



**Which one of these variables is most critically regulated:  
extracellular fluid (ECF) volume or ECF osmolality or ECF pH or  
effective arterial blood volume?**

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The question stated in the title of this article arises because there are several clinical conditions characterized by abnormalities in three or all of these variables. When hypovolemia, occurring as a result of vomiting, is accompanied by metabolic alkalosis, the kidneys avidly reabsorb sodium, chloride and bicarbonate, and urine may become acidic ('paradoxical aciduria'). [1] This suggests that regulation of ECF volume overrides mechanisms defending changes in ECF pH.

Release of antidiuretic hormone (ADH) is triggered by increases in sodium concentration of ECF as well as decreases in ECF or blood volume. [2-4] Primary adrenocortical insufficiency (Addison's disease) is characterized by hyponatremia, a decrease in plasma osmolality, and may additionally be characterized by hyperkalemia and metabolic acidosis. [4-7] The cause of hyponatremia in primary adrenocortical insufficiency is mainly a decrease in the content and concentration of sodium and chloride in ECF secondary to deficiency of glucocorticoids and mineralocorticoids. Since sodium is the dominant osmole in ECF, these individuals must have ECF volume contraction especially in the absence of compensatory or pathologic elevation in secretion and or activity of ADH. Several reports document elevated plasma arginine vasopressin (AVP) in Addison's disease [6-9]. However, some investigators have found AVP levels to be normal in this condition [10-11]; symptoms and signs depend on the extent and rapidity of destruction of the adrenal cortex and may not be clinically apparent until about 90% of adrenocortical function is lost. [5]

Individuals with adrenocortical insufficiency have also been shown to have raised plasma renin activity despite replacement therapy with fludrocortisone and cortisone acetate [12]. Plasma renin concentration has been shown to be elevated in those with Addison's disease receiving glucocorticoids and a placebo, and is reduced in a dose dependent fashion in those treated with fludrocortisone [13]. All of these observations point to a decrease in ECF volume in untreated primary adrenocortical insufficiency.

Leaf and Mamby [14] have described a female patient with Addison's disease inadequately treated with 5 mg of deoxycorticosterone acetate who responded to an oral water load of 500 ml with a fall in plasma osmolality, a rise in urine osmolality, and a demonstrable rise in antidiuretic activity in the serum. Clearly, the osmoregulatory mechanisms were not showing the 'expected' response to a decrease in plasma osmolality. In contrast, in a euvoletic individual, a water diuresis would be expected. In the same article [14], these authors report an identical pattern in dogs depleted of 130 meq of extracellular electrolyte and volume by peritoneal dialysis so as to result in hyponatremia. These animals were then given a 300 ml water load by a stomach tube. In contrast to the hypotonic diuretic response to the 300 ml water load in the euvoletic normonatremic dog, the response observed in the hypovolemic hyponatremic dog to the same water load was a 6-7 fold lower urine flow rate, a significantly higher antidiuretic activity in serum, and urine osmolality remained twice as high as plasma osmolality. With all these observations taken together, it appears that under conditions of hypovolemia, maintenance of the amount of salt and thereby the volume of ECF is prioritized over control of osmolality of ECF.

Goldsmith et al. [15] have examined responses to oral water load of 15-20 ml/kg body weight in patients with congestive heart failure and healthy control subjects. The decrease in urinary osmolality following water load was significantly lower in patients with congestive heart failure compared to healthy subjects, and urine remained concentrated in relation to plasma. Following water load, plasma AVP levels in patients with congestive heart failure reduced to a much smaller extent than in control subjects.

A decrease in effective arterial blood volume (the volume of blood contained in the systemic arteries) and a decrease in atrial pressure induce release of ADH though osmolality may be normal. [16] Effective arterial blood volume is the volume of arterial blood in the systemic circulation that perfuses tissues. It is possible that effective arterial blood volume is reduced while ECF volume is elevated. 'Arterial underfilling' accompanied by an increase in ECF volume is known to occur in three states: congestive heart failure with edema; cirrhosis complicated by portal hypertension and ascites; and nephrotic syndrome with edema.

There is evidence that release of ADH is regulated in part by arterial baroreceptors and low-pressure baroreceptors. When atrial pressures are raised but effective arterial blood volume and arterial blood pressure are reduced as may happen in low cardiac output heart failure, arterial baroreflex mediated stimulation of ADH release dominates low-pressure baroreceptor mediated suppression of ADH release. [17] The afferent pathways for intravascular volume mediated regulation of ADH release are the neural pathways from the arterial baroreceptors and or low-pressure baroreceptors to the nucleus of the tractus solitarius (NTS) via branches of the glossopharyngeal nerves and the vagi respectively. From the NTS, impulses reach the paraventricular nucleus via the caudal ventrolateral medulla. [3,4] A decrease in effective arterial blood volume leads to a decrease in renal blood flow, this activates the renin-angiotensin system, [16] and angiotensin II is a stimulator of ADH release. [4]

As for comparing tolerance to deviations in hydrogen ion concentration and osmolality of ECF from normal, I do not know of a clinical situation in which both plasma osmolality and hydrogen ion concentration change in the absence of a significant change in ECF volume. The normal range of hydrogen ion concentration in arterial plasma is 35-45 nM (a variation of 12.5% either way

from 40 nM), and the osmolality of normal human plasma ranges from 280 to 296 mOsm/Kg H<sub>2</sub>O, a variation of 2.5% [3], significantly smaller compared to normal variations in hydrogen ion concentration of arterial plasma. On this basis, it may be reasonable to infer that osmolality of ECF is more rigorously controlled than the hydrogen ion concentration of ECF.

The arguments presented are summarized below:

<b>Clinical Situation</b>	<b>Observation</b>	<b>Inference</b>
Vomiting leading to hypovolemia and metabolic alkalosis	Kidneys conserve Na, Cl and HCO <sub>3</sub> and the urine may become 'paradoxically' acidic.	ECF volume is more critically controlled than ECF pH.
Untreated or inadequately treated adrenocortical insufficiency, characterized by hypovolemia	Administration of a water load is associated with antidiuresis rather than diuresis, and urine osmolality remains elevated compared to plasma.	ECF volume is more critically controlled than ECF osmolality.
Untreated congestive heart failure	Administration of a water load is associated with antidiuresis rather than diuresis, plasma level of AVP falls less compared to that observed in healthy euvoletic subjects, and urine osmolality remains elevated compared to plasma.	Effective arterial blood volume is more critically controlled than ECF volume and ECF osmolality.

It seems reasonable to infer that homeostatic mechanisms prioritize defense of ECF volume over control of either osmolality or pH of ECF; also, it is clear that effective arterial blood volume is more critically regulated than ECF volume. Teleologically, under conditions of hypovolemic hyponatremia, conservation of ECF volume by antidiuretic mechanisms or its repletion by water drinking may allow for eventual normalization of ECF osmolality by intake of salt in the diet. [14] The practical importance of this knowledge is the possibility that changes in ECF and or blood volume might underlie seemingly paradoxical changes in either osmolality and or pH of ECF in clinical conditions such as those discussed above. It is helpful to bear this in mind since blood or ECF volume is rarely if ever measured in clinical practice, and physical signs and symptoms are not very sensitive indicators of mild hypovolemia [18].

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