Body Fluid Volume Regulation in Health and Disease: A Unifying Hypothesis

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In studies in experimental animals and in edematous patients, the nonosmotic release of vasopressin has been found to be consistently associated with activation of the sympathetic nervous and renin-angiotensin-aldosterone systems. Moreover, the sympathetic nervous system is known to modulate the nonosmotic release of vasopressin and activation of the renin-angiotensin-aldosterone system. These findings led to our proposal that body fluid volume regulation involves dynamic interaction between cardiac output and peripheral arterial resistance. In this context, neither total extracellular fluid volume nor total blood volume are determinants of renal sodium and water excretion. With a decrease in effective arterial blood volume (EABV) initiated by either decreased cardiac output or peripheral arterial vasodilation, the acute response involves vasoconstriction mediated by angiotensin, sympathetic mediators, and vasopressin. The renal vasoconstriction, which accompanies either decreased cardiac output or peripheral arterial vasodilation, causes a decreased distal tubular delivery of sodium and water, thus maximizing the water-retaining effect of vasopressin and impairing normal escape from the sodium-retaining effect of aldosterone. The elevated glomerular filtration rate and filtered sodium load seen in pregnant women allow increased distal sodium and water delivery despite a decrease in EABV, thus limiting edema formation during gestation.

Annals of Internal Medicine. 1990;**113**:155-159.

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Body fluid volume regulation is critically important in maintaining life and has been intensely studied for over a century. In the nineteenth century, the French physiologist, Claude Bernard, wrote that "The constancy of the internal environment is the condition of free and independent existence" (1). Yet there remain many perplexing dilemmas and apparent paradoxes about body fluid volume regulation in humans.

In normal humans, expansion of the extracellular fluid (ECF) volume, including expansion of the interstitial fluid (ISF) and intravascular (IV) volumes, is associated with an increase in renal sodium and water excretion with resultant restoration of normal ECF volume. This observation suggested that there must be specific volume receptors that monitor the volume of either the ISF or IV compartments or both. The exact location of such volume receptors has, however, been debated. Observations made of patients with various sodium- and water-retaining disorders raise questions about the exact nature of this volume regulatory system.

The Concept of Effective Blood Volume

There is now little doubt that there are many circumstances in which, despite expansion of total ECF, ISF, and IV volumes, avid renal sodium and water retention persists. For example, patients with advanced congestive heart failure or cirrhosis have increased ECF volumes, including interstitial edema, and expanded total plasma and blood volumes (2). These observations led Peters (3) to coin the enigmatic term "effective blood volume." This term implies that there must be a body fluid compartment that is "underfilled," despite the expansion of total ECF and blood volume that occurs in patients who have cardiac failure or cirrhosis and yet continue to exhibit renal sodium and water retention. Extrarenal reflexes that enhance tubular sodium and water reabsorption by the otherwise normal kidney therefore must be initiated by this decrease in "effective blood volume." In this regard, it is clear that renal sodium and water retention can occur in patients with cardiac or liver disease before any diminution in glomerular filtration rate. Moreover, transplantation of a kidney from a cirrhotic patient with ascites and peripheral edema to a recipient with normal liver function totally reverses renal sodium and water retention (4). The transplantation of a normal liver into an edematous, cirrhotic patient also has been shown to abolish renal sodium and water retention, thus further implicating extrarenal mechanisms in the pathogenesis of the edema formation in these patients (5).

Borst and deVries (6) first suggested cardiac output as the primary modulator of renal sodium and water excretion. In this context, the level of cardiac output would constitute "effective blood volume." Although this concept was attractive, it is clear that profound renal sodium and water retention may occur in the presence of an increase in cardiac output. For example, a significant elevation in cardiac output may occur in the presence of avid renal sodium and water retention and expansion of ECF and blood volumes in association with cirrhosis, pregnancy, a large arteriovenous fistula, or other causes of high output cardiac failure such as thyrotoxicosis and beriberi (2).

Primacy of Arterial Circulation in Volume Regulation

A series of investigations in experimental animals and humans led to our proposing a unifying hypothesis for body fluid volume regulation in health and disease (7-17). Our hypothesis states that total ECF, ISF, or IV volumes are not primary determinants of renal sodium and water excretion. According to our hypothesis, the venous component of IV volume is also excluded as the primary determinant of sodium and water excretion.

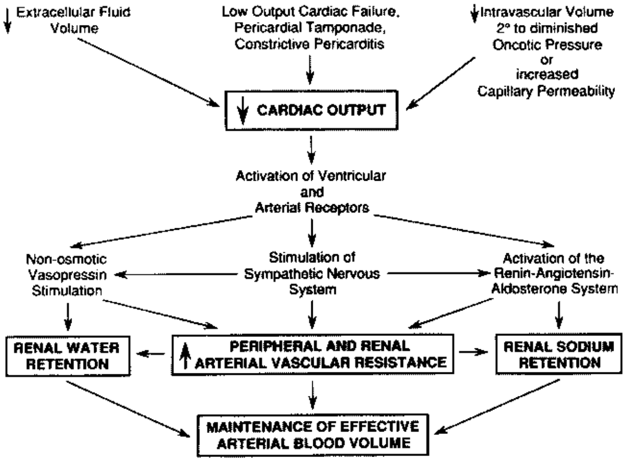

Figure 1. Sequence of events in which reduced cardiac output initiates renal sodium and water retention.

However, in some experimental and clinical circumstances, selective rises in right and left or left atrial pressure stimulate the release of atrial natriuretic peptide (ANP) (18) and the suppression of arginine vasopressin (AVP) (19), respectively, which results in enhanced sodium and water excretion. These events, however, must be subservient to more potent determinants of body fluid volume regulation, because the patient with advanced left or right ventricular dysfunction or both exhibits avid sodium and water retention despite markedly elevated atrial pressures.

Our unifying hypothesis of body fluid regulation in health and disease proposes that the arterial circulation is the primary body fluid compartment modulating renal sodium and water excretion. In a 70-kg man, total body water approximates 42 L, of which only 0.7 L or 1.7% resides in the arterial circulation. From a teleologic viewpoint, it is attractive to propose that the primacy for regulation of renal sodium and water excretion (and, thus, body fluid volume homeostasis) is modulated by a very small body fluid compartment, such as the arterial circulation. This endows the volume regulatory system with exquisite sensitivity to relatively small changes in body fluid volume, and locates it in the fluid compartment that is responsible for arterial perfusion of the body's vital organs and tissues.

Cardiac Output and Peripheral Arterial Resistance as Determinants of Integrity of Arterial Circulation

Our body fluid volume regulation hypothesis indicates that there are two primary determinants of overfilling or underfilling of the arterial circulation: cardiac output and peripheral arterial resistance. In this context, we propose that all renal sodium- and water-retaining states that occur in the absence of intrinsic renal disease are initiated by either decreased cardiac output (Figure 1) or peripheral arterial vasodilation (Figure 2).

The Neurohumoral Response to Arterial Underfilling

The neurohumoral response that defends against arterial underfilling involves rapid activation of the renin-angiotensin-aldosterone and sympathetic nervous systems and nonosmotic release of AVP (Figures 1 and 2). The sympathetic nervous system is the primary integrator of this response, because nonosmotic AVP release involves sympathetic stimulation of the supraoptic and paraventricular nuclei in the hypothalamus (20) and activation of the renin-angiotensin-aldosterone system involves renal beta-adrenergic stimulation (21). There is considerable evidence that this rapid neurohumoral compensatory response is essential to maintaining the integrity of the arterial circulation in sodium- and water-retaining states. Specifically, as previously reviewed (2), the administration of alpha-adrenergic blocking agents, angiotensin antagonists, or converting enzyme inhibitors and V_1 (vascular) antagonists to AVP has been shown to diminish arterial blood pressure in states of arterial underfilling, whether initiated by either decreased cardiac output or peripheral arterial vasodilation.

With peripheral arterial vasodilation, an increase in cardiac output secondary to afterload reduction constitutes another compensatory response to underfilling of the arterial circulation (Figure 2). Some patients who have had cardiac surgery, patients with cardiac failure receiving vasodilating agents, and septic patients, despite having measured cardiac output within the normal range, have avid renal sodium and water retention. In such cases, however, the presence of ventricular dysfunction limits the increase in cardiac output that is seen for comparable afterload reduction in normal subjects. This sequence of events therefore causes arterial underfilling which is accompanied by both activation of the neurohumoral response to arterial underfilling and renal sodium and water retention.

Importance of Divergent Neurohumoral Profiles

Because patients with altered arterial circulation are most frequently seen after compensatory responses to changes in arterial filling have occurred, evaluation of their hemodynamic variables including mean arterial pressure, cardiac output, and peripheral vascular resistance may be insufficient to assess the fullness of the arterial circulation. For example, volume expansion

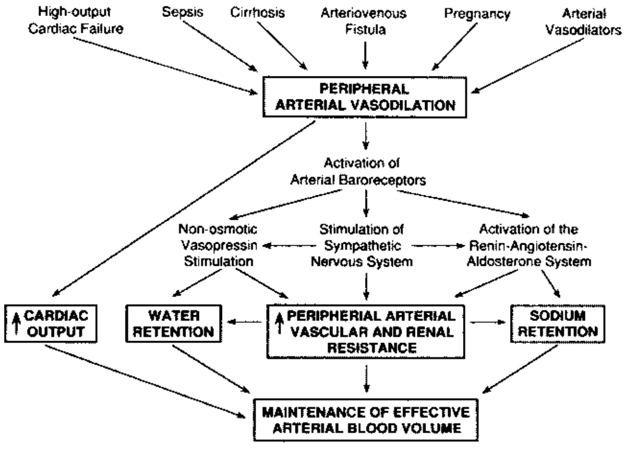

Figure 2. Sequence of events in which peripheral arterial vasodilation is the central initiator of renal sodium and water retention.

with arterial overfilling is associated with an increase in cardiac output and a secondary decrease in peripheral vascular resistance so that the steady-state mean arterial pressure may be within the normal range. On the other hand, primary peripheral arterial vasodilation may cause arterial underfilling with a secondary increase in cardiac output and a steady-state blood pressure within the normal range. However, in the former situation of arterial overfilling, the neurohumoral profile will be suppressed; whereas, in the circumstance of arterial underfilling, the neurohumoral profile will be stimulated (Figure 3).

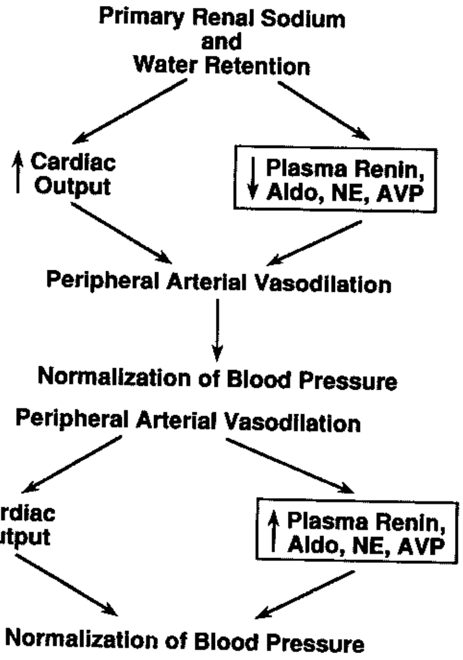

Figure 3. Neurohumoral and hemodynamic profile for increased (*top*) and decreased (*bottom*) effective arterial blood volume. Thus, in the compensated patient, blood pressure, cardiac output, and peripheral vascular resistance may be indistinguishable between states of increased and decreased effective arterial blood volume. However, the neurohumoral profiles and urinary sodium and water excretion clearly distinguish these conditions. Aldo = aldosterone; NE = norepinephrine; AVP = arginine vasopressin.

Renal Sodium and Water Excretion: Sensitive Index of Arterial Underfilling versus Overfilling

With changes in arterial filling, the rapid neurohumoral response and changes in renal excretion of sodium and water thus provide the primary diagnostic monitors for the adequacy of the arterial circulation. The renal excretory response to arterial underfilling constitutes the slower compensatory response as compared with the vasoconstrictor effects of angiotensin, AVP, and the adrenergic nervous system. It also seems likely that this generalized systemic vasoconstrictor response is the primary reason for the renal vasoconstriction that consistently occurs in the sodium- and water-retaining disorders. This renal vasoconstriction is critical in enhancing the sodium and water retention associated with arterial underfilling. Specifically, renal vasoconstriction diminishes the amount of sodium and water delivered to the distal nephron, and this decreased distal delivery rate is a major determinant of sodium and water retention in the presence of nonosmotic release of AVP and stimulation of the renin-angiotensin-aldosterone system. In addition, ANP exerts its primary tubular action on the collecting duct, and the hormone's natriuretic response is therefore influenced by the rate of distal tubule sodium delivery.

Impaired Aldosterone Escape and Atrial Natriuretic Peptide Resistance as Features of Arterial Underfilling

Administration of adequate doses of spironolactone relative to the endogenous plasma concentrations of aldosterone in patients with the edematous disorders has shown that aldosterone is an important sodium-retaining hormone in this setting (22, 23). In contrast to in normal subjects or patients with primary hyperaldosteronism, however, escape from the sodium-retaining effect of aldosterone does not occur in persons with edematous disorders such as advanced cirrhosis and congestive heart failure (2). The "aldosterone escape" from the hormone's sodium-retaining effect in normal subjects depends on enhanced sodium delivery to the distal collecting duct site of aldosterone action. This enhanced sodium delivery results from a rise in glomerular filtration rate and, thus, in filtered load of sodium and a decrease in proximal tubule sodium reabsorption (24). In contrast, in circumstances of arterial underfilling, the neurohumoral-mediated renal vasoconstriction enhances proximal sodium reabsorption and may decrease the filtered load of sodium; these events diminish distal sodium delivery and prevent escape from the sodium-retaining effect of aldosterone. These events are summarized in Figure 4.

Recent observations indicate that a normal increase in urinary cyclic guanosine monophosphate (cGMP) accompanies ANP administration to cirrhotic patients; however, there is a profound blunting of the hormone's natriuretic response (25). This resistance to ANP has also been reported in patients with congestive heart failure (26) and the nephrotic syndrome (27). The normal increase in urinary cGMP response to ANP administration but with an impaired natriuretic response is also compatible with the diminished distal sodium delivery to the collecting duct site of ANP action as occurs in states of arterial underfilling.

Receptors Monitoring Arterial Circulation

Because the maintenance of adequate arterial perfusion of the body's vital organs is of paramount importance, several receptors monitor the integrity of the arterial circulation. The carotid and aortic arch baroreceptors sense mean arterial pressure (28). With arterial underfilling, a baroreceptor-mediated diminution in glossopharyngeal and vagal tone to the nucleus tractus solitorius in the midbrain results in increased efferent adrenergic discharge at the level of the supraoptic and paraventricular nuclei in the hypothalamus and nonosmotic release of AVP (9). An increased systemic adren-

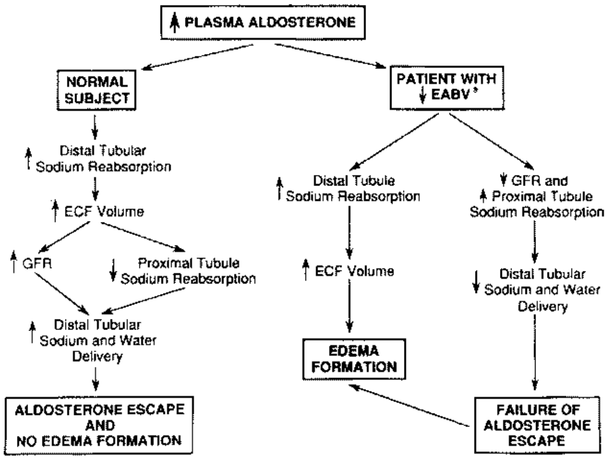

Figure 4. Summary of events involved in aldosterone escape in normal subjects (*left*) and impaired aldosterone escape in arterial underfilling (*right*). * Pregnancy is the only circumstance of arterial underfilling in which glomerular filtration rate (*GFR*) rises and thus allows aldosterone escape. EABV = effective arterial blood volume; ECF = extracellular fluid.

ergic tone also occurs and stimulates beta receptors in the kidney with activation of the renin-angiotensin-aldosterone system. The baroreceptors in the renal afferent arteriole also modulate renin release. Other receptor sites on the high-pressure side of the circulation are located in the left ventricle (29). For example, cardiac afterload reduction that enhances cardiac output may be associated with suppression of the neurohumoral profile of arterial underfilling in the absence of a rise in mean arterial pressure. Although the ventricular receptors seem most likely to initiate this response, arterial baroreceptors have also been shown to sense stroke volume or pulse pressure (30). If vasodilator therapy in patients with cardiac failure is excessive, however, blood pressure decreases and a state of arterial underfilling occurs. Lastly, it seems possible that other receptor sites, perhaps in the microcirculation or liver, that monitor the integrity or fullness of the arterial circulation may also exist.

Importance of Capillary Leak Associated with Peripheral Arterial Vasodilation

Results of experimental studies suggest that peripheral arterial vasodilation is associated with events at the capillary level, events that predispose patients to interstitial edema and thus perpetuate arterial underfilling. Dilatation of the precapillary arterioles increases capillary surface area and, presumably, capillary hydrostatic pressure. In studies done in rats using a subcutaneous capsule to estimate interstitial pressure, an increase in compliance of the interstitial space during saline loading in experimental cirrhosis (31) and vasodilator (minoxidil) therapy (32) has been shown. Moreover, in contrast to in normal rats, the albumin space is considerably larger than the vascular space in cirrhotic rats as well as in rats receiving minoxidil treatment. Thus, peripheral vasodilation favors interstitial edema by increasing capillary surface area and capillary hydrostatic pressure; increasing interstitial compliance, thus minimizing a rise in interstitial pressure during saline loading; and enhancing albumin leak across capillary surfaces, thereby increasing interstitium oncotic pressure. It is these events which may explain why saline loading alone does not correct arterial underfilling in circumstances such as cirrhosis, arterial vasodilation therapy, sepsis, and pregnancy.

Potential Mediators of Peripheral Arterial Vasodilation in States of Arterial Underfilling

The specific mediators of peripheral arterial vasodilation in the various states of arterial underfilling remain to be defined. For example, in cirrhosis, portal hypertension may open existing portosystemic shunts and stimulate collateral portosystemic shunt formation so that as much as 80% of hepatic blood flow is shunted past the liver. In addition to splanchnic arterial vasodilation and shunting, there is evidence of arteriovenous shunting in the lungs, skin, and muscles of cirrhotic patients. The exact mediator (or mediators) of the peripheral arterial vasodilation remains to be defined; prostaglandins, substance P, endotoxins, calcitonin gene-related peptide, vasoactive intestinal peptide, and endorphins are just a few of the substances that have been proposed (33).

In normal pregnancy, vasodilating prostaglandins, resistance to angiotensin II, and the arteriovenous placental shunt appear to be involved in the primary arterial vasodilation that is associated with stimulation of the renin-angiotensin-aldosterone system, AVP release at a lower than normal ECF osmolality, a secondary rise in cardiac output, and sodium and water retention leading to a 30% to 50% increase in blood volume and ECF volume (2, 34). Other, undefined factors, however, must be involved in the primary arterial vasodilation of normal pregnancy. Specifically, an undefined humoral substance (or substances) has been proposed to cause the renal vasodilation, including a 30% to 50% rise in glomerular filtration rate which occurs within the first 2 weeks of pregnancy. This increase in glomerular filtration rate in pregnancy probably provides sufficient distal sodium delivery to allow aldosterone escape despite arterial underfilling. Thus, pregnant women are less edematous than are persons in other states of arterial underfilling. In patients with thyrotoxicosis and high-output cardiac failure, the primary peripheral arterial vasodilation may be due primarily to increased tissue metabolism and its consequences.

Conclusions

Considering the body fluid volume regulatory system as primarily involving the adequacy of the arterial circulation, as determined by the relation between cardiac output and peripheral arterial vascular resistance, creates a framework for further study of virtually all sodium- and water-retaining states. Although once useful to describe a previously undefined compartment involved in body fluid volume regulation, the term "effective blood volume" should probably be discarded. The pertinent question is whether there is evidence of arterial vascular underfilling or overfilling.

If there is no evidence of intrinsic renal disease, renal sodium and water retention virtually always occurs as a compensatory response to arterial underfilling in association with the well-defined neurohumoral, vasoconstrictor response; these mechanisms combine in an effort to restore normal arterial circulatory integrity. The magnitude of the neurohumoral response and the avidity of renal sodium and water retention is an index of the initial degree of arterial underfilling. For example, as cirrhosis progresses from the compensated state without ascites to the decompensated state with ascites and then to the hepatorenal syndrome, the degree of peripheral arterial vasodilation increases; blood pressure diminishes; the renin-angiotensin-aldosterone, adrenergic, and AVP systems are progressively stimulated; renal vasoconstriction worsens; and the avidity of sodium and water retention becomes more severe (35). It is thus pathogenetically sound and not by chance that in the absence of diuretics, the hyponatremic, high-renin patient with cirrhosis or cardiac failure has the worst prognosis (17, 36).

In cirrhosis, the primary cause of arterial underfilling is peripheral arterial vasodilation, whereas the initiating event in low-output cardiac failure is the diminution in cardiac output; but the compensatory renal and neurohumoral responses are identical, even though cardiac output changes in opposite directions in these two important edematous disorders. Thus, our unifying hypothesis of body fluid volume regulation explains many such previous enigmas, including the definition of "effective blood volume."

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