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Role of sodium in hemodialysis

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Role of sodium in hemodialysis. Sodium chloride is the most abundant salt in extracellular fluid. In normal individuals, the tonicity exerted by dissolved sodium chloride determines plasma osmolality and indirectly determines intracellular tonicity and cell volume. Uremic patients retain nitrogenous wastes and have an elevated plasma osmolality. While urea exhibits osmotic activity in serum, no sustained gradient can be established across cell boundaries because it readily diffuses through cell membranes. Thus, sodium remains the major indicator of body tonicity and determines the distribution of water across the intracellular–extracellular boundary, subsequent cell volume, thirst, and, among patients with renal insufficiency, systemic blood pressure. As a result of highly conserved plasma tonicity control systems, uremic subjects demonstrate remarkable stability of their serum sodium. Dialysate is a synthetic interstitial fluid capable of reconstituting extracellular fluid composition through urea extraction and extremely efficient solute and solvent (salt and water) transfer to the patient. Subtle transdialyzer gradients deliver and remove large quantities of trace elements, solvent, and solute to patients, creating a variety of dialysis "disequilibrium" syndromes manifest as cellular and systemic distress. Every dialysis patient uses dialysate, and the most abundant chemicals in dialysate are salt and water. Despite its universal use, no consensus on dialysate composition or tonicity exists. This can only be explained if we believe that dialysate composition is best determined by matching unique dialysis delivery system characteristics to specific patient requirements. Such a paradigm treats dialysate as a drug and the dialysis system as a delivery device. Understanding the therapeutic and toxic profiles of this drug (dialysate) and its delivery device (the dialyzer) is important to safe, effective, goal-directed modifications of therapy. This article explores some of the historical rationale behind choosing specific dialysate tonicities.

Dialysis is a complex, albeit empiric, therapy. Typically envisioned as a washing or cleansing process, dialysis uses dialysate, a synthetic plasma water component, to remove soluble wastes from the blood. The ideal dialysate contains all of the elements of normal plasma and is devoid of any excesses that accumulate during uremia. This permits soluble wastes to diffuse from the patient into the dialysate and normalizes the patient's plasma composition. In reality, dialysate is a plasma water-like solution capable of both removing toxins and delivering solute and solvent to the patient. Early dialysis physicians identified the capacity of dialysate to intoxicate patients through the unintentional delivery of toxic trace elements and mistaken compounding [1–3]. Similarly, depletion syndromes could be precipitated by dialysate devoid of critical plasma constituents (hypoglycemia). In reality, dialysate is the only drug used by all dialysis patients and is critical to safe, effective extracorporeal renal replacement [4, 5]. It is understandable, therefore, that early physicians formulated dialysate specifically to meet the unique needs of their patients and the technology available to them [6].

Advanced renal failure typically results in sodium retention [7–10] and hypertension [11–14]. Early dialysis systems used relatively small surface area dialyzers, impermeate cellulosic membranes, and open dialysate reservoirs. Dialyses of the era were prolonged, lasting 8 to 24 hours, and the delivery systems were incapable of regulated hydrostatic "ultrafiltration." Thus, in the 1960s and 1970s, dialysis prescriptions required that interdialytic salt and water accumulations be removed by diffusion and osmosis rather than by regulated hydrostatic transmembrane pressure "ultrafiltration." Diet prescriptions limited sodium intake to 45 to 90 mmol/day and fluid to less than 1 L/day. In order to remove the salt and water that accumulated between dialyses, early investigators used dextrose containing hyponatremic dialysate to create osmotic and diffusive transmembrane gradients. Dialysate compounded with a sodium content of approximately 126 mEq/L permitted removal of the 250 to 450 mmol of salt and 5 to 8 L of water ingested weekly [15]. This hyponatremic dialysate controlled blood pressure in 70 to 90% of patients, suppressed thirst, and helped control interdialytic weight gain [16–18].

In the 1970s, improved dialyzer construction and delivery system design permitted increasing dialysis efficiency and hydrostatic transmembrane pressure-driven "ultrafiltration." Physicians began to report a dialysis precipitated, potentially fatal "disequilibrium" syndrome. The manifestations of "dialysis disequilibrium" included fatigue, nausea, lethargy, headache, muscle cramps, and

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occasionally intracranial hypertension complicated by seizures and death [19]. As the biochemical efficiency of dialysis, increased "dialysis disequilibrium" became a more prominent concern, and by the late 1970s, "dialysis discomfort" was an anticipated consequence of dialysis. The "discomfort" and "disequilibrium" syndromes were variously attributed to electrolyte imbalance, osmotic disequilibria, tissue hypoxia, acetate intolerance, and cytokine stimulation. The most serious problem, brain edema, was believed to be the result of an acute reduction in serum urea or osmolality and could be ameliorated by limiting dialysis efficiency or infusing osmotic agents [19–21].

The advent of blood pumps, durable large surface area dialyzers, and negative-pressure dialysis delivery systems dramatically altered hemodialysis. Hydrostatic ultrafiltration became a safe effective reality. By 1980, mechanical hydrostatic fluid removal could exceed 1 L/hour, and osmotic convective forces were no longer required. Simultaneously, the National Cooperative Dialysis Study revealed that "short" dialysis could achieve biochemical adequacy [22]. Combining durable large surface area dialyzers with "ultrafiltration"-regulated dialysis delivery systems would theoretically permit uremia control and salt and water regulation during "short," efficient hemodialysis. Furthermore, because hydrostatic ultrafiltration was both potent and flexible, dietary salt and water restrictions could be relaxed. Technology had achieved a true breakthrough. Dietary privations could be relieved, and dialysis treatment times decreased from six to eight hours to four to five hours thrice weekly! These events would greatly facilitate patient rehabilitation.

By 1980, "hypotonic dialysate" was no longer crucial to dialysis salt and water removal, and because "high" sodium dialysate diminished the severity of "dialysis disequilibrium" [21], dialysate sodium concentrations drifted upward from 126 mmol/L to a more physiologic range of 130 to 135 mmol/L [15, 16]. In this era of rapid, "short" dialysis, the incidences of "dialysis discomfort" were substantial [23]. Hypotension, nausea, vomiting, cephalgia, and muscle cramps occurred in 15 to 70% of all dialysis sessions and were so frequent that they became virtually synonymous with the hemodialysis process [24, 25]. It was proposed that the large surface area dialyzers needed for "short" dialysis removed bicarbonate and delivered acetate to patients at rates exceeding their metabolic capacity. This presumably resulted in acetate accumulation, symptomatic intoxication, and "discomfort" with hypotension, headache, nausea, vomiting, dizziness, and muscle cramps [24, 26]. Following reports of lessened hypoxia and improved vascular stability, bicarbonate concentrates for single-pass dialysis proportioning systems were developed [26–28].

In the early 1980s, the University of Iowa was primarily an in-hospital acute dialysis provider. In an attempt to maximize the hemodynamic stability and minimize the "disequilibrium" of these acutely ill dialysis patients, we produced a "eunatremic," high-calcium, bicarbonate dialysate with a sodium content of 140 mEq/L and a calcium of 1.75 mmol/L. During testing, we found that stable maintenance hemodialysis patients preferred and vociferously requested bicarbonate dialysate because they believed it improved dialysis comfort. We also discovered that patients blinded to the dialysate composition could not reliably distinguish between bicarbonate dialysate and a specially prepared 140 mEq/L "high"-sodium, acetate-based dialysate. Additional experiences suggested that dialysate tonicity played a substantial role in the "superior hemodynamic stability" of bicarbonate dialysis [29–35]. Presumably, as blood is dialyzed, plasma osmolality drops from approximately 310 mOsm/L to approximately 290 mOsm/L. When reinfused in the patient whose osmolality is 310 mOsm/L, the osmotic gradient is dissipated when water moves out of the plasma and into the interstitial and intracellular spaces [15]. This process reduces plasma volume and incites intracellular edema even in the absence of ultrafiltration. Recurrent descriptions of improved dialysis comfort, reduced disequilibrium, and better ultrafiltration tolerance made "high"-sodium, bicarbonate-based dialysate a requisite for "rapid," "high-efficiency" hemodialysis therapy [36–39].

Changes in plasma osmolarity were once thought to be the primary determinants of both dialysis "disequilibrium" and hemodynamic instability [40]. If dialysis "disequilibrium" and "discomfort" are the result of cellular osmotic distress, then abolishing the translocation of water from the extracellular to the intracellular space should obviate the disorder; a number of osmotic substances, including mannitol, glycerol, urea, and sodium, successfully achieved this goal [19, 25]. Alternatively, the symptoms of dialysis "disequilibrium" are reminiscent of "water intoxication," and the syndrome itself became obscure with the introduction of more physiologic dialysates [41]. Agents that restore plasma volume and tissue perfusion relieve dialysis "discomfort." A serum sodium change of 1 mEq/L is the osmotic equivalent of a 6 mg/dL change in blood urea nitrogen (2 mmol urea) or the oncotic gradient produced by 10 g/dL of serum protein [42]. Thus, between 1980 and 1995, as the average dialysate sodium increased from approximately 132 mmol to the present day 140 to 145 mmol, we eliminated an osmotic shift equivalent to a 50 to 70 mg/dL fall in blood urea nitrogen (14 to 26 mmol urea) and greatly diminished the likelihood of significant cerebral edema or "disequilibrium." Additionally, it is likely that dialysis-induced plasma volume depletion and hemodynamic instability are not the result of urea-induced osmotic disequilibria nor of aberrant vascular tone, but are a function of the dialysate to plasma tonicity gradient and the ultrafiltration/plasma refilling paradigm. It is tonicity and not urea

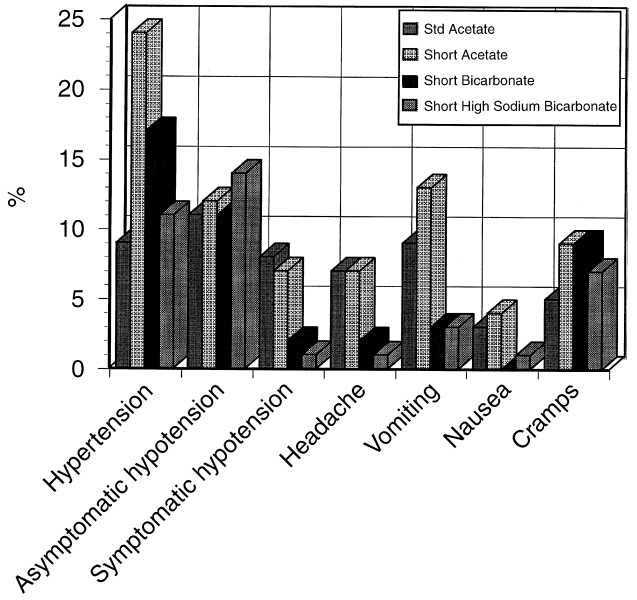

Fig. 1. Incidence of complications noted during several dialysis protocols assessing the benefits of acetate and bicarbonate buffer and 140 mmol and 145 mmol sodium dialysate during hemodialysis [36]. Standard dialysis lasted approximately four hours, and rapid therapy lasted 2.75 hours. Mean weight loss was 2.0 kg for standard dialysis using a 140 mmol sodium 40 mmol acetate dialysate and 1.6 kg using the same acetate dialysate for 2.75 hours. Bicarbonate dialyses achieved weight losses of 1.9 kg using a 140 mmol sodium and 35 mmol bicarbonate dialysate and 2.4 kg using a 145 mmol sodium 35 mmol bicarbonate dialysate for a 2.75-hour dialysis. Predialysis blood pressure increased in the "short, high-efficiency" treatments unless ultrafiltration was increased. There were fewer episodes of symptomatic hypotension using bicarbonate dialysate. Ultrafiltration tolerance was improved by using higher sodium dialysate.

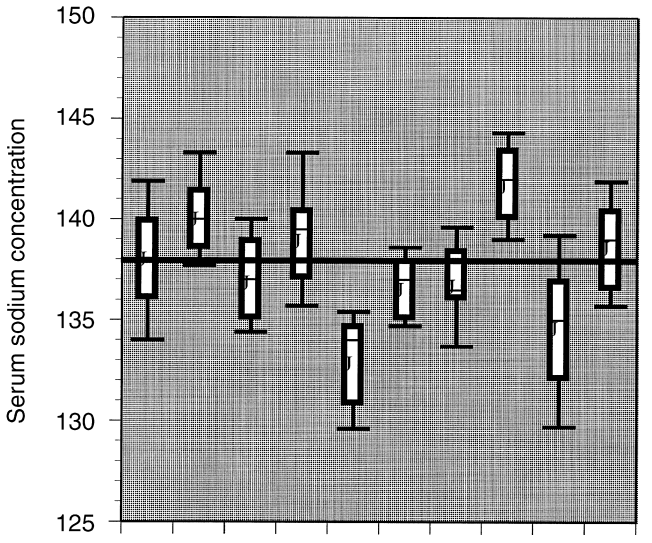

Fig. 2. Midweek serum sodium for 12 consecutive months in 10 nondiabetic dialysis patients. The box and whiskers plot represents the mean (□), 25th and 75th percentile (box), and 10th and 90th percentile (whiskers) sodium values for each individual. The group mean is 138 ± 3.4 mEq/L and is represented by the straight line. Each patient has a relatively fixed and stable serum tonicity with a narrow range of variation (±2%). These patients use a bicarbonate dialysate with a delivered sodium concentration of 140 ± 2 mmol/L measured by indirect potentiometry and had a wide range of interdialytic weight gains (0.2 kg to 5.6 kg).

osmolality that determines water movement across cell membranes to influence plasma refilling and subsequent intradialysis comfort [23, 24, 25, 41, 43–46].

What are the benefits of "high"-sodium dialysate? High-sodium dialysate minimizes dialysis disequilibrium, and by abstracting water from the intracellular into the interstitial and plasma compartments reduces the frequency and severity of dialysis hypotension. By avoiding tissue hypoperfusion, "high"-sodium dialysate ameliorates the common manifestations of dialysis "discomfort," including nausea, vomiting, headache, chest pain, hypotension, and perhaps cramps [29, 44]. In most reports, "short," "high-efficiency," and "ultra-high-efficiency" dialysis with a "high"-sodium, bicarbonate-based dialysate actually produces less intradialysis discomfort and hypotension than does standard therapy [23, 36–38]. "Short," "high-efficiency" dialysis with "high"-sodium dialysate, however, is regularly associated with an increased interdialytic weight gain and, as Figure 1 illustrates, an increased incidence of predialysis hypertension [23, 24, 36, 38, 47]. It has also been proposed that the improved intradialysis comfort of "short," "high-efficiency" therapy may be partially offset by greater interdialytic distress [23].

WHAT CONSTITUTES "HIGH"-SODIUM DIALYSATE?

Sodium chloride is the predominant extracellular salt and the primary determinant of plasma and hence intracellular tonicity. While plasma volume is relatively elastic, plasma tonicity is highly conserved. When Gotch et al changed dialysate sodium from a low of 132 mEq/L to a high of 146 mEq/L, he found that the predialysis serum sodium of his patients remained constant [25]. Similarly, Figure 2 illustrates that over a one-year interval, nondiabetic dialysis patients have extremely little variation in their serum tonicity. While the mean predialysis serum sodium of these patients is 138 ± 3.4 mEq/L, individual values vary from 132 to 144 mEq/L. However, the predialysis sodium of any individual patient varies by less than 2 mEq/L from month to month, a degree of variability within the laboratory's analytical error (relative error ± 1%). Furthermore, when these patients dialyze with a 140 mEq/L sodium dialysate, their serum sodium increases. Figure 3 reveals that the predialysis to postdialysis sodium increases 2.3 ± 3.6 mEq/L but can vary from −2.0 to 8.0 mEq/L, and in at least one patient, the postdialysis serum sodium concentration was 145 mEq/L [47]. This suggests that while dialysis successfully removes the patient's interdialytic weight gain (or water intake = water removal), it fails to restore salt balance because the interdialytic dietary sodium is in-

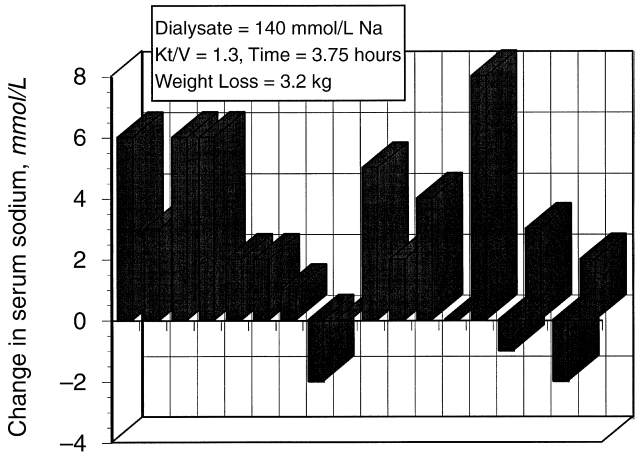

Fig. 3. Patients using a dialysate sodium of 140 mmol/L have an increase in their serum sodium during dialysis. This finding, combined with the data in Figure 2, suggests that each patient has a unique "osmostat" setting and will drink water to restore plasma tonicity to some nominal value. Thus, dialysis salt loading presumably leads to excessive thirst and subsequent increased interdialytic weight gain.

completely removed. Failure to achieve isonatric dialysis results in a tonicity increase equivalent to the unanticipated retention of 80 mmol of NaCl. How and why did this happen?

SODIUM FLUXES ACROSS THE DIALYSIS MEMBRANE

The physical characteristics determining diffusion and convection across the dialyzer have been described. Simply increasing the membrane surface area to achieve high efficiency does not produce discrepant solvent and solute movement. Rather, the membrane's intrinsic resistance to solute and solvent (water) flow and the concentration or activity gradients across the membrane are the variables responsible for the relative transmembrane fluxes of salt and water [4, 25, 48–50].

THE CONCENTRATION GRADIENT

Dialysate containing 140 mEq/L sodium reduces dialysis discomfort, and because the sodium concentration is in the "normal" range, it is anticipated that isonatric dialysis will be achieved. The classic thermodynamic law of entropy predicts that as energy is put into a system, matter will disperse uniformly to a state of maximal disorder. Diffusion is a manifestation of this disorder, and we expect dissolved substances to disperse uniformly in solution. In reality, chemical systems are seldom ideal, and dissolved substances interact with both solvent and other solutes. The sodium ions present in plasma interact with water and other dissolved materials, particularly proteins, bicarbonate, carbonate, and sulfate. These interactions are a form of structure or failure to achieve maximum disorder. Since only infinitely dilute solutions exhibit "ideal behavior," chemists describe reactions by modifying the chemical concentration (c) with a "fudge factor" or activity coefficient (f) to derive an activity or apparent concentration (a) [51, 52]. This recognizes that not all the sodium ions present are immediately available to enter into a reaction and that only free noncomplexed ions are electrochemically active. Furthermore, sodium activity (a) changes with the composition and temperature of the solution. Thus f, the activity coefficient, changes when the solution composition is altered. Changing solution pH or adding other ions, such as carbonate, bicarbonate, or phosphate, effectively lowers the number of free, noncomplexed sodium ions in solution and reduces the activity and activity coefficient of sodium.

$$a = f \times c$$

$$\text{activity} = \text{activity coefficient} \times \text{concentration}$$

Distinguishing between concentration and activity is paramount to understanding why patients fail to achieve simultaneous salt and water balance during dialysis. Only chemically active sodium is able to move across a dialysis membrane by diffusion, and it is the difference between the activity of sodium in the blood and the activity of sodium in the dialysate that drives diffusion across the dialysis membrane. Patients with a predialysis serum sodium concentration of 134 mEq/L can end treatment with a serum sodium concentration of 144 mEq/L and a postdialysis serum sodium activity of 148 mEq/L despite using dialysate with a sodium concentration of 140 mEq/L [5, 49, 53–56].

There are substantial differences between the serum sodium concentration and activity. First, we need to examine the measurement process [51, 52, 54, 57]. If a liter of blood is placed in a beaker, we can measure its sodium content by burning or ashing the sample, dissolving the ash in dilute hydrochloric acid, and performing emission flame spectroscopy to find a whole blood sodium content of 84 mEq/L. If we then place 10 mL of blood into a dialysis sac and suspend that sac in a liter of salt solution containing 84 mmol of NaCl, we would be surprised to find the sac swell and even burst as fluid flows across the membrane into the blood sample. This occurs because blood is a complex fluid in which 40% of the volume is occupied by red cells devoid of sodium. Thus, all of the 84 mEq/L sodium concentration measured in whole blood is present in the plasma, a volume of 0.6 L rather than 1.0 L. That means that the sodium content of plasma is 140 mEq/L, a value much higher than that of our hypothetical dialysis solution, and thus, sodium diffuses out of plasma into the bathing solution, while water diffuses down its activity gradient into the dialysis bag. The hematocrit in our dialysis bag does not change appreciably because water is distributed across cell mem-

branes entering both red cells and plasma, causing the total blood volume to increase from 10 to 16 mL as the red cells swell. Sodium diffusion is not between blood and dialysate but between the salt-containing solutions: plasma and dialysate. Had we spun down our blood sample and measured the sodium content of plasma, we would have reported a plasma sodium concentration of 140 mEq/L. While sodium is restricted to moving between the plasma water and our dialysis solution, water freely traverses cell membranes and enters red cells causing them to swell and perhaps lyze as intracellular tonicity is diluted to equal that of the extracellular bathing solution.

Alternatively, if we had measured the whole blood sodium with an ion-selective sodium electrode (direct potentiometry), we would have directly measured the electrochemical activity of sodium in whole blood and found it to be equal that of plasma and plasma water. This measurement differs from the serum sodium concentration reported by emission flame spectrophotometer and the clinical laboratory because plasma contains proteins and lipids, which occupy space in the plasma volume. Thus, if we ultracentrifuge plasma, ≅6% of plasma is colloidal protein and lipid, and all 140 mEq of sodium are in 0.94 L of plasma water. Thus, the plasma water sodium concentration is 149 mEq/L. Indeed, any time we add protein or lipid to a saline solution, we find that sodium concentration measurements made by flame spectrophotometer decrease in proportion to the amount of protein added, yet direct activity measurement using an ion-selective electrode remains constant [51]. Ion-selective electrodes sense the electrochemical activity of sodium ions and not the volume in which they are dissolved. They can match activities but cannot determine concentrations (that is, the total mass of ions present in a sample).

The laboratory method used to measure serum sodium affects our perception of isonatric dialysate (that is, the dialysate sodium concentration that results in no net sodium diffusion) [4, 54, 57]. When the laboratory uses flame photometry to measure plasma and dialysate sodium concentration, it underestimates the concentration of sodium in plasma water, and it would be preferable to convert these readings into activities to determine when the dialysate sodium activity equals the blood sodium activity. Since plasma is ≅94% water the mean sodium content of plasma water for patients in Figures 2 and 3 would be ≅147 mEq/L [(138 mEq/L plasma) × (1 L plasma/0.94 L water) = 147 mEq/L of water], and the dialysate sodium concentration predicted to prevent diffusive sodium transfer would be 147 mEq/L. (Using plasma standards to calibrate ion-selective electrodes performing indirect potentiometry adds further uncertainty to the situation because dialysate sodium content is overestimated [5]).

THE DIALYSIS MEMBRANE

Using a semipermeable membrane for dialysis further complicates achieving balanced salt and water removal through isonatric dialysis. Based solely on activity measurements, a 140 mEq/L "high"-sodium dialysate is hyponatremic to the patients' plasma water sodium of 147 mEq/L, and sodium ions should diffuse from the patient into the dialysate, a prediction not fulfilled in vivo. Dialysis membranes are functional gels, and analogous to gel electrophoresis, the charge density of the membrane interacts with molecules as they move through its structure. Under conditions of high ultrafiltration pressure (greater than 1 atmosphere) and high perfusate flow, these membranes can function as reverse osmosis systems. As charged ions approach the membrane, they are repelled from the membrane gel and form a junctional layer that is relatively rich in ionic charge. This shell further repels ions and concentrates them in the perfusate producing a water-enriched ultrafiltrate. This is the general principle behind reverse osmosis, and when charge dense, small pore membranes are used in high-pressure settings, ion rejection can exceed 90%. Under in vitro conditions, the sieving effect for sodium ions across most dialysis membranes is negligible [54]. However, in vivo, as plasma approaches and enters the membrane, charged proteins are restricted from crossing this barrier and form a "shell" within the membrane. This shell is an electrochemical boundary that interacts with other ions impeding their flow across the dialyzer to produce a water-enriched, ion-poor plasma ultrafiltrate. Furthermore, because electrical neutrality must be maintained, negatively charged proteins retained in the membrane and plasma water trap accompanying cations (sodium, calcium, magnesium), causing them to be retained in the plasma water. Thus, salts are restrained from isotonic flow across the dialyzer membrane. This protein induced transport asymmetry is termed the Gibbs-Donnan effect and results in the production of a hypotonic ultrafiltrate in which the sodium activity is less than that of the source plasma water [4, 25, 46, 50, 53, 55, 58, 59].

The overall membrane sieving or Donnan coefficient has been estimated to equal a sodium activity gradient of −5 to −10 mEq/L and is influenced by the composition of the dialysis membrane (total in vivo membrane sieving coefficients, which include the Donnan coefficient, are generally below 0.95). The Donnan effect predicts that isonatric dialysis will occur only if dialysate sodium activity is 5 to 10 mmol less than the plasma water sodium activity. This offset is very close to the discrepancy between the flame spectrophotometer determined plasma sodium concentration and the plasma water sodium activity [46].

What are "high" and "low" dialysate sodiums? The term "low"-sodium dialysate refers to a dialysate sodium

activity that permits diffusive transport of salt out of the patient and into the dialysate. If a single dialysate is to achieve this goal for more than 70% of all dialysis patients, then that dialysate will need to be compounded with sodium content one standard deviation below the mean sodium concentration of all dialysis patients, or approximately 135 mEq/L. Similarly, a "high"-sodium dialysate would have a sodium concentration of approximately 141 mEq/L. This "high"-sodium dialysate would avoid diffusive sodium abstraction from approximately 90% of patients, but because patients exhibit a normal distribution of basal plasma sodium values, this "high"-sodium dialysis will salt load 50% of subjects and contribute to dialysis hypertension [60]. "High," "low," and "isonatric" dialysate sodium can only be accurately defined for individuals. Generic dialysis compounding results in inappropriate sodium abstraction or delivery for more than 50% of the dialysis population. When dialysate sodium modeling is practiced to achieve isonatric dialysis, the incidence of dialysis discomfort is remarkably low [25, 50, 61–64]. Furthermore, isonatric dialysis should avoid postdialysis hypertonicity and might therefore improve both intradialysis and interdialysis comfort [23].

Because mechanical ultrafiltration inherently produces a hypotonic ultrafiltrate, it uncouples salt and water balance during dialysis, and patients are salt loaded in direct proportion to their dialysis weight loss. This creates an ever spiraling cycle of hypertonicity, excess thirst, and larger interdialytic weight gain requiring greater ultrafiltration and escalated dialysis salt loading. Achieving salt balance requires either abstracting excessive quantities of extracellular fluid and subsequent volume depletion or exploiting diffusive sodium removal. Thus, to achieve isonatric dialysis during combined ultrafiltration/dialysis, it is likely that dialysate sodium activity must fall below that of the plasma water. Therapy directed toward dialysis comfort requires the use of isonatric to hypertonic dialysate to preserve plasma volume, minimize cellular edema, and sustain tissue perfusion. Achieving these goals without gross salt loading requires that dialysate be compounded for the individual patient, dialyzer combination. If isonatric dialysis becomes a reality, perhaps it can relieve postdialysis thirst, reduce interdialytic weight gain, and control predialysis hypertension [47, 9, 65, 66]. If these goals can be met, then it may be possible to achieve extracellular fluid volume control and drug-free blood pressure control without resorting to long-slow, or daily therapy [47, 67–70]. Proponents of sodium modeling believe that delivering comfortable isonatric dialysis through closed loop-control systems and dialysis–ultrafiltration profiling will achieve these goals.

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REFERENCES

1. *Technical Report: Investigation of the Risks and Hazards Associated with Hemodialysis Devices*. An FDA Medical Device Standards Publication, Washington D.C., U.S. Department of Health, Education, and Welfare, Public Health Service/Food and Drug Administration/Bureau of Medical Devices; U.S. Government Printing Office, O=625–146/1864, 1980
2. Jochimsen EM, Carmichael WW, An JS, Cardo DM, Cookson ST, Holmes CE, Antunes MB, de Melo Filho DA, Lyra TM, Barreto VS, Azevedo SM, Jarvis WR: Liver failure and death after exposure to microcystins at a hemodialysis center in Brazil. *N Engl J Med* 338:873–888, 1998
3. Ward RA: Water processing for hemodialysis. I. A historical perspective. *Semin Dial* 10:26–31, 1997
4. Locatelli F, Ponti R, Pedrini L, Di Filippo S: Sodium and dialysis: A deeper insight. *Int J Artif Organs* 12:71–74, 1989
5. Flanigan MJ: Sodium flux and dialysate sodium in hemodialysis. *Semin Dial* 11:298–304, 1998
6. Grimsrud L, Cole JJ, Lehman GA, Babb AL, Scribner BH: A central system for the continuous preparation and distribution of hemodialysis fluid. *Trans Am Soc Artif Intern Organs* 10:107–109, 1964
7. Dorhout Mees EJ: Volemia and blood pressure in renal failure: Have old truths been forgotten? *Nephrol Dial Transplant* 10:1297–1298, 1995
8. Brennan BL, Yasumura S, Letteri JM, Cohn SH: Total body electrolyte composition and distribution of body water in uremia. *Kidney Int* 17:364–371, 1980
9. Matsuoka H, Kimura G, Sanai T, Kojima S, Kawano Y, Imanishi M, Kuramochi M, Omae T: Normalization of increased sodium sensitivity by maintenance hemodialysis. *Am J Hypertension* 3(8 Pt 1): 628–631, 1990
10. Ritz E, Koomans HA: New insights into mechanisms of blood pressure regulation in patients with uremia. *Nephrol Dial Transplant* 11(Suppl 2):52–59, 1996
11. Agarwal A, Anand IS, Sakhuja V, Chugh KS: Effect of dialysis and renal transplantation on autonomic dysfunction in chronic renal failure. *Kidney Int* 40:489–495, 1991
12. Kooman JP, Leunissen KML, Luik AJ: Salt and hypertension in end-stage renal disease. *Blood Purif* 16:301–311, 1998
13. Rahman M, Dixit A, Donley V, Gupta S, Hanslik T, Lacson E, Ogundipe A, Weigel K, Smith MC: Factors associated with inadequate blood pressure control in hypertensive hemodialysis patients. *Am J Kidney Dis* 33:498–516, 1999
14. Converse RL Jr, Jacobsen TN, Toto RD, Jost CM, Cosentino F, Fouad-Tarazi F, Victor RG: Sympathetic overactivity in patients with chronic renal failure. *N Engl J Med* 327:1912–1918, 1992
15. Stewart W: The composition of dialysis fluid, in *Replacement of Renal Function by Dialysis* (3rd ed), edited by Maher JF, Dordrecht, Kluwer Academic Publishers, 1989, pp 199–217
16. Barbour BH: Hemodialysis equipment, in *Clinical Aspects of Uremia and Dialysis*, edited by Massry SG, Sellers AL, Springfield, Charles C. Thomas, 1976, pp 659–670
17. Weidmann P, Maxwell MH: Hypertension, in *Clinical Aspects of Uremia and Dialysis*, edited by Massry SG, Sellers AL, Springfield, Charles C. Thomas, 1976, pp 100–145
18. Klooker P, Bommer J, Ritz E: Treatment of hypertension in dialysis patients. *Blood Purif* 3:15–26, 1985
19. Arieff AI, Massry SG: Dialysis disequilibrium syndrome, in *Clinical Aspects of Uremia and Dialysis*, edited by Massry SG, Sellers AL, Springfield, Charles C. Thomas, 1976, pp 34–52
20. Henrich WL, Woodard TD, Blanchley JD, Gomez-Sanchez C, Pettinger W, Cronin RE: Role of plasma osmolality in blood pressure stability after dialysis and ultrafiltration. *Kidney Int* 18:480–488, 1980
21. Port FK, Johnson WJ, Klass DW: Prevention of dialysis disequilibrium syndrome by use of high sodium concentration in the dialysate. *Kidney Int* 3:327–333, 1973
22. Gotch FA, Sargent JA: A mechanistic analysis of the National Cooperative Dialysis Study. *Kidney Int* 28:526–534, 1985
23. Skroeder NR, Jacobson SH, Lins LE, Kjellstrand CM: Acute symptoms during and between hemodialysis: The relative role of

speed, duration, and biocompatibility of dialysis. *Artif Organs* 18:880–887, 1994
24. Schilling H, Lehmann H, Hampl H: Studies on circulatory stability during bicarbonate hemodialysis with constant dialysate sodium verses acetate hemodialysis with sequential dialysate sodium. *Artif Organs* 9:17–21, 1985
25. Gotch FA, Lam MA, Prowitt M, Keen M: Preliminary clinical results with sodium-volume modeling of hemodialysis therapy. *Proc Clin Dial Transplant Forum* 10:12–17, 1980
26. Graefe U, Milutinovich J, Follette WC, Babb AL, Scribner BH: Improved tolerance to rapid ultrafiltration with the use of bicarbonate in dialysate. *Proc EDTA* 14:153–159, 1977
27. Graefe U, Milutinovich J, Follette WC, Vizzo JE, Babb AL, Scribner BH: Less dialysis-induced morbidity and vascular instability with bicarbonate in dialysate. *Ann Intern Med* 88:332–336, 1978
28. Vonbrecht JH: Liquid bicarbonate dialysate: Interdialytic and storage characteristics. *Dial Transplant* 14:75–81, 1985
29. Raja R, Kramer M, Barber K, Chen S: Sequential changes in dialysate sodium during hemodialysis. *Trans Am Soc Artif Intern Organs* 29:649–651, 1983
30. Cybulsky AVE, Matni A, Hollomby DJ: Effects of high sodium dialysate during maintenance hemodialysis. *Nephron* 41:57–61, 1985
31. Krishna GG, Denneberg BS, Stom MC, Belber A, Deuter G, Spann JF, Narins RG: Effects of hemodialysis on myocardial contractility. *Trans Am Soc Artif Intern Organs* 31:678–682, 1985
32. Shimizu AG, Taylor DW, Sackett DL, Smith EKM, Barnes CC, Hoda P, Lennox G, Martin J, McNeaney H, Mukherjee J, Uniyal B: Reducing patient morbidity from high-efficiency hemodialysis: A double-blind crossover trial. *Trans Am Soc Artif Intern Organs* 29:666–668, 1983
33. Henrich WL, Woodard TD, Meyer BD, Chappell TR, Rubin LJ: High sodium bicarbonate and acetate hemodialysis: Double-blind crossover comparison of hemodialysis and ventilatory effects. *Kidney Int* 24:240–245, 1983
34. Diamond SM, Henrich WL: Acetate dialysate verses bicarbonate dialysate: A continuing controversy. *Am J Kidney Dis* 9:3–11, 1987
35. Leunissen KML, van Hooff JP: Acetate or bicarbonate for haemodialysis? *Nephrol Dial Transplant* 3:1–7, 1988
36. Keshavaih P, Berkseth R, Ilstrup K, McMichael C, Collins A: Reduced treatment time: hemodialysis verses hemofiltration. *Trans Am Soc Artif Organs* 31:176–182, 1985
37. Miller JH, von Albertini B, Gardner PW, Schinaberger JH: Technical aspects of high-flux hemofiltration for adequate short (under 2 hours) treatment. *Trans Am Soc Artif Intern Organs* 30:377–381, 1984
38. Collins A, Ilstrup K, Hanson G, Berkseth R, Keshaviah P: Rapid high-efficiency hemodialysis. *Artif Organs* 10:185–188, 1986
39. von Albertini B, Miller JH, Gardner PW, Shinaberger JH: High-flux hemodiafiltration: Under six hours/week treatment. *Trans Am Soc Artif Intern Organs* 30:227–231, 1984
40. Henrich WL, Woodard TD, Blanchley JD, Gomez-Sanchez C, Pettinger W, Cronin RE: Role of osmolality in blood pressure stability after dialysis and ultrafiltration. *Kidney Int* 18:480–488, 1980
41. Mann H, Stiller S: Urea, sodium, and water changes in profiling dialysis. *Nephrol Dial Transplant* 11(Suppl 8):10–15, 1996
42. *Geigy Scientific Tables* (vol 3): *Physical Chemistry Composition of Blood Hematology Somatometric Data,* edited by Lentner C, West Caldwell, Medical Education Division, Ciba-Geigy Corporation, pp 48, 68, 1984
43. van Kuijk WHM, Wirtz JJJM, Grave W, de Heer F, Menheere PPCA, van Hooff JP, Leunissen KML: Vascular reactivity during combined ultrafiltration-haemodialysis: Influence of dialysate sodium. *Nephrol Dial Transplant* 11:323–328, 1996
44. Zucchelli P, Santoro A: Dialysis-induced hypotension: A fresh look at pathophysiology. *Blood Purif* 11:85–98, 1993
45. Bogaard HJ, de Vries JPPM, de Vries PMJM: Assessment of refill and hypovolaemia by continuous surveillance of blood volume and extracellular fluid volume. *Nephrol Dial Transplant* 9:1283–1287, 1994
46. Kimura G, Van Stone JC, Bauer JH, Keshaviah PR: A simulation study on transcellular fluid shifts induced by hemodialysis. *Kidney Int* 24:542–548, 1983
47. Flanigan MJ, Khairullah QT, Lim VS: Dialysate sodium delivery can alter chronic blood pressure management. *Am J Kidney Dis* 29:383–391, 1997
48. Locatelli F, Ponti R, Pedrini L, Consanzo R, Di Filippo S, Marai P, Possi C: Sodium kinetics across dialysis membranes. *Nephron* 18:174–177, 1984
49. Pedrini LA, Ponti R, Faranna P, Cozzi G, Locatelli F: Sodium modeling in hemodiafiltration. *Kidney Int* 40:525–532, 1991
50. Sancipriano GP, Negro A, Amateis C, Calitri V, Cantone F, Deabate MC, Della Casa M, Fidelio T, Iacono G, Licata C, Serra A, Susa I: Optimizing sodium balance in hemodialysis. *Blood Purif* 14:115–127, 1996
51. Worth HGJ: A comparison of the measurement of sodium and potassium by flame photometry and ion-selective electrode. *Ann Clin Biochem* 22:343–350, 1985
52. Christian GD: Ion selective electrodes, in *Analytical Chemistry* (2nd ed), edited by Christian GD, New York, John Wiley and Sons, 1977, pp 362–364
53. Locatelli F, Di Filippo S, Manzoni C: Sodium kinetics during dialysis. *Semin Dial* 12(Suppl 1):S41–S44, 1999
54. Gotch FA, Evans MC, Keen ML: Measurement of the effective dialyzer Na diffusion gradient in vitro and in vivo. *Trans Am Soc Artif Intern Organs* 31:354–358, 1985
55. Funck-Brentano JL, Man NK: Optimization of Na content in dialysis fluid. *Nephron* 36:197–200, 1984
56. Petitclerc T: Estimation of mass transfer through a hemodialyzer: Theoretical approach and clinical applications. *Artif Organs* 22:601–607, 1998
57. Waniewski J, Heimburger O, Werynski A, Lindholm B: Aqueous solute concentration and evaluation of mass transport coefficients in peritoneal dialysis. *Nephrol Dial Transplant* 7:50–56, 1992
58. DiFilippo S, Conti M, Andrulli S, Pontorieo G, Manzoni C, Locatelli F: Optimization of sodium removal in paired filtration dialysis and conductivity kinetic models. *Blood Purif* 15:34–44, 1997
59. Kotyk P, Lopot F, Blaha J: Study on sodium and potassium balance during hemodialysis. *Artif Organs* 19:185–193, 1995
60. Thylen P, Ericsson F, Odar-Cederlof I, Kjellstrand CM: Hypertension profiling by total body water (TBW) determinations in patients on chronic hemodialysis. *Int J Artif Organs* 14:18–22, 1991
61. Santoro A, Mancini E, Paolini F, Cavicchioli G, Bosetto A, Zucchelli P: Blood volume regulation during hemodialysis. *Am J Kidney Dis* 32:739–748, 1998
62. Coli L, Bonomini M, La Manna G, Dalmastri V, Ursino M, Ivonovich P, Bonomini V: Clinical use of profiled hemodialysis. *Artif Organs* 22:724–730, 1998
63. Petitclerc T, Trombert JC, Coevoet B, Jacobs C: Electrolyte modeling: Sodium: Is dialysate sodium profiling actually useful? *Nephrol Dial Transplant* 11(Suppl 2):35–38, 1996
64. Locatelli F, Andrulli S, Di Filippo S, Redaelli B, Mangano S, Navino C, Ariano R, Tagliaferri M, Fidelio T, Corti M, Civardi S, Tetta C: Effect of on-line conductivity plasma ultrafiltrate kinetic modeling on cardiovascular stability of hemodialysis patients. *Kidney Int* 53:1052–1060, 1998
65. Krautzig S, Janssen U, Koch KM, Granolleras C, Shaldon S: Dietary salt restriction and reduction of dialysate sodium to control hypertension in maintenance hemodialysis patients. *Nephrol Dial Transplant* 13:552–553, 1998
66. Raj Dominic SC, Ramachandran S, Somiah S, Mani K, Dominic SS: Quenching the thirst in dialysis patients. *Nephron* 73:597–600, 1996
67. Katzarski KS, Charra B, Luik AJ, Nisell J, Divino Filho JC, Leypoldt JK, Leunissen KML, Laurent G, Bergström J: Fluid state and blood pressure control in patients treated with long and short haemodialysis. *Nephrol Dial Transplant* 14:369–375, 1999
68. Leypoldt JK, Cheung AK: Extracellular, in nocturnal hemodialysis. *Semin Dial* 12(Suppl 1):S50–S54, 1999
69. Rahmann M, Dixit A, Donley V, Gupta S, Hanslik T, Lacson E, Ogundipe A, Weigel K, Smith M: Factors associated with inadequate blood pressure control in hypertensive hemodialysis patients. *Am J Kidney Dis* 33:495–508, 1999
70. Ozkahya M, Toz H, Unsal A, Ozerkan F, Asci G, Gurgun Akcicek F, Dorhout Mees EJ: Treatment of hypertension in dialysis patients by ultrafiltration: Role of cardiac dilatation and time factor. *Am J Kidney Dis* 34:218–221, 1999