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Review Article

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Sodium-Based Osmotherapy in Continuous Renal Replacement Therapy: a Mathematical Approach

Jerry Yee[1], *Naushaba Mohiuddin*,[2] *Tudor Gradinariu*,[1] *Junior Uduman*,[1] *and Stanley Frinak*[1]

Abstract

Cerebral edema, in a variety of circumstances, may be accompanied by states of hyponatremia. The threat of brain injury from hypotonic stress-induced astrocyte demyelination is more common when vulnerable patients with hyponatremia who have end stage liver disease, traumatic brain injury, heart failure, or other conditions undergo overly rapid correction of hyponatremia. These scenarios, in the context of declining urinary output from CKD and/or AKI, may require controlled elevations of plasma tonicity *vis-à-vis* increases of the plasma sodium concentration. We offer a strategic solution to this problem *via* sodium-based osmotherapy applied through a conventional continuous RRT modality: predilution continuous venovenous hemofiltration.

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Introduction

Generally, sodium-based osmotherapy (SBO) is tonicity therapy with the aim of reducing cerebral edema during states of hypotonic hyponatremia. Depending on the circumstance, plasma tonicity may be increased or decreased. Because the sodium concentration ([Na]) in the plasma at any time (t), $P_{Na}(t)$, and accompanying anions constitute the bulk of plasma tonicity, SBO is predicated on gradual alteration of P_{Na}, in contrast to the relatively rapid P_{Na} increases imposed by steep dialysate-to-plasma [Na] gradients associated with conventional hemodialysis. Generally, osmotherapy is carried out when there is severe hyponatremia, oligo-anuria, and inability to excrete sufficient electrolyte-free water to maintain isotonicity (1–3). Thus, SBO has played a role in patients with end stage liver disease and advanced heart failure.

Osmotic demyelination syndrome may transpire in patients who are hyponatremic with end stage liver disease after abrupt P_{Na} elevations during orthotopic liver transplantation (4,5). Correspondingly, presurgical elevation of P_{Na} among individuals prone to osmotic demyelination may be prophylactic. Less commonly, supranormal P_{Na} elevations have been imposed during traumatic brain injury or intracerebral hemorrhage to reduce brain swelling (6,7).

To rectify severe plasma hypotonicity, a relatively hypertonic/hypernatric solution is administered in a controlled fashion during continuous renal replacement therapy (CRRT), and P_{Na} is increased at rates consistent with consensus guidelines (8). Controlled P_{Na} elevations can be achieved by hemodialysis, but special device- and protocol-specific modifications are required to avoid dialysis disequilibrium syndrome (9). Sustained low-efficiency dialysis or slow continuous ultrafiltration with simultaneous infusion of a solution relatively hypernatric to P_{Na} is also feasible (10). In terms of CRRT, SBO has been conducted with continuous venovenous hemofiltration (CVVH) (11,12), continuous venovenous hemodialysis (13), or continuous venovenous hemodiafiltration (14).

General Principles of SBO

SBO can be implemented as a stepwise approach based on established biophysical principles governing sodium transit *via* predilution CVVH. The following urea- and sodium-based kinetic methodology involves six steps: (*1*) establishing a time-dependent [Na] gradient [$\nabla Na(t)$] between the plasma and a replacement fluid (RF) based on a sodium concentration adjustment ratio (NaAR) (Figure 1), (*2*) estimation of total body water (TBW), (*3*) determination of sodium ion dialysance (D_{Na}) that approximates the urea hemofilter transfer rate, (*4*) on-treatment prediction of $P_{Na}(t)$, (*5*) determination of sodium balance, and (*6*) troubleshooting.

Predilution CVVH

RF is infused postblood pump and prehemofilter at a specified rate (Q_{RF}) into the plasma flow (Q_P) to raise (or lower) P_{Na} from its pretreatment level, Na_{Pre} or $P_{Na}(0)$, to its post-treatment level, Na_{Post} or $P_{Na}(t)$ (Figure 1). Employing a fixed-volume model where TBW volume is constant and analogizing to established urea kinetic principles, the rate change of P_{Na} can be computed over a specified time interval (15,16). Thus, sodium advected from the RF gradually increases Na_{Pre} to Na_{Post}, with their difference equaling ΔNa (Equation 1).

To produce an [Na] gradient, a stock RF (RF1) of nominal [Na] Na_{RF1} is adjusted to Na_{RF2}, thereby establishing $\nabla Na(0)$, the maximal [Na] gradient at time (0) (Equation 2). ΔNa is also the product of $\nabla Na(0)$ and NaAR, and NaAR is the ratio of ΔNa to $\nabla Na(0)$ (Equation 3).

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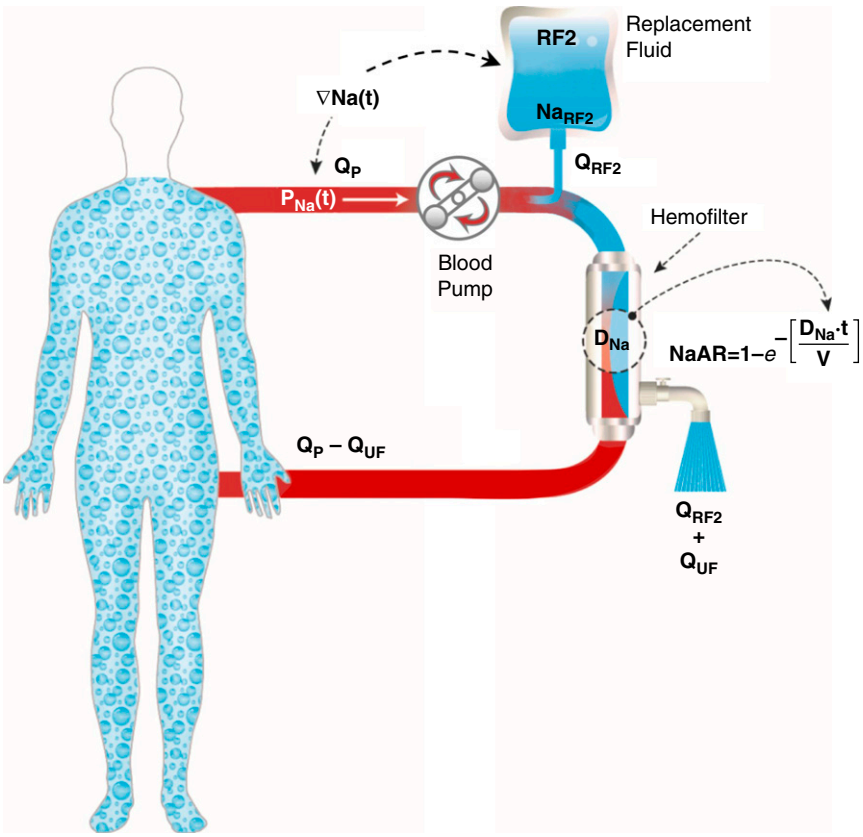

Figure 1. | Plasma sodium concentration is exponentially changed by the replacement fluid sodium concentration and flow rates of plasma, replacement fluid, and ultrafiltration. The extracorporeal circuit is comprised of a hemofilter and replacement fluid. The plasma inflow rate (Q_P) is advected by a sodium concentration [Na]-adjusted replacement fluid (Na_{RF2}). The sodium concentration [Na] gradient, ∇Na(t), equals the [Na] difference between Na_{RF2} and plasma sodium concentration at any time (t), $P_{Na}(t)$. The sodium concentration adjustment ratio (NaAR) is defined by sodium ion dialysance (D_{Na}), time, and total body water volume (Watson volume, V). Hemofilter effluent equals the sum of RF2 flow rate (Q_{RF2}) and net ultrafiltration flow rate (Q_{UF}). ∇Na(t), [Na] gradient at time (t) or $P_{Na}(t)$-to-Na_{RF2} difference; RF2, [Na]-adjusted replacement fluid 2.

$$\Delta Na = Na_{Post} - Na_{Pre} \quad \text{(Equation 1)}$$

$$\nabla Na(0) = Na_{RF2} - Na_{Pre} \quad \text{(Equation 2)}$$

$$NaAR = \Delta Na/\nabla Na(0) = (Na_{Post} - Na_{Pre})/(Na_{RF2} - Na_{Pre}) \quad \text{(Equation 3)}$$

Sodium Kinetic Principles

The NaAR is a function of treatment time (t), TBW (V, Watson volume), and D_{Na}. The NaAR is similar to the urea reduction ratio (URR, Equation 4), with equivalence of D_{Na} to the urea clearance constant, K_{Urea} (Equation 4, A and B).

$$URR = (BUN(0) - BUN(t))/(BUN(0) - BUN_{Dialysate}) = URR = 1 - e^{-K_{Urea}\cdot t/V} \quad \text{(Equation 4A)}$$

$$NaAR = 1 - e^{-D_{Na}\cdot t/V} \quad \text{(Equation 4B)}$$

Step 1: Establishing the Sodium Concentration Gradient

Replacement Fluids

To generate ∇Na(0), the sodium-adjusted RF [Na], Na_{RF2}, is often simply assigned an [Na] that is 6–10 mM greater than Na_{Pre}. However, Na_{RF2} can be more rationally determined from intrinsic parameters of predilution CVVH (Tables 1 and 2). First, by predetermining a target Na_{Post}, ΔNa is defined. Second, estimation of NaAR from URR (Equations 3 and 4) and rearrangement of Equation 3 yields Na_{RF2} as Equation 5.

$$Na_{RF2} = Na_{Pre} + (\Delta Na/NaAR) \quad \text{(Equation 5)}$$

In summary, urea kinetics function to approximate NaAR. These principles are illustrated by the following example.

Case 1. A 42-year-old man, 178 cm and 90 kg, is anuric with stage 3 AKI. He has no peripheral edema. Laboratory data: Na_{Pre}, 116 mM; BUN(0), 80 mg/dl; hematocrit, 0.25. The target BUN and P_{Na} after 24 hours of CVVH are 48 mg/dl and 124 mM, respectively. First, NaAR approximating URR is calculated, with $BUN_{Dialysate}$ as "zero."

Table 1. Sodium-based osmotherapy parameters

Row	Parameter	Definition	Units
1	ΔNa	Post-treatment [Na] minus pretreatment [Na]	mmol/l, mM
2	∇Na(0)	[Na] gradient at time (t)=0	mmol/l, mM
3	[Na]	Sodium concentration	mmol/l, mM
4	ΣNa	Sodium balance	mmol
5	D_{Na}	Dialysance of sodium ion	ml/min
6	Eff-Na_{RF}	Effective replacement fluid [Na] from combined infusions of Na_{RF1} and Na_H	mmol/l, mM
7	NaAR	Sodium concentration adjustment ratio	Dimensionless
8	Na_H	[Na] of a defined hypo-, iso-, hypertonic solution H	mmol/l, mM
9	Na_{Pre}	Pretreatment P_{Na}, *i.e.*, $P_{Na}(0)$	mmol/l, mM
10	Na_{Post}	End treatment P_{Na}	mmol/l, mM
11	Na_{RF1}	RF1 [Na], unadjusted replacement fluid	mmol/l, mM
12	Na_{RF2}	RF2 [Na], sodium-adjusted replacement fluid	mmol/l, mM
13	$P_{Na}(t)$	Plasma [Na] at time (t)	mmol/l, mM
14	Q_H	Solution H flow rate	ml/min
15	Q_B, Q_P	Respective blood and plasma fluid flow rates	ml/min
16	Q_{RF}	Replacement fluid flow rate	ml/min
17	Q_{UF}	Net ultrafiltration flow rate	ml/min
18.	Q_{Eff}	Combined flow rate of Q_{RF1} and Q_H	ml/min
19	RF1	Replacement fluid 1	—
20	RF2	Replacement fluid 2	—
21	t	Time	min
22	URR	Urea reduction ratio	Dimensionless
23	V	Total body water, *i.e.*, Watson volume	ml, L
24	V_{4M}	Volume of added hypertonic saline (23.4%, 4 M)	ml, L
25	V_{RF1}	Volume of RF1	ml, L
26	V_{RF2}	Volume of RF2	ml, L
27	V_W	Volume of added sterile water	ml, L

Variables and abbreviations used in text and equations.

$$\text{NaAR} \approx \text{URR} = (\text{BUN}(0) - \text{BUN}(1440))/\text{BUN}(0) = (80 - 48)\text{mg/dl}/80\text{mg/dl} = 0.4$$

Second, after NaAR is determined, ΔNa, ∇Na(0), and Na_{RF2} are calculated.

$$\Delta\text{Na} = \text{Na}_{\text{Post}} - \text{Na}_{\text{Pre}} = 124\ \text{mM} - 116\ \text{mM} = 8\ \text{mM}$$
$$\nabla\text{Na}(0) = \Delta\text{Na}/\text{NaAR} = 8\ \text{mM}/0.4 = 20\ \text{mM}$$
$$\text{Na}_{\text{RF2}} = \text{Na}_{\text{Pre}} + (\Delta\text{Na}/\text{NaAR}) = 116\ \text{mM} + 8\ \text{mM}/0.4 = 116\ \text{mM} + 20\ \text{mM} = 136\ \text{mM}$$
$$\text{NB:}\ \ \nabla\text{Na}(0) = \text{Na}_{\text{RF2}} - \text{Na}_{\text{Pre}} = 136\ \text{mM} - 116\ \text{mM} = 20\ \text{mM}$$

The time dependencies of Na_{Post}, NaAR, and ΔNa during prolonged SBO are tabulated in Table 3. Figure 2 demonstrates the effect of increasing ∇Na(0) on P_{Na} at NaAR of 0.4 over 1440 minutes of treatment. The random assignment of a 6–10 mM ∇Na(0) would have suboptimally elevated P_{Na}, underscoring this approach of using NaAR to determine Na_{RF2}. Note the relatively low NaAR complements the large ∇Na(0). Importantly, a low URR of 0.4 provides a therapeutic advantage by mitigating the risk of inducing cerebral edema by lowering overall urea flux.

Replacement Fluid Manipulation

In predilution CVVH SBO, the Na_{RF1} is frequently lowered from a nominal level of 130 or 140 mM. For *Case 1*, Na_{RF1} can be adjusted to an Na_{RF2} of 136 mM by several methods (Figure 3) (11,12): method 1, diluting RF1 (Na_{RF1} 140 mM) with 147 ml sterile water; method 2, exchanging 143 ml of RF1 (Na_{RF1} 140 mM) for sterile water; and method 3, addition of 7.8 ml of 4 M saline (23.4%) to 5 L of RF1 solution (Na_{RF1} 130 mM).

Effective Replacement Fluid Sodium Concentrations

If institutional policy prohibits RF manipulations, an effective RF [Na] (Eff-Na_{RF}) equal to the desired Na_{RF2} must be generated *via* flow-rate adjustments of an unadjusted RF1 and a separate solution (H; Figure 3, method 4) (14,17–19). Peripheral infusion of 5% dextrose in water (D_5W) or sterile water by central vein may be used as "0" mM [Na] solutions (20).

Step 2: Estimating TBW as Watson Volume

Watson Volume

NaAR is a function of time, D_{Na}, and TBW (V, Watson volume). Hence, accurate determination of V is critical. Consequently, the Watson volume, representing TBW as urea space, is used in subsequent calculations because it is a

Table 2. Sodium-based osmotherapy equations

Row	Description	Equation
1	Dialysance of sodium ion	$D_{Na} = -(V/t) \times LN(1 - NaAR)$ $D_{Na} = Q_P \times [(Q_{UF} + Q_{RF})/(Q_P + Q_{RF})]$
2	Method 1 calculation of added water volume	$V_{RF2} = V_{RF1} \times (Na_{RF1}/Na_{RF2})$ $V_W = V_{RF1} \times [(Na_{RF1} - Na_{RF2})/Na_{RF2}]$
3	Method 2 calculation of water exchange volume	$V_X = V_{RF1} \times (Na_{RF1} - Na_{RF2})/Na_{RF1}]$
4	Method 3 volume calculation of added 4 M hypertonic saline volume (23.4%)	$V_{4M} = V_{RF1} \times (Na_{RF2} - Na_{RF1})/(Na_{4m} - Na_{RF2})$
5	Method 4 calculation of solution H fluid flow rate	$Q_H = Q_{Eff} \times (Na_{RF1} - Eff\text{-}Na_{RF})/(Na_{RF1} - Na_H)$
6	Method 4 replacement fluid 1 (RF1) flow rate	$Q_{RF1} = Q_{Eff} \times (Eff\text{-}Na_{RF} - Na_H)/(Na_{RF1} - Na_H)$
7	Plasma flow rate calculation	$Q_P = Q_B \times (1 - \text{hematocrit})$
8	Sodium concentration at treatment time (t)	$P_{Na}(t) = P_{Na}(0) + \nabla Na(0) \times (1 - e^{-D_{Na} \cdot t/V})$; $P_{Na}(0) = Na_{Pre}$ $P_{Na}(t) = P_{Na}(0) + (Na_{RF2} - Na_{Pre}) \times (1 - e^{-D_{Na} \cdot t/V})$ $P_{Na}(t) = Na_{Pre} + ([Na_{RF2} - Na_{Pre}] \times NaAR)$
9	Replacement fluid flow rate	$Q_{RF} = Q_P \times (D_{Na} - Q_{UF})/(Q_P - D_{Na})$; $Q_{UF} = 0$
10	Sodium balance at time (t)	$\Sigma Na(t) = P_{Na}(t) \times (V - Q_{UF} \times t) - (Na_{Pre} \times V)$ $\Sigma Na(t) = P_{Na}(t) \times (V - Q_{UF} \times t) - (P_{Na}(0) \times V)$
11	Sodium concentration adjustment ratio	$NaAR = 1 - e^{-D_{Na} \cdot t/V}$ $NaAR = \Delta Na/\nabla Na(0) = (Na_{Post} - Na_{Pre})/(Na_{RF2} - Na_{Pre})$
12	Sodium concentration change at end-treatment time (t)	$\Delta Na = \nabla Na(0) \times NaAR$ $\Delta Na = Na_{Post} - Na_{Pre}$
13	Sodium concentration gradient, initial	$\nabla Na(0) = Na_{RF2} - Na_{Pre}$
14	Sodium concentration of RF2	$Na_{RF2} = Na_{Pre} + (\Delta Na/NaAR)$ $Na_{RF2} = Na_{Pre} + [\Delta Na/(1 - e^{-D_{Na} \cdot t/V})]$
15	Time at which specified P_{Na} occurs (t_X)	$t_X = -(V/D_{Na}) \times LN[(Na_{RF2} - P_{Na}(t_X))/(Na_{RF2} - Na_{Pre})]$
16	Ultrafiltration rate to achieve net zero sodium balance at time (t)	$Q_{UF}(t) = ([Na_{Post} \times V] - [Na_{Pre} \times V])/(Na_{Post} \times t)$ $Q_{UF}(t) = (\Delta Na \times V)/(Na_{Post} \times t)$
17	Urea reduction ratio	$URR = 1 - e^{-K_{Urea} \cdot t/V}$ $URR = (BUN(0) - BUN(t))/(BUN(0) - BUN_{Dialysate})$
18	Watson volume	$V_{Man} = 2.447 - 0.09156 \times (\text{age, yr})$ $+0.1074 \times (\text{height, cm}) + 0.3362 \times (\text{weight, kg})$ $V_{Woman} = -2.097 + 0.1069 \times (\text{height, cm}) + 0.2466 \times (\text{weight, kg})$

See Table 1 for definitions of variables.

superior estimate of TBW compared to multiplication of body weight by an arbitrary factor, *i.e.*, 0.5–0.6 (2,21). For *Case 1*, initial estimates of V for a 178-cm, 90-kg man and woman are 48.0 L and 39.1 L, respectively. For initial estimates of V, considerations of edema and third spacing of extracellular fluid are excluded, but accommodations for these factors can be made (see *Additional Considerations*).

Step 3: Dialysance of Sodium Ion

Sodium Ion Dialysance

Dialysance of sodium ion (D_{Na}) comprises three flow rates: plasma (Q_P), RF (Q_{RF}), and net ultrafiltration (Q_{UF}) (22). Q_P has the greatest influence on D_{Na} by virtue of its greater magnitude. D_{Na} is also the product of Q_P and the filtration fraction as follows.

$$D_{Na} = Q_P \times [(Q_{UF} + Q_{RF})/(Q_P + Q_{RF})] \qquad \text{(Equation 6)}$$

We recommend a blood flow (Q_B) of 250–300 ml/min to promote clearance and prevent filter clotting (23). As shown, at a Q_B of 300 ml/min and hematocrit (Hct) of 0.25, Q_P is 225 ml/min (Equation 7).

$$Q_P = Q_B \times (1 - Hct) = 300 \text{ ml/min} \times (1 - 0.25) = 225 \text{ ml/min} \qquad \text{(Equation 7)}$$

Application

In *Case 1*, NaAR at 1440 minutes equals 0.4. Thus, D_{Na} is resolved by specifying V and t and rearranging Equation 4B as Equation 8.

$$\begin{aligned} D_{Na} &= -(V/t) \times LN(1 - NaAR) = -(48,000 \text{ ml}/1440 \text{ min}) \\ &\quad \times LN(1 - 0.4) \\ &= -33.3 \text{ ml/min} \times -0.51 = 17.0 \text{ ml/min} \end{aligned} \qquad \text{(Equation 8)}$$

With D_{Na} known, Q_{RF} is determined by rearranging Equation 6 as Equation 9.

$$\begin{aligned} Q_{RF} &= Q_P \times (D_{Na} - Q_{UF})/(Q_P - D_{Na}); Q_{UF} = 0 \\ &= (225 \text{ ml/min} \times 17 \text{ ml/min})/(225 \text{ ml/min} - 17 \text{ ml/min}) \\ &= 18.4 \text{ ml/min} = 1.1 \text{ L/h} \end{aligned} \qquad \text{(Equation 9)}$$

In summary, steps 1–3 determine an NaAR of 0.4 and a $\nabla Na(0)$ of 20 mM that yield a ΔNa of 8 mM. Similar results are obtained by increasing D_{Na} (*i.e.*, greater NaAR) and proportionally decreasing $\nabla Na(0)$. For example, if NaAR is 0.6, $\nabla Na(0)$ becomes 13.3 mM and Na_{RF2} becomes 129.3

Table 3. Time-dependencies of plasma sodium concentration and sodium concentration adjustment ratio during sodium-based osmotherapy

Time (t, min)	$P_{Na}(0)$	NaAR	ΔNa(t) (mM)	$P_{Na}(t)$ (mM)
0	116.0	0.0 (0.0)	0.0 (0.0)	116.0 (116.0)
360	116.0	0.12 (0.14)	2.4 (2.9)	118.4 (118.9)
720	116.0	0.23 (0.27)	4.5 (5.4)	120.5 (121.4)
1080	116.0	0.32 (0.37)	6.4 (7.5)	122.4 (123.5)
1440	116.0	0.40 (0.47)	8.0 (9.3)	124.0 (125.3)
2880	116.0	0.64 (0.71)	12.8 (14.3)	128.8 (130.3)
4320	116.0	0.78 (0.85)	15.7 (16.9)	131.7 (132.9)

Predilution continuous venovenous hemofiltration is carried out on a hypothetical 42-year-old, 178-cm, 90-kg man with $P_{Na}(0)$ 116 mM and Watson volume 48.0 L for times shown. The replacement fluid is adjusted from a nominal [Na] of 140 mM to 136 mM to achieve a 20 mM [Na] gradient. Values in parentheses are those of a 42-year-old woman with a Watson volume of 39.1 L, treated with the same parameters. P_{Na}, plasma sodium concentration; NaAR, sodium concentration adjustment ratio; ΔNa(t), $P_{Na}(t)$ minus $P_{Na}(0)$; $P_{Na}(t)$, P_{Na} at time (t); [Na], sodium concentration; $P_{Na}(0)$, P_{Na} at time (t) = 0.

mM. Also, the Na_{RF2} that produces a specified ΔNa at time (t) is calculated from Equations 4B and 5 (Equation 10).

$$Na_{RF2} = Na_{Pre} + \left[\Delta Na \Big/ \left(1 - e^{-D_{Na}\cdot t/V}\right)\right] \quad \text{(Equation 10)}$$

Step 4: Plasma Sodium Concentration during Osmotherapy

Targeting the Plasma Sodium Concentration

Because D_{Na} and TBW are constants within the constraints of a fixed-volume model, $P_{Na}(t)$ can be projected over a specified treatment interval (t) (Equation 11).

$$P_{Na}(t) = Na_{Pre} + \left[(Na_{RF2} - Na_{Pre}) \times \left(1 - e^{-D_{Na}\cdot t/V}\right)\right] \quad \text{(Equation 11)}$$

This concept is depicted in Figure 4 where time- and volume-dependencies of $P_{Na}(t)$ are displayed for a man and woman of equal height and weight. The greater $P_{Na}(t)$ of the woman throughout treatment is attributable to a lesser Watson volume. The time (t_X) when a specified $P_{Na}(t_X)$ occurs is ascertained by substituting t_X into Equation 11 and solving for it.

$$t_X = -(V/D_{Na}) \times LN[(Na_{RF2} - P_{Na}(t_X))/(Na_{RF2} - Na_{Pre})] \quad \text{(Equation 12)}$$

Step 5: Sodium Balance during Osmotherapy

In a fixed-volume model of SBO, sodium accrual is inevitable as P_{Na} increases. If patient vulnerability to volume overload is present, net ultrafiltration is advised. Consequently, real-time net sodium balance (ΣNa) monitoring is critical and computed by Equation 13.

$$\Sigma Na(t) = P_{Na}(t) \times (V - Q_{UF} \times t) - (Na_{Pre} \times V)$$
$$\Sigma Na(t) = P_{Na}(t) \times (V - Q_{UF} \times t) - (P_{Na}(0) \times V) \quad \text{(Equation 13)}$$

In *Case 1*, ΣNa(1440) is +384 mmol if Q_{UF} = 0 but –62.4 mmol if Q_{UF} is 0.15 L/h or 3.6 L per day.

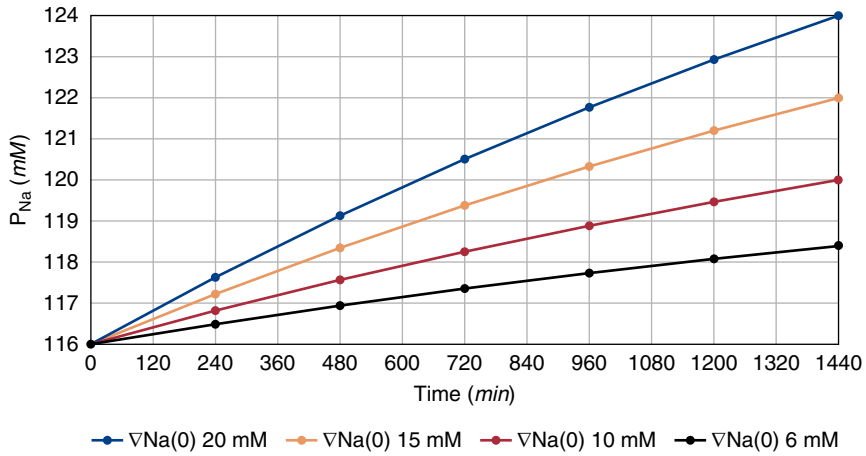

Figure 2. | Plasma sodium concentration increases are time- and sodium concentration gradient-dependent. Data are modeled from a hypothetical 42-year-old, 178-cm, 90-kg man with Watson volume 48.0 L (see text, *Case 1*). Plasma sodium concentration (P_{Na}) is 116 mM before predilution continuous venovenous hemofiltration is carried out at four different [Na] gradients. NaAR equals 0.4 after 1440 minutes of sodium-based osmotherapy. At end treatment, P_{Na} increases in direct proportion to ∇Na(0). ∇Na(0), [Na] gradient between plasma and replacement fluid at time (0).

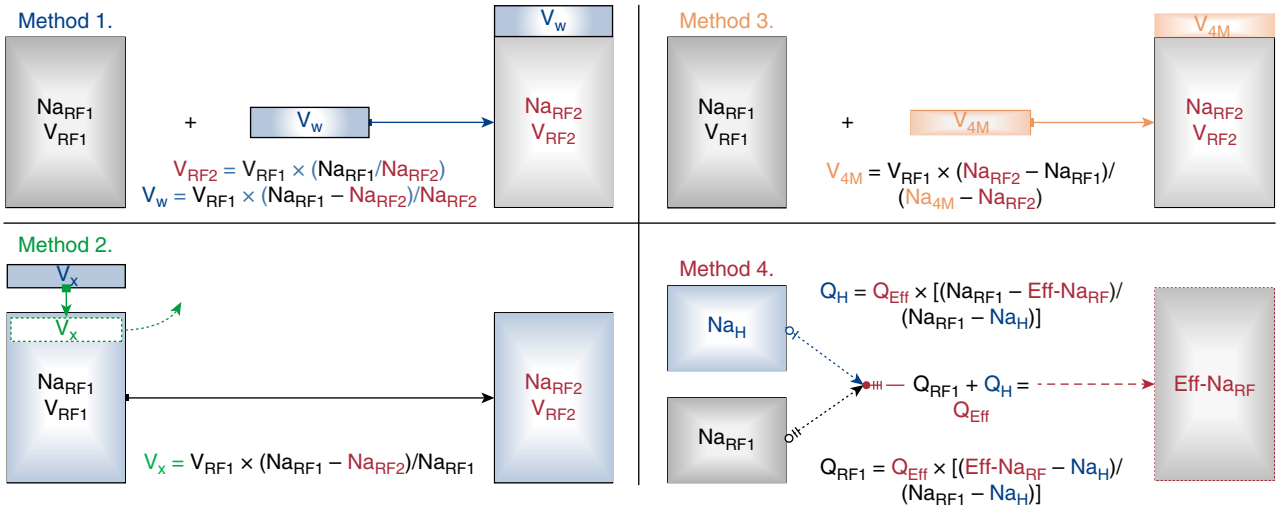

Figure 3. | **Replacement fluid sodium concentration adjustment.** Method 1: Sterile water is added to replacement fluid 1 (RF1) of volume V_{RF1} and sodium concentration Na_{RF1} to produce replacement fluid 2 (RF2) of volume V_{RF2} and sodium concentration Na_{RF2}. Method 2: A volume from RF1 (V_X) is exchanged with sterile water to produce Na_{RF2}. Method 3: A volume of 4 M sodium chloride solution (V_{4M}) is added to RF1 to produce RF2 volume V_{RF2} and Na_{RF2}. Method 4: Solution H is infused postblood pump and prehemofilter at flow rate Q_H in parallel with RF1 at flow rate Q_{RF1} to produce a blended solution with an effective [Na] (Eff-Na_{RF}) at flow rate Q_{Eff}. H, solution of defined [Na]; Eff-Na_{RF}, effective-[Na] of RF1 and solution H; Na_H, solution H [Na]; Q_{Eff}, additive flow rate of Q_{RF1} and Q_H; Q_H, solution H flow rate; Q_{RF1}, RF1 flow rate; Q_{RF2}, RF2 flow rate; V_{4M}, 4 M saline volume; V_W, water volume added to RF1; V_X, RF1 exchange volume.

$$\Sigma Na(t) = (P_{Na}(t) \times V) - (Na_{Pre} \times V);\ Q_{UF} = 0\ ml/min$$
$$\Sigma Na(1440) = (124\ mM \times 48.0\ L) - (116\ mM \times 48.0\ L)$$
$$= +384\ mmol$$
$$\Sigma Na(t) = P_{Na}(t) \times (V - Q_{UF} \times t) - (Na_{Pre} \times V)$$
$$\Sigma Na(1440) = 124\ mM \times (48.0\ L - 0.15\ L/h \times 24\ h)$$
$$- (116\ mM \times 48.0\ L) = -62.4\ mmol$$

The Q_{UF} that "zeroes" the sodium load at time (t) is calculated as 3.1 L per 24 hours by Equation 14.

$$Q_{UF}(t) = [(Na_{Post} \times V) - (Na_{Pre} \times V)]/(Na_{Post} \times t)$$
$$= (V \times \Delta Na)/(Na_{Post} \times t)$$
$$Q_{UF}(t) = (V \times \Delta Na)/(Na_{Post} \times t)$$
$$= (48\ L \times 8\ mM)/(124\ mM \times 1440\ min)$$
$$0.00215\ L/min = 3.1\ L\ per\ 24\ hours$$

(Equation 14)

Modeling Sodium Balance

For patients vulnerable to volume excess/overload, ΣNa should be modeled *a priori*, and we demonstrate this concept as follows.

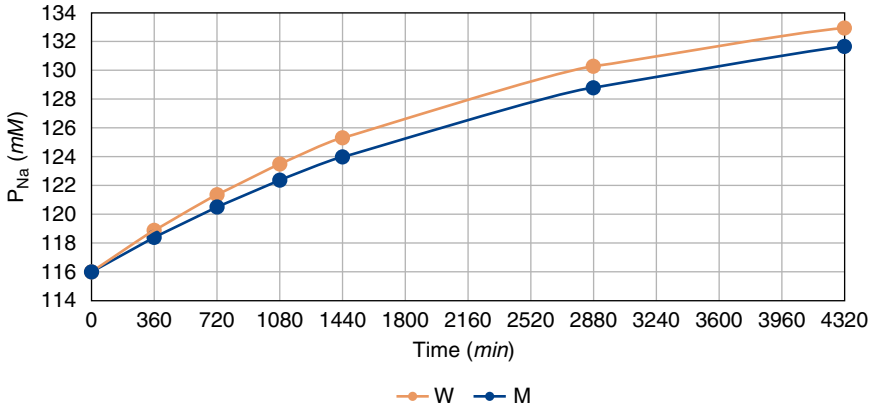

Figure 4. | **Plasma sodium concentration increases are time- and volume-dependent.** Data are derived from a hypothetical 42-year-old, 178-cm, 90-kg man (M; see text, *Case 1*) with Watson volume 48.0 L and a 42-year-old woman (W) with Watson volume 39.1 L. The baseline plasma and replacement fluid sodium concentrations of both patients are 116 mM and 136 mM, respectively. Continuous venovenous hemofiltration treatment parameters are as follows: Q_P, 225 ml/min; Q_{RF}, 18.3 ml/min; Q_{UF}, 0 ml/min; and treatment time, 4320 minutes. The P_{Na} of the woman is greater at all time points due to her smaller Watson volume. Q_P, plasma flow rate; Q_{RF}, replacement fluid rate; Q_{UF}, net ultrafiltration fluid rate; P_{Na}, plasma sodium concentration.

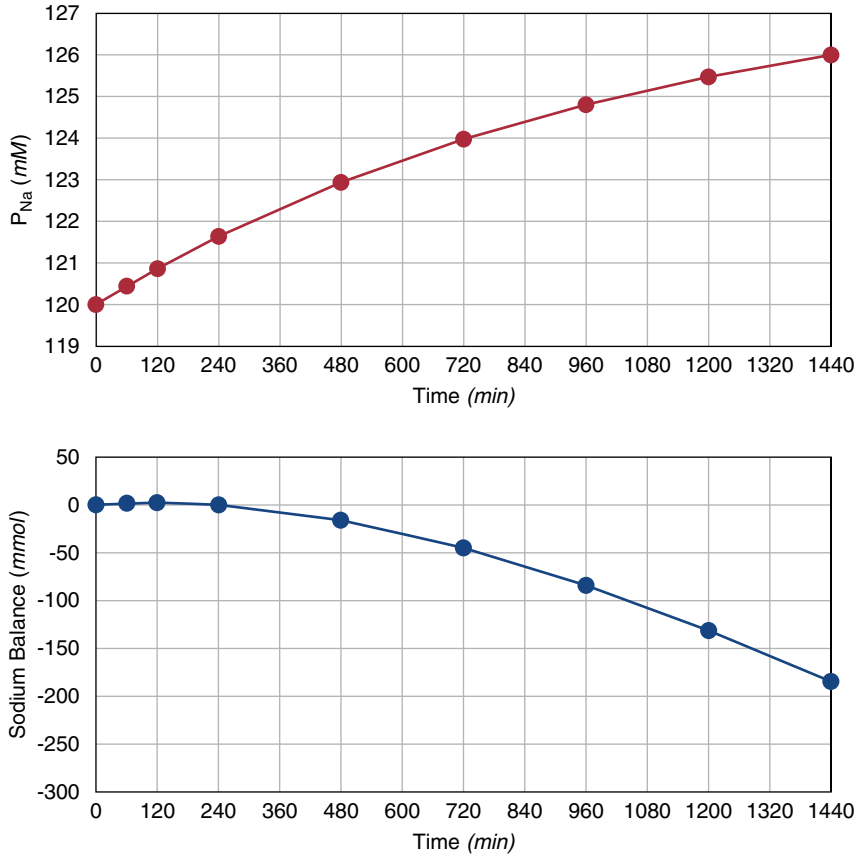

Figure 5. | Plasma sodium concentration elevation without sodium accumulation is achieved by net ultrafiltration during predilution continuous venovenous hemofiltration. Treatment parameters during predilution continuous venovenous hemofiltration of a hyponatremic, 170-cm, 80-kg, 30-year-old man with Watson volume 44.85 L are as follows (see text, *Case 2*): Na_{RF2}, 128 mM; Q_P, 200 ml/min; Q_{RF2}, 50 ml/min; Q_{UF}, 2.5 ml/min; and treatment time, 1440 minutes. At end treatment, NaAR is 0.74 and P_{Na} increases from 120 mM to 126 mM (top plot). Negative sodium balance begins at t = 240 minutes. Cumulative sodium loss is 185 mmol at end treatment (bottom plot).

Case 2. A 30-year-old man with heart failure and stage 3B CKD develops AKI and dyspnea. The admission weight is 2 kg more than his last-reported hospital discharge weight. His vital signs are as follows: height, 170 cm; weight, 80 kg; temperature, 36.5°C; heart rate, 118 bpm; blood pressure 130/80 mm Hg; respiratory rate, 18 per minute; and Watson volume, 44.85 L. His laboratory data are as follows: Na_{Pre}, 120 mM; BUN, 50 mg/dl; serum creatinine, 4.2 mg/dl; and hematocrit, 0.33. Urine output is <0.05 ml/kg·h. A 24-hour Na_{Post} target of 126 mM is planned. Predilution CVVH is begun with parameters of Q_P 200 ml/min, Q_{RF} 50 ml/min, Q_{UF} 2.5 ml/min, and NaAR 0.74. An NaRF2 of 128 mM is formulated by adding 79 ml sterile water to an RF1 of 130 mM. To achieve net sodium balance of zero after 24 hours, net

Table 4. Effects of intravenous solutions and urine output on the effective replacement fluid sodium concentration

Solution	RF	0.45%	Solution A	Solution B	UO	4-Hour Results[a]
Flow rate, L/h	2.0	Single dose	Single dose	Single dose	−0.1	—
Time, h	4.0	4.0	—	—	4.0	—
[Na], mM	130.0	77.0	154.0	40.0	50.0	—
Volume, L	8.0	0.10	0.10	0.25	−0.40	8.05
Cation, mmol	1040.0	7.7	15.4	10.0	−20.0	1053.1
Eff-Na_{RF}, mM[b]	130.0	129.3	130.3	127.3	134.2	130.8

The replacement fluid is infused simultaneously with three separate solutions as shown, with ongoing urine output. To simplify calculations, the RF-potassium concentration is assumed equal to plasma potassium concentration and not described. RF, replacement fluid with [Na] 130 mM; UO, urine output; [Na], sodium concentration; Eff-Na_{RF}, effective [Na] of RF and one of the solutions listed and/or UO.
[a]Aggregate effect of solutions and urine output on Eff-Na_{RF}.
[b]Isolated effect of each solution or urine output on Eff-Na_{RF}.

Table 5. Theoretical effects of a posthemofilter 5% dextrose infusion on glucose metabolism during pre-/post-dilution continuous venovenous hemofiltration

Parameter	Value				
D_5W infusion, ml/h	30	80	160	240	300
CHO load, mg/kg·min	0.28	0.74	1.48	2.22	2.78
P_{Glu}, without carbohydrate metabolism for 24-h, mg/dl	125	500	1100	1700	2150
Maintenance metabolic rate, mg/kg·min	0.15	0.62	1.36	2.10	2.65
Prehemofilter P_{Na}, mM	117.0	117.0	116.9	116.8	116.8

The effects of a 5% dextrose infusion on glucose metabolism in a hypothetical, nondiabetic, 42-year-old, 178-cm, 90-kg man with Watson volume 48 L and $P_{Na}(0)$ 116 mM (see text, *Case 1*) after 24 hours of CVVH are displayed. CVVH parameters are: Na_{RF}, 130 mM; Q_P, 225 ml/min; combined prehemofilter RF and posthemofilter D_5W flow rate, 1.1 L/h (18.3 ml/min); and net ultrafiltration rate, 0 ml/min. Calculations are based on an extracellular fluid volume of 16 L (48 L × 0.33), without expansion of the extracellular fluid space from glucose accumulation. All CHO metabolism is assumed to originate from the D_5W infusion. With no CHO metabolism, increasing the CHO load (row 2) by increasing the D_5W infusion rate from 0 to 300 ml/h rapidly increases P_{Glu} (row 3). The respective glucose metabolic rates required to maintain P_{Glu} at 100 mg/dl for increasing D_5W infusion rates are shown (row 4). The minimal dilutional effect of the increasing D_5W infusion rate on hemofilter inlet P_{Na} is shown (row 5). CVVH, continuous venovenous hemofiltration; D_5W, 5% dextrose solution; CHO, carbohydrate; P_{Glu}, plasma glucose concentration; $P_{Na}(0)$, plasma [Na] at time (t) = 0; Na_{RF}, RF [Na]; Q_P, plasma flow rate; RF, unadjusted replacement fluid; [Na], sodium concentration.

ultrafiltration of 2.14 L per 24 hours is required, as shown below. Ultrafiltration beyond 24 hours produces net total body sodium loss. Figure 5 depicts the evolution of $P_{Na}(t)$ and $\Sigma Na(1440)$ if Q_{UF} is 3.6 L per 24 hours.

$$Q_{UF}(1440) = (V \times \Delta Na)/(Na_{Post} \times t)$$
$$= (44.85\ L \times 6\ mM)/(126\ mM \times 1440\ min)$$
$$= 0.00148\ L/min = 2.14\ L\ per\ 24\ hours$$

Sodium Balance with Edema

If the entire 2-kg excess weight is assumed isotonic to plasma, total body sodium balance must be recalculated. The Watson volume of the 78-kg man was 44.18 L and increased to 46.18 L from 2 L of edema. Achieving zero sodium balance requires just 0.06 L more net ultrafiltration. However, there is a 160-mmol sodium excess if edema is considered isotonic plasma (Equation 15). To shed the sodium surfeit, an additional 1.27 L of net ultrafiltration is required. Overall, net ultrafiltration of 3.47 L attains a $P_{Na}(1440)$ of 126 mM at 76.53 kg.

$$Q_{UF}(1440) = (V \times \Delta Na)/(Na_{Post} \times t)$$
$$= (46.18\ L \times 6\ mM)/(126\ mM \times 1440\ min)$$
$$= 0.00153\ ml/min = 2.2\ L\ per\ 24\ h \quad \text{(Equation 15)}$$

$$\Sigma Na(0) = P_{Na}(0) \times (adjusted\ V + edema\ [kg])$$
$$= 120\ mM \times (44.18 + 2)L = 5542\ mmol$$
$$\Sigma Na(0) = P_{Na}(0) \times (unadjusted\ V)$$
$$= 120\ mM \times 44.85\ L = 5382\ mmol$$
$$\Delta Total\ body\ sodium = 5542\ mmol - 5382\ mmol = 160\ mmol$$
$$Additional\ ultrafiltration\ volume = 160\ mmol/126\ mM$$
$$= 1.27\ L$$

Influence of Exogenous Fluids and Urine Output on Replacement Fluid Sodium Concentration

During SBO, the influence of exogenous cation (sodium and potassium)-containing fluids on P_{Na} and ΣNa must be tallied. Only cationic effects require analysis as anions follow *pari passu*. The RF [Na] is altered by infusions of exogenous fluids and/or urine output and produces a blended solution with an effective [Na] (Eff-Na_{RF}). Table 4 illustrates the 4-hour effects on Eff-Na_{RF} in a patient who receives three intravenous fluids, 0.45% saline and hypothetical solutions A and B. By evaluating a short time interval, the singular and collective effects of each fluid on Eff-Na_{RF} are exposed early on. In aggregate, with consideration of all inputs and outputs, the 4-hour effects on Eff-Na_{RF} and extracellular fluid volume are +0.8 mM and +0.05 L, respectively. Extrapolation of this analysis to a 24-hour interval may obligate readjustments of Na_{RF1} and/or Q_{UF}. Lastly, elaboration of hypotonic urine increases Eff-Na_{RF} minimally, unless urine output is copious, *i.e.*, >4 L per day.

Acute Sodium Loading

Sodium loading can benefit individuals who are normonatremic with acute brain swelling. In patients who are hyponatremic and hypovolemic, sodium loading may be carried out abruptly by delivery of several small-volume, hypertonic saline boluses (*e.g.*, 100-ml boluses of 23.4% saline) (7,23). Subsequent maintenance of the hypertonic state can be achieved with CRRT modalities. Importantly, the gradual sodium loading of SBO should not supplant urgent volume resuscitation where indicated. In brief, the associated risk of sodium loading must be weighed at the outset of SBO, particularly in patients who are volume overloaded or edematous.

Step 6: Troubleshooting

Slow or No Plasma Sodium Concentration Elevation

If P_{Na} fails to increase during SBO, the osmotherapy prescription must be reexamined. Equipment and extracorporeal circuit integrity must be checked, and the effects of all fluid inputs and outputs must be reevaluated. If V is underestimated, the rise of P_{Na} is mathematically inhibited by an NaAR that is lower than calculated. A Q_{UF} increase will not remedy the situation because D_{Na} and NaAR are essentially

Table 6. Effect of pre- and posthemofilter replacement fluid infusion on end treatment plasma sodium concentration

Variable	Units	Predilution Only	Pre-/Postdilution	Pre-/Postdilution
Q_P	ml/min	200.0	200.0	200.0
Q_{RF}	ml/min	50.0	50.0	50.0
Replacement fluid Pre-/postdilution ratio	—	1.0/0.0	0.5/0.5	0.3/0.7
D_{Na}	ml/min	40.0	44.4	46.5
NaAR	—	0.76	0.80	0.81
$P_{Na}(1440)$	mM	127.6	128.0	128.1

A hypothetical patient with Watson volume 40 L and $P_{Na}(0)$ 120 mM undergoes 24 hours of continuous venovenous hemofiltration with the following parameters: Na_{RF}, 130 mM; Q_P, 200 ml/min, and Q_{RF}, 3 L/h. Three simulations are shown: predilution only and pre- and postdilution with Q_{RF} pre- and postdilution ratios of 0.5/0.5 and 0.3/0.7. D_{Na}, NaAR, and $P_{Na}(1440)$ increase with an increasing proportion of postdilution Q_{RF}. The maximal $P_{Na}(1440)$ difference among the three pre-/posthemofilter combinations is 0.5 mM. Q_P, plasma flow rate; Q_{RF}, replacement fluid flow rate; D_{Na}, dialysance of sodium; NaAR, sodium concentration adjustment ratio; $P_{Na}(0)$, P_{Na} at t (0); $P_{Na}(1440)$, P_{Na} at t = 1440 minutes; Na_{RF}, replacement fluid [Na].

unchanged. NaAR must be augmented by increasing Q_P and/or Q_{RF}. In parallel, $\nabla Na(0)$ can be increased to rectify suboptimal P_{Na} elevations. When P_{Na} increases more rapidly than expected *per se* >1 mM per hour for 4–6 hours, the aforementioned maneuvers should be attenuated, stopped, or even reversed.

Inaccurate NaAR

When BUN is relatively low, *e.g.*, 30–40 mg/dl, calculation of NaAR may be inaccurate. This may transpire when sodium ion and urea clearance are discordant, *i.e.*, abnormal rate of urea metabolism. Accordingly, a D_{Na} of 25–40 ml/min can be prespecified by empirically establishing ∇Na, Q_P, Q_{RF}, and, optionally, Q_{UF}.

Additional Considerations

Hyperglycemia from Dextrose-Containing Solutions

If RF solutions cannot be altered, delivery of a parallel, posthemofilter D_5W infusion in pre-/postdilution CVVH may provoke concern for induction of hyperglycemia. However, this concern is unwarranted. A maximal rate of carbohydrate infusion of 4 mg/kg·min has been suggested to prevent lipogenesis (24). At this metabolic threshold, the patient of *Case 1* can tolerate a posthemofilter D_5W infusion of 300 ml/h, without hyperglycemia (Table 5). Absent carbohydrate metabolism, this infusion rate, in an extracellular volume of 16 L, increases plasma glucose (P_{Glu}) from 100 to 2150 mg/dl. However, at a submaximal rate of glucose metabolism of 2.65 mg/kg·min, P_{Glu} remains stable at 100 mg/dl. Notably, the effective P_{Na} entering the hemofilter is changed minimally. Prefilter D_5W infusions have minimal potential for generating severely elevated P_{Glu} due to rapid glucose sieving through the hemofilter. If D_5W or sterile water infusion rates are eschewed, less hypotonic solutions can be used, *e.g.*, 0.225% or 0.45% saline solution.

Regional Citrate Anticoagulation

Regional citrate anticoagulation with trisodium citrate (TSC) solutions of 4% ([Na], 408 mM) or 2.2% ([Na], 224 mM) have been used during SBO (25–27). Nevertheless, hypertonic TSC infusions can greatly increase plasma tonicity, necessitating reduction of RF [Na] and/or dialysate [Na] to prevent untoward elevations of P_{Na}. If TSC is used during SBO, *a priori* sodium modeling is advised with appropriate laboratory monitoring at 4- to 8-hour intervals, including ionized calcium levels that will decline with untoward P_{Na} elevations if hypercitratemia occurs.

SBO by Other CRRT Modalities

Aside from predilution CVVH, other CRRT modalities and protocols are available, and some employ pre- and posthemofilter RF delivery (19). When Q_{RF} is partitioned pre- and postfilter versus prefilter alone, there is an incremental postfilter P_{Na} elevation. Table 6 represents a quantitative analysis for pre- and posthemofilter CVVH and reveals only a 0.5-mM increment with a 30/70 division of Q_{RF} between pre- and postfilter fractions. TSC has been exploited to increase P_{Na} from normal to supranormal levels in patients with cerebral edema (6). However, in acute cerebral edema, rapid induction of hypertonicity *via* hypertonic saline boluses (4 M) is favored when prompt elevation of plasma tonicity is critical (7).

Summary

In conclusion, advective SBO by predilution CVVH may be therapeutically exploited in hypotonic conditions with hyponatremia and oligo-anuria. We recommend a six-step protocol based on calculation of NaAR to achieve a time-targeted P_{Na}. A failure of SBO signifies potential miscalculation(s) and/or the influences of external input and output solutions. Recurrent laboratory monitoring and quantitative analysis of these variables is imperative for safe and successful implementation of SBO. Modeling the plasma sodium concentration, sodium balance, and ultrafiltration with our *mise en place* approach prevents treatment-based sodium loading (Box 1).

Author Contributions

S. Frinak was responsible for methodology; S. Frinak, T. Gradinariu, N. Mohiuddin, and J. Yee were responsible for formal analysis; S. Frinak, J. Uduman, and J. Yee conceptualized the manuscript S. Frinak and J. Yee were responsible for supervision and validation; N. Mohiuddin and J. Yee were responsible for visualization; all authors wrote the original draft of the manuscript, and reviewed and edited the manuscript.

Box 1. Osmotherapy by Predilution Continuous Venovenous Hemofiltration

(*1*) Define ΔNa from time (0) to time (t) by defining Na_{Post}, *e.g.*, 8 mM after 24 hours
$\Delta Na = Na_{Post} - Na_{Pre}$; $Na_{Pre} = P_{Na}(0)$; t = end treatment time
(*2*) Define sodium concentration adjustment ratio (NaAR) from time (0) to t *via* urea reduction ratio (URR), *e.g.*, 30%–70% over 24 hours
$NaAR \approx URR = (BUN(0) - BUN(t))/(BUN(0) - BUN_{Dialysate})$
(*3*) Define ∇Na(0)
$\nabla Na(0) = \Delta Na/NaAR = (Na_{Post} - Na_{Pre})/NaAR = Na_{RF2} - Na_{Pre}$
(*4*) Calculate Na_{RF2}
$Na_{RF2} = Na_{Pre} + \nabla Na(0)$
(*5*) Adjust Na_{RF1} to Na_{RF2} by methods 1–4 (Figure 3)
(*6*) Calculate dialysance of sodium (D_{Na}) from NaAR, Watson volume (V), and t
$D_{Na} = -(V/t) \times LN(1 - NaAR)$
(*7*) Calculate plasma flow rate (Q_P) from blood flow rate (Q_B) and hematocrit (Hct)
$Q_P = Q_B \times (1–Hct)$
(*8*) Calculate Q_{RF} from D_{Na} and Q_P
$Q_{RF} = Q_P \times (D_{Na} - Q_{UF})/(Q_P - D_{Na})$; $Q_{UF} = 0$
(*9*) Model predilution continuous venovenous hemofiltration at specified Q_P and Q_{RF} to determine $Q_{UF}(t)$ (see below)
Monitor P_{Na} at 4- to 6-hour intervals
(*10*) Calculate sodium balance Σ Na from time (0) to (t)
$\Sigma Na(t) = P_{Na}(t) \times (V - Q_{UF} \times t) - (Na_{Pre} \times V)$
Note: Adjust for additional inputs and outputs and edema (see text)
(*11*) Calculate $Q_{UF}(t)$ for zero sodium balance at time (t)
$Q_{UF}(t) = [(Na_{Post} \times V) - (Na_{Pre} \times V)]/(Na_{Post} \times t) = (\Delta Na \times V)/(Na_{Post} \times t)$

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