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Sodium-based osmotherapy for hyponatremia in acute decompensated heart failure

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Abstract
Acute decompensated heart failure (ADHF) accounts for more than 1 million hospital admissions annually and is associated with high morbidity and mortality. Decongestion with removal of increased total body sodium and total body water are goals of treatment. Acute kidney injury (AKI) or chronic kidney disease (CKD) is present in two-thirds of patients with ADHF. The pathophysiology of ADHF and AKI is bidirectional and synergistic. AKI and CKD complicate the management of ADHF by decreasing diuretic efficiency and excretion of sodium and water. Among patients hospitalized with ADHF, hyponatremia is the most common electrolyte abnormality and is classically encountered with volume overload. ADHF represents an additional therapeutic challenge particularly when oligoanuria is present. Predilution continuous venovenous hemofiltration with sodium-based osmotherapy can safely increase plasma sodium concentration without deleteriously increasing total body sodium. We present a detailed methodology that addresses the issue of hypervolemic hyponatremia in patients with ADHF and AKI.

Keywords Hyponatremia · Acute decompensated heart failure · Osmotherapy · Ultrafiltration

Introduction

Acute decompensated heart failure (ADHF) accounts for greater than 1 million hospital admissions annually [1]. Currently in the USA, 5.7 million patients have HF that is responsible for an estimated expenditure of $37.2 billion USD. The prevalence of HF is projected to be 8 million persons by 2030, a 46% increase [2]. Fluid congestion now accounts for more than 90% of hospital admissions for ADHF [3]. Persistent congestion is present in 40% of ADHF patients at discharge [4] and leads to a major proportion of rehospitalizations [5]. Therefore, decongestion is the principal treatment goal for ADHF [6]. The foremost reason for fluid accumulation in patients with ADHF is persistent renal sodium and water retention. Because renal water reabsorption is disproportionately greater than sodium reabsorption in many ADHF patients, hyponatremia occurs and is a poor prognostic factor [7]. However, excessive sodium retention is the reason for congestion, and reduction of total body sodium (TBNa) is an obligate component of HF therapy. This review provides a pathophysiological cardiorenal outline of oligo-anuric ADHF complicated by hyponatremia and describes a specific treatment model that utilizes continuous renal replacement therapy.

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Hyponatremia

Hyponatremia is the most common electrolyte disorder in hospitalized patients, occurring in 15–30% of cases [8]. Acute hyponatremia is defined as a plasma sodium concentration (P_{Na}) < 130 mEq/L that transpires within 48 h. Chronic hyponatremia is defined as P_{Na} < 130 mEq/L for > 48 h or at presentation for care. Hyponatremia is present in up to 7% of patients in ambulatory settings and is discovered in nearly 23% of all patients presenting to emergency departments [9]. Among outpatients with HF, the prevalence of hyponatremia is 17% [10]. In patients admitted for ADHF, hyponatremia, defined as P_{Na} < 135 mEq/L, is

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the most common electrolyte abnormality and is frequently accompanied by volume overload [11, 12]. Depending on the rapidity and magnitude of change of P_{Na}, clinical features of hyponatremia may range from generalized fatigue, falls with potential fractures, and altered mentation and cognitive dysfunction [13].

In the meta-analysis by Wang et al. that assessed patients with ADHF, the correction of hyponatremia [14] during hospital admission was associated with lower cardiovascular mortality compared to patients who experienced no or minimal improvement of hyponatremia. The improvement of hyponatremia in ADHF patients was associated with reductions in short-term and long-term all-cause mortality [14] and hospital readmission [15]. In a study of HF patients by Madan et al. that had a median follow-up of 610 days, a positive correlation between increased P_{Na} and survival was observed. [16]. Unfortunately, hyponatremia is corrected in only 19% of ADHF patients by the time of hospital discharge, even after the application of traditional therapeutic management strategies, including fluid restriction, diuretics, and/or saline administration. [17]. In summary, hyponatremia in ADHF patients is an easily identifiable and modifiable factor, and its correction with decongestion is recommended and salutary.

Renal function and ADHF

The kidneys are frequently affected by ADHF, and concomitant acute kidney injury (AKI) or chronic kidney disease (CKD) is present in 67% of patients [18]. Moderate CKD with glomerular filtration rates (GFRs) of 30–59 mL/min per 1.73 m^2 was documented in 43.5% of patients hospitalized with ADHF and in 13% of patients with severe CKD had GFRs of 15–29 mL/min per 1.73 m^2. Kidney failure defined by GFR <15 mL/min per 1.73 m^2 developed in 7% of patients [18]. Concurrent AKI and CKD at admission or during hospitalization with ADHF is associated with a worse prognosis [18–21]. Healthy kidneys have a tremendous capacity to excrete water, up to 15 L daily, and water retention and hyponatremia are infrequent findings until the GFR is quite depressed. Even at a GFR of 10 mL/min per 1.73 m^2, a normal amount of water ingestion will not provoke hyponatremia [22].

Hyponatremia in heart failure patients is mediated by an exaggerated neurohormonal axis that tightly regulates TBNa and total body water (TBW) in the normal physiologic state. Derangements in atriorenal reflexes, the sympathetic nervous system (SNS), the renin-angiotensin-aldosterone system (RAAS), glomerular filtration, tubular flow, and nonosmotic arginine vasopressin (AVP) release, collectively result in disproportionate renal reabsorption of salt and water producing hypervolemic hyponatremia.

In the normal heart, atrial natriuretic peptide is secreted in response to increased atrial stretch and high systemic blood pressure. These stimuli enhance glomerular filtration and augment renal excretion of sodium and water. With depression of effective arterial blood volume (EABV) during ADHF, SNS overstimulation from high-pressure baroreceptors amplify inotropic and chronotropic effects to maintain circulatory hemodynamics and perfusion at systemic and renal levels [23]. SNS hyperactivity potentiates release of renin and activates the RAAS, with consequent upregulation of sodium-hydrogen exchanger in proximal tubule cells [24]. The net effect of this cascade is increased filtration fraction in conjunction with sodium and water retention at the proximal tubular level, mediated by angiotensin II (AngII) [25, 26] and aldosterone. In addition, Ang II activates the thirst center and increases AVP release, thereby promoting water retention in the distal nephron.

Under normal conditions, AVP release increases linearly in response to increasing plasma tonicity, [27, 28] with subsequent rapid degradation by liver and kidney. In HF patients, elevated AVP concentrations stem from non-osmotic release attributable to decreased EABV sensed by arterial baroreceptors, increased Ang II plasma concentrations, augmented alpha-2 adrenergic receptor stimulation, and decreased hormone degradation from hepatic and renal dysfunction [29–31]. AVP signaling via the vasopressin type 2 receptor (V2R) upregulates aquaporin-2 channel expression in the medullary collecting duct and increases water reabsorption [32]. Increased circulating AVP also activates V1a receptors in the liver and vasa recta, respectively, increasing hepatic urea production and urea absorption in the medullary collecting duct which enhances the interstitial corticomedullary osmotic gradient [33]. The summative consequences of the hydro-osmotic effect of AVP in the collecting duct are greater water reabsorption devoid of electrolyte with reduced tubular flow and reduced urine volume.

Free water excretion is dependent on the tubular function of distal and collecting tubules, which are low water- and high sodium-permeable segments [34]. Decreased cardiac output results in reduced renal blood flow and GFR which decreases renal tubular flow, with less sodium reabsorption and water excretion. [35, 36]. Decreased blood flow within the vasa recta further enhances water absorption. Elevated central venous pressures from HF elevate right-sided cardiac pressures and renal vein pressures. The consequences of the latter are reduction of the transrenal pressure gradient and renal congestion. The heightened renovascular resistance decreases renal blood flow and the compensatory increase in filtration fraction resulting in decreased GFR.

In summary, hyponatremia in patients with ADHF is promoted by maladaptive responses that eventually worsen renal function, with disproportional renal sodium and water reabsorption. Decreased free water excretion occurs despite increased TBW and TBNa, the clinical consequences of which are pulmonary congestion and peripheral edema with hypotonic, hypervolemic hyponatremia.

Treatment of hyponatremia

The treatment of hyponatremia can be categorized as reduction of access to water, promotion of urinary water excretion, and supraphysiological addition of sodium to the plasma compartment. Oral fluid restriction is classically limited to 1000–1500 mL of total fluids per day. Adherence to this regimen is practically difficult. Fluid restriction generally results in a modest P_{Na} increase of 2 mEq/L or less per 24 h. Thus, diuretic treatment that targets the diluting segment of the nephron is usually necessary.

In the thick ascending limb of Henle's loop, the site of the sodium–potassium-chloride cotransporter, loop agents increase urinary electrolyte-free water loss by disrupting maximization of the corticomedullary gradient via inhibition of the cotransporter. Urine electrolyte-free water is the portion of urine devoid of sodium and potassium ions but contains urea. The net result of loop diuresis is greater loss of electrolyte-free water. High dose loop diuretics are required for patients with underlying kidney disease because its efficacy is limited by decreased GFR and the induction of diuretic resistance during long-term treatment [37].

V2R antagonists such as conivaptan and tolvaptan also increase free water excretion. By interrupting the lumen-to-plasma transit of urea and water at the collecting duct, these agents produce hypotonic urine. V2R antagonists facilitate correction of hyponatremia by reducing the denominator of the Edelman equation. However, despite increasing P_{Na}, agents have minimal impact on TBNa attributable to their locus of action (i.e., minimal sodium reabsorption occurs in the inner medullary collecting duct). These "aquaretic" agents have not been proven salutary in ADHF or for patients with chronic HF [38, 39].

Hypertonic saline as solutions of 2% to 23.4% saline are administered to increase P_{Na}. As a corrective measure for hyponatremia, hypertonic saline represents a double-edged sword. Salutary P_{Na} elevation proceeds at the expense of increasing TBNa, which may aggravate cardiopulmonary congestion. Nonetheless, hypertonic saline combined with high-dose diuretics has been advocated for refractory cases of ADHF with severe symptomatic and very low or rapidly declining P_{Na} [40, 41]. If this combination therapy is used, careful monitoring and accounting of sodium and water inputs and outputs is mandatory to prevent worsening congestion from sodium-loading. If the diuretic response of congested, hypervolemic patients is inadequate, mechanical ultrafiltration is advised. The current American College of Cardiology guidelines recommend ultrafiltration in patients who have obvious fluid overload or patients who do not respond adequately to diuretics [6].

In the following review, we outline a therapeutic solution for hyponatremic patients who have ADHF and limited urine output—sodium-based osmotherapy (SBO). We model predilution continuous venovenous hemofiltration (CVVH) as the therapeutic vehicle that increases P_{Na} without increasing TBNa.

Osmolality and tonicity

Osmolality is defined as the number of milliosmoles of solute per kilogram of solvent, and the solvent is water for biological systems. Optimal cell function and cell volume homeostasis occurs at plasma osmolality of 275 to 290 mOsm/kg H_2O, with no osmotic gradient between the intracellular and extracellular milieus [36, 42]. Tonicity, or effective osmolality, is the concentration of effective osmoles that are impermeant to cell membranes and that displace water, thus regulating cell volume. Because sodium with its accompanying anions is the most abundant extracellular osmole, sodium represents the major determinant of plasma tonicity. However, urea, permeates cells readily and is not an effective osmole at osmotic equilibrium. With plasma as the referent solution, hypotonicity indicates that water will flow into cells, whereas hypertonicity implies cell shrinkage. An abrupt reduction in plasma tonicity from hyponatremia is acutely reconciled by egress of electrolytes from cells. Chronic hypotonicity induces a reduction of intracellular osmolyte concentration that is required to preserve cell volume to prevent untoward cell volume expansion, e.g., cerebral edema [43].

Sodium and total body water

The ubiquitous, electrogenic Na-K-ATPase maintains a high extracellular sodium concentration and a high intracellular potassium concentration to preserve cellular osmotic equilibrium. This concept is delineated by Eqs. 1 and 2 in which P_{Na} is the ratio of the sum of exchangeable TBNa ($TBNa_e$) and potassium (TBK_e) ions to TBW [44]. TBW is determined from anthropometric data as the urea space [45].

$$P_{Na} = (1.11 \times \frac{TBNa_e + TBK_e}{TBW}) - 25.6 \quad (1)$$

The modified Edelman equation is commonly simplified as follows:

$$P_{Na} = \frac{TBNa_e + TBK_e}{TBW} \quad (2)$$

As exchangeable potassium is quantitatively minor compared to exchangeable sodium, Eq. 2 is further simplified to Eq. 3 for general clinical application.

$$P_{Na} = \frac{TBNa_e}{TBW} \quad (3)$$

And

$$TBNa_e = TBW \times P_{Na} \quad (4)$$

The hyponatremia that occurs during ADHF is hypervolemic and attributable to the greater increase of the denominator (TBW) relative to the numerator $TBNa_e$.

Exchangeable and non-exchangeable sodium

TBNa is distributed within several compartments: 65% plasma, 5–10% intracellular fluid, and 25% bone and interstitial tissues. In healthy individuals, fluid accumulation in tissues is opposed by a reduction of interstitial compliance that exerts a hydrostatic pressure that promotes return of fluid into the systemic circulation via lymphatic networks [46, 47]. Sodium is also segregated from TBNa by interstitial glycosaminoglycans, particularly in skin and muscle, and escapes osmotic regulation by pituitary osmoreceptors and kidney [48]. This minimally exchangeable sodium pool may be important in HF and CKD [49]. Accordingly in ADHF, sodium radiolabeling studies have demonstrated sodium accrual without weight (water) gain [50]. ^{23}Na-MRI has also demonstrated sodium accumulation in muscle, brain, and skin. Conversely, in patients with hyperaldosteronism, there is ^{23}Na-MRI confirmation of this non-exchangeable ion pool [51], which can be mobilized without weight loss. This pool of non-exchangeable sodium can be mobilized by diuretic therapy [52] or ultrafiltration [53]. Essentially, these sequestered sodium stores represent a reservoir that contributes to persistently high TBNa and congestion.

Myocardial contractility in hyponatremia

Hyponatremia adversely affects myocyte function and contractility by multiple mechanisms. The sodium-calcium exchanger and Na-K-ATPase modulate calcium entry into cardiomyocytes which regulates myocardial contractility [54]. Plasma concentrations of sodium, potassium, calcium, and magnesium regulate RUNX1 gene transcription that accelerates proliferation and differentiation of injured myocytes. Hyponatremia may impair RUNX1-mediated cardiomyocyte remodeling following myocardial infarction [55]. L-type calcium channels are responsible for the release of intracellular calcium from the sarcoplasmic reticulum, with myocyte activation and contraction. L-channel activity is downregulated by the rapid induction of acute hyponatremia with reduced cardiomyocyte contractility [56, 57] However, such short-term studies do not reflect the time course during which hyponatremia typically develops in patients with ADHF. Moreover, the contribution of hyponatremia to ADHF has not been quantified rigorously. Nonetheless, severe hyponatremia remains a potential risk factor for impaired cardiac contractility in ADHF.

Hyponatremia-induced arrhythmia

P_{Na} is a major determinant of the cardiomyocyte resting membrane potential. Since ventricular arrhythmia results from disruption of cardiomyocyte depolarization or repolarization and/or action potential conduction, hyponatremia is a potential risk factor for arrhythmogenesis. Clinically, the frequency and complexity of ventricular extrasystoles are associated with worsening hyponatremia [56]. Voltage-gated sodium channels and gap junction proteins retard action potential conduction velocity and may contribute to arrhythmia. Gain-of-function mutations that prolong activation of fast sodium channels increase ventricular depolarization and arrhythmias, e.g., long QT syndrome. In Brugada syndrome, loss-of-function mutations of slow and fast sodium channels produce sodium channel inactivation and sustained repolarization, triggering ventricular arrhythmias [56, 58]. Atrial arrhythmias such as atrial fibrillation occur more frequently in patients with hyponatremia who present to emergency departments [59] and who undergo open heart surgery [60]. Hyponatremia in heart failure patients with reduced ejection fraction has been independently associated with atrial fibrillation. [61]. Cases of complete heart block in patients with hyponatremia and without cardiac disease have shown improvement after correction of hyponatremia [62].

Osmotherapy for hyponatremia in hypervolemic heart failure

Most hyponatremic ADHF patients have chronic hyponatremia. Slow correction of P_{Na} is recommended for these patients to prevent rapid fluctuation of osmotic gradients and attenuate the risk of iatrogenic neurologic sequelae, e.g., osmotic demyelination syndrome (ODS), which results from overly rapid correction of hyponatremia [43]. Current consensus guidelines recommend correction of the chronic hyponatremic state by 6–8 mEq/L per 24 h [63]. Individuals with a history of severe alcohol abuse, particularly those with complicating features of hypokalemia, malnutrition, low TBW, and liver disease, are at increased risk for ODS. ODS has occurred in older HF patients with a history of alcohol abuse who manifested severe hyponatremia [64].

Several modalities of renal replacement therapy, including hemodialysis, sustained low-efficiency dialysis (SLED), and CVVH a form, of continuous renal replacement therapy (CRRT), have been employed to correct hyponatremia and treat hypervolemic ADHF patients with oligo-anuric AKI [65]. The constellation of hypervolemia, AKI with oligo-anuria, and hyponatremia poses a therapeutic challenge, especially in hemodialysis. In this circumstance, rapid reduction of urea can be complicated by neurological symptoms, e.g., dialysis disequilibrium syndrome [66] from generation of an osmotic gradient that favors rapid ingress of water into the brain.

Mitigating the risk of brain injury during correction of hyponatremia by CRRT involves strategic flow rate adjustments of plasma and replacement fluid [67, 68] and monitoring of net sodium mass balance. Compared to hemodialysis, continuous therapy affords gradual correction of P_{Na} and decongestive treatment by ultrafiltration. We provide a readily available and implementable solution for patients with ADHF, hyponatremia, and kidney failure.

CVVH setup and implementation

We utilize predilution CVVH because of its simplicity and modeling characteristics. CVVH utilizes an extracorporeal circuit that maintains a closed loop between the patient's blood and a hemofilter (Fig. 1) [68]. A blood pump regulates plasma flow (Q_P) into a conventional hemofilter (F). A sodium-based replacement fluid (RF) of sodium concentration Na_{RF} is advected into the fluid flow prehemofilter. The ultrafiltration flow rate (Q_{UF}) is determined by the operator such as a nephrologist or intensive care specialist. Commercial RF solutions are supplied at sodium concentrations of 130 and 140 mEq/L and may be customized to

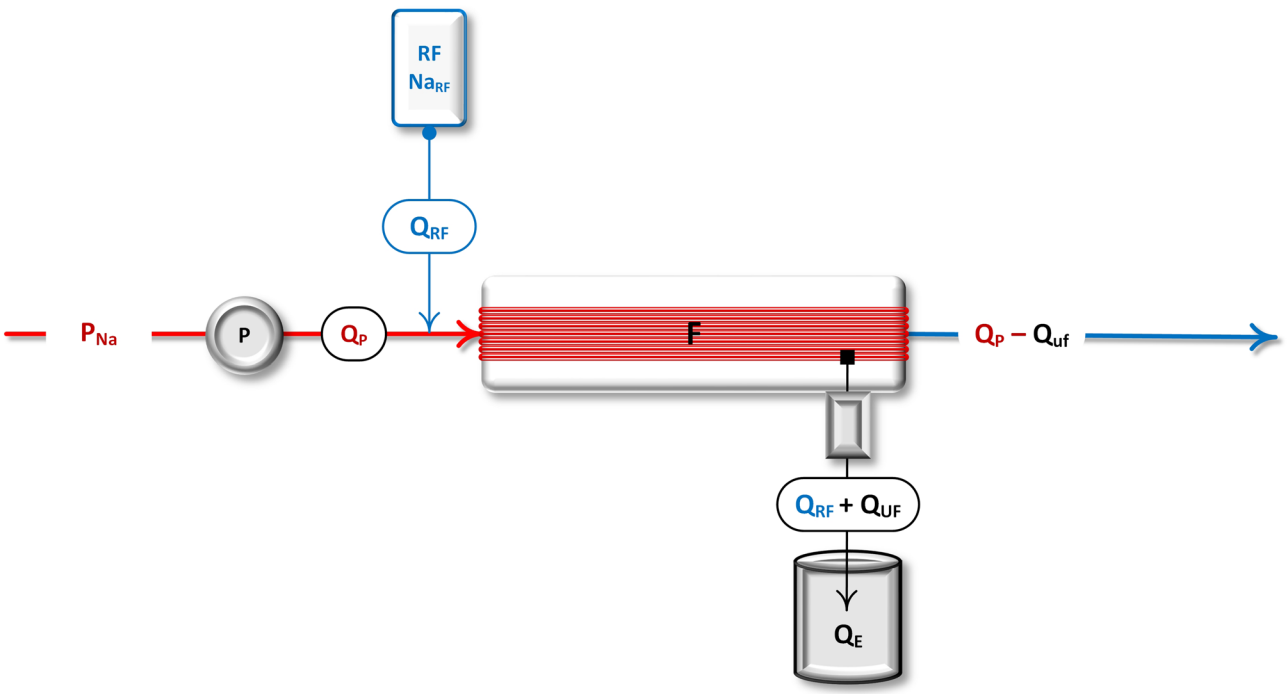

Fig. 1 Sodium-based osmotherapy with predilution continuous venovenous hemofiltration (CVVH) setup. A blood pump (P) delivers plasma at sodium concentration P_{Na} at rate Q_P and replacement fluid (RF) at flow rate Q_{RF} with a sodium concentration (Na_{RF}) into the hemofilter (F). The effluent flow rate (Q_E) is the sum of Q_{RF} and the ultrafiltration flow rate (Q_{UF}). The plasma flow rate exiting the filter that is returned to the patient (→) is the difference between Q_P and Q_{UF}. P_{Na} is gradually increased by the addition of RF that has a greater sodium concentration (Na_{RF}) than P_{Na}

specific sodium concentrations (Na_{RF}) by the addition or subtraction of water or hypertonic saline [68]. P_{Na} is raised by the relatively hypertonic RF while TBW is reduced by ultrafiltration. Therefore, the numerator of the Edelman Equation is increased while the denominator is decreased, thereby raising P_{Na}. During SBO, P_{Na} is incrementally elevated toward the target P_{Na}, avoiding dangerous and rapid elevations of cerebral and cardiac tonicity.

Case

We present a hypothetical, illustrative case of a 54-year-old man with HF and reduced ejection fraction. He has dyspnea, progressive, bilateral lower extremity swelling, and has gained 6 kg in 1 week. The admission height and weight are 170 cm and 78 kg, respectively. Admission laboratory data are plasma sodium 118 mEq/L, potassium 5.2 mEq/L, blood urea nitrogen 92 mg/dL, creatinine 6.4 mg/dL (baseline, 3.0 mg/dL), and hematocrit (Hct) 0.30. No urogenital obstruction was identified by ultrasonography, and a furosemide stress test was negative (urine output < 200 mL 2 h after 1.5 mg/kg intravenous furosemide) [69]. The TBW at admission (V_0) is calculated using the patient's sex, height, age, and weight by the Watson volume formula (Eqs. 4 and 5) and yields $V_0 = 42L = 42{,}000$ mL.

$$TBW(male) = 2.447 - (0.09156 \times age) + (0.1074 \times height) + (0.3362 \times weight) \quad (5)$$

$$TBW(female) = -2.097 + (0.1069 \times height) + (0.2466 \times weight) \quad (6)$$

The proposed treatment is predilution CVVH-SBO for HF with oligoanuric AKI and poor response to diuretics [6, 68, 70]. Therapy is planned by a stepwise mathematical approach and based on urea- and sodium-based kinetic modeling [71]. First, urea clearance (K_{Urea}) is estimated assuming a minimal, recommended effluent clearance of 20 mL/kg/h per Eq. 7 [72, 73] (Table 1).

$$K_{Urea} = (78kg \cdot 20mL/kg/h)/60\,\text{min}/h = 26mL/min \quad (7)$$

SBO therapy will have a treatment time tx = 24 h = 1440 min. Urea kinetic modeling defines BUN at any treatment time (t) as BUN(t) (Eq. 8).

$$BUN(t) = BUN_0 \cdot e^{-\frac{K_{Urea} \cdot t}{V_0}} \quad (8)$$

The BUN at end treatment at time tx can be calculated. Here, tx is 1440 min.

$$BUN(1440) = 92 \cdot e^{-\frac{26 \cdot 1440}{42000}} = 37.7mg/dL \quad (9)$$

Once K_{Urea} is established, SBO treatment parameters are specified. Since urea (mol wt, 60 g/mol) and sodium (mol wt, 23 g/mol) freely pass through the filter membrane, the dialysance of sodium (D_{Na}) is essentially equivalent to urea clearance or K_{Urea} [74, 75]. D_{Na} is subsequently defined by Eq. 10.

$$(BUN)D_{Na} = K_{Urea} = \frac{Q_P}{(Q_P + Q_{RF})} \cdot (Q_{RF} + Q_{UF}) = 26mL/min \quad (10)$$

Q_{RF} is the predilution RF flow rate; Q_{UF} is the ultrafiltration rate; the extracorporeal circuit plasma flow rate, Q_P, is derived from the blood flow rate Q_B and hematocrit (Hct) per Eq. 11 (Fig. 1):

$$Q_P = Q_B \cdot (1 - Hct) = 200mL/min \cdot (1 - 0.30) = 140mL/min \quad (11)$$

SBO modeling may be used to increase or decrease the P_{Na}. The value of the initial plasm sodium (Na_{Pre}) is 118 mEq/L. A safe and desired change of P_{Na} (ΔNa) is + 6 mEq/L, and this value defines the post-treatment plasma sodium (Na_{Post}) per Eq. 12.

$$Na_{Post} = Na_{Pre} + \Delta Na = 118 + 6 = 124mEq/L \quad (12)$$

Using this method, any feasible value for Q_{UF} can be used during treatment. For this case, the Q_{UF} that achieves "zero" sodium balance is chosen. $TBNa_0$ and $TBNa_{tx}$ are, respectively, pre- and post-treatment TBNa levels (mEq). If Q_{UF} is > 0 mL/min, the volume at end-treatment is ($V_0 - Q_{UF} \cdot$ tx). Equation 13 defines $TBNa_0$ and Eq. 14 defines $TBNa_{tx}$.

Table 1 Proposed mechanisms of arrythmia due to hyponatremia

Ventricular arrhythmia	Atrial fibrillation
Disrupts cellular depolarization and repolarization	Blocks inhibitory function of AV node accessory pathway
Increases ventricular electrical activity	Prevents depolarization phase of AV node
Decreases conduction velocity	Decreased NCX activity increases intracellular calcium, diastolic PV distension, and PV burst firing
Prolongs activation and deactivation of action potential channels	

AV atrioventricular, *NCX* sodium-calcium exchanger, *PV* pulmonary vein

$$TBNa_0 = Na_{Pre} \cdot V_0 \tag{13}$$

$$TBNa_{tx} = Na_{Post} \cdot (V_0 - Q_{UF} \cdot tx) \tag{14}$$

At zero sodium balance, $TBNa_{tx} - TBNa_0 = 0$ mEq (Eq. 15).

$$Na_{Post} \cdot (V_0 - Q_{UF} \cdot tx) - (Na_{Pre} \cdot V_0) = 0 \tag{15}$$

Equation 15 can be solved for the ultrafiltration rate that achieves zero sodium balance (Eq. 16).

$$Q_{UF} = \frac{V_0 \cdot (Na_{Post} - Na_{Pre})}{Na_{Post} \cdot tx} = \frac{42000 \cdot (124 - 118)}{124 \cdot 1440} = 1.41 mL/min = 2.03 L/24h \tag{16}$$

The value of the replacement fluid flow rate is calculated by solving Eq. 10 for Q_{RF}, which yields Eq. 17.

$$Q_{RF} = \frac{Q_P \cdot (Q_{UF} - D_{Na})}{(D_{Na} - Q_P)} = \frac{140 \cdot (1.41 - 26)}{26 - 140} = 30.2 mL/min \tag{17}$$

P_{Na} at any time (t) is defined as $P_{Na}(t)$ and calculated by Eq. 18.

$$P_{Na}(t) = Na_{Pre} + (Na_{RF} - Na_{Pre}) \cdot \left(1 - e^{-\frac{D_{Na} \cdot t}{V_0}}\right) \tag{18}$$

The proportional change of P_{Na} from beginning to end of treatment is the sodium adjustment ratio (NaAR) and provided by Eq. 19.

$$NaAR = 1 - e^{-\frac{D_{Na} \cdot t}{V_0}} = 1 - e^{-\frac{26 \cdot 1440}{42000}} = 0.59 \tag{19}$$

Na_{Post}, which equals $P_{Na}(1440)$ at treatment-end is determined by Eq. 20.

$$Na_{Post} = Na_{Pre} + (Na_{RF} - Na_{Pre}) \cdot NaAR \tag{20}$$

Equation 20 can now be solved for the required value of replacement fluid sodium concentration Na_{RF} Eq. 21.

$$Na_{RF} = \frac{Na_{Post} - Na_{Pre} \cdot (1 - NaAR)}{NaAR} = \frac{124 - 118 \cdot (1 - 0.59)}{0.590} = 128.2 mEq/L \tag{21}$$

Substituting Na_{Pre}, Na_{RF}, V_0, and D_{Na} into Eq. 18 and solving for the final plasma sodium at the end of the treatment is determined in Eq. 22.

$$P_{Na}(1440) = 118 + (128.17 - 118) \cdot \left(1 - e^{-\frac{26 \cdot 1440}{42000}}\right) = 124\, mEq/L \tag{22}$$

The change in TBNa (ΔTB_{Na}) can be defined as a continuous function of time (t) using the equation for $P_{Na}(t)$. The value of $\Delta TBNa(t)$ is the product of the current $P_{Na}(t)$ and volume ($V_0 - Q_{UF}\, t$) (Eq. 23).

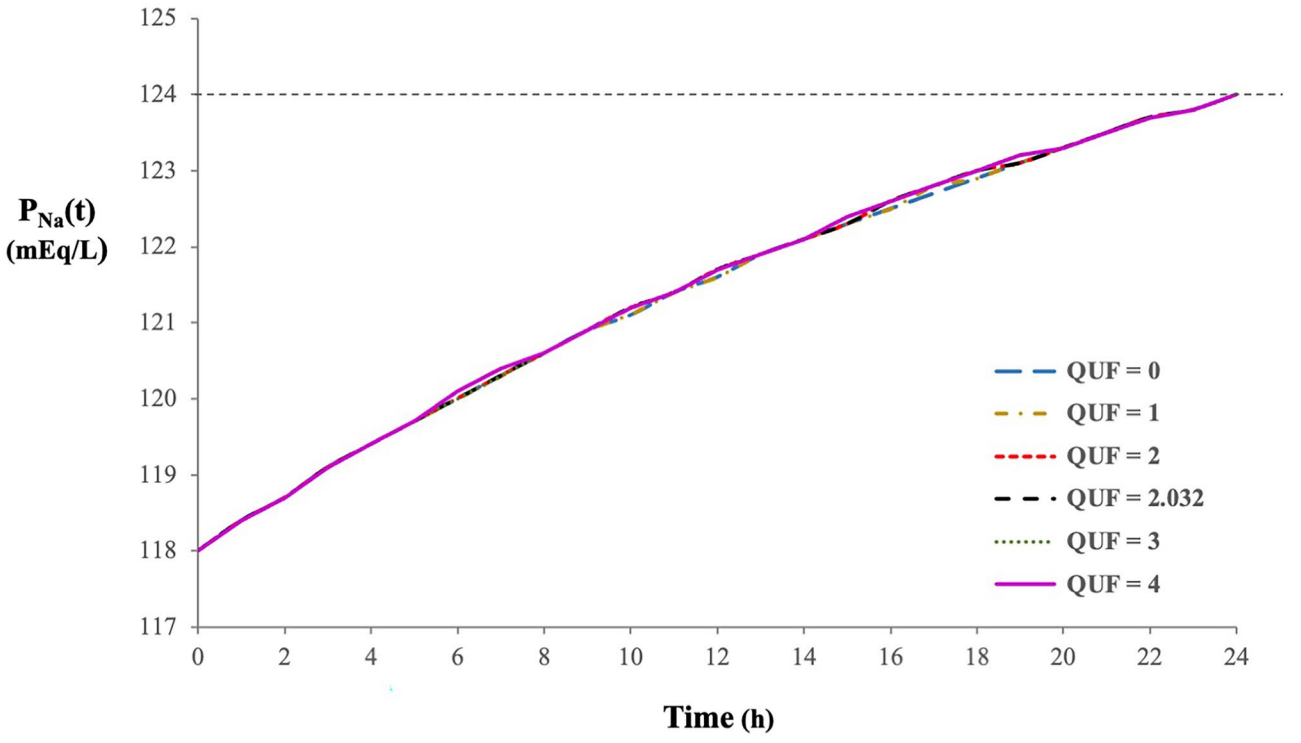

Fig. 2 Sodium-based osmotherapy modeling calculations for continuous venovenous hemofiltration show that the plasma sodium concentration increases at the same rate regardless of ultrafiltation rate (Q_{UF}, L/24h)

$$\Delta TBNa(t) = P_{Na}(t) \cdot \left(V_0 - Q_{UF} \cdot t\right) - Na_{Pre} \cdot V_0 \quad (23)$$

In Eq. 23, the zero change in TBNa is calculated per Eq. 24.

$$\Delta TBNa(1440) = 124 \cdot \left(42 - \frac{1.411}{1000} \cdot 1440\right) - 118 \cdot 42 = 0mEq \quad (24)$$

Figure 2 illustrates that when D_{Na} and Na_{RF} are adjusted for a specified Q_{UF}, the change in $P_{Na}(t)$ over 24 h is equal at final volumes, ranging from 42 L at Q_{UF} of 0 L/24 h to 38 L at Q_{UF} of 4 L/24 h. Figure 3 shows the corresponding changes in ΔTBNa(t) for the same range of Q_{UF} values 0 to 4 L/24 h. For Q_{UF} of 0 L/24 h, TBNa increases by 252 mEq and for Q_{UF} 4 L/24 h, TBNa decreases by 244 mEq by the end of treatment. The Q_{UF} (1.41 mL/min, 2.03 L/24 h) that achieves zero sodium balance demonstrates a maximal ΔTBNa(t) that is 32 mEq greater than the initial TBNa of 4956 mEq. ΔTBNa(t) returns to 0 mEq after 24 h, sidestepping the intrinsic sodium accrual that attends a positive change of P_{Na}. SBO modeling parameters and calculations for the first 24 h are summarized in Table 2.

Since P_{Na} should be increased by no more than 6–8 mEq/L in 24 h, computations must be repeated every 24 h and CVVH parameters changed accordingly, while P_{Na} is monitored at 2- to 4-h intervals. To achieve the new target P_{Na} of 130 mEq/L, treatment parameters must be calculate using a reduced body water ($V_0 - Q_{UF} \cdot tx$). Modeling parameters for the second 24-h time period are provided in Table 3. Calculations in Table 3 are identical to those in Table 2 except for the first and second rows.

For the second SBO modeling, a lesser URR value of 0.4 is chosen, and urea removal is reduced from 59 to 40% for the second treatment. K_{Urea} is next determined from the value of URR using the formula in Table 3 (line 2, column 2) and reduced from 26 to 14.37 mL/min. Using the reduced value of K_{Urea}, the new value of BUN_0 is 37.7 mg/dL. BUN_{tx} from the previous treatment is reduced to 23.2 mg/dL (Table 3, line 3). Since D_{Na} is equivalent to K_{Urea}, which equals 14.19 mL/min, SBO modeling for the second treatment is changed. Now, the Q_{UF} that achieves zero sodium balance declines from 1.411 to 1.282 mL/min and Q_{RF} decreases from 30.2 to 14.37 mL/min. The SBO modeling equations compensate for the decrease in D_{Na} by increasing Na_{RF} from 128.2 to 139 mEq/L. Accordingly, the sodium concentration gradient between plasma and replacement fluid must increase from 10.2 to 15 mEq/L. At the end of the second treatment, P_{Na} equals 130 mEq/L and TBW is 38.2 L. The final computed TBNa of 4960 mEq is essentially equal to the TBNa of 4956 mEq at the start of

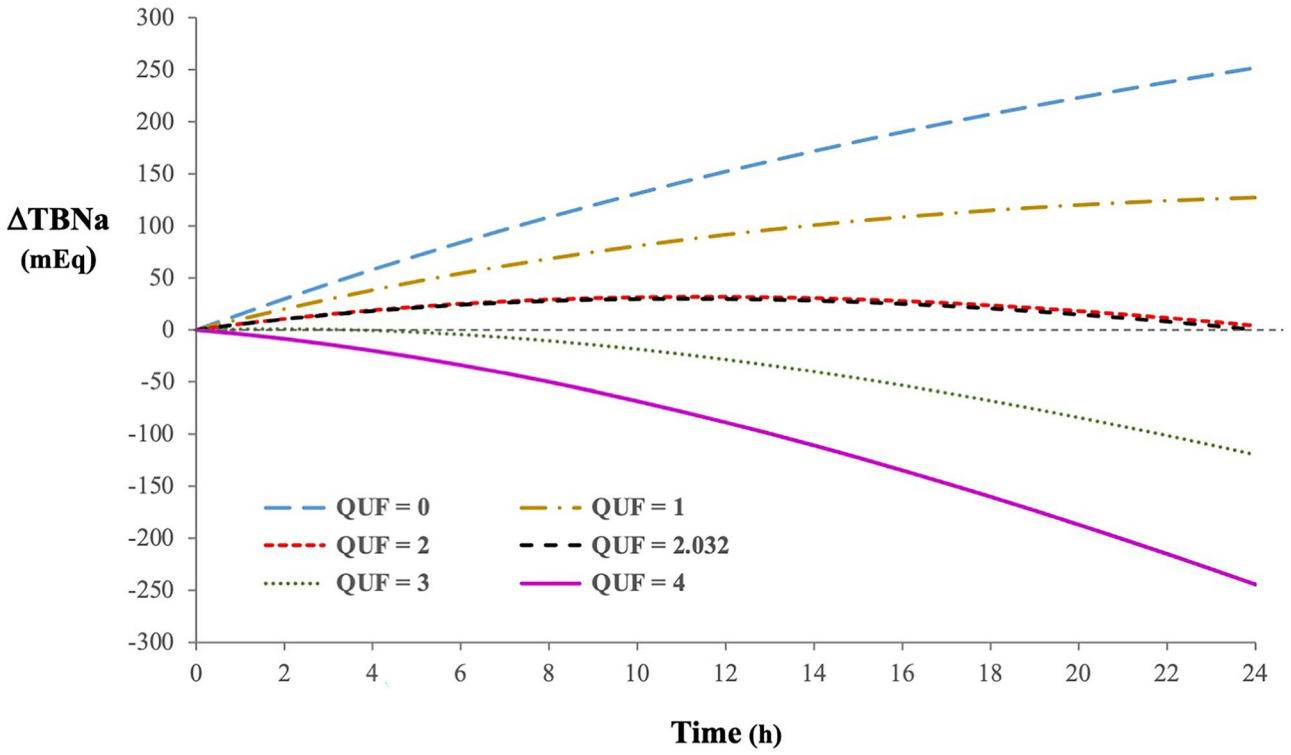

Fig. 3 The change in total body sodium (ΔTBNa) varies with ultrafiltration rate (Q_{UF}). For $Q_{UF}=0$, ΔTBNa is continuously positive because sodium is added to the TBW without removal. For $Q_{UF}=2.032$ L/24 h, calculated to achieve zero sodium balance, plasma sodium concentration increases to 124 mEq/L without increasing TBNa. For $Q_{UF}>2.032$ L/24 h, ΔTBNa is negative and sodium loss occurs

Table 2 CVVH parameters during a 24-h treatment

Parameter	Equation	Calculation	Value
Urea clearance (K_{Urea}. mL/min) calculated from patient weight at 20 mL/kg/h	$\frac{Weight(kg)\times 20ml/kg/h}{60min/h}$	$\frac{78(kg)\times 20ml/kg/h}{60min/h}$	*26.0 mL/min*
Urea reduction ratio (URR) (percent as a fraction)	$1-e^{-\frac{K_{Urea}\bullet tx}{V_0}}$	$1-e^{-\frac{26\times 1440}{42000}}$	*0.590*
BUN Post (BUN_{tx}, mg/dL)	$BUN_0\times e^{-\frac{K_{Urea}\bullet tx}{V}}$	$BUN_0\times e^{-\frac{26\times 1440}{42000}}$	*37.7 mg/dL*
Final sodium (Na_{Post}) calculated from initial sodium (Na_{Pre})	$Na_{Pre}+6\ mEq/L$	$118+6$	*124 mEq/L*
Ultrafiltration rate (Q_{UF}, mL/min) for zero sodium balance	$\frac{V_0\times(Na_{Post}-Na_{Pre})}{Na_{Post}\bullet tx}$	$\frac{42000\times(124-118)}{124\times 1440}$	*1.411 mL/min* *0.0847 L/h* *2.032 L/24 h*
Plasma flow (Q_P, mL/min) calculated from blood flow rate (Q_B)	$Q_B\times(1-Hct)$	$200\times(1-0.3)$	*140 mL/min*
Sodium dialysance (D_{Na}, mL/min)	$D_{Na}=K_{Urea}$		*26.0 mL/min*
Replacement fluid flow rate (Q_{RF}, mL/min)	$\frac{Q_P\times(Q_{UF}-D_{Na})}{(D_{Na}-Q_P)}$	$\frac{140\times(1.411-26)}{26-140}$	*30.2 mL/min* *1512 mL/h*
Sodium adjustment ratio (NaAR)	$1-e^{-\frac{D_{Na}\bullet tx}{V_0}}$	$1-e^{-\frac{26\times 1440}{42000}}$	*0.590*
Replacement fluid sodium concentration (NaRF, mL/min)	$\frac{Na_{Post}-Na_{Pre}\times(1-NaAR)}{NaAR}$	$\frac{124-118\times(1-0.590)}{0.590}$	*128.2 mEq/L*
Sodium concentration gradient (∇Na, mEq/L)	$Na_{RF}-Na_{Pre}$	$128.2-118$	*10.2 mEq/L*
Plasma Na at time (t) during treatment (P_{Na}(t), mEq/L)	$Na_{Pre}+\nabla Na\times\left(1-e^{-\frac{D_{Na}\bullet t}{V_0}}\right)$	*for* $t=1440$ $118+10.2\times(NaAR)$ $118+10.2\times(0.590)$	*124 mEq/L*
Total body sodium (TBNa, mEq)	$Na_{Pre}\cdot V_0$	118×42	*4956 mEq*
Change in total body Na at time (t) ΔTBNa(t), milliequivalents (mEq)	$P_{Na}(t)\cdot\left(V_0-Q_{UF}\cdot t\right)-Na_{Pre}\cdot V_0$	$V_0=L$ *and* $Q_{UF}=L/h$ $124\times(42-0.0847\times 24)-118\times 42$	*0 mEq*

Table 3 CVVH parameters for treatment time from 24 to 48 h, using case example

Parameter	Equation	Calculation	Value
Urea reduction ratio (URR, percent as a fraction)	Specified variable		0.40
Urea clearance (K_{Urea}, mL/min)	$\frac{-V_0\times LN(1-URR)}{1440}$	$\frac{-40000\times LN(1-0.40)}{1440}$	14.19 mL/min
BUN Post (BUN_{tx}, mg/dL)	$BUN_0\times e^{-\frac{K_{Urea}\bullet tx}{V_0}}$	$37.7\times e^{-\frac{14.19\times 1440}{40000}}$	>23.2 mg/dL
(Na_{Post}, mEq/L)	$Na_{Pre}+6\ mEq/L$	$124+6$	*130 mEq/L*
Ultrafiltration rate that achieves zero sodium balance (Q_{UF}, mL/min)	$\frac{V_0\times(Na_{Post}-Na_{Pre})}{Na_{Post}\bullet tx}$	$\frac{40000\times(130-124)}{130\times 1440}$	*1.28 mL/min* *0.077 L/h* *1.85 L/24 h*
Plasma flow (Q_P, mL/min)	$Q_B\times(1-Hct)$	$200\times(1-0.30)$	*140 mL/min*
Sodium dialysance (D_{Na}, mL/min)	$D_{Na}\approx K_{Urea}$		*14.19 mL/min*
Replacement fluid flow rate (Q_{RF}, mL/min)	$\frac{Q_P\times(Q_{UF}-D_{Na})}{(D_{Na}-Q_P)}$	$\frac{140\times(1.28-14.19)}{14.19-140}$	*14.37 mL/min* *861.8 mL/h*
Sodium reduction ratio (NaAR, percent as a fraction)	$1-e^{-\frac{D_{Na}\bullet tx}{V_0}}$	$1-e^{-\frac{14.19\times 1440}{40000}}$	*0.400*
Replacement fluid sodium concentration (Na_{RF}, mEq/L)	$\frac{Na_{post}-Na_{Pre}\times(1-NaAR)}{NaAR}$	$\frac{130-124\times(1-0.40)}{0.400}$	*139 mEq/L*
Sodium gradient (∇Na, mEq/L)	$Na_{RF}-Na_{Pre}$	$139-124$	*15 mEq/L*
Plasma sodium concentration at time (t, min) during treatment (P_{Na}(t), mEq/L)	$Na_{Pre}+\nabla Na\times\left(1-e^{-\frac{D_{Na}\bullet t}{V_0}}\right)$	*for* $t=1440$ $124+15\times(NaAR)$ $124+15\times(0.400)$	*130 mEq/L*
Total body Na (TBNa, mEq)	$Na_{Pre}\cdot V_0$	124×40	*4960 mEq*
Change in total body Na at time (t) ΔTBNa(t), mEq)	$P_{Na}(t)\cdot\left(V_0-Q_{UF}\cdot t\right)-Na_{Pre}\cdot V_0$	$V_0=L$ *and* $Q_{UF}=L/h$ $130\times(40-0.077\times 24)-124\times 40$	*0 mEq*

Table 4 Day 2 treatment parameters

Parameter	Admission	Day 1	Day 2
Weight, kg	78	*75*	72
P_{Na}, mEq/L	118	124	130
TBW, L	42	39	36.2
TBNa, mEq	4956	4836	4706
Ultrafiltration, mL/h	0	125	118
Net change of TBNa, mEq	0	−122	−252

the first treatment. Therefore, ΔTBNa equals 0 for the 48 h of treatment, and volume overloading does not occur. Thus, targeting net fluid loss with simultaneous correction of P_{Na} and no sodium gain is the desired treatment goal in the setting of ADHF, hyponatremia, fluid overload, and increased TBNa.

Troubleshooting

Baseline (t = 0 min) and 2–4-hourly lab monitoring that includes plasma sodium, potassium, chloride, total carbon dioxide, blood urea nitrogen, creatinine, and glucose concentrations is recommended to evaluate the efficacy of SBO. A failure of P_{Na} to increase within 4 h requires reexamination of calculations and checking equipment and the extracorporeal circuit for proper functioning. For example, inaccurately low determination of Na_{RF} will prevent elevation of P_{Na}. Accurate calculation of TBW at the beginning of therapy is important because underestimating TBW results reduces the rate of rise of P_{Na}. If this occurs, increasing Q_P, Q_{RF}, and increasing the sodium concentration gradient between plasma and replacement fluid will increase P_{Na} at a more rapid rate. Rapid increases of P_{Na}, (e.g., > 1 mmol/L per hour for 4–6 hours) are rectified by decreasing Q_P, and Q_{RF} and decreasing the sodium gradient between P_{Na} and RF [68].

Achieving net negative sodium and fluid balance

Applying the above equations while establishing a goal of net negative fluid balance prevents the inevitable increase of TBNa that accompanies P_{Na} elevation. In our example, TBNa excess is averted by increasing ultrafiltration by 1 L per day. This maneuver produces a cumulative loss of 6 L of fluid and P_{Na} of 130 mEq/L after 48 h. An additional 1 L of ultrafiltration volume removes an additional 122 mEq on day 1 of treatment. The additional removal of 1 L of ultrafiltrate on day 2 removes an additional 130 mEq of sodium, and a net sodium loss of 252 mEq is realized. The changes of TBNa and P_{Na}(t) are tabulated (Table 4).

Conclusion

Predilution CVVH-SBO therapy controls the rate of urea removal and the rate of increase (or decrease) of P_{Na}. SBO modeling provides an advantage for the treatment of hyponatremia in patients with oligoanuric ADHF. Implementation of CVVH-SBO provides simple and smooth regulation of TBNa through judicious determination of ultrafiltration. When properly implemented, predilution CVVH-SBO alleviates the congestion and corrects the hyponatremia of ADHF in a safe and controlled fashion.

Disclosures

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