF. Dialysis patients have "un-physiological" perturbations in extracellular volume, and are frequently salt and water overloaded as a result of dietary indiscretion and/or inadequate ultrafiltration. Longitudinal studies of this population show, for the most part, that LV mass either steadily increases or at best fails to regress over time, at least for those receiving conventional dialysis (18–21). Persistently elevated blood pressure (BP) and fluid overload due to positive salt and water balance appear to be the main risk factors for this worsening condition (22–25).

There are some data to suggest that a reduction (but not to normal) of LV mass can be achieved by aggressive BP control and ultrafiltration during dialysis (26). However, the most effective intervention involves the use of frequent or extended hours hemodialysis. In a randomized controlled trial, Culleton et al. demonstrated a 7.7% reduction in LV mass over a 6-month period in patients dialyzed in this manner, as opposed to stable LV mass in those dialyzed conventionally (18). Similar findings were reported in the recent Frequent Hemodialysis Network trial (20). In both studies, regression in LV mass paralleled improvements in BP control and markers of extracellular fluid volume.

Potentially, regression of LV hypertrophy might also be achieved by altering salt balance through use of lower Na+ exposure during dialysis. Sodium loading, either by excessive dietary intake or excessive diffusion via dialysate, increases both BP and inter-dialytic weight gain (27–30). In particular, there is consistent evidence from the literature suggesting that lower dialysate [Na+] relative to plasma water [Na+] is beneficial for these outcomes. The large majority of studies show that relatively lower dialysate [Na+] is associated with less thirst (31–35), lower inter-dialytic weight gain (31,36–46), and lower BP (35,38,41,44,45,47–50); only a few studies have been negative (33,51–55). Aside from altering salt and water balance, elevation in serum [Na+] (above

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135 mM) can also invoke other physiological changes affecting BP through "stiffening" of vascular endothelium, in part by impairing the release of vasodilatory nitric oxide in the microcirculation (56). Combinations of lower dialysate [Na+], dietary sodium restriction, and the use of non-sodium containing fluids for extracorporeal circuit priming and treatment of intra-dialytic hypotension might therefore be useful (57,58). However, to our knowledge, there have only been two studies examining the effect of lower dialysate [Na+] on LV structure and function (59,60). One showed an association between lower dialysate [Na+] and decreased LV volumes on echocardiography, although the duration of both studies was too short to assess for changes in LV mass.

These arguments all lead to the paradigm illustrated in Fig. 1. This paradigm is clearly appealing: it makes clinical common-sense, and is consistent with our day-to-day observations in routine medical practice. It is easy to implement in models of care, which can then be used with a clear expectation of improved patient CV outcomes. In most espousals of dialysate [Na+], this is where the story ends. So what motivates the clinical equipoise around sodium? The most compelling cautionary data are from the Dialysis Outcome and Practice Patterns Study (DOPPS) (61). In an analysis of 1727 patients and 12,274 patients years, patients with a serum [Na+] of <137 mM had a 45% higher death rate over a 12-month follow-up compared to those with a serum [Na+] of ≥ 140 mM, even after statistical adjustment for a large number of demographic and medical co-morbid factors. In terms of dialysate [Na+], there was no decrease in mortality risk in those exposed to lower dialysate [Na+] at any level of serum [Na+]. Moreover, in patients with a serum [Na+] of <137 mM there was actually a possible benefit in those exposed to higher dialysate [Na+]: a 35% lower mortality risk was observed in those exposed to dialysate [Na+] of >142 mM relative to other groups. The associations between low serum or dialysate [Na+] and increased mortality have been confirmed in reports from other groups (62–64), as well as a more recent report from the DOPPS using a different analytical approach (65).

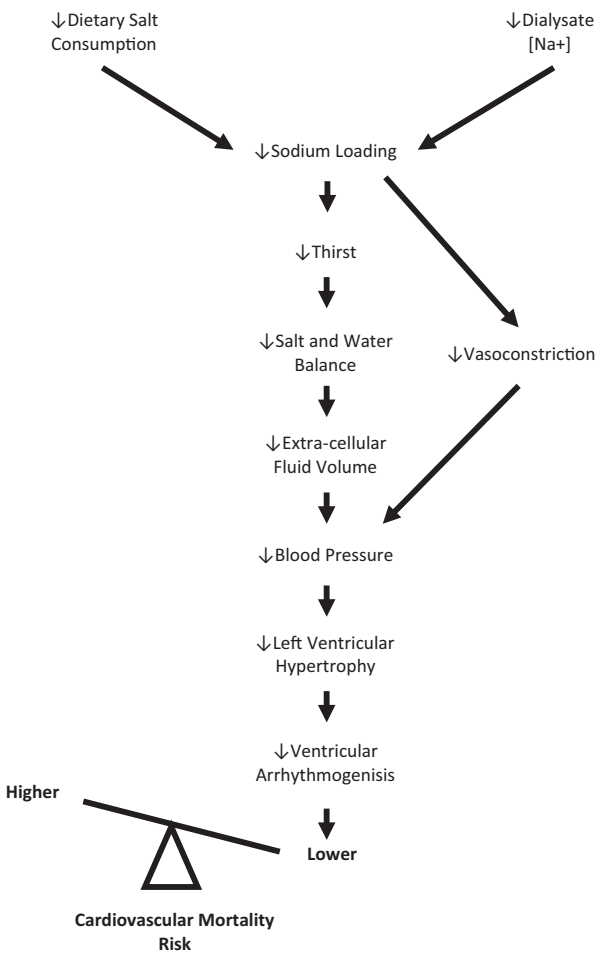

FIG. 1. Simplistic causal diagram relating low salt exposure hemodialysis to cardiovascular mortality risk.

There are several possible reasons for these counter-intuitive observations. Firstly, an important element is missing from the simplistic paradigm in Fig. 1, that of intra-dialytic hypotension. The survival advantage of higher dialysate [Na+] might plausibly be related to improved intra-dialytic hemodynamic stability: intra-dialytic hypotension is less likely to occur with higher dialysate [Na+], and hence higher dialysate [Na+] may be protective in patients prone to intra-dialytic hypotension (60). Intra-dialytic hypotension is unquestionably bad (66). It is probably as deleterious (if not more so) as inter-dialytic hypertension, and associated with myocardial stunning and all-cause patient mortality (67–69). In the DOPPS data referred to above, the authors described a definite "frail" phenotype that was associated with lower serum [Na+] in their study sample. Those patients with lower serum [Na+] were more likely to have diabetes mellitus, coronary artery disease, CV disease, congestive health failure, cerebrovascular disease, lung disease, and cancer. It is these types of patients who are prone to intra-dialytic hypotension, and less physiologically tolerant of its consequences. It would therefore not be surprising if such "frail" patients were to benefit from a higher rather than lower dialysate [Na+] (70).

Another concern that arises is whether or not dialysate [Na+] might also influence serum [Na+]. The traditional wisdom is that humans have an individual natremic set point, and studies such as the DOPPS data referred to above have generally not shown any cross-sectional correlation between dialysate and serum [Na+] (41,61,71–76). However, it is likely that natremic adaptation does in fact occur, at least to some degree. Pre-dialysis serum [Na+] did decline in several small prospective clinical trials after lowering of dialysate [Na+] (35,44,45,49,77–79), albeit after a lag of several months in some reports possibly due to the time taken to desalinate large reservoirs of non-osmotic sodium in skin and bone (80–82). Given the positive association between pre-dialysis serum [Na+] and patient survival, an intervention that might lower serum [Na+] should be carefully tested since it may have unexpected deleterious effects.

Finally, lessons may be gleaned from studies of reduced dietary salt intake on CV outcomes. The call for

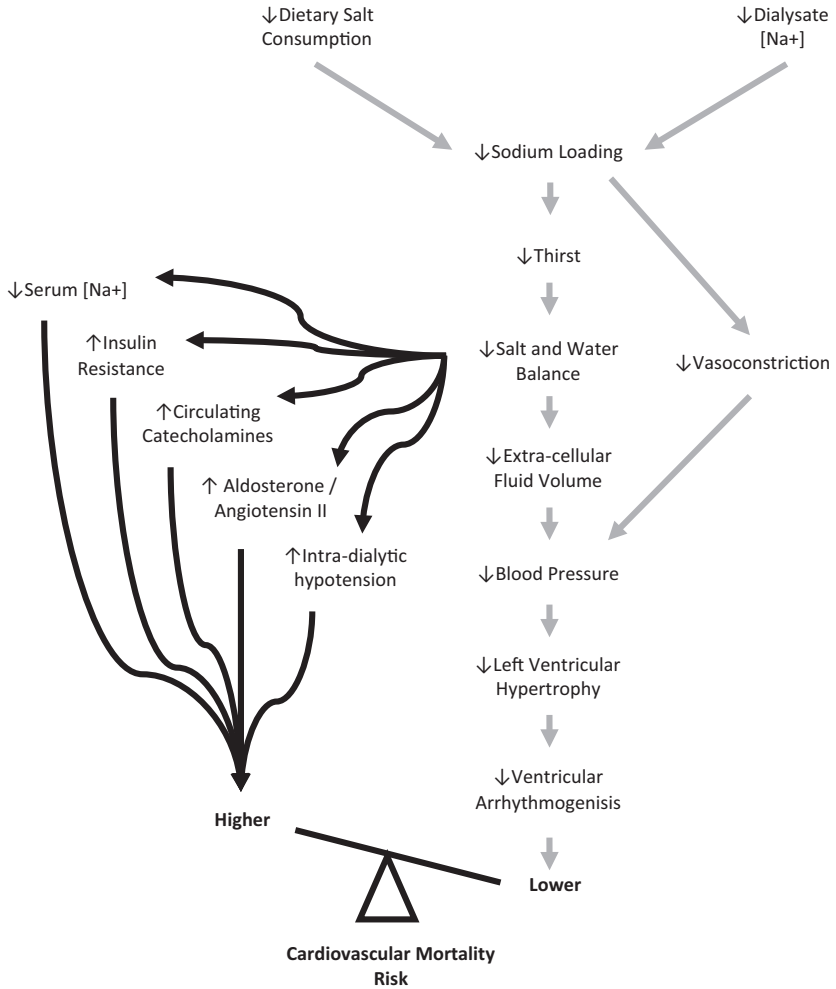

Fig. 2. More realistic causal diagram relating low salt exposure hemodialysis to cardiovascular mortality risk.

a population health intervention of universal salt restriction is predicated by two well accepted paradigms: reduced salt intake lowers blood pressure, and reduced blood pressure lowers CV risk. However, a recent meta-analysis has highlighted the ongoing clinical equipoise in this area (83,84). Despite collating more event data than previous systematic reviews (665 deaths, 6250 participants), Taylor et al. concluded that there was "still insufficient power to exclude clinically important effects of reduced dietary salt on CV mortality or morbidity." An accompanying editorial highlighted the biological plausibility of a J-shaped relationship between dietary salt intake and CV health (85). The author of an accompanying editorial makes a strong case for a true "J" shaped relationship between salt exposure and health, with a "safe" range of dietary salt intake between either extreme. He calls attention to consistent data showing negative associations between reduced dietary salt intake and outcomes, especially in the setting of generally low salt consumption (85). There are several plausible biological mechanisms to explain these observations. Reduced dietary salt intake activates a number of metabolic and neurohormonal pathways in a potentially deleterious fashion, including the sympathetic nervous and renin–angiotensin systems (86). Studies have shown increased levels of catecholamines, aldosterone and angiotensin II, total and LDL-cholesterol, and reduced peripheral insulin sensitivity (87–89).

These data all reflect the multiple physiological consequences of reducing salt exposure. Therefore, the overall effect on CV outcomes will likely be the net result of these competing and often conflicting physiological responses as shown in Fig. 2. Research agendas in both ESKF and non-ESKF populations should define the "safe" range of salt exposure, and test initiatives to ameliorate the effects of both deficient and excess salt exposure beyond an ostensible "safe" range. Moreover, it is likely that the effects of reduced salt exposure will differ between "healthy" and "frail" phenotypes and both groups should be studied.

The question of optimal dialysate [Na+] will only be answered by experimental testing in clinical trials. Although there have been a number of randomized clinical trials of dialysate [Na+], their results are not definitive. These trials have been small, short-term, and fraught with internal validity problems. Most importantly, few of the studies consider in detail the dark side of lower dialysate [Na+], which is potentially a greater degree of intra-dialytic hypotension. Few address the confounding effect of dietary salt intake, and changes in

consumption that may occur in response to alterations in dialysate [Na+]. Fewer yet use a physiologically appropriate measure of diffusible sodium which is plasma water [Na+] as measured by direct ionometry, further corrected with an additional factor to account for the Gibbs-Donnan effect (90). These corrections are important since patients who are hypoproteinemic will usually have higher diffusible sodium for any given serum [Na+] as a result of both of these factors. Finally, none address the issue of non-osmotic sodium either by direct measurement or by consideration within some quantitative physiological model. The area of non-osmotic sodium is an involved one, and detailed discussion is outside the scope of this article but is an area that should be considered in future clinical trials of dialysate [Na+].

Are typical dialysate sodium [Na+] levels too high? The truth is that we do not know. One obvious difficulty that arises with research in this area is our uncertainty as to optimal blood pressure targets for our dialysis patients: definitive randomized controlled trials of blood pressure targets in this population are wholly lacking, and the value of blood pressure as a surrogate outcome in dialysis populations is not established (91). As such, studies of dialysate [Na+] should probably not use this study endpoint, and more suitable measures should be chosen (92). Ideally, studies should also quantify the extent of the roles of inter-dialytic blood pressure and intra-dialytic hypotension, and determine their place in the hierarchy of the various important factors that lead to CV mortality and morbidity. Should these studies show lower dialysate [Na+] to result in more frequent intra-dialytic hypotension (unresponsive to the usual preventative measures), any benefit from lower salt exposure may well be offset. There are a number of studies of lower dialysate [Na+] underway or proposed, and these are shown in Table 1.

What are reasonable clinical recommendations for dialysate [Na+] while we await definitive evidence? As a default, most patients on short schedule thrice-weekly dialysis should do well with a "typical" setting for dialysate [Na+] of between 138–142 mM. However, it is important to consider whether a given patient is within a specific clinical subset that may benefit from manipulation of dialysate [Na+]. The first of these clinical subsets contain those that have clear clinical evidence of positive salt and water balance through either high dietary salt consumption or excessive diffusion via dialysate. This condition is manifested by large inter-dialytic weight gains (> 3–5% of body weight) and/or high pre-dialysis BP (> 160/90). As an adjunct to dietary measures, these patients may benefit from a lower dialysate [Na+] to offset or mitigate their positive salt and water balance.

There are two approaches to selecting a specific dialysate [Na+] setting for such patients. It has been previously estimated that low sodium hemodialysis is characterized by a dialysate [Na+] of ~135 mM in most populations, and one approach might be to select this as an empirical setting (72). Alternatively, it has also been estimated that isonatremic hemodialysis is characterized by a dialysate [Na+] that is between 0.1 and 3.0 mM lower than pre-dialysis serum [Na+] (depending on

Table 1. Currently active clinical trials with an intervention of lower dialysate [Na+], according to the WHO Registry Network of primary and partner clinical trials registries

Clinical trial registration number	Estimated enrollment, study duration	Key inclusions	Key exclusions	Intervention	Control	Primary outcome
ACTRN12611000975998	118 patient, 12 months	Adults on home HD, mean pre-dialysis serum [Na+] ≥135 mM	HD > 3.5 times/week, HDF, life expectancy < 12 months, frequent intra-dialytic hypotension, significant structural heart disease	Dialysate [Na+] 135 mM	Dialysate [Na+] 140 mM	LV mass index (cardiac MRI)
NCT01015313	40 patients, 12 months	Adults on 3 times/week HD	Pacemaker, amputation, artificial joint, life expectancy < 5 months	Dietary sodium restriction, Dialysate [Na+] equal to patient's pre-dialysis serum [Na+], avoiding saline solutions and Na+ profiling	"Standard" care	Feasibility
NCT00724633	75 patients, 3 months	Adults on 3 times/week HD > 3 months, hypertension, dialysate sodium [Na+] 140 mM, mean pre-dialysis serum [Na+] < 140 mM	Frequent intra-dialytic hypotension, significant residual renal function, life expectancy < 1 year	Dialysate [Na+] equal to patient's pre-HD serum [Na+] OR Dialysate [Na+] lower than patient's pre-dialysis serum [Na+]	Dialysate [Na+] 140 mM	Change in pre-dialysis systolic BP (home monitoring)
ISRCTN14411549	13 patients, 18 months	Adults on 3 times/week HD	Frequent intra-dialytic hypotension	"Low' dialysate [Na+]	"Standard" dialysate [Na+]	Change in intracellular and extracellular fluid volumes (bioimpedance spectroscopy)

laboratory method), and hence another approach might be to select a dialysate [Na+] setting that is somewhat lower than this (45,50,93–98). A clinical trial of low dialysate [Na+] using either intervention is reasonable, bearing in mind that a result in terms of inter-dialytic weight gain and blood pressure may only be observed after a lag of several weeks or even a few months. The second of these clinical subsets contains patients with a low serum [Na+] (<137 mM) or with the "frail phenotype" described previously. For these patients, a reasonable recommendation can be made for a higher (≥140 mM) rather than lower dialysate [Na+], especially for those with more severe forms of CV disease or intra-dialytic hypotension.

Before concluding, we should return to the issue of excess CV risk in our dialysis patients. As discussed, the most cardioprotective form of dialysis is frequent or extended hours HD. An important characteristic of this modality is enhanced intra-dialytic hemodynamic stability. Slower rates of fluid and solute removal minimize the risk of both intra-dialytic hypotension and solute disequilibrium due to rapid changes in solute concentrations (99,100). A recent small randomized cross-over study has shown that lower dialysate [Na+] at 134–136 mM during extended hours HD is effective and safe (101). The investigators demonstrated a mean decrease in inter-dialytic weight gain of 0.6 kg, and a mean decrease in pre-dialysis systolic blood pressure of 8.3 mmHg. There were no increases in the frequency of intra-dialytic hypotension or symptoms of disequilibrium. This dialysis regimen perhaps represents the future of cardioprotective dialysis, and might allow the safe application of two co-interventions aimed at better CV health: frequent or extended hours HD in combination with low dialysate [Na+]. Additional study of this promising approach is needed in the form of suitably powered clinical trials with accepted surrogate or clinical endpoints. Ironically, this approach is a re-invention of early dialysis strategies: long hour dialysis with hypotonic dialysate (dialysate [Na+] <130 mM) was the standard approach to achieve a negative sodium balance during extended hour hemodialysis in the 1970s, with dialysate [Na+] increasing only after the advent of short schedule hemodialysis and the introduction of negative-pressure hydrostatic ultrafiltration (72,102).

In summary, dialysate [Na+] is a fundamental component of hemodialysis that can be easily modified. However, more research is needed to determine the safe and effective use of lower dialysate [Na+]. An interim recommendation is to manipulate dialysate [Na+] in two clinical subsets: firstly, in those with clear evidence of positive salt and water balance by decreasing dialysate [Na+], and secondly in those with frail phenotypes characterized by more severe CV disease and intra-dialytic hypotension by increasing dialysate [Na+]. Ultimately, frequent or extended hours HD using low dialysate [Na+] may provide the greatest cardioprotection. However, the multiple physiological consequences of manipulating salt exposure mean that even the most appealing concepts still need to be assessed by experimental testing in clinical trials. The lack of overall clarity on relative benefits and risks of lower dialysate [Na+] does not support the argument for empirical 'across the board' change, nor support those clinicians who have already voted with their feet by embracing this practice in the absence of definitive evidence.

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