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PERSPECTIVES IN BASIC SCIENCE

# Evolving concepts in the quantitative analysis of the determinants of the plasma water sodium concentration and the pathophysiology and treatment of the dysnatremias

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**Evolving concepts in the quantitative analysis of the determinants of the plasma water sodium concentration and the pathophysiology and treatment of the dysnatremias.** The physiologic and clinical implications of the empirical formula originally discovered by Edelman et al [*J Clin Invest* 37:1236–1256, 1958] relating the plasma water sodium concentration ($[Na^+]_{pw}$) to the total exchangeable sodium ($Na_e$), total exchangeable potassium ($K_e$), and total body water (TBW) have recently been elucidated. It is quite remarkable that the full significance of the Edelman equation discovered almost 50 years ago had remained unrecognized by clinicians and physiologists until recently. Although Edelman and colleagues had shown that the $[Na^+]_{pw}$ is proportional to the magnitude of $(Na_e + K_e)$/TBW, the linear equation relating $[Na^+]_{pw}$ to $(Na_e + K_e)$/TBW had a slope greater than unity of 1.11, and a non-zero y intercept of –25.6 whose significance was unrecognized and more often than not ignored. It has recently been demonstrated that the slope and y intercept in this equation are quantitatively determined by several additional physiologic parameters, which in addition to $(Na_e + K_e)$/TBW, play a role both in modulating the $[Na^+]_{pw}$ and in the generation of the dysnatremias. Even more remarkably, based only on the theoretical principles of Gibbs-Donnan and osmotic equilibrium, all the physiologic parameters that determine the magnitude of the $[Na^+]_{pw}$ can be incorporated into a simple conceptual and mathematical framework that sheds light on a broad of range of seemingly unrelated topics that have heretofore been treated separately clinically, including (*1*) effect of changes in the mass balance of $Na^+$, $K^+$, and $H_2O$ on the $[Na^+]_{pw}$; (*2*) modulation of $[Na^+]_{pw}$ in hyperglycemic states; (*3*) definition of an isonatric solution; (*4*) current formulas used to quantitate electrolyte-free water excretion; (*5*) complex role of $K^+$ in modulating the $[Na^+]_{pw}$; and (*6*) quantitative analysis of the generation and treatment of the dysnatremias. Moreover, this analysis has also proven to be an indispensable tool for deriving new formulas to aid the clinician in both interpreting the pathogenesis and treating the dysnatremias.

**Key words:** plasma water sodium concentration, Gibbs-Donnan equilibrium, osmotic equilibrium, hyponatremia, hypernatremia.

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Understanding the pathogenesis and treatment of the dysnatremias is a challenge encountered frequently by most physicians [1]. Although the dysnatremias are the most common electrolyte disorders in hospitalized patients, the complexity of their pathogenesis from a physiologic standpoint often creates conceptual difficulties for medical students and experts alike. These difficulties arise in part from the fact that unlike many substances in the plasma space whose concentration is altered simply by changes in their mass balance, the mass balance of $Na^+$ alone cannot account for changes in the $[Na^+]_{pw}$ [2–5]. Deming and Gerbode [6] first showed definitively that the plasma $Na^+$ concentration ($[Na^+]_p$) was modulated not only by the mass balance of $Na^+$, but also by the mass balance of $K^+$ and $H_2O$. To add to this complexity, in addition to changes in whole body mass balance, the $[Na^+]_{pw}$ is affected by intercompartmental $H_2O$ shifts as for example in hyperglycemic states [7, 8]. The multiplicity of factors that can modulate the $[Na^+]_{pw}$ are depicted schematically in Figure 1.

In 1958, Edelman et al [9] solved the difficult problem of determining how the major physiologic factors that modulate the $[Na^+]_{pw}$ were interrelated quantitatively. In this study, Edelman et al determined the interrelationship between $[Na^+]_{pw}$, and exchangeable sodium ($Na_e$), exchangeable potassium ($K_e$), and total body water (TBW). Using linear regression methodology which accounted for the variance in both the dependent and independent variables, it was demonstrated that

$$[Na^+]_{pw} = 1.11(Na_e + K_e)/TBW - 25.6 \quad \text{(Equation 1)}$$

where $[Na^+]_{pw}$ is plasma $H_2O$ sodium concentration; $Na_e$ is total exchangeable sodium; $K_e$ is total exchangeable potassium; and TBW is total body water. We have named this equation the "Edelman equation" after its original discoverer [10].

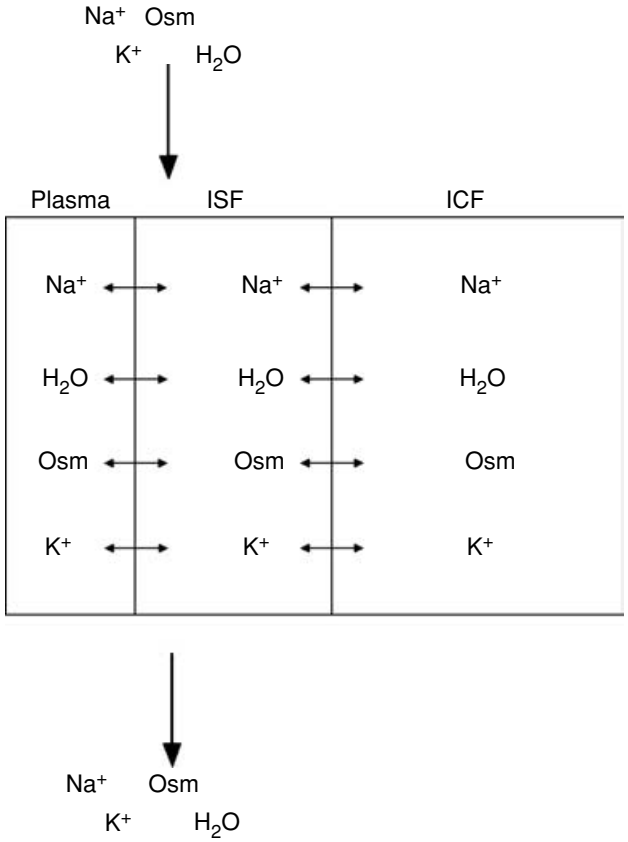


**Fig. 1. Schematic diagram depicting the complexity of factors that modulate the $[Na^+]_{pw}$.** At any given time point, all the terms in equation 4 determine the value of the $[Na^+]_{pw}$. The magnitude of the terms in equation 4 is altered by changes in the mass balance of $Na^+$, $K^+$, non-$Na^+$ non-$K^+$ osmoles, $H_2O$, and subsequent intercompartmental water shifts.

## GENERALIZED EQUATION DEPICTING THE PHYSIOLOGIC TERMS THAT MODULATE $[Na^+]_{pw}$

The Edelman equation is a linear equation of the form $y = mx + b$ where y represents the $[Na^+]_{pw}$, the independent variable (x) is represented by $(Na_e + K_e)/TBW$, the slope (m) has a value of 1.11, and y intercept (b) has a value of −25.6. Given that clinical laboratories report $[Na^+]_p$ rather than $[Na^+]_{pw}$, this equation has more recently been rewritten [10] in a more clinically convenient form in terms of $[Na^+]_p$ where

$$[Na^+]_p = 1.03(Na_e + K_e)/TBW - 23.8 \quad \text{(Equation 2)}$$

assuming that plasma is 93% $H_2O$ [11]. In most references, however, equation 1 appears in a simplified version in terms of $[Na^+]_p$ (rather than $[Na^+]_{pw}$) where

$$[Na^+]_p = (Na_e + K_e)/TBW \quad \text{(Equation 3)}$$

implying that the slope and y intercept in the Edelman equation have values of 1 and 0, respectively (Fig. 2) [12–14].

In part because of the difficulty in measuring $Na_e$ and $K_e$ clinically, the perceived lack of clinical applicability, and the duration of time since the original report, the findings of Edelman et al [9] remained a physiologic curiosity. As long as one held the belief that the $[Na^+]_p$ was determined solely by the value of $(Na_e + K_e)/TBW$ (equation 3), it remained difficult to explain quantitatively using equation 3 how several known factors that do not alter the value of the $(Na_e + K_e)/TBW$ term were theoretically capable of modulating the $[Na^+]_{pw}$. These factors included (*1*) changes in the $[Na^+]_{pw}$ due to intercompartmental $H_2O$ shifts in hyperglycemic states [7, 8]; (*2*) transcellular shifts of $Na^+$ and $K^+$ in hypokalemia-induced hyponatremia [15–17]; and (*3*) a component of the total $Na_e$ and $K_e$ is osmotically inactive and incapable of modulating the $[Na^+]_{pw}$ [9, 18–25]. This osmotically inactive reservoir must be subtracted from the $(Na_e + K_e)/TBW$ term.

These considerations prompted our recent mathematical analysis of all the physiologic parameters modulating the $[Na^+]_{pw}$ and their specific role in the generation and treatment of the dysnatremias [10, 26–28]. Surprisingly, all that was required to resolve the difficulty discussed earlier was the recognition that additional physiologic parameters that modulate the $[Na^+]_{pw}$ were components of the slope and y intercept of the Edelman equation. This insight provided the opportunity to incorporate all factors that modulate the $[Na^+]_{pw}$ into a single quantitative and conceptual framework.

Using well-established theoretical principles based on osmotic and Gibbs-Donnan equilibrium as a starting point in our analysis, we proved that the equation relating $[Na^+]_{pw}$ and its physiologic parameters have a slope greater than 1 with a non-zero value for the y intercept [10, 28]. Moreover, we demonstrated that in addition to the explicit $(Na_e + K_e)/TBW$ term in equation 1, the magnitude of the slope of 1.11 and y intercept of −25.6 were determined by several physiologic parameters that independently modulate the $[Na^+]_{pw}$ [10, 28]. The mathematical relationship between the $[Na^+]_{pw}$ and all its physiologic determinants in normal individuals and patients with the dysnatremias is depicted in the following important equation [28]:

$$[Na^+]_{pw} = G/\emptyset\left(\frac{Na_e + K_e}{TBW}\right) - G/\emptyset\left[\left(\frac{Na_{osm\ inactive} + K_{osm\ inactive}}{TBW}\right) - \left(\frac{osmol_{ICF} + osmol_{ECF}}{TBW}\right) + [K^+]_{pw} + \frac{osmol_{pw}}{V_{pw}}\right]. \quad \text{(Equation 4)}$$

where $G$ is Gibbs-Donnan effect; Ø is average osmotic coefficient of $Na^+$ salts; $Na_{osm\ inactive}$ is osmotically inactive $Na^+$; $K_{osm\ inactive}$ is osmotically inactive $K^+$; $osmol_{ECF}$ is osmotically active, extracellular non-$Na^+$ and non-$K^+$ osmoles; $osmol_{ICF}$ is osmotically active, intracellular non-$Na^+$ and non-$K^+$ osmoles; $[K]_{pw}$ is plasma water $K^+$ concentration; and $osmol_{pw}$ is osmotically active, plasma water non-$Na^+$ non-$K^+$ osmoles.

This equation can be viewed conceptually as an expansion of equation 1 with all the terms on the right side of the equation depicted explicitly. In addition to the $(Na_e + K_e)/TBW$ term that is present in the original Edelman equation, equation 4 contains additional terms that modulate the $[Na^+]_{pw}$. Furthermore, specific terms in equation 4 determine the magnitude of the slope and y intercept in equation 1, which appear in the latter equation as constants. It is important to realize that the equation holds true irrespective of the specific value of any of the individual physiologic parameters. A change in the magnitude of any of the parameters on the right side of equation 4 will alter the $[Na^+]_{pw}$ clinically.

**Table 1.** Physiologic parameters that determine the plasma water $[Na^+]$ ($[Na^+]_{pw}$)

| Parameter | Effect of increase in the parameter on $[Na^+]_{pw}$ |
|---|---|
| G/Ø | Increase |
| $\frac{(Na_e + K_e)}{TBW}$ | Increase |
| $\frac{(Na_{osm\ inactive} + K_{osm\ inactive})}{TBW}$ | Decrease |
| $\frac{(osmol_{ECF} + osmol_{ICF})}{TBW}$ | Increase |
| $[K^+]_{pw}$ | Decrease |
| $\frac{osmol_{pw}}{V_{pw}}$ | Decrease |

Abbreviations are: $G$, Gibb-Donnan effect on the $[Na^+]_{pw}$; Ø, average osmotic coefficient of $Na^+$ salts; $Na_e$, total exchangeable $Na^+$; $K_e$, total exchangeable $K^+$; TBW, total body water; $Na_{osm\ inactive}$, osmotically inactive $Na^+$; $K_{osm\ inactive}$, osmotically inactive $K^+$; $osmol_{ECF}$, osmotically active, extracellular non-$Na^+$ and non-$K^+$ osmoles; $osmol_{ICF}$, osmotically active intracellular non-$Na^+$ and non-$K^+$ osmoles; $[K^+]_{pw}$, plasma water $[K^+]$; $osmol_{pw}$, osmotically active, plasma water non-$Na^+$ non-$K^+$ osmoles; $V_{pw}$, plasma water volume.

## SIGNIFICANCE OF THE $(Na_e + K_e)/TBW$ TERM AND ITS EFFECT ON THE $[Na^+]_{pw}$

Armed with this generalized equation (equation 4), one can systematically address the role of each of the physiologic parameters in modulating the $[Na^+]_{pw}$ in various clinical situations. The $(Na_e + K_e)/TBW$ term varies linearly with the $[Na^+]_{pw}$ [9]. Moreover, of the parameters in equation 4, the $(Na_e + K_e)/TBW$ term has greatest quantitative effect in determining the magnitude of the $[Na^+]_{pw}$. Alterations in the $(Na_e + K_e)/TBW$ term typically occur clinically because of simultaneous changes in $Na_e$, $K_e$, and TBW as a result of gastrointestinal or renal losses of $H_2O$ and electrolytes. Changes in the mass balance of $Na^+$ and/or changes in the mass balance of $K^+$ can alter the $[Na^+]_{pw}$. By increasing the value of the $(Na_e + K_e)/TBW$ term, positive total body $Na^+$ and/or $K^+$ balance increases the $[Na^+]_{pw}$. Conversely, negative $Na^+$ and/or $K^+$ balance results in a decrement in the $[Na^+]_{pw}$ by decreasing the $(Na_e + K_e)/TBW$ term. $Na_e$ and $K_e$ are distributed throughout the TBW in the plasma space, interstitial space (ISF), and intracellular space (ICF); however, the majority of exchangeable sodium is in the ISF, while the majority of exchangeable potassium is in the ICF [29]. Mathematically, the location of $Na_e$ and $K_e$ is irrelevant since individual body fluid compartments do not appear explicitly in the $(Na_e + K_e)/TBW$ term.

Importantly, not all exchangeable $Na_e$ and $K_e$ is osmotically active [9, 18–25, 29]. Since the $(Na_e + K_e)/TBW$ term refers to total exchangeable $Na_e$ and $K_e$ (osmotically active plus osmotically inactive), the osmotically inactive component needs to be subtracted in order to prevent overestimation of the $[Na^+]_{pw}$. As is discussed below, it has recently been proven that the osmotically inactive exchangeable $Na_e$ and $K_e$ term is one of several physiologic components determining the magnitude of the y intercept in equation 1 [10]. Subtracting the y intercept in equation 1 ensures that only the osmotically active exchangeable $Na^+$ and $K^+$ play a role in modulating the $[Na^+]_{pw}$.

## COMPONENTS OF THE SLOPE IN THE EDELMAN EQUATION: EFFECT OF GIBBS-DONNAN EQUILIBRIUM AND THE OSMOTIC COEFFICIENT OF $Na^+$ SALTS ON THE $[Na^+]_{pw}$

As demonstrated in equation 4 [28], the slope of 1.11 in the Edelman equation is determined by the ratio of the magnitude of the Gibbs-Donnan effect ($G$) [30, 31] to the value of the osmotic coefficient of $Na^+$ salts at normal physiologic concentrations (Ø) [32]. The Gibbs-Donnan effect alters the distribution of $Na^+$ and its associated anions due to the presence of negatively charged, impermeant plasma proteins [30, 31]. As a result, the $[Na^+]_{pw}$ is 152.7 mmol/L $H_2O$, whereas the sodium concentration in ISF ($[Na^+]_{ISF}$) is 145.1 mmol/L $H_2O$ (i.e., $[Na^+]_{ISF} = 0.95 \times [Na^+]_{pw}$). In contrast, the plasma water chloride concentration ($[Cl^-]_{pw}$) is lower than the ISF chloride concentration ($[Cl^-]_{ISF}$) (i.e., 111.9 mmol/L $H_2O$ versus 117.4 mmol/L $H_2O$). $Na^+$ and $Cl^-$ ions distribute such that at equilibrium, the product of the concentrations of $Na^+$ and $Cl^-$ ions is the same in both body fluid compartments [30, 31]: $[Na^+]_{pw} \times [Cl^-]_{pw} = [Na^+]_{ISF} \times [Cl^-]_{ISF}$. In addition, the distribution of non-$Na^+$ cations and anions between the plasma and ISF will also be altered by the presence of negatively charged, impermeant plasma proteins. Furthermore, due to Gibbs-Donnan equilibrium, the plasma osmolality is typically 1 mOsm/L greater

**Table 2.** Osmolar substances in the extracellular and intracellular compartments[a]

| | Plasma[b] (mOsm/L $H_2O$) | Interstitial (mOsm/L $H_2O$) | Intracellular[c] (mOsm/L $H_2O$) |
|---|---|---|---|
| $Na^+$ | 142 | 139 | 14 |
| $K^+$ | 4.2 | 4.0 | 140 |
| $Ca^{2+}$ | 1.3 | 1.2 | 0 |
| $Mg^{2+}$ | 0.8 | 0.7 | 20 |
| $Cl^-$ | 108 | 108 | 4 |
| $HCO_3^-$ | 24 | 28.3 | 10 |
| $HPO_4^{2-}$, $H_2PO_4^-$ | 2 | 2 | 11 |
| $SO_4^{2-}$ | 0.5 | 0.5 | 1 |
| Phosphocreatine | 45 | | |
| Carnosine | 14 | | |
| Amino acids | 2 | 2 | 8 |
| Creatine | 0.2 | 0.2 | 9 |
| Lactate | 1.2 | 1.2 | 1.5 |
| Adenosine triphosphate | 5 | | |
| Hexose monophosphate | 3.7 | | |
| Glucose | 5.6 | 5.6 | |
| Protein | 1.2 | 0.2 | 4 |
| Urea | 4 | 4 | 4 |
| Other | 4.8 | 3.9 | 10 |
| Total mOsm/L | 301.8 | 300.8 | 301.2 |
| Corrected osmolar activity *mOsm/L* | 282.0 | 281.0 | 281.0 |
| Total osmotic pressure at 37°C *mm Hg* | 5443 | 5423 | 5423 |

[a]Adapted from [33].
[b]In the plasma, the Gibbs-Donnan effect results in an additional osmotic pressure generated by diffusible ions plus the plasma anionic proteins that exceeds the interstitial fluid (ISF) osmolality by 1 mOsm/L. This plasma osmotic pressure is opposed in the steady state by the capillary hydrostatic pressure.
[c]Cells contain impermeant anionic proteins that also exert a Gibbs-Donnan effect. In the absence of other opposing factors, cells would swell and rupture. However, the $Na^+$-$K^+$-adenosine triphosphatase (ATPase) pumps 1 net cation out of cells per cycle (3 $Na^+$ out/2 $K^+$ in), and opposes the intracellular Gibbs-Donnan effect, thereby prevent cells from swelling.

than that of the interstitial fluid and intracellular compartment, which have the same osmolality [33] (Table 2). The total osmotic pressure generated by diffusible ions plus the plasma anionic proteins tends to cause more water to move into the plasma compartment than would be predicted from the plasma protein concentration alone. A steady state is achieved because the capillary hydrostatic pressure opposes the osmotic movement of water into the plasma space.

Quantitatively, $G$ is a function of the volumes of the plasma and ISF since the distribution of $Na^+$ ions between the plasma and ISF at equilibrium will depend upon the respective volumes of these compartments [28]. Therefore, more $Na^+$ ions are distributed in the ISF at equilibrium than that in the plasma by virtue of the fact that the ISF volume exceeds the plasma volume. We have previously shown that $G$, which normally has a value of 1.04, and is related to the plasma volume ($Vol_{pw}$), ISF volume ($Vol_{ISF}$), and the Gibbs-Donnan ratio for the distribution of univalent cations in the plasma and ISF ($R$) according to [28]:

$$G = \frac{Vol_{pw} + Vol_{ISF}}{Vol_{pw} + R(Vol_{ISF})} \qquad \text{(Equation 5)}$$

The second determinant of the slope of the Edelman equation is the osmotic coefficient of $Na^+$ salts under normal physiologic conditions (Ø) [28]. Due to the ionic interactions, the osmotic activity of most ions is slightly less than one. Specifically, NaCl has an osmotic coefficient of 0.93, whereas $NaHCO_3$ has an osmotic coefficient of 0.96 in the physiologic range of $[Na^+]_{pw}$ values [32]. Since $Na^+$ is present in the plasma predominantly as NaCl and $NaHCO_3$, and the normal $[Cl^-]$ and $[HCO_3^-]$ is 104 mmol/L and 24 mmol/L, respectively, the average osmotic coefficient of $Na^+$ salts is estimated to be 0.94 ($104/128 \times 0.93 + 24/128 \times 0.96$). The value of the slope in the Edelman equation is determined by the ratio $G/Ø$ ($1.04/0.96 = 1.11$). Therefore, the theoretical value for the slope in the Edelman equation is in excellent agreement with the experimentally determined value.

## PHYSIOLOGIC PARAMETERS COMPRISING THE Y INTERCEPT IN THE EDELMAN EQUATION: EFFECT ON $[Na^+]_{pw}$

As shown below, the y intercept of –25.6 in equation 1 is determined by several physiologic parameters [10, 28]:

$$\text{y intercept} = -G/Ø\left[\left(\frac{Na_{osm\ inactive} + K_{osm\ inactive}}{TBW}\right) - \left(\frac{osmol_{ICF} + osmol_{ECF}}{TBW}\right) + [K^+]_{pw} + \frac{osmol_{pw}}{TBW}\right]$$

Therefore, the $G/Ø$ term that determines the slope of the Edelman equation has an additional independent effect on the $[Na^+]_{pw}$ since it is also a determinant of the magnitude of the y intercept. This is not surprising because the components of the y intercept must be similarly

affected by the Gibbs-Donnan effect and the osmotic coefficient of $Na^+$ salts. Specifically, the distribution of non-$Na^+$ cations and anions between the plasma and ISF (as represented by the terms $osmol_{ECF}$, $[K^+]_{pw}$, and $osmol_{pw}$) will also be altered by the presence of negatively charged, impermeant plasma proteins. Furthermore, the magnitude of the y intercept is also determined by the osmotic coefficient of $Na^+$ salts (Ø) since anions that interact electrostatically with $Na^+$ are represented by the terms $osmol_{ECF}$ and $osmol_{pw}$.

In addition to the *G*/Ø term, there are four more physiologic parameters comprising the y intercept, each of which plays a role in determining the value of the $[Na^+]_{pw}$ [10, 28]. Changes in these parameters can account for (*1*) the alteration in $[Na^+]_{pw}$ following intercompartmental water shifts in hyperglycemic states; (*2*) the transcellular shift of $Na^+$ and $K^+$ in hypokalemia-induced hyponatremia; and (*3*) the effect of osmotically inactive $Na_e$ and $K_e$ on the $[Na^+]_{pw}$. The four parameters in the y intercept are (*1*) total body osmotically inactive exchangeable $Na^+$ and $K^+$ concentration $(Na_{osm\ inactive} + K_{osm\ inactive})$/TBW; (*2*) total body osmotically active non-$Na^+$ and non-$K^+$ osmolar concentration $(osmol_{ECF} + osmol_{ICF})$/TBW; (*3*) plasma water osmotically active exchangeable $[K^+]$ $[K^+]_{pw}$; and (*4*) plasma water osmotically active non-$Na^+$ and non-$K^+$ osmolar concentration: $osmol_{pw}/V_{pw}$. Each of these parameters can independently modulate the $[Na^+]_{pw}$. The value of the y intercept in equation 1 reported by Edelman et al [9], can also be independently calculated using known values [33] (Table 2) for the y intercept terms in equation 4, and initially solving for $(Na_{osm\ inactive} + K_{osm\ inactive})$/TBW where $140 = 1.11\ (148.6) - 1.11\ [(Na_{osm\ inactive} + K_{osm\ inactive})/TBW + 151.3 + 4.2 + 155.6]$. Of note, the mean $[Na^+]_{pw}$ of 140 mmol/L and $(Na_e + K_e)$/TBW of 148.6 mmol/L used in the calculations were obtained from the data of Edelman [9]. The values of the last three terms of the y intercept (−151.3, 4.2, 155.6) are calculated from the data in Table 2 [33]. Therefore, $(Na_{osm\ inactive} + K_{osm\ inactive})/TBW = 14$ and the calculated value of the y intercept is therefore –25. The latter value is in agreement with the value of the y intercept determined by Edelman et al [9].

The simplified version of the Edelman equation appearing in most textbooks, $[Na^+]_p = (Na_e + K_e)/TBW$ (equation 3), tacitly assumes that all exchangeable $Na^+$ and $K^+$ are osmotically active. However, there is strong evidence for the existence of exchangeable $Na^+$ and $K^+$ reservoirs that are osmotically inactive. Recently, Heer et al [20] in a well-conducted balance study provided strong evidence for osmotic inactivation of exchangeable $Na^+$ in subjects who had net positive $Na^+$ balance without a change in body weight, expansion of the extracellular space, or plasma sodium concentration. Moreover, Titze et al [21] provided evidence for osmotic inactivation of $Na^+$ in subjects studied in a terrestrial space station. In rats, skin and to a lesser extent bone appear to be the major reservoirs of osmotically inactive $Na^+$ [22]. Glycosaminoglycan polymerization may regulate osmotically inactive $Na^+$ skin storage [23]. Interestingly, salt-sensitive Dahl rats have a reduced osmotically inactive sodium storage capacity in comparison to Sprague-Dawley rats, thereby resulting in fluid accumulation and high blood pressure [24]. In addition to $Na^+$, there is also evidence for a $K^+$ reservoir that is exchangeable but osmotically inactive [25]. Importantly, since osmotically inactive exchangeable $Na^+$ and $K^+$ cannot contribute to the distribution of water between the extracellular and intracellular compartments, osmotically inactive exchangeable $Na^+$ and $K^+$ cannot contribute to the modulation of the $[Na^+]_{pw}$, and therefore from a quantitative perspective, must be subtracted from the $(Na_e + K_e)$/TBW term that represents the total (osmotically active and inactive) exchangeable $Na^+$ and $K^+$. The osmotically inactive exchangeable $Na^+$ and $K^+$ are accounted for quantitatively by the $(Na_{osm\ inactive} + K_{osm\ inactive})$/TBW term in the y intercept.

The $(osmol_{ECF} + osmol_{ICF})$/TBW term in the y intercept represents the total body osmotically active non-$Na^+$ and non-$K^+$ osmolar concentration. Osmotically active non-$Na^+$ and non-$K^+$ osmoles are present in the plasma space, ISF, and ICF. Examples of these osmoles are calcium, magnesium, chloride, bicarbonate, phosphate, organic anions, organic cations, and glucose. The $[Na^+]_{pw}$ varies directly with the $(osmol_{ECF} + osmol_{ICF})$/TBW term. Non-$Na^+$ and non-$K^+$ osmoles in the plasma space tend to lower the $[Na^+]_{pw}$ by promoting the movement of water from the ISF to the plasma space. In contrast, osmotically active, non-$Na^+$ and non-$K^+$ osmoles in the ISF and ICF have the opposite effect on the $[Na^+]_{pw}$ by promoting the movement of water out of the plasma space. Since the $[Na^+]_{pw}$ varies directly with the $(osmol_{ECF} + osmol_{ICF})$/TBW term, the effect of non-$Na^+$ and non-$K^+$ osmoles in the ISF and ICF must predominate.

The $[K^+]_{pw}$ term in the y intercept represents the osmotically active plasma water exchangeable $K^+$ concentration. Potassium therefore appears in three separate terms in equation 4, each of which can quantitatively alter the $[Na^+]_{pw}$ [34]. These terms are $(Na_e + K_e)$/TBW, $(Na_{osm\ inactive} + K_{osm\ inactive})$/TBW, and $[K^+]_{pw}$. The latter two terms appear in the y intercept. The $[Na^+]_{pw}$ varies inversely with both of these physiologic parameters. Potassium represented by $K_{osm\ inactive}$ in the $(Na_{osm\ inactive} + K_{osm\ inactive})$/TBW term is osmotically inactive and therefore does not play a role in inducing $H_2O$ movement between body fluid compartments. In contrast, the $[K^+]_{pw}$ term represents an osmotically active pool of $K^+$ in the plasma space. Although $K^+$ is present in all body fluid compartments, only the $[K^+]_{pw}$ term appears explicitly as a separate term in the y intercept. Osmotically active $K^+$ in the plasma space is also represented along with $K^+$ in the ISF and ICF by $K_e$ in the $(Na_e + K_e)$/TBW term. Importantly, the effect of $K^+$ on the $[Na^+]_{pw}$ must

differ depending on which body fluid compartment one is referring. In the ISF and ICF, $K^+$ tends to increase the $[Na^+]_{pw}$ by promoting the movement of water from the plasma space into the ISF and ICF, respectively. In contrast, plasma $K^+$ tends to lower the $[Na^+]_{pw}$ by inducing the movement of water from the ISF and ICF into the plasma space. Quantitatively, unlike the $[K^+]_{pw}$ term, $K_e$ in the $(Na_e + K_e)/TBW$ term varies directly with the $[Na^+]_{pw}$ because the majority of exchangeable $K^+$ is present in the ISF and ICF and therefore the effect of $K^+$ in these latter compartments will predominate in promoting the movement of $H_2O$ out of the plasma space.

The $osmol_{pw}/V_{pw}$ term in the y intercept represents the plasma $H_2O$ osmotically active non-$Na^+$ and non-$K^+$ osmolar concentration. Non-$Na^+$ and non-$K^+$ osmoles therefore appear in two separate terms in equation 4, each of which can independently alter the $[Na^+]_{pw}$ [i.e., $(osmol_{ECF} + osmol_{ICF})/TBW$ and $osmol_{pw}/V_{pw}$]. These terms have opposing effects on the $[Na^+]_{pw}$ since unlike the $(osmol_{ECF} + osmol_{ICF})/TBW$ term, $[Na^+]_{pw}$ varies inversely with the $osmol_{pw}/V_{pw}$ term. The presence of plasma osmotically active non-$Na^+$ and non-$K^+$ osmoles ($osmol_{pw}$) promote the shift of water from the ISF and ICF into the plasma space, thereby lowering the $[Na^+]_{pw}$. Osmotically active, non-$Na^+$, and non-$K^+$ osmoles distributed throughout the extracellular compartment ($osmol_{ECF}$) are present in both the plasma and interstitial compartments. In this case, $osmol_{ECF}$ will have a net effect of increasing the $[Na^+]_{pw}$ since only approximately one fifth of the ECF compartment is confined to the plasma space.

## NEW INSIGHTS INTO THE ROLE OF HYPERGLYCEMIA IN THE MODULATION OF THE $[Na^+]_{pw}$

In the setting of hyperglycemia, the $[Na^+]_{pw}$ decreases as a result of the net movement of $H_2O$ into the plasma space [8]. In addition to intercompartmental water flux, $[Na^+]_{pw}$ is altered as a result of changes in the mass balance of $Na_e$, $K_e$, and TBW due to renal losses during an osmotic diuresis. The simplified form of the Edelman equation (equation 3) contains the $(Na_e + K_e)/TBW$ term that is altered during hyperglycemia-induced changes in the mass balance of $Na^+$, $K^+$ and $H_2O$. However, equation 3 does not contain any parameters that are altered during intercompartmental shifts. Katz [8] originally showed that the $\Delta[Na^+]_p$ due to intercompartmental water flux could be calculated using a separate formula according to $\Delta[Na^+]_p = -(1.6/100)(\Delta[glucose]_p)$. More recently, it has been suggested that the factor of 1.6 is only valid over a restricted range of plasma glucose concentrations [35]. Above a plasma concentration of 400 mg/dL, these authors suggested that a correction factor of 4.0 should be used instead. However, in deriving this

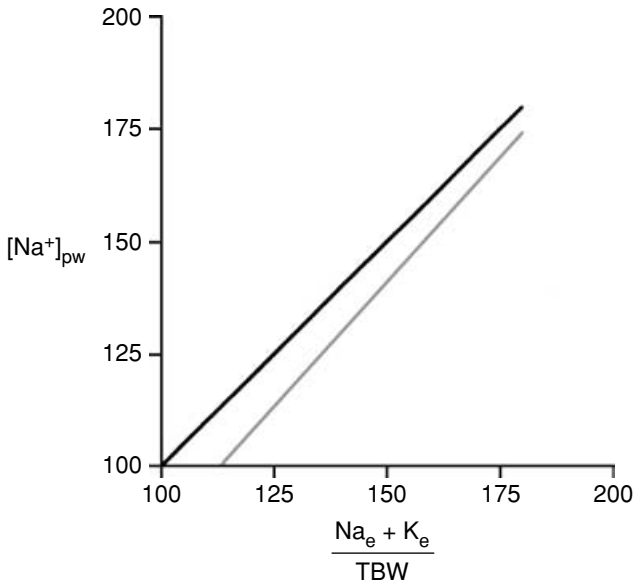


**Fig. 2. Quantitative effect of the slope and y intercept in the Edelman equation on the $[Na^+]_{pw}$.** The slope of 1.11 and y intercept of −25.6 in the Edelman equation are determined by several parameters that have physiologic and clinical significance. The quantitative significance of the slope and y intercept in the Edelman equation can be graphically depicted by comparing the value of $[Na^+]_{pw}$ (mmol/L) at a given $(Na_e + K_e)/TBW$ (mmol/L) as calculated according to the abbreviated form of the equation: $[Na^+]_{pw} = (Na_e + K_e)/TBW$ (upper line) and the complete equation $[Na^+]_{pw} = 1.11(Na_e + K_e)/TBW - 25.6$ (lower line).

factor, there was no correction made for changes in mass balance of $Na^+$, $K^+$ and $H_2O$ that could have modulated the $[Na^+]_p$ during the course of the study independent of transcellular $H_2O$ shifts. Specifically, at a plasma glucose concentration greater than 400 mg/dL, changes in the mass balance of $Na^+$, $K^+$, and $H_2O$ must have occurred due to a significant glucose-induced osmotic diuresis. Moreover, on the input side of the mass balance determination, variable amounts of 20% dextrose/0.45% saline were infused to induce hyperglycemia. As a result, significantly greater volumes of 20% dextrose/0.45% saline would be required to increase the $[glucose]_p$ above 400 mg/dL. Consequently, dilution of the $[Na^+]_p$ by the infusate could have led to an overestimation of the degree of dilutional hyponatremia at $[glucose]_p$ exceeding 400 mg/dL. Therefore, because of these technical considerations, there is a need to replicate these findings in the absence of any documented mass balance changes in $Na^+$, $K^+$ and $H_2O$.

By inducing intercompartmental water shifts, hyperglycemia alters three of the parameters in the y intercept in equation 4 [10, 26]. The $[Na^+]_{pw}$ is altered because of the net change in the magnitude of these terms during hyperglycemia. Mathematically, the problem of how to account quantitatively for both the effect of hyperglycemia-induced changes in mass balance and intercompartmental water shifts has recently been solved [10, 26]. The following formula is utilized to determine the

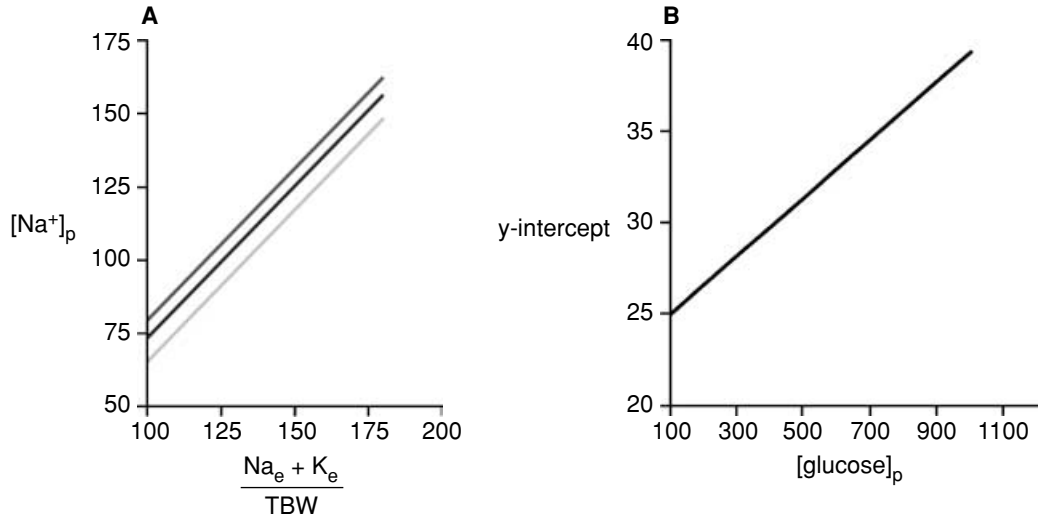


**Fig. 3. (*A*) Dependence of the $[Na^+]_p$ on the plasma glucose concentration as calculated according to $[Na^+]_p = 1.03(Na_e + K_e)/TBW - 23.8 - (1.6/100)([glucose]_p - 120)$.** The formula demonstrates that the value of the y intercept changes in hyperglycemia. An increase in the plasma glucose concentration results in a predictable increase in the magnitude of the y intercept, thereby decreasing the $[Na^+]_p$ (mmol/L). Upper line is glucose 120 mg/dL; middle line is glucose 500 mg/dL; and lower line is glucose 1000 mg/dL. (*B*) Theoretical dependence of the y intercept on the $[glucose]_p$. Hyperglycemia causes an intercompartmental water shift, resulting in a change in the value of several of the parameters in the y intercept of equation 4. The theoretical dependence of the magnitude of the y intercept on the $[glucose]_p$ is depicted.

effect of a given $[glucose]_p$ on the $[Na^+]_p$ [6]:

$$[Na^+]_p = 1.03(Na_e + K_e)/TBW - 23.8 - (1.6/100)([glucose]_p - 120) \quad \text{(Equation 6)}$$

The formula demonstrates that the y intercept is not constant in hyperglycemia and is altered in a predictable manner by changes in the $[glucose]_p$ [10, 26] (Fig. 3).

During an osmotic diuresis, the $(Na_e + K_e)/TBW$ term will increase due to renal excretion of $H_2O$ in excess of $Na^+$ and $K^+$. Of the terms in the y intercept, hyperglycemia results in an increase in the ratio $(osmol_{ECF} + osmol_{ICF})/TBW$. During the hyperglycemia-induced osmotic shift of water from the intracellular compartment to the extracellular space, the TBW remains constant since the change in intracellular volume is equal to the change in extracellular volume. The $(osmol_{ECF} + osmol_{ICF})/TBW$ term in the y intercept increases because hyperglycemia increases the $osmol_{ECF}$ term whereas the TBW remains unchanged (ignoring the change in TBW due to the osmotic diuresis). Second, the $[K^+]_{pw}$ will also be affected by the hyperglycemia-induced osmotic shift of $H_2O$ as well as the magnitude of subsequent cellular $K^+$ efflux induced by the decrease in $[K^+]_{pw}$ and hyperosmolality. Finally, the plasma water concentration of osmotically active non-$Na^+$ and non-$K^+$ osmoles represented by the term $osmol_{pw}/V_{pw}$ increases in hyperglycemia, thereby lowering the $[Na^+]_{pw}$ by promoting the osmotic movement of $H_2O$ into the plasma space. Therefore, changes in the parameters in the y intercept quantitatively account for the decrease in the $[Na^+]_{pw}$. The increase in the $(Na_e + K_e)/TBW$ term due to the osmotic diuresis lessens the severity of the hyponatremia in these patients.

## TRANSCELLULAR FLUXES OF $Na^+$, $H^+$, AND $K^+$ IN HYPOKALEMIA-INDUCED HYPONATREMIA: DIFFERENTIAL CHANGES IN THE PHYSIOLOGIC PARAMETERS IN THE EDELMAN EQUATION THAT ALTER THE $[Na^+]_{pw}$

In clinical states characterized by negative potassium balance, the decrease in the $(Na_e + K_e)/TBW$ term accounts quantitatively for the majority of the decrement in the $[Na^+]_{pw}$. Cellular $K^+$ loss could theoretically be accompanied by equimolar $H^+$ influx, $Na^+$ influx, or anion efflux. It has previously been recognized that these transport processes have different predictable effects on the number of osmotically active particles lost from the body in hypokalemic states [34, 36]. We have recently extended this analysis by demonstrating that these transport processes differentially impact the various parameters in equation 4 [34]. Moreover, the magnitude of the change in the $[Na^+]_{pw}$ as reflected by the parameters in equation 4 differs depending on which of the above transcellular mechanisms mediates cellular $K^+$ efflux [34].

Previous studies have invoked a role for cellular $Na^+$ influx as a mechanism for decreasing the $[Na^+]_{pw}$ during hypokalemia associated with negative $K^+$ balance [15–17]. The concept that a decrease in intracellular $K^+$ may

result in the flux of $Na^+$ into the ICF is supported by the finding of an increase in intracellular $Na^+$ and increased ratio of intracellular $Na^+$ to exchangeable $Na^+$ in patients with diuretic-induced hyponatremia [17]. However, the cellular uptake of extracellular $Na^+$ per se (without concomitant $K^+$ exit) cannot be responsible for the decrease in the $[Na^+]_{pw}$ because the subsequent movement of $H_2O$ out of the plasma space would tend to normalize the $[Na^+]_{pw}$. In contrast, the equimolar exchange of cellular $K^+$ for $Na^+$ will not be associated with the movement of $H_2O$ out of the plasma space since $K^+$ is as osmotically active as $Na^+$. In this instance, the $[Na^+]_{pw}$ is predicted to decrease because the flux of $K^+$ into the plasma space increases the $[K^+]_{pw}$ term in the y intercept. Specifically, the decrease in the $[Na^+]_{pw}$ is not due to the entry of $Na^+$ into the ICF per se, but rather that $K^+$ efflux into the ECF prevents water from entering the ICF with $Na^+$, resulting in a dilution of the $[Na^+]_{pw}$.

Cellular $K^+$ efflux into the ISF can also potentially be accompanied by $H^+$ influx into the ICF and/or cellular anion efflux into the ISF [34, 36]. The mechanisms of cellular $K^+$ loss will affect the $(osmol_{ECF} + osmol_{ICF})/TBW$ term and therefore the $[Na^+]_{pw}$ differently [34]. For instance, $H^+$ that enters cells in exchange for $K^+$ is buffered predominantly by intracellular proteins and bicarbonate. When $H^+$ entering cells binds to intracellular proteins, the total number of osmotically active, intracellular non-$Na^+$ and non-$K^+$ particles remains constant since $H^+ + Prot^- \rightarrow HProt$ and the $osmol_{ICF}$ term remains unchanged. The cellular efflux of $K^+$ and subsequent urinary $K^+$ loss, however, will result in the loss of osmotically active $K^+$ particles, which will be reflected in the $K_e$ component of the $(Na_e + K_e)/TBW$ term. Although this cellular $K^+$ loss is accompanied by the excretion of extracellular $Cl^-$ in the urine, there will be no change in the quantity of osmotically active, extracellular non-$Na^+$ and non-$K^+$ particles ($osmol_{ECF}$) since the $H^+$ entering the cells are produced along with $HCO_3^-$ in the ECF by the following reaction: $CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$. Therefore, the increase in ECF $HCO_3^-$ is equal to the decrement in ECF $Cl^-$. Therefore, if $H^+$ flux into the ICF (in exchange for equimolar $K^+$ exit) binds to intracellular proteins, each mmol of cellular $K^+$ loss from the body represents a net loss of 1 mmol from the ICF (1 mmol of $K^+$) [34, 36].

$H^+$ flux into the ICF in exchange for equimolar $K^+$ exit can also bind to an intracellular bicarbonate according to the following reaction: $H^+ + HCO_3^- \rightarrow H_2CO_3 \rightarrow CO_2 + H_2O$. The effect of this reaction is to decrease intracellular $HCO_3^-$, which is a non-$Na^+$ and non-$K^+$ osmole. The equimolar loss of intracellular $K^+$ will result in the loss of 2 mmol of osmotically active particles (1 mmol of $HCO_3^-$ and 1 mmol of $K^+$) from the ICF per mmol of cellular $K^+$ lost from the body. The loss of intracellular $HCO_3^-$ (excreted as $CO_2$) will result in a decrease in $osmol_{ICF}$ component of the $(osmol_{ECF} + osmol_{ICF})/TBW$ term. The loss of $K^+$ in the urine will be reflected by a decrease in the $K_e$ component of the $(Na_e + K_e)/TBW$ term. The subsequent cellular $K^+$ loss along with extracellular $Cl^-$ in the urine, however, will not result in a change in the quantity of osmotically active, extracellular non-$Na^+$ and non-$K^+$ particles ($osmol_{ECF}$) since the $H^+$ entering the cells are produced along with $HCO_3^-$ in the ECF by the reaction: $CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$. Therefore, the increase in ECF $HCO_3^-$ is equal to the decrement in ECF $Cl^-$. Therefore, when $H^+$ binds to intracellular $HCO_3^-$ rather than intracellular $Prot^-$, the additional decrease in the $osmol_{ICF}$ term will result in a greater decrease in the $[Na^+]_{pw}$ due to the shift of $H_2O$ out of the cells.

If total body $K^+$ loss results from cellular $K^+$ loss accompanied by equimolar cellular anion loss, the nature of the anion will determine whether there will also be a reduction in the $(osmol_{ECF} + osmol_{ICF})/TBW$ term due to a decrease in the $osmol_{ICF}$ component of the $(osmol_{ECF} + osmol_{ICF})/TBW$ term. For each mmol of cellular $K^+$ loss along with intracellular phosphate in the urine, the net loss is only 1 mmol from the ICF (1 mmol of $K^+$) since phosphate is derived from an intracellular macromolecule such as RNA [34, 36]. The loss of $K^+$ in the urine will be reflected by a decrease in the $K_e$ component of the $(Na_e + K_e)/TBW$ term. There will be no change in the $(osmol_{ECF} + osmol_{ICF})/TBW$ term in this setting. On the other hand, the loss of cellular $K^+$ along with intracellular $Cl^-$ [31] in the urine will result in a net loss of 2 mmol from the ICF (1 mmol of $K^+$ and 1 mmol of $Cl^-$) and a decrease in both the $K_e$ component of the $(Na_e + K_e)/TBW$ term and the $osmol_{ICF}$ term. Therefore, when cellular $K^+$ loss is accompanied by cellular $Cl^-$ loss, rather than cellular phosphate loss, the additional decrease in the $osmol_{ICF}$ term will result in a greater decrease in the $[Na^+]_{pw}$ due to the shift of water out of the cells.

## NEW FORMULAS FOR QUANTITATIVELY GUIDING THE TREATMENT OF THE DYSNATREMIAS

Several limitations are inherent in previous formulas used to predict the effect of a given infusate on the change in $[Na^+]_p$. These limitations have recently been reviewed in detail [37]. A new formula has recently been derived that is based on the theoretical principles outlined above and overcomes previous limitations in accurately determining the amount of a given infusate required to induce a change in the $[Na^+]_p$ [27]:

$$V_{IVF} = [([Na]_1 + 23.8) \times TBW_1 - ([Na]_2 + 23.8) \times (TBW_1 + V_{NET}) + 1.03([E]_{input} \times V_{input} - [E]_{output} \times V_{output})]/[[Na]_2 + 23.8 - 1.03[E]_{IVF}] \quad \text{(Equation 7)}$$

where V iv volume; IVF is intravenous fluid; $[Na]_1$ is initial plasma sodium concentration; $[Na]_2$ is target plasma sodium concentration; $TBW_1$ is initial total body water; and $V_{NET}$ is mass balance of water excluding the volume of intravenous fluid ($V_{IVF}$) which is being solved for: $V_{NET}$ is $(V_{oral} + V_{tube\ feed} + V_{TPN} + V_{oxidation}) - (V_{urine} + V_{GI} + V_{sweat} + V_{insensible})$; $[E]_{input} \times V_{input} = [E]_{oral} \times V_{oral} + [E]_{tube\ feed} \times V_{tube\ feed} + [E]_{TPN} \times V_{TPN}$; $[E]_{output} \times V_{output} = [E]_{urine} \times V_{urine} + [E]_{GI} \times V_{GI} + [E]_{sweat} \times V_{sweat}$; and $[E] = [Na^+ + K^+]$

This formula has several advantages: (*1*) it accounts for all input and output sources of $Na^+$, $K^+$, and $H_2O$ (mass balance) that can result in a $\Delta[Na^+]_p$; (*2*) it takes into consideration the fact that plasma is 93% $H_2O$ [11] and that the $[Na^+]_{pw} = 1.11(Na_e + K_e)/TBW - 25.6$ [9]; (*3*) it considers the therapy-induced change in TBW; (*4*) it is applicable for both hyponatremia and hypernatremia; (*5*) it calculates directly the amount of the infusate necessary to induce a given $\Delta[Na^+]_p$; and (*6*) it may also be used to determine the inappropriateness of the selected fluid prescription in a given clinical situation.

This formula is not applicable in predicting the change in $[Na^+]_p$ in severe symptomatic syndrome of inappropriate antidiuretic hormone secretion (SIADH) in clinical situations where intravenous therapy (hypertonic saline ± furosemide) is used to increase the $[Na^+]_p$ more rapidly than $H_2O$ restriction alone. This formula as well as previous formulas cannot be used since they fail to consider the neutral $Na^+ + K^+$ balance maintained in these patients [27]. Indeed, correction of hyponatremia in SIADH occurs by the attainment of negative $H_2O$ balance while maintaining neutral $Na^+$ and $K^+$ balance. Therefore, an additional formula has recently been derived that is applicable in the treatment of severe symptomatic SIADH requiring intravenous therapy [27]:

$$V_{IVF} = [TBW_1 \times [1 - (([Na]_1 + 23.8)/([Na]_2 + 23.8))] + V_{input} - ([E]_{input} \times V_{input})/([E]_{urine})]/[([E]_{IVF}/[E]_{urine}) - 1]$$

(Equation 8)

where $[E]_{input} \times V_{input}$ is $[E]_{oral} \times V_{oral} + [E]_{tube\ feed} \times V_{tube\ feed} + [E]_{TPN} \times V_{TPN}$; $V_{input}$ is $V_{oral} + V_{tube\ feed} + V_{TPN} + V_{oxidation}$; $[E]_{IVF}$ is intravenous fluid $[Na^+ + K^+]$; and $[E]_{urine}$ is urinary $[Na^+ + K^+]$.

## DEFINITION OF AN ISONATRIC SOLUTION DICTATED BY THE EDELMAN EQUATION: A NEW ELECTROLYTE FREE-WATER CLEARANCE FORMULA

In evaluating the renal mechanisms responsible for the generation of the dysnatremias, an analysis of electrolyte free-water clearance (EFWC) is often utilized to characterize the rate of urinary free-water excretion in these disorders [12, 36, 38, 39]. The classic EFWC formula, $V(1 - [Na^+ + K^+]_{urine}/[Na^+]_p)$, implicitly assumes that the urine is isonatric (i.e., its addition or loss from the plasma will not result in an alteration in the $[Na^+]_p$) when $[Na^+ + K^+]_{urine} = [Na^+]_p$ [12, 38]. In a variant of this formula reported by Shoker [39] and subsequently Mallie, Bichet, and Halperin [36] where $V(1 - [Na^+ + K^+]_{urine}/([Na^+]_p + [K^+]_p)$, urine is implicitly assumed to be isonatric when $[Na^+ + K^+]_{urine} = [Na^+]_p + [K^+]_p$. However, we have recently shown that given the empirical and theoretical basis for the non-zero values of the slope and y intercept in equation 1, the definition of an isonatric solution requires modification [40]. Specifically, this equation dictates that a solution be isonatric if its $[Na^+ + K^+] = (Na_e + K_e)/TBW$. The addition or loss from the plasma of a solution with this property does not result in an alteration in the $[Na^+]_p$. $(Na_e + K_e)/TBW$ is difficult to measure clinically, however, based on equation 2, $(Na_e + K_e)/TBW = ([Na^+]_p + 23.8)/1.03$, and therefore urine is isonatric when $[Na^+ + K^+]_{urine} = ([Na^+]_p + 23.8)/1.03 = 0.97[Na^+]_p + 23.1$ [40].

Utilizing this definition of isonatricity as our basis for further theoretical considerations, we have recently derived a modified electrolyte free-water clearance formula (MEFWC) that meets the requirements dictated by equation 1 [40]:

$$MEFWC = V\left(1 - \frac{1.03[Na^+ + K^+]_{urine}}{[Na^+]_p + 23.8}\right)$$

(Equation 9)

This new formula incorporates the relationship between the $[Na^+]_{pw}$ and $Na_e$, $K_e$, and TBW in equation 1 in its derivation and takes into consideration the effects of Gibbs-Donnan equilibrium, osmotic coefficient of $Na^+$ salts at physiologic concentrations, and osmotic equilibrium on the $[Na^+]_{pw}$. Unlike previous EFWC formulas, the MEFWC formula also incorporates in its derivation the fact that plasma is 93% $H_2O$ [11]. In addition, the MEFWC formula predicts correctly that urine is isonatric only when $[Na^+ + K^+]_{urine} = (Na_e + K_e)/TBW$ as required by equation 1.

In the setting of hyperglycemia, the MEFWC formula must be generalized to account for the dilutional effect of blood glucose on the $[Na^+]_p$ [40] as follows:

$$MEFWC = V\left(1 - \frac{1.03[Na^+ + K^+]_{urine}}{[Na^+]_p + 23.8 + (1.6/100)([glucose]_p - 120)}\right)$$

(Equation 10)

According to this modified formula, MEFWC is 0 (i.e., urine is isonatric to the $[Na^+]_p$) when the $[Na^+ + K^+]_{urine} = (Na_e + K_e)/TBW = \{[Na^+]_p + 23.8 + (1.6/100)([glucose]_p - 120)\}/1.03 = 0.97\,[Na^+]_p + 23.1 + 0.0155\,([glucose]_p - 120)$.

## QUANTITATIVE ANALYSIS OF THE GENERATION OF THE DYSNATREMIAS: ADVANTAGE OF CATEGORIZING THE DYSNATREMIAS MECHANISTICALLY BASED ON CHANGES IN $E_{MB}$ AND $V_{MB}$

Although the MEFWC formula is clinically useful in defining the renal contribution to the generation of the dysnatremias, an analysis of electrolyte free-water excretion is limited in that it is unable to quantitatively account for both the input and nonurinary output of $Na^+$, $K^+$, and $H_2O$. Therefore, in a patient with extrarenal causes for alterations in the mass balance of $Na^+$, $K^+$, and $H_2O$, the MEFWC formula cannot be used to predict the magnitude of the change in $[Na^+]_{pw}$. Recently, the goal of incorporating all known factors responsible for generating the dysnatremias into a single equation has been accomplished [26] where

$$[Na^+]_{p2} = \frac{([Na^+]_{p1} + y_1)TBW_1 + 1.03 \times E_{MB}}{TBW_1 + V_{MB}} - y_2$$

(Equation 11)

where y is $23.8 + (1.6/100)([glucose]_p - 120)$; [E] is $[Na^+ + K^+]$; $E_{MB}$ is $(Na^+ + K^+)_{input-output}$ = mass balance of $Na^+ + K^+$ in a chosen duration of time; and $V_{MB}$ is $V_{input} - V_{output}$ = mass balance of $H_2O$ in a chosen duration of time.

This formula can be used to explain retrospectively and predict prospectively the generation of the dysnatremias. In euglycemic patients, equation 11 can be simplified as follows:

$$[Na^+]_{p2} = \frac{([Na^+]_{p1} + 23.8)TBW_1 + 1.03 \times E_{MB}}{TBW_1 + V_{MB}} - 23.8$$

(Equation 12)

Importantly, the difficult problem of measuring $Na_e$ and $K_e$ clinically can be overcome since when solving for $Na_e$ and $K_e$ in the derivation of equations 11 and 12, these terms drop out mathematically [26]. TBW is usually estimated from anthropomorphic measurements according to Watson, Watson, and Batt [41]. Equations 11 and 12 are also extremely useful in that they provide a more intuitive understanding of the essential role that simultaneous changes in the mass balance of $Na^+$, $K^+$, and $H_2O$ and intercompartmental shifts have on the generation of the dysnatremias. Additional formulas for specifically analyzing the pathogenesis of the generation of the dysnatremias in patients on dialysis have also recently been reported [42].

Clinically, the dysnatremias are often categorized based on the predicted ECF volume status of patients [13, 14]. Although descriptively useful, in teaching the pathophysiology of the generation of the dysnatremias, certain misconceptions are commonly perpetuated regarding the physiologic mechanisms involved. We have therefore previously argued that a more quantitatively useful approach in categorizing the dysnatremias mechanistically is to determine the changes in $E_{MB}$ (mass balance of $Na^+ + K^+$) and $V_{MB}$ (mass balance of $H_2O$) [26]. For example, hypovolemic hyponatremia is often considered to be a disorder of positive water balance rather than a disorder of altered $Na^+ + K^+$ balance. As shown in Table 3, in hypovolemic hyponatremia, patients tend to have an $E_{MB}$ that is negative and is therefore the primary cause of the hyponatremia [26]. $V_{MB}$ that is also typically negative in these patients is actually contributing to the partial correction of the hyponatremia. Therefore, hypovolemic hyponatremia should be viewed from a pathophysiologic standpoint as a disorder of negative $Na^+$ and $K^+$ balance with inadequate negative water balance to normalize the $[Na^+]_p$. In contrast, in euvolemic hyponatremia, the positive $V_{MB}$ is the cause of the decrease in $[Na^+]_p$, whereas the $E_{MB}$ is negligible. Similarly, in hypervolemic hyponatremia, the positive $V_{MB}$ is the cause of the hyponatremia. The positive $E_{MB}$ is contributing to the partial correction of the hyponatremia. Although the positive $E_{MB}$ would tend to raise the $[Na^+]_p$, its incremental effect is less than the depressive effect of the positive $V_{MB}$ on the $[Na^+]_p$. A similar analysis of changes in $E_{MB}$ and $V_{MB}$ can be utilized for determining the mechanisms underlying the generation of hypernatremia in various clinical disorders (Table 3).

**Table 3.** Classification of the dysnatremias

| | $V_{MB}$ | $E_{MB}$ | Relative effects of $E_{MB}$ and $V_{MB}$ on $[Na^+]_p$ |
|---|---|---|---|
| Hyponatremia | | | |
| Hypovolemic | Negative | Negative | $E_{MB} > V_{MB}$ |
| Euvolemic | Positive | Negligible | $V_{MB} > E_{MB}$ |
| Hypervolemic | Positive | Positive | $V_{MB} > E_{MB}$ |
| Hypernatremia | | | |
| Hypovolemic | Negative | Negative | $V_{MB} > E_{MB}$ |
| Euvolemic | Negative | Negligible | $V_{MB} > E_{MB}$ |
| Hypervolemic | Positive | Positive | $E_{MB} > V_{MB}$ |

Abbreviations are: $V_{MB}$, mass balance of $H_2O$; $E_{MB}$, mass balance of $Na^+ + K^+$.

## FUTURE CONSIDERATIONS

The conceptual and theoretical advances in our understanding of the dysnatremias has been made possible by the empirical relationship between the $[Na^+]_{pw}$, $Na_e$, $K_e$, and TBW discovered by Edelman et al approximately half a century ago [9]. The full implications of the Edelman equation have recently come to light as a result of the recent elucidation of the mathematical relationship between the physiologic parameters incorporated into the slope and y intercept that modulate the $[Na^+]_{pw}$. Simply stated, all questions regarding the cause of an alteration in the $[Na^+]_{pw}$ can be addressed theoretically

**Table 4.** Summary of formulas and mathematical tools

| Formula | Description |
|---|---|
| $[Na^+]_{pw} = 1.11(Na_e + K_e)/TBW - 25.6$ | Edelman equation |
| $[Na^+]_p = 1.03(Na_e + K_e)/TBW - 23.8$ | Edelman equation in terms of $[Na^+]_p$ |
| $[Na^+]_p = 1.03(Na_e + K_e)/TBW - 23.8 - (1.6/100)([glucose]_p - 120)$ | Hyperglycemia-induced changes in the magnitude of the y intercept |
| $[Na^+ + K^+]_{urine} = 0.97[Na^+]_p + 23.1$ | Definition of an isonatric urine |
| $[Na^+ + K^+]_{urine} = 0.97\,[Na^+]_p + 23.1 + 0.0155\,([glucose]_p - 120)$ | Definition of an isonatric urine in hyperglycemia |
| $MEFWC = V(1 - \frac{1.03[Na^+ + K^+]_{urine}}{[Na^+]_p + 23.8})$ | Modified electrolyte free-water clearance |
| $MEFWC = V(1 - \frac{1.03[Na^+ + K^+]_{urine}}{[Na^+]_p + 23.8 + (1.6/100)([glucose]_p - 120)})$ | Generalized modified electrolyte free-water clearance in hyperglycemia |
| $[Na^+]_{p2} = \frac{([Na^+]_{p1} + 23.8)TBW1 + 1.03xE_{MB}}{TBW_1 + V_{MB}} - 23.8$ | Generation of the dysnatremias |
| $[Na^+]_{p2} = \frac{([Na^+]_{p1} + y_1)TBW1 + 1.03xE_{MB}}{TBW_1 + V_{MB}} - y_2$ | Generation of the dysnatremias in hyperglycemia |
| $V_{IVF} = [([Na]_1 + 23.8) \times TBW_1 - ([Na]_2 + 23.8) \times (TBW_1 + V_{NET}) + 1.03([E]_{input} \times V_{input} - [E]_{output} \times V_{output})]/[[Na]_2 + 23.8 - 1.03[E]_{IVF}]$ | Calculation of infusate volume |
| $V_{IVF} = [TBW_1 \times [1 - (([Na]_1 + 23.8)/([Na]_2 + 23.8))] + V_{input} - ([E]_{input} \times V_{input})/([E]_{urine})]/[([E]_{IVF}/[E]_{urine}) - 1]$ | Calculation of infusate volume in SIADH |

Abbreviations are: $E_{MB}$, mass balance of $Na^+ + K^+$; IVF, intravenous fluid; $K_e$, total exchangeable $K^+$; MEFWC, modified electrolyte free-water clearance; $Na_e$, total exchangeable $Na^+$; $[Na^+]_p$, plasma $[Na^+]$; $[Na^+]_{pw}$, plasma water $[Na^+]$; SIADH, syndrome of inappropriate antidiuretic hormone secretion; TBW, total body water; V, volume; $V_{MB}$, mass balance of $H_2O$; $V_{NET}$, mass balance of water excluding the volume of intravenous fluid; $V_{IVF}$, volume of intravenous fluid.

by determining which parameter(s) in equation 4 have been altered. Importantly, clinically useful formulas that have incorporated this analysis in their derivation have recently been reported. These new formulas are useful in that they do not require the difficult measurement of $Na_e$ and $K_e$ clinically. Armed with these new quantitative tools (Table 4), clinicians are now able to approach both the generation and the treatment of the dysnatremias more quantitatively and accurately than was previously possible. Additional studies are needed to determine the role that various physiologic parameters in Equation 4 play in certain disease states. For example, in nephrotic patients, the decrease in serum albumin concentration must modulate the G/Ø term, thereby altering the magnitude of the slope and y intercept. In addition, recent findings in rats indicating that the osmotically inactive exchangeable $Na^+$ and $K^+$ reservoir in skin is decreased in models of hypertension could have important implications clinically if these results are applicable to human hypertension [24]. The difficult experimental task of directly measuring the osmotically inactive exchangeable $Na^+$ and $K^+$ reservoir will likely be overcome by the development of newer methodologies that can be utilized clinically.

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## REFERENCES

1. Anderson RJ: Hospital-associated hyponatremia. *Kidney Int* 29:1237–1247, 1986
2. Welt LG: Edema and hyponatremia. *Arch Intern Med* 89:931–942, 1952
3. Warner GF, Sweet NJ, Dobson EL: "Sodium space" and body sodium content, exchangeable with sodium$^{24}$, in normal individuals and patients with ascites. *Circ Res* 1:486–490, 1953
4. Moore FD, Edelman IS, Olney JM, *et al*: Body sodium and potassium. III. Interrelated trends in alimentary, renal and cardiovascular disease; lack of correlation between body stores and plasma concentration. *Metabolism* 3:334–350, 1954
5. Wilson GM, Edelman IS, Brooks L, *et al*: Metabolic changes associated with mitral valvuloplasty. *Circulation* 9:199–219, 1954
6. Deming Q, Gerbode F: Observations on sodium balance in patients undergoing mitral valvotomy. *Surg Forum* 4:18–22, 1953
7. Arieff AI, Carroll HJ: Nonketotic hyperosmolar coma with hyperglycemia: Clinical features, pathophysiology, renal function, acid-base balance, plasma-cerebrospinal fluid equilibria and the effects of therapy in 37 cases. *Medicine* 51:73–94, 1972
8. Katz M: Hyperglycemia-induced hyponatremia. Calculation of expected sodium depression. *N Engl J Med* 843–844, 1973
9. Edelman IS, Leibman J, O'Meara MP, Birkenfeld LW: Interrelations between serum sodium concentration, serum osmolality and total exchangeable sodium, total exchangeable potassium and total body water. *J Clin Invest* 37:1236–1256, 1958
10. Nguyen MK, Kurtz I: Are the total exchangeable sodium, total exchangeable potassium and total body water the only determinants of the plasma water sodium concentration? *Nephrol Dial Transplant* 18:1266–1271, 2003
11. Davis FE, Kenyon K, Kirk J: A rapid titrimetric method for determining the water content of human blood. *Science* 118:276, 1953

12. Rose BD: New approach to disturbances in the plasma sodium concentration. *Am J Med* 81:1033–1040, 1986
13. Halperin ML, Goldstein MB (editors): Hyponatremia, in *Fluid, Electrolyte and Acid-Base Physiology—A Problem-Based Approach*, Philadelphia, WB Saunders, 1994, pp 253–288
14. Rose BD (editor): *Clinical Physiology of Acid-Base and Electrolyte Disorders*, New York, McGraw-Hill, 1994, pp 219–234, 638–650, 651–694, 695–736
15. Laragh JH: The effect of potassium chloride on hyponatremia. *J Clin Invest* 33:807–818, 1954
16. Fuisz RE, Lauler DP, Cohen P: Diuretic induced hyponatremia and sustained antidiuresis. *Am J Med* 33:783–791, 1962
17. Fichman MP, Vorherr H, Kleeman CR, Telfer N: Diuretic-induced hyponatremia. *Ann Intern Med* 75: 853–863, 1971
18. Edelman IS, James AH, Brooks L, Moore FD: Body sodium and potassium—The normal total exchangeable sodium; its measurement and magnitude. *Metabolism* 3:530–538, 1954
19. Edelman IS, James AH, Baden H, Moore FD: Electrolyte composition of bone and the penetration of radiosodium and deuterium oxide into dog and human bone. *J Clin Invest* 33:122–131, 1954
20. Heer M, Baisch F, Kropp J, *et al*: High dietary sodium chloride consumption may not induce body fluid retention in humans. *Am J Physiol Renal Physiol* 278:585–595, 2000
21. Titze J, Maillet A, Lang R, *et al*: Long-term sodium balance in humans in a terrestrial space station simulation study. *Am J Kidney Dis* 40:508–516, 2002
22. Titze J, Lang R, Ilies C, *et al*: Osmotically inactive skin $Na^+$ storage in rats. *Am J Physiol Renal Physiol* 285:F1108–F1117, 2003
23. Titze J, Shakibaei M, Schafflhuber M, *et al*: Glycosaminoglycan polymerization may enable osmotically inactive $Na^+$ storage in the skin. *Am J Physiol Heart Circ Physiol* 287:H203–H208, 2004
24. Titze J, Krause H, Hecht H, *et al*: Reduced osmotically inactive Na storage capacity and hypertension in the Dahl model. *Am J Physiol Renal Physiol* 283:F134–F141, 2002
25. Cameron IL, Hardman WE, Hunter KE, *et al*: Evidence that a major portion of cellular potassium is "bound." *Scan Micros* 4:89–102, 1990
26. Kurtz I, Nguyen MK: A simple quantitative approach to analyzing the generation of the dysnatremias. *Clin Exp Nephrol* 7:138–143, 2003
27. Nguyen MK, Kurtz I: A new quantitative approach to the treatment of the dysnatremias. *Clin Exp Nephrol* 7:125–137, 2003
28. Nguyen MK, Kurtz I: Determinants of the plasma water sodium concentration as reflected in the Edelman equation: Role of osmotic and Gibbs-Donnan equilibrium. *Am J Physiol Renal Physiol* 286:F828–F837, 2004
29. Edelman IS, Leibman J: Anatomy of body water and electrolytes. *Am J Med* 27:256–277, 1959
30. Pitts RF (editor): Volume and composition of the body fluids, in *Physiology of the Kidney and Body Fluids*, Chicago, Year Book Medical Publishers, 1974, pp 11–34, 1974
31. Sperelakis N: Gibbs-Donnan equilibrium potentials, in *Cell Physiology Sourcebook: A Molecular Approach*, 3rd ed., San Diego, CA, Academic Press, 2001, pp 243–247
32. Kutchai HC: Cellular membranes and transmembrane transport of solutes and water, in *Physiology*, edited by Berne RM, Levy MN, Koeppen BM, Stanton BA, St. Louis, Mosby, 2004, pp 3–21
33. Guyton AC, Hall JE (editors): The body fluid compartments: Extracellular and intracellular fluids; interstitial fluid and edema, in *Textbook of Medical Physiology*, Philadelphia, WB Saunders, 2000, pp 264–278
34. Nguyen MK, Kurtz I: An analysis of the role of potassium in hypokalemia-induced hyponatremia. *Clin Exp Nephrol* 8:98–102, 2004
35. Hillier TA, Abbott RD, Barrett EJ: Hyponatremia: Evaluating the correction factor for hyperglycemia. *Am J Med* 106:399–403, 1999
36. Mallie JP, Bichet DG, Halperin ML: Effective water clearance and tonicity balance: The excretion of water revisited. *Clin Invest Med* 20:16–24, 1997
37. Nguyen MK, Kurtz I: Analysis of current formulas used for treatment of the dysnatremias. *Clin Exp Nephrol* 8:12–16, 2004
38. Goldberg M: Hyponatremia. *Med Clin North Am* 65:251–269, 1981
39. Shoker AS: Application of the clearance concept to hyponatremic and hypernatremic disorders: A phenomenological analysis. *Clin Chem* 40:1220–1227, 1994
40. Nguyen MK, Kurtz I: Derivation of a new formula for calculating urinary electrolyte-free water clearance based on the Edelman equation. *Am J Physiol Renal Physiol* 288:F1–F7, 2005
41. Watson PE, Watson ID, Batt RD: Total body water volumes for adult males and females estimated from simple anthropometric measurements. *Am J Clin Nutr* 33:27–39, 1980
42. Nguyen MK, Kurtz I: A new formula for predicting alterations in plasma sodium concentration in peritoneal dialysis. *Am J Physiol Renal Physiol* [Epub December 29, 2004]