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Water and Sodium Retention in Edematous Disorders: Role of Vasopressin and Aldosterone

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ABSTRACT

This article discusses the pathophysiology of sodium and water retention in edematous disorders with a particular focus on cardiac failure, cirrhosis, and pregnancy. The body fluid volume hypothesis, which emphasizes the dominant role of arterial baroreceptors in renal sodium and water excretion, is reviewed. With arterial underfilling, either due to a decrease in cardiac output or peripheral arterial vasodilation, the normal central inhibition of the sympathetic nervous system activity and baroreceptor-mediated, nonosmotic arginine vasopressin (AVP) release is attenuated. The resultant increase in renal adrenergic activity stimulates the renin-angiotensin-aldosterone system. Although the resultant increase in systemic vascular resistance compensates for the primary arterial underfilling, this activation of the neurohumoral axis results in diminished sodium and water delivery to the renal collecting duct sites of aldosterone, AVP, and natriuretic peptide action. This diminished distal sodium and water delivery will be discussed as an important factor in the failure to escape from the sodium-retaining effects of aldosterone, the resistance to the natriuretic and diuretic effects of natriuretic peptides, and the diminished maximal solute-free water excretion in patients with edema. The role of the nonosmotic AVP release in water retention and hypo-osmolality/hyponatremia has been demonstrated in patients and experimental animals by administering nonpeptide, orally active vasopressin V_2 receptor antagonists. These agents have been found to increase solute-free water excretion in patients with water-retaining, hyponatremic edema as well as in experimental animals.

KEYWORDS: Cardiac failure; Cirrhosis; Pregnancy; Vasopressin

In 1922 Niels Bohr, a Nobel Laureate in physics, wrote, "We shall never understand anything until we have found some contradictions." The hyponatremia and hypo-osmolality that occur in edematous disorders, including cardiac failure, cirrhosis, and pregnancy, have several apparent contradictions.[1–4] In 1947, Verney[5] demonstrated the extreme sensitivity of the osmotic regulation of the antidiuretic hormone, arginine vasopressin (AVP). A 1% to 2% increase in plasma osmolality stimulates AVP release, whereas a 1% to 2% decrease in plasma osmolality suppresses AVP release. In spite of much larger decreases in plasma sodium and osmolality, patients with advanced cardiac failure[6] and cirrhosis[7] do not have suppressed plasma AVP concentrations measured by radioimmunoassay.

The water retention and hyponatremia in edematous disorders are always associated with sodium retention. The renal water and sodium retention occurs in edematous disorders in spite of an increase in the major body fluid compartments, including total blood volume and extracellular fluid (ECF) volume. In contrast, the intact kidney normally increases urinary water and sodium excretion when total blood volume and ECF volume are expanded. Yet, the patients with hyponatremic edema and cardiac failure or cirrhosis are known to have normal kidneys. Specifically, the kidneys of the patient with edematous cardiac failure no longer retain water and sodium when the patient receives

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a successful heart transplant. Similarly, when water- and sodium-retaining kidneys from patients with end-stage liver disease are successfully transplanted into patients with end-stage renal disease who have normal liver function, they no longer retain water and sodium.

For several decades the explanation for these dilemmas was that some compartment of the circulation, termed "effective blood volume," must be decreased in patients with edema because their total blood volumes are expanded. Although undefined and enigmatic, the term *effective blood volume* has been in common use in the medical community for many years. An attempt to define the effects of effective blood volume also has been plagued with contradictions. Although the glomerular filtration rate (GFR) may be decreased in advanced cardiac and liver disease, it is clear that early sodium and water retention occurs with these diseases when GFR is still normal. Aldosterone is the sodium-retaining hormone that is elevated in the plasma of patients with advanced cardiac failure and cirrhosis, but does not cause edema when administered in pharmacologic doses to control subjects. This is because of the aldosterone escape phenomenon in which, after initial sodium retention, urinary sodium excretion increases so that a further positive sodium balance no longer occurs.[8] There is also the phenomenon of vasopressin escape, in which, after initial renal water retention secondary to pharmacologic doses of vasopressin, urinary water retention is ameliorated.[9] Thus, if aldosterone and vasopressin are mediators of sodium and water retention in edematous disorders, there are apparent contradictions when compared with the actions of these hormones in normal subjects. Two natriuretic peptides, atrial and brain natriuretic hormones, are increased in patients with edema who have cardiac failure and cirrhosis, yet there is a relative resistance to their action when compared with controls, which represents another contradiction.

ARTERIAL UNDERFILLING AS A UNIFYING HYPOTHESIS FOR EDEMATOUS DISORDERS

In recent years, a hypothesis explaining many of these contradictions with respect to water and sodium retention in edematous disorders has emerged in several reports.[1–4,10,11] Total blood volume consists of approximately 85% of blood on the venous side of the circulation, with the remaining 15% on the arterial side of the circulation. Although there are low-pressure receptors on the venous side of the circulation, the unifying hypothesis of body fluid volume regulation focused on the integrity of the arterial circulation as the primary modulator of the efferent determinants of renal water and sodium regulation. The hypothesis proposed that underfilling of the arterial circulation could occur secondary to either a decrease in cardiac output (**Figure 1**)[3] or a relative underfilling due to arterial underfilling (**Figure 2**).[3] This hypothesis of body fluid regulation is only applicable in the absence of renal parenchymal disease, thus excluding edema associated with chronic renal diseases and/or nephrotic syndrome.

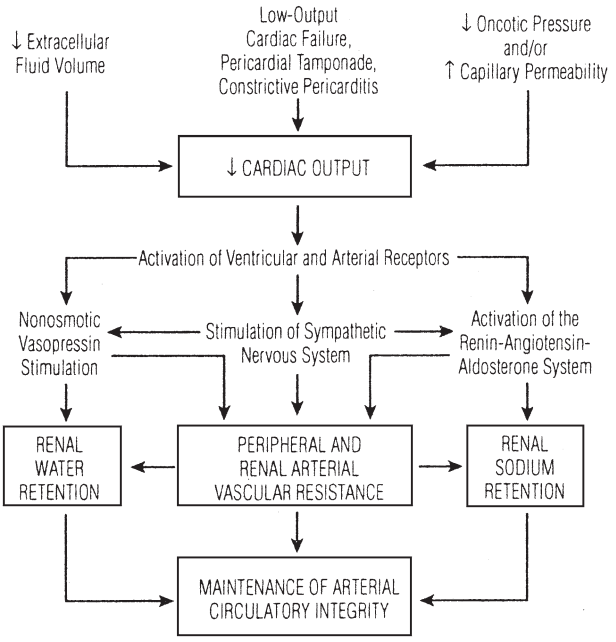

Figure 1 Neurohumoral activation in response to arterial underfilling secondary to a decrease in cardiac output. ↓ = decreased; ↑ = increased. (Adapted from *Ann Intern Med.*[3])

In the context of this hypothesis, if the increase occurred predominantly on the venous side of the circulation, sodium and water retention could increase total blood volume despite arterial underfilling. Because of the importance of arterial perfusion of vital organs, there are several relevant receptors in the high-pressure arterial circulation. Specifically, baroreceptors that respond to stretch are located in the left ventricle, carotid sinus, aortic arch, and juxtaglomerular apparatus. A series of experimental studies have demonstrated a baroreceptor-mediated, nonosmotic pathway for AVP release is less sensitive, but more potent, than the osmotic path of AVP regulation.[12,13] In neurophysiologic studies, single magnocellular neurons in the supraoptic nucleus of the hypothalamus were found to respond to both osmotic and nonosmotic stimuli.[14] Thus, a hypo-osmotic effect to suppress AVP synthesis and release may be overridden by the nonosmotic AVP stimulation of arterial underfilling. Normally, a tonic inhibition of nonosmotic vasopressin release and central sympathetic outflow is present via the vagal and glossopharyngeal nerves. With a decrease in arterial baroreceptor stretch during low-output cardiac failure (Figure 1) or arterial vasodilation that occurs with cirrhosis, high-output failure (e.g., beriberi, thyrotoxicosis), or pregnancy (Figure 2), there is nonosmotic vasopressin release[6,7,15] and an increase in sympathetic tone.[16] The increase in sympathetic tone stimulates the renin-angiotensin-aldosterone system (RAAS) via renal β-adrenergic stimulation[17]; both the sympathetic and angiotensin pathways increase systemic vascular resistance to maintain arterial circulatory integrity by attenuating the arterial underfilling. The increased nonosmotic vasopressin release stimulates V_{1a} receptors (V_{1a}Rs) on vascular smooth muscle

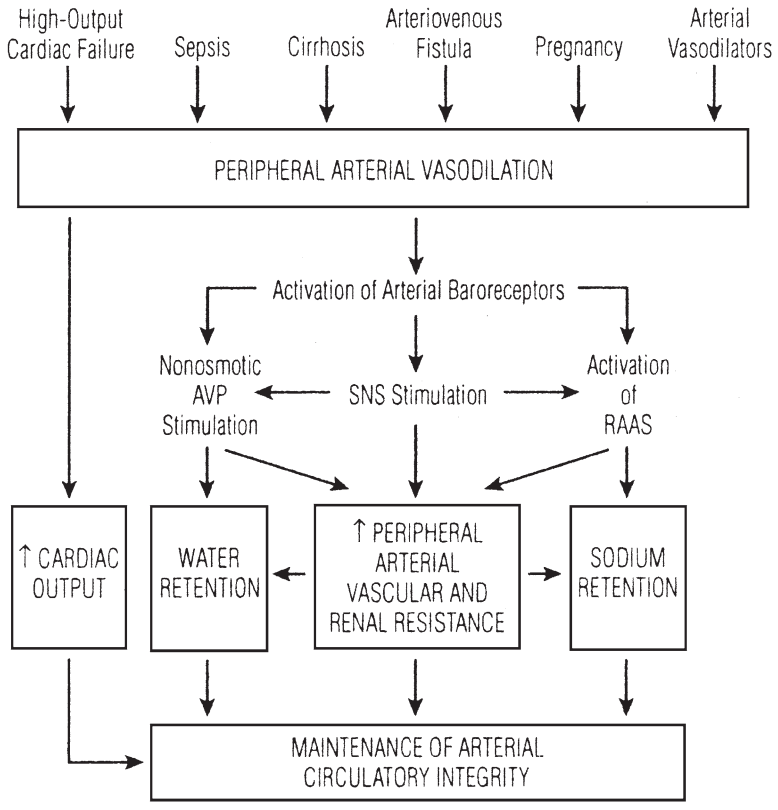

Figure 2 Neurohumoral activation in response to relative arterial underfilling secondary to systemic arterial vasodilation. Cardiac output increases secondary to the diminished cardiac afterload. AVP = arginine vasopressin; RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system. ↑ = increased. (Adapted from *Ann Intern Med.*[3])

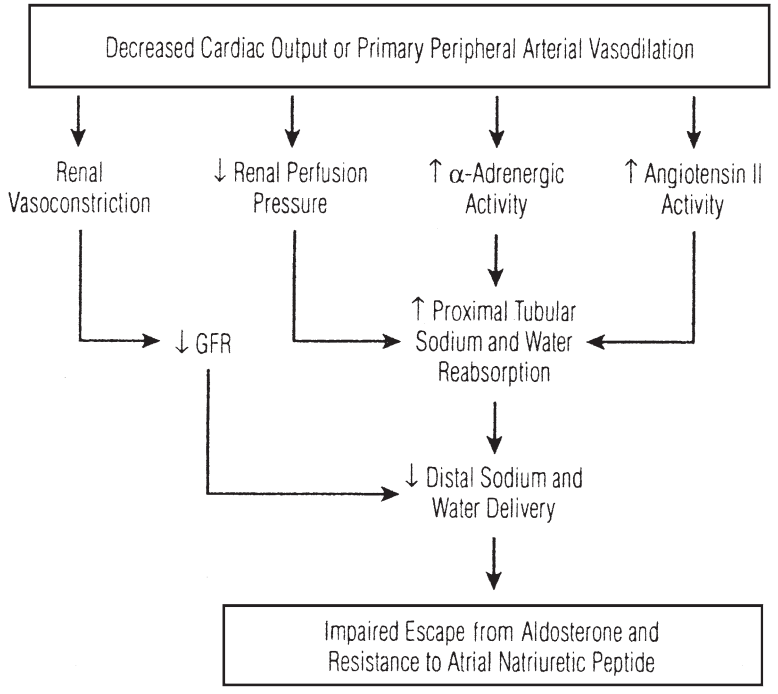

Figure 3 During arterial underfilling the renal consequences lead to decreased distal sodium and water delivery to the collecting duct with resultant impaired aldosterone escape and resistance to natriuretic peptides. ↓ = decreased; ↑ = increased; GFR = glomerular filtration rate. (Adapted from *J Am Coll Cardiol.*[23])

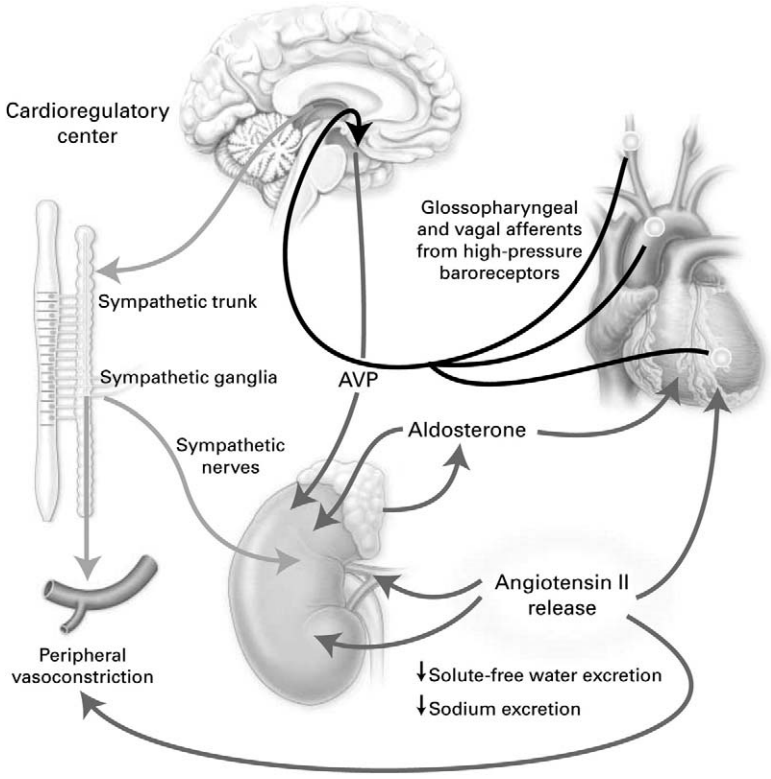

Figure 4 Unloading of high-pressure baroreceptors in the left ventricle, carotid sinus, and aortic arch generates afferent signals that stimulate cardioregulatory centers in the brain, resulting in the activation of efferent pathways in the sympathetic nervous system. The sympathetic nervous system appears to be the primary integrator of the neurohumoral vasoconstrictor response to arterial underfilling. Activation of renal sympathetic nerves stimulates renin release, thus activating the renin-angiotensin-aldosterone system. Concomitantly, sympathetic stimulation of the supraoptic and paraventricular nuclei in the hypothalamus results in the nonosmotic synthesis and release of arginine vasopressin (AVP). Sympathetic activation also causes peripheral and renal vasoconstriction, as does angiotensin II. Angiotensin II also stimulates the release of aldosterone from the adrenal gland and increases tubular sodium reabsorption in addition to remodeling cardiac myocytes. Aldosterone enhances cardiac fibrosis and increases sodium reabsorption of sodium and the secretion of potassium and hydrogen ions in the collecting duct. *Gray arrows* designate circulating hormones. ↓ = decreased. (Reprinted with permission from *N Engl J Med.*[15])

cells and contributes to this compensatory vascular response to arterial underfilling.[18] When the vasopressin V_2 receptors (V_2Rs) on the collecting duct are stimulated, the resultant activation of the adenylate-cyclic AMP pathway increases aquaporin-2 (AQP2) water channel trafficking to the apical membrane of the collecting duct. This sequence of events leads to an increase in water reabsorption and can cause hyponatremia in edematous disorders.[19–22]

The collecting duct in the distal nephron is also the site of aldosterone action and the natriuretic peptides. Thus, the ultimate effects of these hormones on sodium and water excretion depend on the amount of sodium and water delivered to these distal nephron sites. **Figure 3**[23] demonstrates the compensatory events occurring with arterial underfilling that diminish distal sodium and water delivery to the collecting duct.[24] As a consequence, there is a failure to escape from the sodium-retaining effects of aldosterone and there is resistance to natriuretic peptides in the edematous disorders that occur secondary to arterial underfilling. In experimental models of cardiac failure and cirrhosis, renal denervation, which enhances distal sodium and water delivery to the collecting duct, has been shown to reverse the resistance to atrial natriuretic peptide.[25,26] Moreover, in patients with cirrhosis, an increase in distal fluid delivery with mannitol administration, as assessed by lithium clearance, has been demonstrated to reverse the resistance to atrial natriuretic peptide.[27]

NONOSMOTIC STIMULATION OF ATRIAL VASOPRESSIN SECRETION

The first demonstration of a role of nonosmotic vasopressin release in congestive heart failure was published in 1981 in *The New England Journal of Medicine*.[6] Some 30 of 37 patients with cardiac failure who had hyponatremia and hypo-osmolality, of a degree that would have suppressed plasma AVP to undetectable levels in normal subjects, revealed "nonosmotic" plasma AVP concentrations measured by radioimmunoassay. In earlier studies, a bioassay for measuring plasma AVP was used, but the sensitivity of this technique was not sufficient to incriminate the nonosmotic release of AVP in edematous disorders. Subsequently, non-

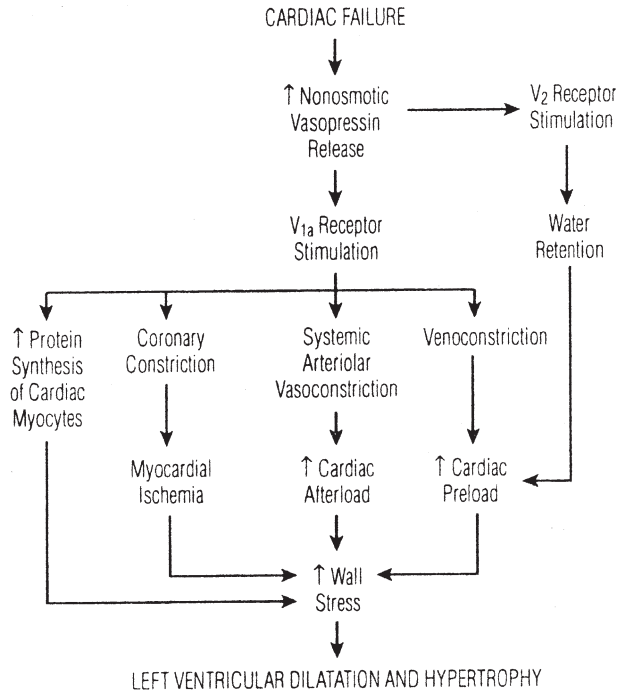

Figure 5 Potential effects of vasopressin on V_1 and V_2 receptors that can worsen cardiac function by increasing cardiac preload and afterload, as well as causing myocardial ischemia and remodeling. ↑ = increased. (Adapted from *J Am Coll Cardiol*.[23])

osmotic release of AVP occurring in 'patients with hyponatremic cirrhosis' was reported.[7] These initial observations have subsequently been confirmed in other studies.

The definitive confirmation of the role of nonosmotic AVP release in edematous disorders has been obtained by the use of nonpeptide, orally active vasopressin V_2R antagonists. In patients with both cardiac failure[28] and cirrhosis,[29] V_2R antagonists have demonstrated an impressive effect to increase solute-free water excretion. In patients with cardiac failure, urinary AQP2 water channels have been shown to be decreased during the administration of V_2 antagonist.[30]

CONTRIBUTION FROM THE RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM

Figure 4 illustrates the pathophysiologic events occurring during heart failure that lead not only to sodium and water retention but also are associated with deleterious effects of angiotensin and aldosterone on cardiac remodeling.[15] Taken together, the enhanced understanding of the pathophysiology of heart failure has been accompanied by several prospective, randomized clinical trials that have reported increased survival in patients with cardiac conditions treated with β-blocker therapy, angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), and mineralocorticoid antagonists (spironolactone and eplerenone). Whereas V_2R antagonists have been found to increase solute-free water excretion in patients with heart failure, their effect on mortality has not been documented. There are also combination $V_{1a}R/V_2R$ antagonists that have the potential for benefit in patients with cardiac failure. The flow chart in **Figure 5** depicts the different pathways of $V_{1a}R$ and V_2R activation by AVP, which may contribute to increased ventricular wall stress, dilation, and hypertrophy.[23] (See also the article by Goldsmith in this supplement.[31])

PATHOPHYSIOLOGIC ROLE OF PRIMARY ARTERIAL VASODILATION

The critical pathophysiologic question in cirrhosis relates to the potential mediators of the splanchnic arterial vasodilation that initiate the arterial underfilling with resultant water and sodium retention.[32] The portal hypertension of cirrhosis is associated with splanchnic dilatation and increased splanchnic blood flow. The increased splanchnic blood flow is associated with an upregulation of endothelial nitric oxide synthase (eNOS) and increased nitric oxide levels.[33] Nitric oxide is a very potent vasodilator and has been proposed to be a major mediator of splanchnic dilatation in cirrhosis. In experimental cirrhosis inhibition of eNOS, of a degree to normalize systemic vascular resistance, has been demonstrated to dramatically reverse the elevation in plasma AVP, renin activity, and aldosterone concentrations.[34] Over a 7-day period the reversal of these hormonal perturbations was accompanied by loss of ascites in 75% of the cirrhotic animals, which occurred secondary to a profound improvement in water and sodium excretion. Taken together, there is now substantial support for the primary arterial vasodilation hypothesis to explain sodium retention, water retention, and ascites in patients with cirrhosis.[32] With the predominance of $V_{1a}Rs$ in the splanchnic circulation, the combination of a V_1 agonist (terlipressin) and albumin over a 7- to 10-day period has been reported to reverse the hepatorenal syndrome in approximately 75% of patients.[35] Moreover, attenuation of the arterial underfilling with albumin and antibiotic administration during spontaneous bacterial peritonitis in patients with cirrhosis has been demonstrated to improve survival as compared with antibiotics alone.[36] Due to the potential for further splanchnic dilation, there is some concern regarding use of a $V_{1a}R/V_2R$ antagonist in patients with cirrhosis.

Pregnancy is an avid sodium- and water-retaining state, independent of that related to conceptus. Studies early in normal pregnancy reveal a decrease in plasma osmolality and arterial vasodilation with a secondary increase in cardiac output. As with other arterial underfilling states, the RAAS is stimulated in early pregnancy, and renal sodium and water retention leads to an expanded total blood volume.[37] The role of nonosmotic vasopressin in the upregulation of AQP2 water channels was demonstrated during the first trimester of pregnancy in the rat, and V_2 antagonists dramatically increased solute-free water excretion.[38] Sodium and water retention in pregnancy occurs in spite of a substantial increase in GFR. Because estrogen upregulates eNOS, inhibition of nitric oxide synthase was examined in pregnant rats, and the systemic and renal vasodilation was reversed.[39] Thus,

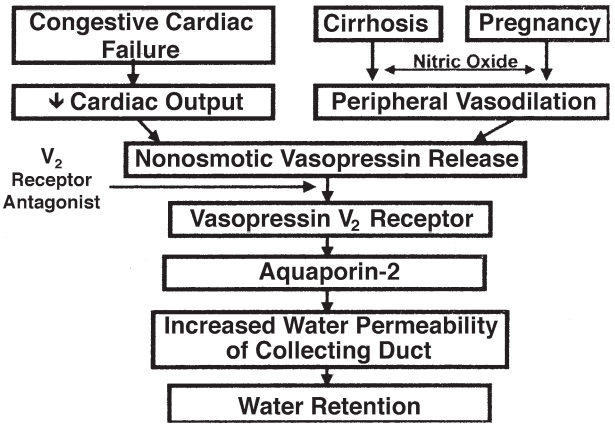

Figure 6 Role of nonosmotic vasopressin release in hyponatremia of edematous disorders. Potential therapeutic role of V_2 receptor antagonists. ↓ = decreased. (Adapted from *Am J Physiol Renal Physiol.*[39])

there are similarities between cirrhosis and pregnancy in which the arterial underfilling occurs owing to systemic vasodilation involving, at least in part, increased nitric oxide. The common pathway and potential effect of V_2 antagonists on the water retention in pregnancy[40] and cirrhosis[32] is illustrated in **Figure 6**.[39,41]

SUMMARY

Absolute arterial underfilling due to a decrease in cardiac output (e.g., low-output cardiac failure), and relative arterial underfilling due to systemic arterial vasodilation (e.g., cirrhosis and/or pregnancy), activate the neurohumoral axis including AVP, RAAS, and the sympathetic nervous system. Although these events initially maintain arterial perfusion in edematous patients, in patients with advanced edematous disorders the resultant sodium and water retention leads to deleterious complications such as pulmonary edema and ascites.

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