Pathophysiology and Clinical Spectrum of Acute Congestive Heart Failure

Mona Shah, MD,* Vaqar Ali, MD,† Sumant Lamba, MD,†
William T. Abraham, MD, FACP, FACC†

*Department of Internal Medicine and †Division of Cardiovascular Medicine, University of Kentucky, Lexington, KY

This article reviews the current understanding of the pathophysiology and clinical spectrum of heart failure. A cascade of hemodynamic and neurohormonal derangements result from a decrease in ventricular performance or cardiac output. Because neurohormonal activation has become a target for intervention in heart failure, the role of selected systems (sympathetic nervous, renin–angiotensin–aldosterone) and of natriuretic peptides is detailed. The spectrum (from compensated to acute decompensated) within which congestive heart failure patients present is reviewed, with special attention paid to the intermediate, transitional group of patients, who pose unique diagnostic and therapeutic challenges. Given these variable presentations, there is an obligation to tailor therapy accordingly. [Rev Cardiovasc Med. *2001;2(suppl 2):S2–S6*]

Key words: Heart failure • Hemodynamics • Neurohormonal factors • Norepinephrine • Renin–angiotensin–aldosterone system • Natriuretic peptides

In terms of incidence, prevalence, morbidity, and mortality, the epidemiological magnitude of congestive heart failure is staggering. The consequent economic and psychosocial implications extract an immeasurable toll on our society. The estimated annual cost of heart failure in the United States is about $60 billion.[1] There are approximately one million hospital admissions each year in America attributable to a primary diagnosis of acutely decompensated heart failure.[1] Ambulatory patients with persistent Class IV symptoms have a 1-year mortality rate that approaches 50%, whereas those who can maintain relief from congestion regain a prognosis more like Class III patients, with a 1-year mortality of approximately 20% to 25%.[2] In patients referred for cardiac

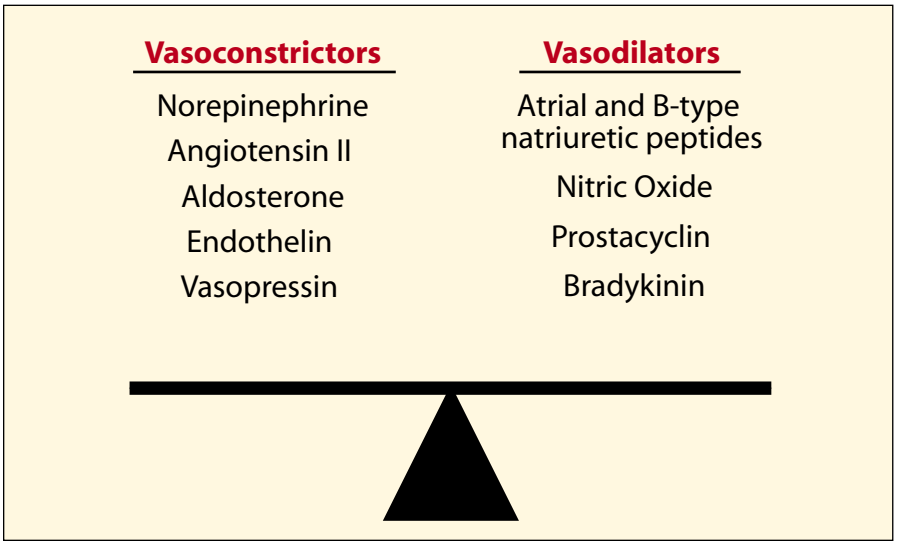


Figure 1. *Neurohoromones associated with homeostatic balance.*

transplantation, 5-year survival with medical therapy is 88% in those whose ventricular filling pressures can be reduced with vasodilators and diuretics.[3] Over the past two decades, the outlook for patients with heart failure has improved through a better understanding of its pathophysiology and clinical spectrum. This review will focus on a current understanding of acute congestive heart failure.

A cascade of hemodynamic and neurohormonal derangements result from a decrease in ventricular performance or cardiac output. The primary response of the body is seen in activation of a variety of neuroendocrine systems, most notably the adrenergic and renin–aldosterone systems. Activation of these systems results in salt and water retention and peripheral vasoconstriction, two of the hallmarks of clinical heart failure. Other vasoactive systems, such as endothelin, vasopressin, and the natriuretic peptide system, are implicated in a variety of ways, resulting in an alteration in the homeostatic balance of vasoconstrictors and vasodilators. Specifically, as heart failure advances and/or becomes decompensated, there is a progressive increase in vasoconstrictor substances and a relative decline in the counter-regulatory effects of endogenous vasodilators, including nitric oxide, prostaglandins, bradykinin, and the natriuretic peptides (Figure 1). This imbalance of neurohormonal factors favors vasoconstriction and thus increased cardiac preload and afterload, cellular proliferation resulting in adverse myocardial and vascular remodeling, and anti-natriuresis contributing to the excess in total body fluid volume commonly seen as heart failure becomes decompensated.

The acute presentation of patients with decompensated heart failure includes one of several hemodynamic profiles.[2] Most patients present with less complex hemodynamic profiles, manifest as an adequate cardiac output with or without clinical congestion. These patients can often be successfully treated with diuretics to achieve an euvolemic status and oral neurohumoral antagonists to modify disease progression. The intermediate or more complex patients (those with reduced or inadequate peripheral perfusion) are best served by hospitalization and the use of vasoactive agents, in addition to diuretics. The choice of vasoactive agents continues to grow and should be dictated by a particular clinical and hemodynamic profile. The neurohormonal and hemodynamic picture of heart failure provides a framework for such treatment selection.

Pathophysiology

Following myocardial injury, the inciting event in congestive heart failure involves adaptation of the cardiac myocyte to increased wall stress, to maintain an adequate cardiac output. The primary myocardial response includes myocyte hypertrophy and remodeling, usually of the eccentric type. Although the hypertrophic state is induced by mechanical distention, there is also humoral control of myocyte hypertrophy, including endothelin (ET-1),[4] angiotensin II (Ang II),[5] and norepinepherine.[6] Myocardial fibrosis and cardiomyocyte apoptosis, along with hypertrophy, contribute to maladaptive changes that eventually lead to adverse ventricular remodeling (Figure 2). Eventually, the ability of the heart to compensate is overwhelmed, and symptomatic heart failure marked by episodes of decompensation ensues. Because neurohormonal activation has become a target for intervention in heart failure, the role of selected systems is detailed below.

Sympathetic nervous system. The consequences of decreased cardiac output and increased filling pressures lead to changes that are initially compensatory and help to restore cardiovascular homeostasis. However, shortly afterward, they are maladaptive and result in progressive neurohumoral activation and

left ventricular remodeling. Systolic and diastolic heart failure result in a decrease in stroke volume. This leads to activation of peripheral and central baro- and chemo-reflexes that are capable of eliciting marked increases in sympathetic nerve traffic. The ensuing elevation in plasma norepinephrine directly correlates with the degree of cardiac dysfunction and has significant prognostic implications.[7] Norepinephrine, while being directly toxic to cardiomyocytes,[8] is also responsible for a variety of signal-transduction abnormalities, such as downregulation of β1 adrenergic receptors, uncoupling of β2 adrenergic receptors, and increased activity of inhibitory G-protein, Gi.[9] Changes in β1 receptors result in over-expression and promote myocardial hypertrophy.[10]

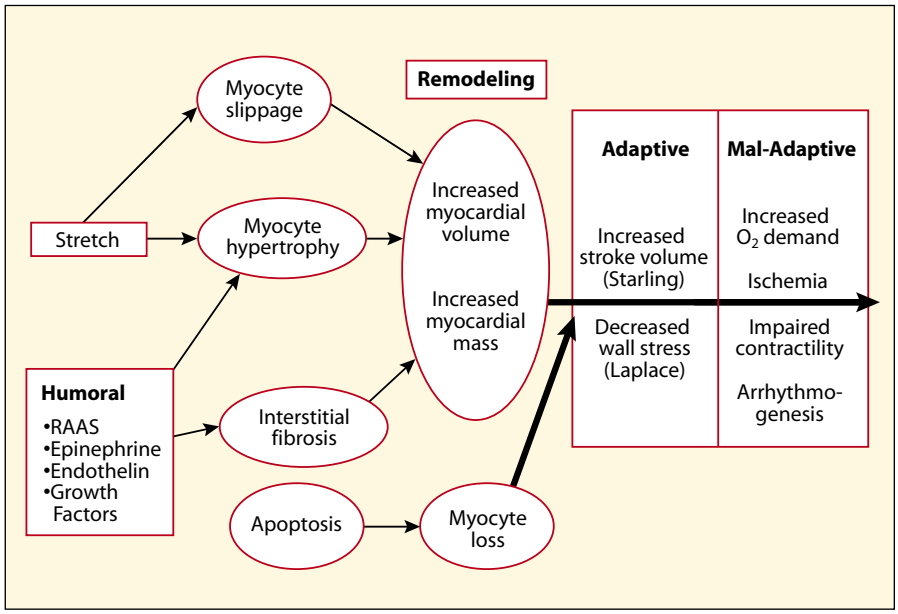
From a hemodynamic standpoint, increased vasoconstriction mediated by norepinephrine, Ang II, endothelin, and vasopressin increases cardiac inotropy and chronotropy, alters renal salt and water handling, and enhances venous tone to facilitate end organ perfusion. The marked increases in cardiac and renal adrenergic activity reaffirms the fact that both the sympathetic and the renin–angiotensin–aldosterone systems are co- activated and co-regulated, in the setting of heart failure.[11]

Renin–angiotensin–aldosterone system. In congestive heart failure, the increased release of renin is mediated by decreased stretch of the glomerular afferent arteriole, reduced delivery of chloride to the macula densa, and increased β1 adrenergic activity. Increased renin induces a cascade of events, which eventually results in an increase of Ang II levels, which in turn allows for stimulation of release of aldosterone. Ang II along with ET-1 are crucial in maintaining effective intravascular homeostasis mediated by vasoconstriction, and aldosterone-induced salt and water retention. In addition to activation of the systemic renin–angiotensin system, there is evidence of local cardiac Ang II production with adverse effects on cardiac function.[12] Ang II has similar actions to norepinephrine in congestive heart failure, increasing sodium reabsorption and inducing systemic and renal vasoconstriction.[12] Ang II mediates myocardial cellular hypertrophy and may promote progressive loss of myocardial function.[13]

Natriuretic peptides. Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are endogenously generated peptides activated in response to atrial and ventricular volume/pressure expansion. ANP and BNP are released from the atria and ventricles to promote vasodilation and natriuresis. Their hemodynamic effects are mediated by decreases in ventricular filling pressures, owing to reductions in cardiac preload and afterload. BNP, in particular, produces selective afferent arteriolar vasodilatation and inhibits sodium reabsorption in the proximal convoluted tubule. It inhibits renin and aldosterone release, and possibly adrenergic activation as well. Both ANP and BNP have been shown to be elevated in chronic heart failure, and BNP in particular has potentially important diagnostic, therapeutic, and prognostic implications.[14,15]

Other vasoactive systems that play a role in the pathogenesis of congestive heart failure include the endothelin receptor system, the adenosine receptor system, vasopressin, and tumor necrosis factor α (TNFα). Endothelin, another substance produced by the vascular endothelium, may contribute to the regulation of myocardial function, vascular tone, and peripheral resistance in congestive heart failure. Endothelin can bind to two recep-

Figure 2. *Myocardial fibrosis and cardiomyocyte apoptosis, along with hypertrophy, contribute to maladaptive changes that eventually lead to adverse ventricular remodeling. Adapted from Baig MK, Mahon N, McKeena WJ, et al. The pathophysiology of advanced heart failure.* Am Heart J. *1998;135:S216–S230, with permission from the publisher, Mosby.*



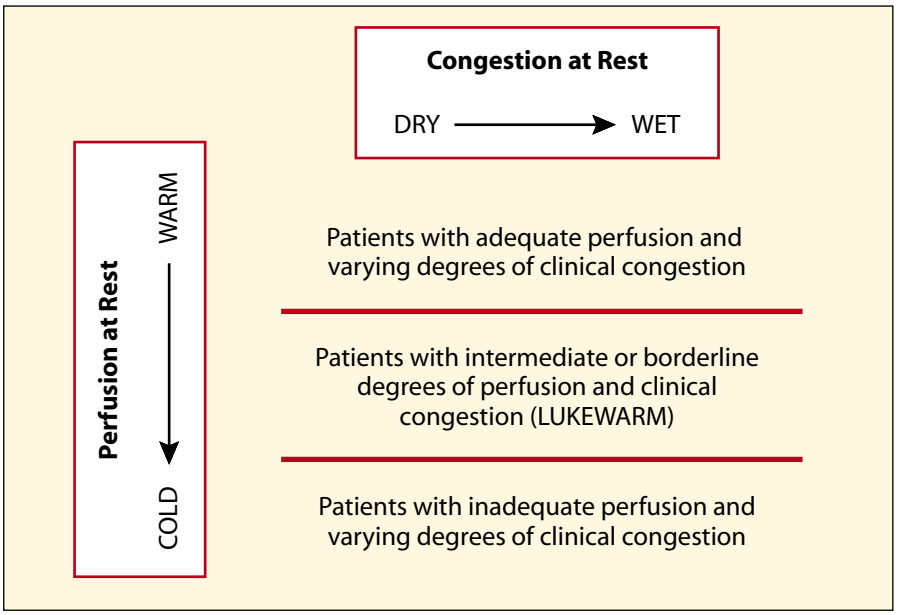


Figure 3. *Spectrum of patients presenting with congestive heart failure. Adapted from Stevenson LW.*[2] Eur J Heart Failure. *1999;1:251–257. With permission from the publisher, Elsevier Science.*

tors: ET-A, which exists in vascular smooth muscle and mediates vasoconstriction, and ET-B, which is found predominantly in endothelial cells and mediates vasodilation through the release of nitric oxide and prostacyclin.[16] Elevated levels of ET-1 have been shown to closely correlate with the severity of heart failure. Endothelin-1 is a potent vasoconstrictor and has exaggerated vasoconstrictive effects in the renal vasculature, reducing renal plasma blood flow, glomerular filtration rate, and sodium excretion.[17] TNFα has been implicated in response to various infectious or inflammatory conditions. Elevations in levels of TNFα have been consistently observed in congestive heart failure and seem to correlate with the degree of myocardial dysfunction.[18] Furthermore, experimental studies suggest that local production of this cytokine may have toxic effects on the myocardium. Genetic factors, including angiotensin-converting enyme gene and β-adrenergic receptor polymorphisms may influence the natural history of disease progression and response to treatment.

Clinical Spectrum

There is a spectrum within which patients with congestive heart failure may present. Varying degrees of activation of neurohormonal systems and a spectrum of hemodynamic derangements leads to a range of symptoms and severity of heart failure. Myocardial ischemia, poorly controlled hypertension, atrial and ventricular arrhythmias, worsening of existing valvular abnormalities, metabolic and endocrine derangements, dietary indiscretion, noncompliance with medications, worsening renal function, and most importantly progression of the natural history of the disease process contribute to either exacerbation of existing congestive heart failure or new-onset heart failure.

The patient with compensated heart failure will be warm and dry, and without symptoms of dyspnea and fatigue at rest. They often present with symptoms of exercise intolerance, usually with moderate or more than moderate degrees of activity. They are generally best served by ambulatory up-titration of neurohumoral antagonists and diuretics to achieve a euvolemic status and optimized chronic drug regimen (Figure 3).

At the other end of the spectrum are complex patients with overt, acute, decompensated congestive heart failure, who are primarily cold and wet, implying very low cardiac output and symptoms and signs of clinical congestion at rest or with minimal exertion. They are often hypotensive and have other signs of low cardiac output, such as pre-renal azotemia, progressive hyponatremia, and an inability to tolerate treatment with vasodilators. This complex group of patients are best served by invasive hemodynamic monitoring, inotropic agents, hemodynamic tailoring of therapy, and finally consideration for mechanical assist devices and cardiac transplantation.

However, it is now being increasingly recognized that a vast majority of patients fall into an intermediate group. They are frequently clinically congested and have symptoms and signs of low cardiac output, but not overtly so (what might be described as “lukewarm” and wet). This transitional group of patients poses unique diagnostic and therapeutic challenges. Ideally, they require treatment with vasoactive agents that have the capacity to increase cardiac performance and decrease filling pressures without increasing myocardial oxygen demand, in combination with diuretics. The use of invasive hemodynamic monitoring in these patients is controversial, and used at the discretion of the managing physician. The decision to invasively monitor such patients

may depend to some extent on the degree of clinical decompensation. Many of these patients may be adequately treated in a sub-acute care environment, such as a step-down or telemetry unit, particularly given the advent of newer intravenous therapies that have been proved safe and effect in this setting.

Summary

The pathophysiology of acute congestive heart failure is becoming increasingly complex and not only involves hemodynamic derangements, but also neurohumoral activation and compensatory immunologic responses. Given the variable presentations of patients with acute congestive heart failure, there is an obligation to understand this pathophysiology and to tailor the therapy to the common presenting clinical and/or hemodynamic profiles. These profiles create novel opportunities for new therapeutic interventions targeted at the predominant forms of decompensation, namely the volume-overloaded patient with either adequate or reduced peripheral perfusion who is not in frank cardiogenic shock. These patients are ideal candidates for diuretics and, in most cases, intravenous vasoactive medications that reduce cardiac preload and afterload, while improving cardiac performance at no increase in metabolic cost. ■

References

1. O'Connell JB. The economic burden of heart failure. *Clin Cardiol*. 2000;23:III6–III10.
2. Stevenson LW. Tailored therapy to hemodynamic goals for advanced heart failure. *Eur J Heart Failure*. 1999;1:251–257.
3. Stevenson LW, Tillisch JH, Hamilton M, et al. Importance of hemodynamic response to therapy in predicting survival with ejection fraction less than or equal to 20% secondary to ischemic or nonischemic dilated cardiomyopathy. *Am J Cardiol*. 1990;66:1348–1354.
4. Wei CM, Lerman A, Rodeheffer RJ, et al. Endothelin in human congestive heart failure. *Circulation*. 1994;89:1580–1586.
5. Baker KM, Chernin MI, Wixson SK, Aceto JF. Renin–angiotensin system involvement in pressure-overload cardiac hypertrophy in rats. *Am J Physiol*. 1990;259:H324–H332.
6. Cohn JN, Levine B, Olivari MT, et al. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med*. 1984;311:819–823.
7. Francis GS, Benedict C, Johnstone EE, et al. Comparison of neuroendocrine activation in patients with left ventricular dysfunction with and without congestive heart failure. A substudy of the studies of left ventricular dysfunction (SOLVD). *Circulation*. 1990;82:1724–1729.
8. Mann DL, Kent RL, Parsons B, Cooper G IV. Adrenergic effects on the biology of the adult mammalian cardiocyte. *Circulation*. 1992;85:790–804.
9. Bristow MR, Ginsberg R, Fowler M, et al. β1- and β2-adrenergic receptor subtype populations in normal and failing human ventricular myocardium. *Circ Res*. 1986;59:297–309.
10. Adams JW, Sakata Y, Davis MG, et al. Enhanced Gαq signaling: a common pathway mediates cardiac hypertrophy and apoptotic heart failure. *Proc Natl Acad Sci U S A*. 1998;95:10140–10145.
11. Lamba S, Abraham WT. Alterations in adrenergic receptor signaling in heart failure. *Heart Failure Rev*. 2000;5:7–16.
12. Lee MA, Bohm M, Paul M, Ganten D. Tissue renin–angiotensin systems. Their role in cardiovascular disease. *Circulation*. 1993;87:IV7–IV13.
13. Dzau VJ. Tissue renin–angiotensin system in myocardial hypertrophy and failure. *Arch Intern Med*. 1993; 153:937–942.
14. Colucci WS, Elkayam U, Horton DP, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. *N Engl J Med*. 2000;343:246–253.
15. Young JB, Abraham WT, Stevenson LW, Horton DP. Results of the VMAC Trial: vasodilation in the management of acute congestive heart failure. *Circulation*. 2000;102:a2794.
16. Fujse K, Stacy L, Beck P, et al. Differential effects of endothelin receptor activation on cyclic flow variations in rat mesenteric arteries. *Circulation*. 1997;96:3641–3646.
17. Wei CM. Endothelin in human congestive heart failure. *Circulation*. 1994;89:1580–1586.
18. Feldman AM, Combes A, Wagner D, et al. The role of tumor necrosis factor in the pathophysiology of heart failure. *J Am Coll Cardiol*. 2000;35:537–544.

Main Points

- As heart failure advances and/or becomes decompensated, there is a progressive increase in vasoconstrictor substances and a relative decline in the counter-regulatory effects of endogenous vasodilators.
- Neurohormonal activation has become a target for intervention in heart failure.
- The elevation in plasma norepinephrine that ensues from systolic and diastolic heart failure directly correlates with the degree of cardiac dysfunction and has significant prognostic implications.
- Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) have been shown to be elevated in chronic heart failure, and BNP in particular has potentially important diagnostic, therapeutic, and prognostic implications.
- Regarding clinical presentation, a vast majority of patients fall between the extremes of compensated and acute decompensated heart failure. They are frequently clinically congested and have symptoms and signs of low cardiac output, but not overtly so. Ideally, they require treatment with vasoactive agents that have the capacity to increase cardiac performance and decrease filling pressures without increasing myocardial oxygen demand, in combination with diuretics.