

## Physiologic basis for understanding quantitative dehydration assessment<sup>1–4</sup>

Samuel N Cheuvront, Robert W Kenefick, Nisha Charkoudian, and Michael N Sawka

### ABSTRACT

Dehydration (body water deficit) is a physiologic state that can have profound implications for human health and performance. Unfortunately, dehydration can be difficult to assess, and there is no single, universal gold standard for decision making. In this article, we review the physiologic basis for understanding quantitative dehydration assessment. We highlight how phenomenologic interpretations of dehydration depend critically on the type (dehydration compared with volume depletion) and magnitude (moderate compared with severe) of dehydration, which in turn influence the osmotic (plasma osmolality) and blood volume–dependent compensatory thresholds for antidiuretic and thirst responses. In particular, we review new findings regarding the biological variation in osmotic responses to dehydration and discuss how this variation can help provide a quantitative and clinically relevant link between the physiology and phenomenology of dehydration. Practical measures with empirical thresholds are provided as a starting point for improving the practice of dehydration assessment. *Am J Clin Nutr* 2013;97:455–62.

### INTRODUCTION

Dehydration (body water deficit) is a common physiologic state that can have profound implications for human health (1–7) and performance (8). Although mild dehydration can be easily corrected and is principally associated with impaired physical performance (8), it may be linked with common public health disorders if left chronically untreated (9, 10). A greater severity of dehydration can result in significant medical costs, morbidity, and mortality across the life span (11, 12). Although the physiology of osmotic and vascular volume responses to dehydration in humans have been well described (13, 14), the phenomenology of dehydration assessment has not. For example, there is no single, universal gold standard method of dehydration assessment for clinical decision making (7, 15, 16), which contributes greatly to the difficulty that clinicians encounter when trying to accurately assess dehydration in practice (17–25). This discordance between the physiology and phenomenology of dehydration is a recognized source of clinical confusion (17) for which clarity is needed to improve the practice of dehydration assessment.

In this review, we highlight how phenomenologic interpretations of dehydration depend critically on the type (dehydration

compared with volume depletion) and magnitude (moderate compared with severe) of dehydration, which, in turn, influence the plasma osmolality (Posm)<sup>5</sup>– and blood volume (BV)–dependent compensatory thresholds for antidiuretic and thirst responses. We also discuss the recent application of biological variation analysis to osmotic responses during dehydration for its novel potential as an adjunct (17) to clinical decision making. Posm is the primary focus of this review because it is the key regulated variable in fluid balance (13, 14, 26–28), and it is commonly used to screen for dehydration and complement more quantitative differential diagnoses of dysnatremias and other diseases (3, 5, 28–30). The osmolality of other body fluids commonly used to assess dehydration (ie, urine and saliva) are also mentioned as is the practical assessment of volume depletion. Descriptions of other potential methods of dehydration and volume-depletion assessment have been provided by other authors (7, 16, 19, 31, 32). Complementary reviews (33) are similarly suggested for detailed information related to sodium (natriuresis and appetite) and nonosmotic contributors (eg, baroreceptors) to osmotic homeostasis.

### FUNDAMENTALS OF OSMOTIC RESPONSES TO DEHYDRATION IN HUMANS

In its simplest form, the net body water balance is generally the zero sum of food (water and solute) and fluid intake minus insensible and obligatory renal water losses (7). Fluid intakes,

<sup>1</sup> From the US Army Research Institute of Environmental Medicine, Natick, MA.

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<sup>3</sup> Supported by the United States Army Medical Research and Materiel Command.

<sup>4</sup> Address correspondence to SN Cheuvront, Thermal and Mountain Medicine Division, US Army Research Institute of Environmental Medicine, Kansas Street, Building 42, Natick, MA 01760-5007. E-mail: samuel.n.cheuvront@us.army.mil.

<sup>5</sup> Abbreviations used: AVP, arginine vasopressin; Bm, body mass; BV, blood volume; Posm, plasma osmolality; PV, plasma volume; Sosm, saliva osmolality; TBW, total body water; Uosm, urine osmolality.

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losses, and needs vary widely in free-living people and are governed heavily by physical activity, environmental stress, and cultural and habitual cues (7, 8, 34–36). Under conditions of ordinary daily body water flux, osmotic constancy is maintained by the secretion of the antidiuretic hormone arginine vasopressin (AVP), which directly influences renal water excretion and conservation in response to intravascular fluid shifts (that result from thermal and positional changes) and ad libitum food and fluid intakes (14, 26, 37–39). Thus, Posm remains stable as the kidneys modify urine osmolal and water excretion in accordance with ordinary living conditions. When a body water deficit in excess of ordinary flux occurs (dehydration), threshold increases in Posm (primary) and decreases in BV (secondary) produce compensatory water-conservation (renal) and water-acquisition (thirst) responses (14, 26). As a result, the discriminatory power of renal excretion measures for the detection of dehydration is always secondary to changes in Posm (28).

AVP is synthesized in supraoptic and paraventricular nuclei of the hypothalamus and is released from the posterior pituitary (14, 26). Basal AVP concentrations can fluctuate considerably in response to ordinary postural and skin-temperature (skin blood flow) shifts in BV (39). However, a threshold reduction in BV >10% is required to elicit greater (compensatory) AVP secretion, whereas smaller reductions in BV primarily act to enhance the sensitivity of the AVP response to changes in Posm (40–42). Osmotic homeostasis (<1–2% deviation in Posm) is also maintained by basal AVP regulation, but compared to BV smaller threshold increases in Posm (>2%) produce intracellular dehydration and compensatory increases in AVP secretion, renal water conservation, and thirst (14, 43).

When the net balance between water intake and output becomes negative (dehydration), renal water conservation is insufficient to restore fluid balance. Obligatory renal water losses persist, and fluid acquisition must occur, to restore the body water balance (28, 44). However, the Posm threshold for thirst is highly variable in people (27, 45, 46), and thirst mechanisms are subject to numerous influences unrelated to the body water balance (47). In humans, fluid losses (because of sweating, vomiting, or diarrhea) can easily outpace oral intakes. Peripheral osmoreceptors (eg, gut) (14) and oropharyngeal cues trigger thirst satiety well before volume is fully restored (26, 48, 49), even when dehydration is substantial (50). This transitory response acts to buffer the presystemic impact of ingested fluids (14) but often leads to involuntary dehydration when water is consumed without food (solute) (47, 51).

## TWO CRITICAL CAVEATS TO UNDERSTANDING OSMOTIC RESPONSES TO DEHYDRATION

### **Caveat 1: a sufficient body water–deficit threshold must be reached before compensatory reactions become reliably engaged**

Percentage reductions in body mass (Bm) that exceed typical human variation are depicted in **Figure 1**, whereby a change in Bm is equated with a change in total body water (TBW). The change in Bm is used as the criterion value for practical purposes but also because the random measurement error for tracer-dilution methods (the change in TBW) is larger than the same for Bm (52). Typical human variation is defined as the day-to-day CV in Bm, which is <1.0% when fluid intake and activity

are tightly controlled (53, 54). As a consequence, day-to-day change in Bm must exceed 1% and approach 2% (ie,  $\sqrt{2} \times 1.65$ ) to be considered truly atypical ( $P < 0.05$ ; 1-tailed test). Therefore, day-to-day fluctuations in Bm <1–2% cannot be reliably associated with perturbations in body water beyond ordinary (sinusoidal) physiologic and behavioral body water regulation (55). Under these circumstances, renal water excretion or conservation is a reflection of the flux produced by fluctuating AVP concentrations in response to widely ranging dietary fluid intakes, osmolar loads, and ordinary compartmental fluid shifts without discernible changes in TBW, Posm, or, by extension, intracellular hydration (26, 37–39, 56). Thus, day-to-day fluctuations in Bm or TBW within this range should be interpreted as euhydrated (the state of normal hydration).

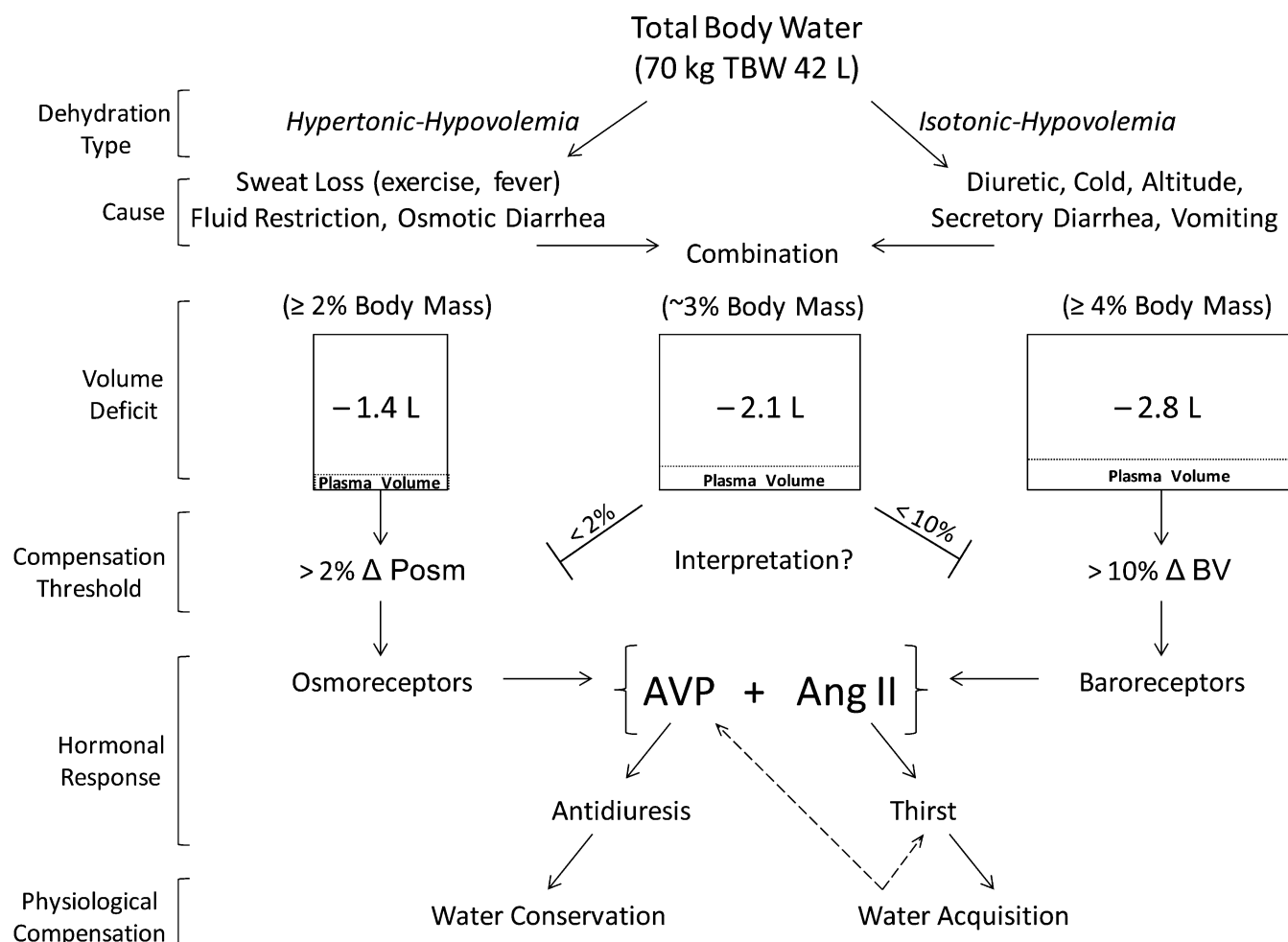
### **Caveat 2: body water–deficit threshold for dehydration depends critically on the type and magnitude of the body water deficit incurred**

A 2% increase in Posm ( $\sim 5$  mmol/kg) and a 10% decrease in BV ( $\sim 0.5$  L) are commonly quoted physiologic thresholds for compensatory water conservation and acquisition (**Figure 1**) (26, 40, 43). Posm increases to greater than  $\sim 5$  mmol/kg in response to dehydration via sweat losses, fluid restriction, or osmotic diarrhea (hypertonic hypovolemia) when those losses exceed  $\sim 2\%$  of Bm (1.4 L at 70 kg) (18, 54, 57–59), which is a threshold that is also consistent with negative physiologic outcomes (7, 8, 60). The variation in sweat sodium losses in people may (61) or may not (62) add uncertainty to the magnitude of the osmotic response to a given water deficit, depending on the delicate balance between sweating rate and sweat sodium concentrations, whereby

$$\text{Volume} \times \text{concentration} = \text{content} \quad (1)$$

Similar considerations may be made of alterations in extracellular volume [plasma volume (PV)], but on the basis of the regression equations shown in **Figure 2**, the anticipated decrease in PV is only  $\sim 0.14$  L at  $\sim 2\%$  dehydration (63) because of the rapid osmotic redistribution of water from the intracellular to the extracellular (interstitial and intravascular) fluid compartment (61, 64). Therefore, hypertonic hypovolemia results in a small ratio of plasma-to-TBW losses ( $\sim 1:10$ ). Hypertonic hypovolemia would not produce intravascular volume losses >10% of BV until a 7% loss of Bm was achieved (**Figure 2**) (63, 65). This effect illustrates the primary influence of Posm as the stimulus for early compensatory water-conservation and -acquisition responses (40–42). Although the osmolalities of other body fluids (eg, urine and saliva) also increase in parallel with Posm and afford a good diagnostic accuracy for dehydration under ideal circumstances (54), they remain secondary (25) and are inferior to Posm for the detection of dehydration for additional reasons.

Isotonic hypovolemia can occur in response to diuretic use, cold or altitude exposure, secretory diarrhea, and vomiting (6, 18, 42, 44, 63, 65–68). The ratio of PV-to-TBW loss is approximately twice as large ( $\sim 1:5$ ) with isotonic hypovolemia than with hypertonic hypovolemia (63, 65, 68). This type of body water loss is often referred to as salt-depletion dehydration (44)



**FIGURE 1.** Body water regulation in response to dehydration. Schematic includes the 2 major types of dehydration, their typical causes, and the estimated magnitude of dehydration required to stimulate a primary osmotic- or volume-dependent response for compensatory water conservation and acquisition (26). A change in TBW was equated with a change in body mass (1 L = 1 kg), whereby dehydration was expressed as a percentage of body mass in accordance with  $(\Delta \text{ body mass} \div \text{ body mass}) \times 100$ . Plasma volume and TBW losses are depicted to scale as are their 1:10 and 1:5 ratios for hypertonic and isotonic hypovolemia, respectively. Dashed arrows represent negative feedback. Ang II, angiotensin II; AVP, arginine vasopressin; BV, blood volume; Posm, plasma osmolality; TBW, total body water.

or volume depletion (24, 30) because the added solute loss produces little change in Posm but proportionally greater PV reductions. When there are large losses of solute from the extracellular space, there is a minimal or no osmotic gradient to pull fluids from the larger intracellular space (61, 64). As a result, a smaller ~4% loss of Bm (2.8 L at 70 kg; 0.56-L PV loss) must be incurred to achieve the 10% BV threshold for compensatory water conservation and acquisition with isotonic hypovolemia (Figures 1 and 2).

Methods for the assessment of volume depletion vary widely, with no single, standard approach advocated in the medical or related literature (16, 19). The use of a simple 20-beats/min sit-to-stand heart-rate response provides high specificity but low sensitivity and only marginal diagnostic accuracy even when dehydration is severe (65, 69). BV losses >10% (~1.0 L), whether measured directly (70) or by using lower body negative pressure to simulate equivalent blood losses (71), are required for an improved test sensitivity. The type of water loss with a gastrointestinal illness can be unpredictable or mixed (18, 44), and thus, the presence of both types of dehydration probably

explains much of the difficulty associated with their interpretation (30, 44), in which neither Posm nor BV thresholds for compensatory responses are reached (Figure 1). Under these circumstances, a more heuristic assessment approach is needed (19, 22, 24, 28).

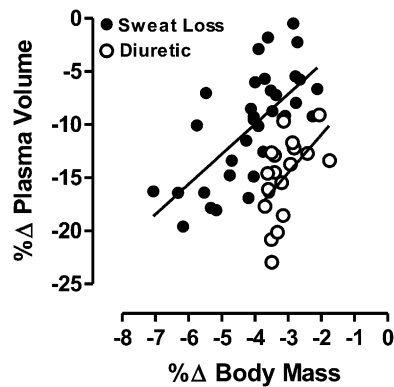
**BIOLOGICAL AND METHODOLOGIC VARIATION**

Human variation in osmotic responses to dehydration is primarily biological, but the methodology used to study osmotic responses can also contribute to variation. An understanding and appreciation for these sources of variation can inform probabilistic decision making related to the diagnosis of dehydration (54, 58, 72) and, likely, volume depletion as well (65).

**Threshold and slope of AVP and thirst responses (biology)**

It is common to refer to both the threshold and slope of the Posm-AVP relation. The threshold Posm value is associated with the initial increase in AVP secretion above baseline, whereas the slope is the responsiveness (or sensitivity) of the AVP system for





**FIGURE 2.** Linear regression of plasma volume change ( $y$ ) and dehydration [ $\% \Delta$  body mass ( $x$ )] after induction of hypotonic (sweat) or isotonic (diuretic) body water losses. Equations for plasma volume contraction are as follows: diuretic,  $y = -3.8 + 3.6x$ ; sweat,  $y = 1.35 + 2.8x$ . From Cheuvront et al (63).

any given increase in Posm above the threshold value. The osmotic control of AVP, when defined by using slope and sensitivity terms, is highly variable. For example, there appears to be a polygenetic basis for the variation in the slope of the AVP-Posm relation and Posm thresholds for AVP and thirst (46). The relations are highly correlated between monozygotic, but not dizygotic, twin pairs (46). For a healthy and heterogeneous population, the individual AVP-Posm slopes vary 10-fold in individuals but are highly correlated within a subject ( $r = 0.94$ ). The osmotic threshold for AVP varies less in individuals ( $\sim 8$  mmol/kg) but shows only a moderate correlation within subjects ( $r = 0.61$ ).

The individual variation of Posm set points and thresholds for both AVP release and unequivocal thirst relative to what has been commonly reported in the literature for group means is illustrated in **Figure 3** (27). The variation contains the potential influences of sex (73), but not age (74), on osmotic responses. Posm thresholds for AVP release and unequivocal thirst differ in subjects by  $\sim 10$  mmol/kg. The largest difference between Posm thresholds for AVP release and unequivocal thirst within an individual was 17 mmol/kg (subject 5). Also of importance is the difference in the Posm set point relative to the Posm threshold for AVP release and unequivocal thirst; for example, subjects 7 and 15 fell on opposite extremes. Taken together, the data in Figure 3 show that plasma osmotic responses (AVP and thirst) vary considerably in people and have a strong genetic component. These data may partly explain the 20-mmol/kg range in Posm often reported for population reference intervals (eg, 280–300 mmol/kg). Differences in health and hydration states must also contribute to this range, but the volume of fluid ingested and its proximity to measurement can also make an important methodologic contribution (43, 75), even in well-controlled laboratory situations.

### Threshold and slope of AVP and thirst responses (methodology)

Some of the variation in the Posm threshold for AVP and thirst is methodologic rather than physiologic. In this context, moderate water loading is one methodology used to standardize Posm and suppress AVP secretion before imposing an intervention such as saline infusion or water restriction (dehydration). However, this

approach produces low basal Posm values and results in threshold and slope calculations dissimilar from studies in which ad libitum water consumption was permitted before testing (13, 43, 45, 76). Suppressed Posm thresholds for AVP release and thirst in studies that used water-loading methodologies, although experimentally sound, may be unrealistic for free-living people.

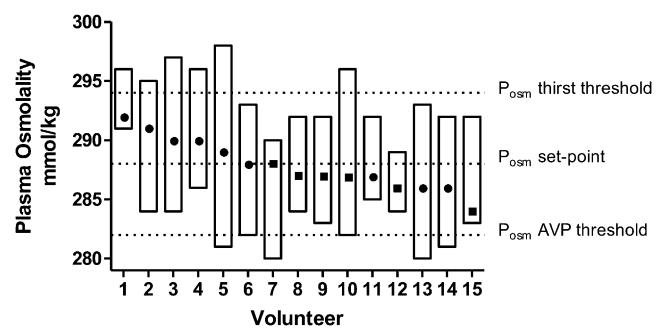
Interpreting osmotic responses after water loading should be approached with caution. For example, the application of regression equations for AVP-Posm and AVP-urine osmolality (Uosm), which has been commonly adopted to explain the physiology of osmotic responses, indicated that a near maximally concentrated urine ( $\sim 1100$  mmol/kg) should occur at a Posm of 292 mmol/kg and AVP value of 4.6 pg/mL (43). This result contrasts with everyday observations but is easily understood from a starting Uosm:Posm ratio of approximately

$$187:282 = 0.66 \quad (2)$$

which can be back calculated from a starting AVP value of 1 pg/mL in these experiments (43). If we assume unity between plasma and urine electrolyte concentrations and accept that urea contributes 40% to Uosm (77), any Uosm:Posm ratio  $\leq 1.5$  is consistent with electrolyte-free renal water clearance and a water-loaded state (77). In contrast, the change in Posm (12 mmol/kg) that is responsible for the 1100-mmol/kg Uosm is entirely consistent with a hyperosmolar state:

$$\begin{aligned} \Delta U_{\text{osm}} &= 250 \times 0.35 \Delta P_{\text{osm}} \text{ or } \Delta 12 \text{ Posm} \\ &= \Delta 1050 \text{ Uosm} \quad (27) \end{aligned} \quad (3)$$

Therefore, both aspects of osmoregulation (ie, the variation and basal set point) are very important considerations when Posm is used to assess dehydration. When a person's true Posm baseline is not known, biological variation analysis can provide confident probabilistic estimates of dehydration by using both single and serial measures of Posm.



**FIGURE 3.** Means [men (●); women (■)] from 4 basal plasma osmolality samples under conditions of ad libitum fluid intake in 15 healthy subjects. Boundaries of rectangular boxes represent osmotic thresholds for unequivocal thirst (top) and AVP secretion (bottom) determined from regression analysis during hypertonic saline infusion. Dashed lines represent group means often cited in the literature. Adapted from reference 13 with permission (copyright 1976; The Endocrine Society). AVP, arginine vasopressin;  $P_{\text{osm}}$ , plasma osmolality.

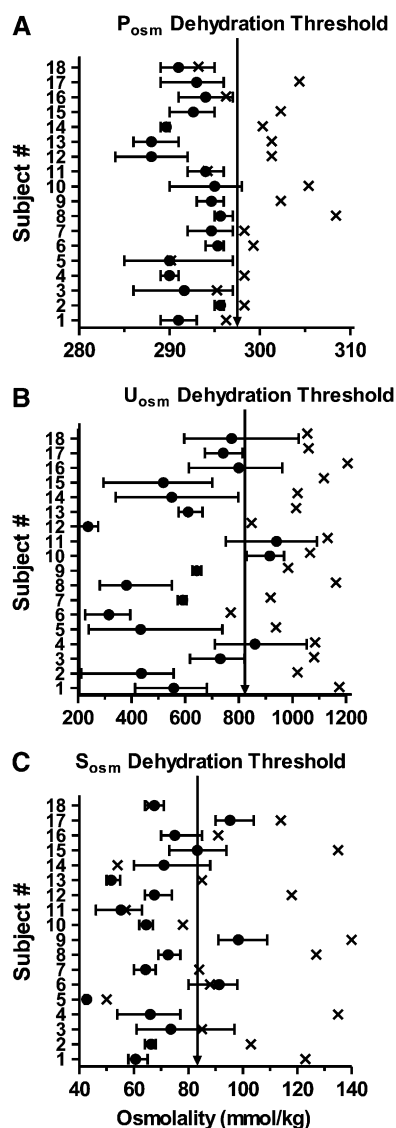
### Biological variation of Posm (single measure)

Claude Bernard's concept of the tightly regulated milieu intérieur is commonly referenced by extension as a narrow 1–2% variation in Posm. Surprisingly few studies have quantified the intraindividual variation in Posm from day to day, but they have been consistent with this concept and reported values that ranged from 0.8% to 1.4% (2–4 mmol/kg), with the exclusion of the analytic (measurement) variation (~0.5% or 1 mmol/kg) (54, 78, 79). These studies (54, 78, 79) were not stratified and, thus, included contributions to the variation because of sex (73) and age (74). Although most measures of physiologic interest have a larger interindividual variation than intraindividual variation (80), the 2 measures are similar for Posm. This outcome seems to contrast with wide population reference intervals until it is considered that the variation between subjects shrinks when measurement methodology and other preanalytic factors are controlled for (80). The ratio of intraindividual to interindividual variation (index of individuality) in Posm ranges from 0.9 to 1.4 (54, 78, 79). The index of individuality provides a statistical framework to distinguish pathologic states such as dehydration from a single measurement. Any atypical value for a given individual, relative to the larger population of individuals, will go unnoticed when the ratio is <0.6 but will be captured when the ratio is >1.4 (80, 81). The probability of identifying an atypical value increases rapidly as the ratio exceeds 0.60 and approaches unity (1.00) (81).

The index of individuality concept for Posm is shown in **Figure 4** and includes Uosm and saliva osmolality (Sosm) for comparison (54, 58). The interindividual variation is depicted by the differences in means (dots), whereas the intraindividual differences (typical day-to-day variation) in body fluid measures are represented by the range (bars) that surrounds each individual mean. "X" values in Figure 4 represent body fluid measures in response to a –2.5-L loss of body water (–3% dehydration). When graphed relative to the respective dehydration thresholds determined empirically by receiver operating characteristic curve analysis, probabilities of false-negative and -positive findings become apparent. The index of individuality for Posm was 0.90. For contrast, ratios for Uosm and Sosm were 0.49 and 0.27, respectively (54). As illustrated in Figure 4, an atypical value for Posm (X, dehydrated) is more easily and accurately detected than an atypical value for Uosm or Sosm, despite the expected linear associations commonly reported when the dehydration level against Sosm or Uosm is regressed. The complete biological variation analysis (54) supports a Posm threshold of  $301 \pm 5$  mmol/kg, which is mathematically identical to the  $-0.56^\circ\text{C}$  depression in the freezing point proposed by Olmstead et al (82) >50 y ago as a positive test for hypernatremia. We recommend the inclusion of a variance term ( $\pm 5$  mmol/kg) to account for biological differences in basal set points (54) and note its consistency to values (295–300 mmol/kg) reached by consensus (24) as consistent with impending dehydration.

### Biological variation of Posm (serial measures)

Reference change values (80) allow the observation of serial changes in Posm to be interpreted in terms of diagnosing dehydration (54, 58). Reference change values can be calculated (when the proper statistical assumptions are met) (80, 83)

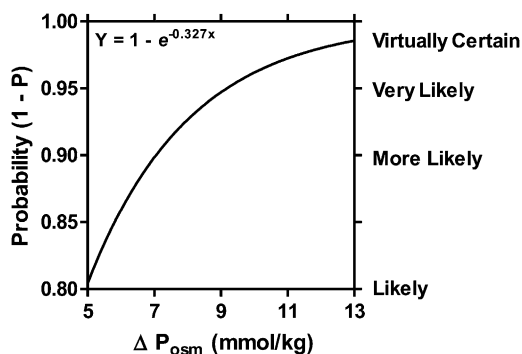


**FIGURE 4.** Means (●) and absolute ranges of plasma (A), urine (B), and saliva (C) osmolality from 3 samples taken from each of 18 normally hydrated (euhydrated) subjects. "X" values represent a single sample from the same subjects after dehydration to  $-3.3 \pm 0.6\%$  of body mass. Dehydration thresholds were determined by using receiver operating characteristic curve analysis (value that provided the highest diagnostic accuracy) with the use of both euhydrated and dehydrated matched pairs. Data are a composite from references 54 and 58. P<sub>osm</sub>, plasma osmolality; S<sub>osm</sub>, saliva osmolality; U<sub>osm</sub>, urine osmolality.

by using the sum of analytic and intraindividual variations in Posm (80). The probability that a measured change in Posm is atypical can then be determined (58, 80). As illustrated in **Figure 5**, atypical changes in Posm begin above the daily 2–4-mmol/kg constancy threshold and provide increasing predictive certainty that dehydration has occurred in accordance with the equation

$$\text{Probability} = 1 - e^{-0.327x} \quad (4)$$

where  $x$  is the measured change in Posm (58). As a result, the probability that a change in Posm reflects the occurrence of dehydration can be gauged in both quantitative and qualitative terms.



**FIGURE 5.** Changes in  $P_{\text{osm}}$  plotted as a function of the statistical probability for dehydration. Semantic descriptors provide a scale that aligned with statistical probability to communicate the likelihood of dehydration in simple terms. The equation (inset) describes the curved line and its ubiquitous  $K$  constant ( $-0.327$ ). From Cheuvront et al (58).  $P_{\text{osm}}$ , plasma osmolality.

### LIMITATIONS OF USE OF OSMOMETRY FOR ASSESSMENT OF DEHYDRATION

It is clear that  $P_{\text{osm}}$  is critical for body water regulation, and plasma is a unique body fluid for use in the assessment of dehydration. Although  $U_{\text{osm}}$  and  $S_{\text{osm}}$  have also been used successfully for this purpose (84, 85), human variation in these body fluids seem to limit their potential utility (Figure 4). The greater variation in  $U_{\text{osm}}$  and  $S_{\text{osm}}$  is not surprising. For example,  $\leq 40\%$  of  $U_{\text{osm}}$  is attributable to urea (compared with only  $\sim 1\%$  for  $P_{\text{osm}}$ ), and thus, the addition of solute in the form of antecedent diet or catabolic byproducts of protein metabolism associated with exercise or illness may increase  $U_{\text{osm}}$  by the addition of solute (86, 87). Similar limitations apply for urine-specific gravity, whereas all urine-concentration measures are subject to timing and uniformity concerns that manifest empirically as differences between first morning, 24-h, and spot urine measures (88) in addition to acute drinking and exercise behaviors (59). The discriminatory power of renal excretion measures for the detection of dehydration is clearly secondary to changes in  $P_{\text{osm}}$  (28), but this does not, in any way, minimize the critical use of  $U_{\text{osm}}$  (and its relation to  $P_{\text{osm}}$ ) in the measurement of renal function related to the phenomenologic interpretation or differential diagnosis of other disorders (5, 28, 29). With regard to saliva,  $S_{\text{osm}}$  is subject to practical use issues related to simple oral artifacts (54, 89).  $S_{\text{osm}}$  may also be affected by anything that affects salivation (salivary flow), which includes a multitude of factors (85). Limitations of the use of  $P_{\text{osm}}$  for the assessment of dehydration must also be acknowledged.

$P_{\text{osm}}$  and plasma tonicity (effective osmolality) are very similar quantities in health (90). However, substances in the blood that raise osmolality but not tonicity (ineffective or penetrating solutes) have the potential to confound dehydration assessment. The calculation of the osmol gap will reveal contributions from ineffective solutes, but the direct measurement of  $P_{\text{osm}}$  is always recommended for dehydration assessment because of the large acceptable error in calculated osmolality ( $\pm 10$  mmol/kg) (90). Fluctuations in the volume of body fluid compartments will also affect  $P_{\text{osm}}$ . For example, consumption of a large meal can increase  $P_{\text{osm}}$  because of the osmolar shift of water out of the vasculature and into the gut (91). In contrast, simple changes in posture (42, 92) and even low-intensity exercise ( $\leq 40\%$  maximal

oxygen uptake) (93, 94) produce little effect, probably because osmotic concordance is not disrupted by the 2-way fluid flow between interstitial and intravascular spaces that share the same osmotic pressures (61, 64, 93). Higher exercise intensities increase  $P_{\text{osm}}$  as a result of greater intravascular volume losses and the presence of lactic acid, but recovery appears complete in  $\leq 20$ – $30$  min (93). Finally, as stated earlier,  $P_{\text{osm}}$  is of no use for the detection of volume depletion. When this distinction is made, coupled with the importance of biological variation and other issues discussed herein, criticisms for adopting  $P_{\text{osm}}$  as a gold standard for dehydration assessment (15, 95–97) are minimal.

### CONCLUSIONS AND FUTURE DIRECTIONS

Dehydration is a common physiologic state with implications for health and performance (1–8). Although the physiology of dehydration is well described, it remains difficult to assess accurately in practice. In this review, we highlighted how the phenomenologic interpretation of dehydration depends critically on the type and magnitude of dehydration, which directly affect threshold osmotic and volume-dependent compensatory anti-diuretic and thirst responses. We also emphasized how knowledge of biological variation improves our broader understanding of the physiology that underpins the osmotic response to dehydration in humans and affords important diagnostic insight for dehydration assessment. To help improve the practice of dehydration assessment, a single, atypical  $P_{\text{osm}}$  threshold value of  $301 \pm 5$  mmol/kg is suggested (54) as a starting point for this purpose, along with a nomogram (58) for the estimation of the probability of dehydration when serial changes in  $P_{\text{osm}}$  are measured as an adjunct to quantitative differential diagnostic procedures. No standard method has been advocated for the assessment of volume depletion (16, 19), but a 20-beats/min sit-to-stand cutoff provides high test specificity for both dehydration and volume depletion (65, 69). Because  $P_{\text{osm}}$  requires the collection of blood and the preparation of plasma, future efforts to identify or develop an acceptable noninvasive surrogate for  $P_{\text{osm}}$  would benefit clinical, sports, and military medicine communities (7). A test with high diagnostic accuracy for moderate volume depletion is also needed.

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