



Pathophysiology of Volume Overload in Acute Heart Failure Syndromes

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ABSTRACT

The inability to effectively regulate volume status is a major consequence of acute heart failure syndromes (AHFS). A variety of pathophysiologic processes contribute to this impairment, most notably neurohormonal activation of the renin-angiotensin-aldosterone system, arginine vasopressin, and the sympathetic nervous system. As a result, addressing volume overload is one of the most challenging aspects of AHFS management. Neurohormonal activation leads to substantial changes in hemodynamics and myocardial remodeling, which further contribute to the severity of heart failure (HF) disease and thereby cyclically increase the risk of further neurohormonal activation. Pulmonary capillary wedge pressure is a dependable reflection of volume status and has been used as a surrogate marker in recent studies to assess disease progression in response to innovative HF treatment strategies. Future approaches to HF treatment should focus on the more accurate assessment and management of volume status in an effort to improve patient care. © 2006 Elsevier Inc. All rights reserved.

KEYWORDS: Atrial natriuretic peptide; B-type natriuretic peptide; Neurohormones; Pulmonary capillary wedge pressure; Renin-angiotensin-aldosterone system

Heart failure (HF) has an overwhelming impact on global health and healthcare costs. In the United States, approximately \$4.0 billion in Medicare reimbursements related to HF were awarded in 2001.¹ This figure is unlikely to decrease in the near future because the disease has a disproportionate effect on the elderly, a growing segment of the US population. The most complex and potentially costly aspect of symptomatic HF care is acute heart failure syndromes (AHFS), which involve the management of altered volume status due to dysfunctional cardiorenal, hemodynamic, and neurohormonal processes.²

PATHOPHYSIOLOGY OF RENAL SODIUM AND WATER RETENTION IN ACUTE HEART FAILURE SYNDROMES

The renal sodium and water retention that leads to volume overload in patients with AHFS occurs in the pres-

ence of an increase in total blood volume. In normal subjects, an increase in total blood volume is associated with an increase in renal sodium and water excretion. The reverse occurs in patients with AHFS because the integrity of the arterial circulation, not total blood volume, is the primary determinant of renal sodium and water excretion.^{3–5} Only an estimated 15% of total blood volume resides in the arterial circulation; thus, total blood volume can be increased primarily by expansion of the blood volume in the venous circulation, because underfilling of the arterial circulation occurs as a result of a decrease in cardiac output (**Figure 1**).⁵

The renal sodium and water retention that occurs in AHFS involves several mediators.⁶ In contrast to normal subjects, patients with AHFS fail to escape from the renal sodium-retaining effect of aldosterone and also experience renal resistance to natriuretic peptides. Increased sodium reabsorption in the proximal tubule, and thus decreased sodium delivery to the collecting duct—sites of action of aldosterone and the natriuretic peptides—occurs in patients with AHFS secondary to renal consequences of arterial underfilling and neurohumoral activation. The decreased

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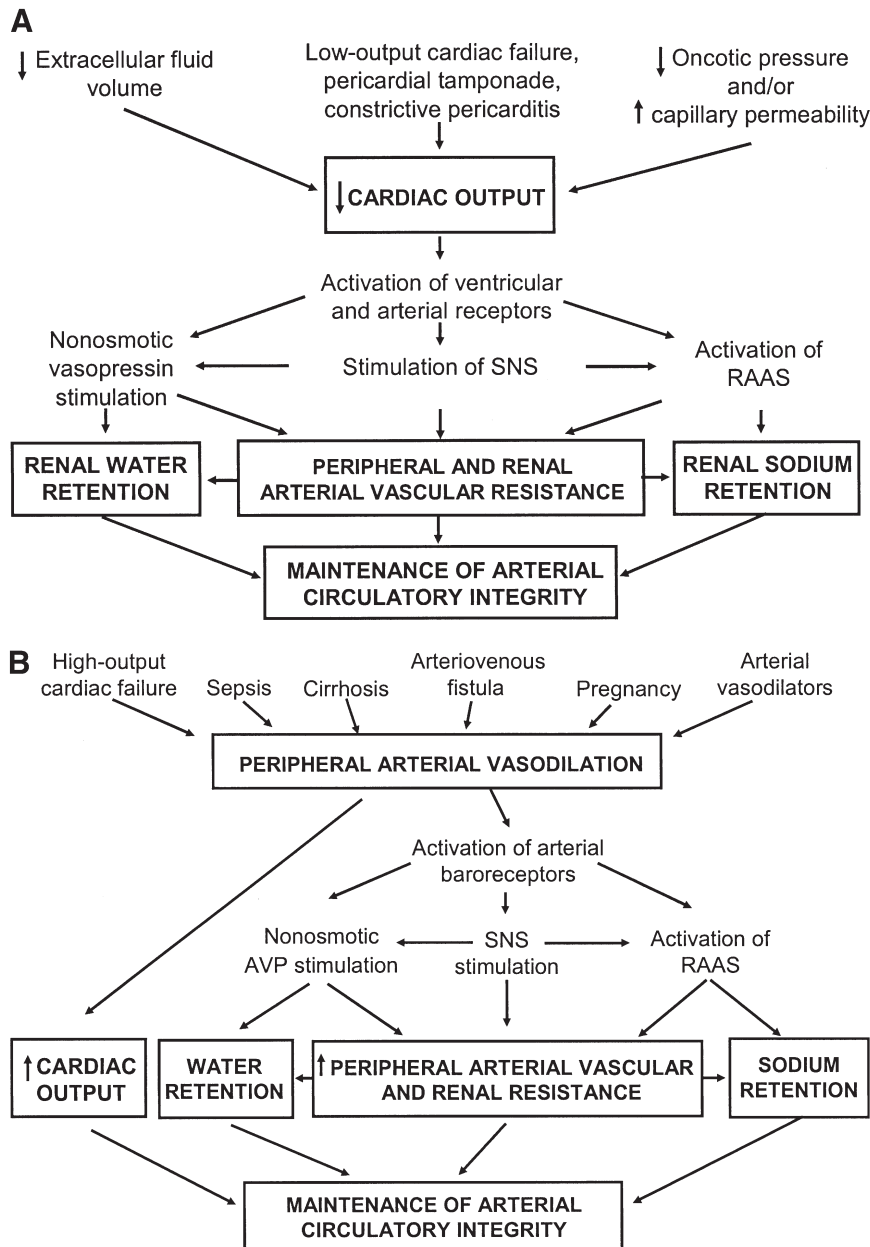


Figure 1 (A) Neurohumoral activation in response to arterial underfilling secondary to a decrease in cardiac output. (B) Neurohumoral activation in response to relative arterial underfilling secondary to peripheral arterial vasodilation. Cardiac output increases secondary to the diminished cardiac afterload. RAAS = renin-angiotensin-aldosterone system; SNS = sympathetic nervous system. (Adapted with permission from *Ann Intern Med.*⁵)

distal sodium delivery in patients with AHFS no doubt contributes to the impaired escape from the sodium-retaining effect of aldosterone and the resistance to the natriuretic effect of atrial and ventricular peptides.

Decreased distention of arterial baroreceptors during arterial underfilling is associated with increased adrenergic discharge from the central nervous system, with resultant activation of the renin-angiotensin-aldosterone system (RAAS) (Figure 2).⁶ Both adrenergic stimulation and increased angiotensin II activate receptors on the proximal tubular epithelium that enhance sodium reabsorption and diminish sodium delivery to the collecting duct. The in-

crease in angiotensin II and aldosterone also increases cardiac remodeling and fibrosis.

Another outcome of the neurohumoral activation that occurs in cardiac failure is the baroreceptor-mediated non-osmotic release of arginine vasopressin (AVP).^{7,8} This non-osmotic AVP stimulation overrides the osmotic regulation of AVP and is the major factor leading to the hyponatremia associated with AHFS.⁹ In addition to activation of the V_2 vasopressin receptors on the collecting duct, which leads to aquaporin 2 water channel-mediated antidiuresis, the vascular V_{1a} receptors on vascular smooth muscle are activated by the nonosmotic release of AVP.¹⁰ Figure 3 illustrates

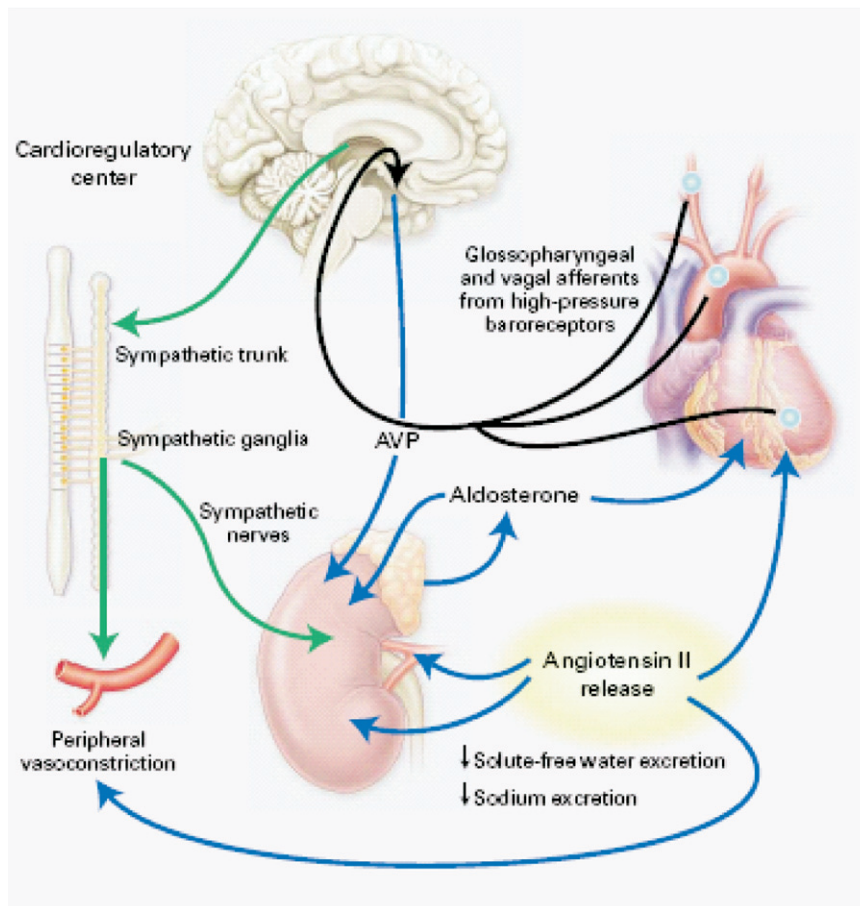


Figure 2 Unloading of high-pressure baroreceptors (blue circles) in the left ventricle, carotid sinus, and aortic arch generates afferent signals (black arrows) that stimulate cardioregulatory centers in the brain, resulting in the activation of efferent pathways in the sympathetic nervous system (green arrows). 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 the reabsorption of sodium and the secretion of potassium and hydrogen ions in the collecting duct. The blue arrows designate circulating hormones. (Reprinted with permission from *N Engl J Med*.⁶)

potential pathways whereby activation of V_2 and V_{1a} vasopressin receptors can increase cardiac preload and afterload, constrict the coronary vessels, stimulate cardiac myocyte proliferation, and thereby enhance ventricular wall stress, dilatation, and hypertrophy.¹¹

PATHOPHYSIOLOGY OF HEART FAILURE

A variety of mechanisms, including myocardial infarction, primary myocardial diseases, or pressure overload, can lead to adverse left ventricular (LV) remodeling with impaired myocardial contraction and/or relaxation and can result in the development of HF. Obstructive coronary artery disease is a major source of LV dysfunction and consequent HF, a fact that is highlighted by a recent meta-analysis of HF treatment trials that reported that coronary artery disease was the underlying cause of HF in >70% of a population of

>20,000 patients.¹² In many cases, a cardiac event such as acute myocardial infarction damages cardiac myocytes, leading to LV dysfunction, cardiac remodeling and fibrosis, and the prevention of normal muscle contraction.² Inherited and acquired cardiomyopathies can also lead to impaired cardiac function and the clinical manifestations of HF.² Major epidemiologic studies have also reported that $\leq 50\%$ of patients with HF have preserved LV systolic function. These patients have LV diastolic dysfunction as a result of hypertension, diabetes mellitus, or other conditions.¹³

Increased cardiac filling pressures, reduced cardiac output, excessive peripheral vasoconstriction, and impaired natriuresis and diuresis are the long-established hallmarks of HF disease that result in volume overload.^{2,14} These changes in volume management and cardiac output lead to a cyclical detrimental process by which impaired cardiac

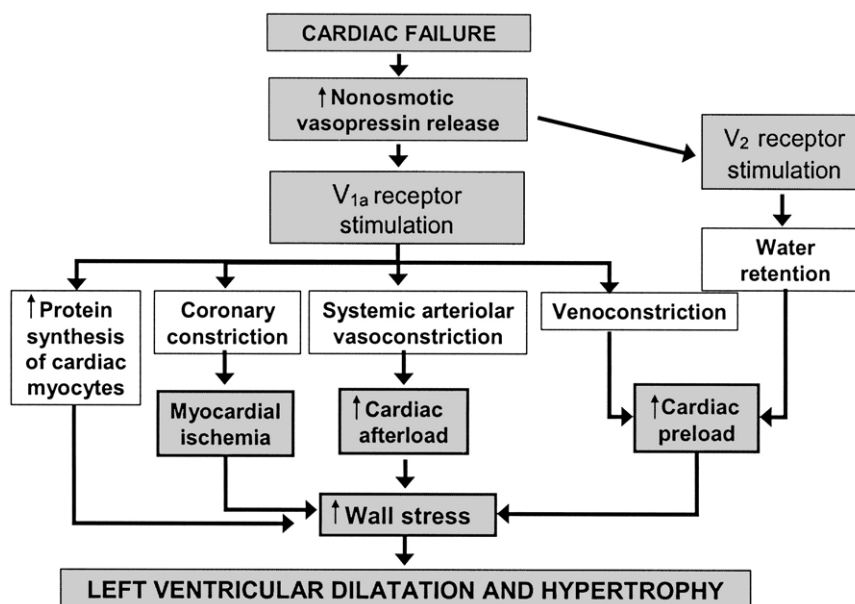


Figure 3 Potential effects of vasopressin on V₁ and V₂ receptors, which can worsen cardiac function by increasing cardiac preload and afterload, as well as causing myocardial ischemia and remodeling. (Adapted with permission from *J Am Coll Cardiol*.¹¹)

output and the inability to maintain normal volume contribute to neurohormonal activation, which in turn exacerbates volume overload and myocardial dysfunction.

Neurohormonal Activation and Volume Overload in AHFS

Cardiorenal, hemodynamic, and neurohormonal mechanisms of HF are currently accepted as accounting for the aggressive and ultimately debilitating nature of the disease. Although cardiorenal and hemodynamic derangements of volume and pressure have been well established as contributing to AHFS,² it has also been recognized that underlying neurohormonal processes are ultimately responsible for the inevitable disease progression that occurs in HF despite the use of diuretic agents that restore volume status and vasodilatory agents that improve hemodynamics.^{2,15}

Neurohormonal activation of the RAAS and sympathetic nervous system are physiologic responses to the reduced cardiac output that occurs in AHFS.^{15,16} Both aldosterone and angiotensin-converting enzyme (ACE) are released from the left ventricle in patients with LV dysfunction¹⁷ in response to RAAS activation. Neurohormonal activation directly increases peripheral vascular resistance¹⁶ and therefore increases afterload. Sodium, potassium, and fluid retention are also increased with neurohormonal activation,² all of which leads to increased preload and a further exacerbation of hemodynamic and volume changes in AHFS. Finally, neurohormonal activation often results in tachycardia due to a variety of causes, leading to tachycardia-induced myopathy.¹⁸ Tachycardia in this setting often creates a harmful cycle in which the condition exacerbates volume overload by causing abnormalities in myocardial calcium cycling and decreasing diastolic filling time,¹⁹ leading to

additional neurohormonal activation and myocardial dysfunction.¹⁸

Neurohormonal activation directly contributes to myocardial dysfunction by substantially affecting cardiac remodeling and disease progression. Angiotensin II has the ability to have a direct impact on myocardial remodeling by stimulating myocyte hypertrophy and fibrosis,^{16,20} leading to further impairment of contractile function and suggesting a vicious circle of neurohormonal activation, remodeling, and disease progression. The fact that HF disease status and survival have been improved with the long-term use of agents that block neurohormonal activation, including ACE inhibitors and β -adrenergic blockers, further supports the neurohormonal model of HF progression.²¹

A counterregulatory response to these neurohormonal effects on volume overload and myocardial remodeling occurs with the activation of natriuretic peptides.^{22–24} Natriuretic peptides, including atrial natriuretic peptide (ANP) and brain-type natriuretic peptide (BNP), act by relaxing vascular smooth muscle and consequently reducing blood pressure and ventricular preload.^{25,26} These peptides have demonstrated the ability to promote vasodilation,²⁵ as well as natriuresis and diuresis,²² thereby ameliorating the volume overload caused by neurohormonal activation. One study reported that infusions of BNP in both healthy subjects and patients with HF reduced norepinephrine spillover, an indication of sympathetic nervous system inhibition, while also modulating renal sympathetic activity,²⁴ although this effect has not been well established in prospective randomized trials or in clinical practice. Natriuretic peptides also counteract the remodeling effects of neurohormonal activation by inhibiting hypertrophy and fibrosis.^{27,28}

At physiologic levels, however, these beneficial effects of natriuretic peptides are quickly overwhelmed by the continued neurohormonal activation that occurs in progressive HF. Both preclinical and human studies have established an association between the development of resistance to natriuretic peptides and the progression of HF. The exact mechanisms that mediate the attenuated response to natriuretic peptides in overt congestive HF remain poorly defined. The clearance of natriuretic peptides occurs by several routes, all of which exist within the kidneys: degradation by neutral endopeptidase, binding to the clearance receptor NPR-C, and clearance by glomerular filtration.²⁹ Decreased distal fluid delivery to the collecting duct site of natriuretic peptide action appears to be involved in natriuretic peptide resistance. Other possibilities include NPR-A receptor downregulation, increased clearance by the NPR-C receptor, increased degradation by neutral endopeptidase, upregulation of phosphodiesterases that hydrolyze cyclic guanosine monophosphate or upregulation of the multidrug resistance protein-5, and export pump for intracellular cyclic nucleotides.²⁹ An altered molecular form of ANP has been described, and it is possible that an altered molecular form of BNP with reduced biological activity in HF also exists.^{29,30} Importantly, the relative resistance can be overcome by exogenous administration of BNP, which can raise the plasma concentration severalfold, resulting in biological action.

Pulmonary Capillary Wedge Pressure and Volume Overload in AHFS

Previous studies have demonstrated that pulmonary capillary wedge pressure (PCWP) corresponds directly to the symptoms, volume status, and cardiovascular risk in patients with HF.^{31–34} One study group concluded that in AHFS, a decrease in cardiac systolic or diastolic performance leads to an acute increase in systemic vascular resistance, an acute decrease in cardiac index, and an increase in LV filling pressures.³¹ These AHFS effects appear clinically, leading to a release of intravascular fluid to the lungs and the overt clinical symptoms of HF congestion.³¹

SUMMARY

Volume overload is one of the most complex pathologic processes confronting those responsible for the daily management of patients with AHFS, a disease that is often confounding, difficult to diagnose, and challenging to manage, and that affects a large population with multiple presentations and comorbidities. Various mechanisms contribute to volume derangements in AHFS, not the least of which is neurohormonal activation and the resultant changes in hemodynamics and myocardial remodeling. PCWP can be a reliable tool to monitor volume and has been used as a surrogate marker in recent studies to assess disease progression in patients receiving innovative treatments. Future AHFS management strategies should focus on the more

accurate assessment and correction of volume in an effort to more effectively care for this diverse patient population.

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