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# The pivotal role of sodium balance in control of blood pressure in dialysis patients

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## Abstract

In hemodialysis patients, as in patients with normal kidney function, sodium balance is the major determinant of changes in extracellular volume, and extracellular volume is an important determinant of blood pressure. The osmotic thresholds for thirst and ADH release are normal in kidney failure; pre-dialysis serum sodium concentration shows a high index of individuality in oliguric hemodialysis patients. Non-osmotic storage of sodium in vascular walls may also amplify the volume-sensitivity of blood pressure. The variable relationship between volume removal and change in blood pressure described in clinical studies reflects a state of permanent volume expansion in those whose blood pressure does not fall, or rises, during dialysis, whereas those whose blood pressure falls during dialysis are those who approach normovolemia. Rigorous control of extracellular volume often results in perfect blood pressure control, but may be difficult to achieve safely other than with long, slow dialysis combined with dietary salt restriction.

**Key words:** Hemodialysis, hypertension, sodium, extracellular volume

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## INTRODUCTION

The management of hypertension among patients on hemodialysis remains problematic, and the available guidelines are based largely on opinion. Several large observational studies have shown U-shaped or J-shaped relationships between blood pressure and subsequent outcome, with the poorest survival being seen among those patients with low predialysis and postdialysis blood pressures.<sup>1–3</sup> Dialysis-related hypotension is known to be associated with an increased risk of death.<sup>4</sup> These findings are probably an example of “reverse epidemiology,” with relatively low blood pressure being a marker of heart failure or other preterminal illness; longer term studies show an association between hypertension and the subsequent risk of heart failure and death.<sup>5,6</sup>

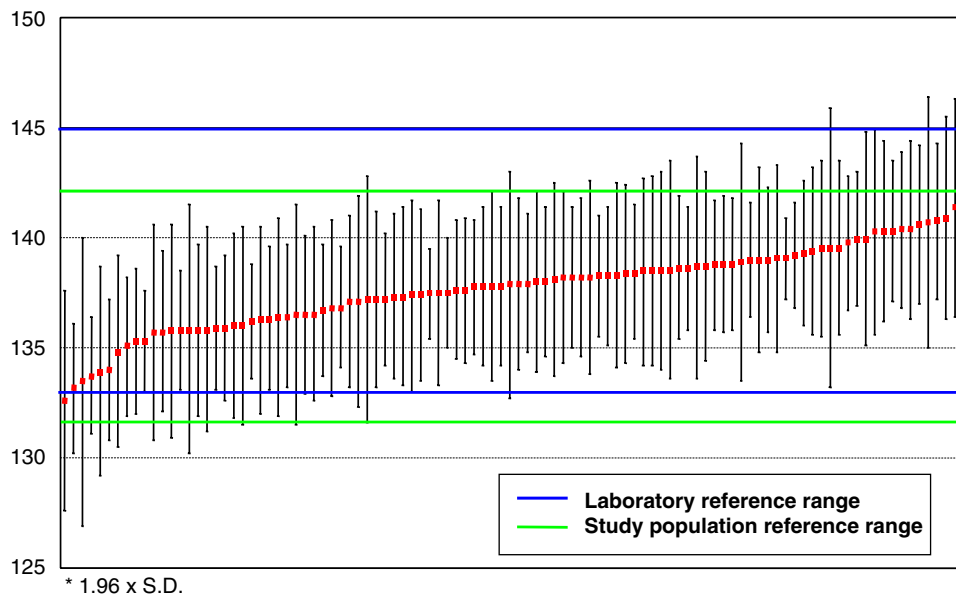
Whether or not complete correction of hypertension is associated with the best outcomes, the question remains: as to what extent is blood pressure determined by volume status (and thus by sodium balance), as opposed to neuroendocrine influences including the renin/angiotensin system, other vasoactive substances released by the kidney, endothelin, and the sympathetic nervous system?

## RELATIONSHIP BETWEEN SODIUM STATUS AND EXTRACELLULAR VOLUME

Sodium is the predominant extracellular cation, and there is no doubt that sodium (and chloride) balance determines changes in extracellular volume in both health and disease. Changes in volume status between hemodialysis sessions are related largely to changes in extracellular volume alone,<sup>7,8</sup> although there is some evidence that hypertonic dialysate (as used in sodium profiling dialysis) can lead to transient intradialytic reduction in intracellular volume.<sup>9</sup>

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**Figure 1** Serial monthly predialysis serum sodium concentrations in 102 stable, nondiabetic hemodialysis patients who had been on dialysis for at least 2 years. Each bar represents the mean and SD of 12 values from an individual patient.

## OSMOREGULATION IN END-STAGE RENAL FAILURE

The osmotic threshold for thirst and ADH release is normal in patients about to start dialysis.<sup>10</sup> Serum sodium concentration shows a very high index of individuality in oliguric nondiabetic dialysis patients, not only remaining within the reference range but also with a narrower range of variation in individual patients (Figure 1). Interdialytic weight gain is directly related to the gradient between individual predialysis sodium concentration and the dialysate sodium concentration<sup>11</sup>—in simple terms, dialyzing sodium into patients makes them thirsty. A lower individual osmotic threshold for thirst is associated with higher interdialytic weight gain.<sup>12</sup> These findings and others support the argument that it is irrational and inhumane to advise dialysis patients on fluid restriction without providing advice on salt restriction<sup>13</sup> and the need for more research on the potential benefits of individualizing dialysate sodium concentration based on usual predialysis serum sodium concentration.

Angiotensin II can also stimulate thirst, and there are occasional reports of severe, nonosmotic, thirst due to hyperreninemia.<sup>14–16</sup> Oldenburg et al. reported that enalapril reduced interdialytic weight gain,<sup>17</sup> but these findings have not been replicated.<sup>18</sup> Xerostomia due to reduced salivary flow has been reported in dialysis patients,<sup>19</sup> and correlates with IDWG;<sup>20</sup> but reduction of

xerostomia with chewing gum, or pilocarpine does not affect IDWG or blood pressure.<sup>21</sup>

## REGULATION OF SALT APPETITE IN END-STAGE RENAL FAILURE

Since the description of salt hunger among patients with Addison's disease, we have known that salt appetite is, in part, biologically determined.<sup>22,23</sup> Fernstrom<sup>24</sup> demonstrated that patients with kidney failure had higher thresholds for salty taste than normal individuals. This finding deserves further investigation. High dialysate sodium has been shown to decrease the ability to taste salt.<sup>25</sup>

## LONG SLOW DIALYSIS

Several reports from Tassin indicate that long, slow, conventional dialysis is associated with drug-free control of hypertension in over 95% of patients,<sup>26</sup> better survival than reported from any other center or Registry,<sup>27</sup> and better survival with lower blood pressure.<sup>28</sup> However, it remains unclear whether these exceptional results are due to patient selection, dietary salt restriction, long slow dialysis, or the policy of rigorous reduction of dry weight, tolerating frequent dialysis-related hypotension and cramps for the first 8 weeks, until drug-free blood pressure control is achieved. A recent report from Turkey

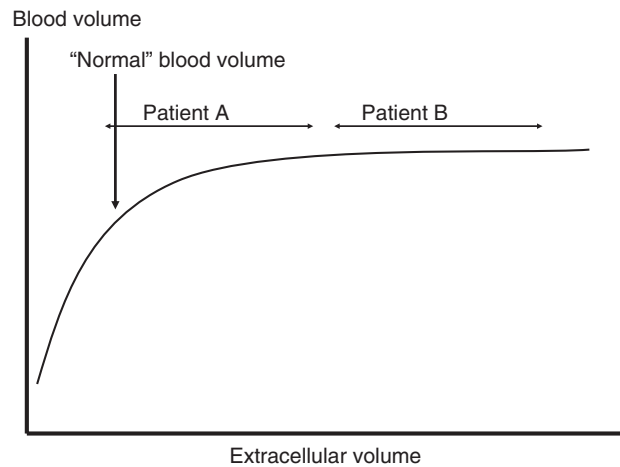
suggests that similar results can be achieved with conventional (4–5 hr thrice weekly) dialysis.<sup>29</sup> Better blood pressure control has been reported in patients undergoing both nightly long dialysis<sup>30</sup> and daily short dialysis.<sup>31–33</sup>

### PARADOXICAL VASODILATATION IN HEMODIALYSIS PATIENTS AFTER SODIUM REMOVAL

A comparison of patients receiving conventional hemodialysis in Maastricht and those receiving long slow hemodialysis in Tassin showed no significant difference in intracellular or extracellular volume or in collapsibility of the inferior vena cava, but a lower systemic vascular resistance in Tassin patients.<sup>34</sup> Similarly, planned reduction in dialysate and dietary sodium, without change in target weight, resulted in lower 48-hr ambulatory blood pressure and systemic vascular resistance.<sup>35</sup> These findings, and the “lag phase” described from Tassin between reduction of extracellular volume and correction of hypertension,<sup>26</sup> may relate to changes in the sodium content of the vascular wall and other structures,<sup>36</sup> rather than directly to changes in extracellular volume. Recent research has demonstrated that positive sodium balance results not only in volume expansion but also in marked accumulation of nonosmotically active sodium, facilitated by the synthesis of glycosaminoglycans (which bind sodium without parallel water retention), as well as by exchange of intracellular potassium for sodium in muscle; this nonosmotic sodium retention is strongly associated with increased volume sensitivity.<sup>37</sup>

### CLINICAL STUDIES RELATING HYPERVOLEMIA TO HYPERTENSION IN DIALYSIS PATIENTS

Early studies in dialysis patients showed a clear relationship between blood volume and blood pressure.<sup>38</sup> However, modern studies using ambulatory blood pressure recording have reached conflicting conclusions on the relationship between interdialytic weight gain and blood pressure, with some showing a clear relationship<sup>39–42</sup> and others showing no relationship.<sup>43–48</sup> One interpretation of these conflicting findings is that the relationship is nonlinear: no reduction in blood pressure as a result of volume removal would be expected among patients who remain significantly fluid-overloaded at the end of dialysis. The clinical assessment of “dry weight” is critically important in this context, and is known to be highly variable. Figure 2 gives a schematic illustration of why blood volume (and, therefore, blood pressure)



**Figure 2** Schematic representation of the relationship between ECF volume and blood volume. Note that normovolemia occurs at a relatively steep point on the curve; arriving at this point safely, without overshooting into hypovolemia, is more difficult the more rapid the rate of reduction of ECF volume. The horizontal arrows represent the fluctuation in ECF volume in 2 patients, each with similar interdialytic weight gains.

changes significantly in patients who approach physiologically appropriate “dry weight” during dialysis, but will remain unaltered in those patients dialyzing to an inappropriately high dry weight. A post hoc analysis of data from the HEMO study confirmed this interpretation: plasma volume actually *increased* in many patients; as a result there was a dissociation between changes in body weight and changes in plasma volume; and a reduction in plasma volume was associated with a reduction in blood pressure, whereas no such relationship was found between body weight and blood pressure.<sup>49</sup>

Several small clinical studies provide convincing evidence that hypertension can, at least in some patients, be caused by saline overload. Fishbane et al., used measurement of plasma atrial natriuretic peptide (ANP) as a marker of ECF volume. In those patients remaining hypertensive before and after dialysis, ANP was high both before and after dialysis; in those whose hypertension was corrected by dialysis, ANP fell significantly; and in those who were normotensive before and after, ANP was low.<sup>50</sup> Reduction of dialysate sodium, combined with dietary salt restriction, results in lower blood pressure with less antihypertensive drugs.<sup>51</sup> Cirit et al. selected patients with “paradoxical” rise in blood pressure during dialysis, often mistakenly attributed to hypovolemia, and demonstrated clear evidence of ECF expansion, with a 64/

22 mmHg reduction in blood pressure after discontinuation of antihypertensive drugs and intensive ultrafiltration.<sup>52</sup> There have been no large-scale trials of systematic approaches to the control of blood pressure by control of extracellular volume, and such trials ought to be carried out. The CLIMB study randomized patients to volume control using online hematocrit monitoring or to usual care, and reported higher mortality in those undergoing hematocrit monitoring—but an unusually low mortality in the usual care group.<sup>53</sup> A post hoc analysis from this study showed higher mortality in those whose blood pressure rose during dialysis compared with those who experienced a fall in blood pressure during dialysis.<sup>54</sup>

The relationship between interdialytic weight gain and blood pressure is determined partly by the mechanical properties of the left ventricle and large vessels: high volume sensitivity is associated with higher elastance of the left ventricle (indicating greater “stiffness”).<sup>55</sup>

## CONCLUSIONS

Alterations in extracellular fluid volume in patients on hemodialysis are largely driven by sodium balance; water intake is determined by osmoregulation of thirst, thus maintaining normal extracellular osmolality at all times. Individual patients vary in their “osmostat” set points; use of a standard dialysate sodium concentration causes positive sodium balance, thirst, and hypertension in patients with low predialysis plasma sodium concentration. The lack of a relationship between fluid removal and blood pressure in many hemodialysis patients nearly certainly reflects a state of permanent saline overload. Correction of this state by hemodialysis is highly likely to result in reduction in blood pressure, and in correction of hypertension in many patients, but whether this can be achieved safely in all patients other than by daily, nightly, or long slow hemodialysis requires further study.

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