The Treatment Targets in Acute Decompensated Heart Failure

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Acute decompensated heart failure is characterized by hemodynamic abnormalities as well as neuroendocrine activation, which contribute to heart failure symptoms, progressive cardiac dysfunction, and sudden death. The therapeutic goals in patients hospitalized with decompensated heart failure are to reverse acute hemodynamic abnormalities, relieve symptoms, and initiate treatment that will slow disease progression and improve long-term survival. Traditional hemodynamic targets in acute heart failure have been reduction in left and right ventricular filling pressures, reduction in systemic vascular resistance, and increase in cardiac output. Treatments aimed at these targets in patients with acute decompensated heart failure include diuretics, vasodilators, and inotropic agents. In patients hospitalized with acute decompensated heart failure, persistently elevated left ventricular filling pressure has been shown to be highly predictive of an increased risk of fatal decompensation and sudden death. Measures of systemic perfusion, arterial pressure, and vascular resistance have not. Thus, there is a more compelling physiologic rationale for the use of vasodilators than for inotropic agents in these patients. An ideal agent for acute decompensated heart failure would be one that rapidly reduces pulmonary wedge pressure, results in balanced arterial and venous dilation, promotes naturiesis, lacks direct positive inotropic effects, and does not result in reflex neuroendocrine activation. [Rev Cardiovasc Med. *2001;2(suppl 2):S7–S12.*]

Key words: Hemodynamics • Heart failure • Pulmonary capillary wedge pressure • Mortality

Despite recent advances in the management of patients with heart failure, morbidity and mortality remain high, with an estimated 5-year mortality rate of 50%. Patients hospitalized with acute decompensated heart failure are burdened with disabling symptoms, an average 6-day duration of hospitalization, and rehospitalization rates over the next 6 months as high as 50%. Hospitalizations for acute decompensated heart failure continue to constitute a major public health burden, increasing from 577,000 in 1985 to 970,000 in 1998 in the United States.[1] The greatest expenditure for heart failure care

is on hospitalizations, with an estimated 23 billion dollars spent on the inpatient management of acute decompensated heart failure. A therapeutic approach targeting the most important hemodynamic abnormalities contributing to acute heart failure would be expected to reverse decompensation, reduce patient morbidity, and help control rising health care costs by reducing length of stay and rate of rehospitalization.

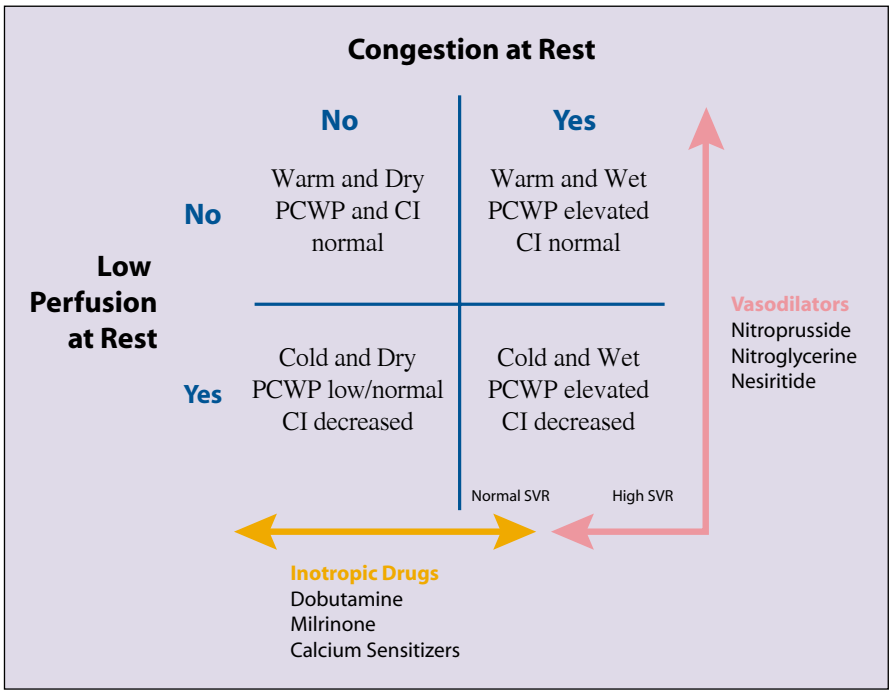
Hemodynamics in Decompensated Heart Failure

Acute decompensated heart failure is characterized hemodynamically by elevated right and left ventricular filling pressures, decreased cardiac output, and increased systemic vascular resistance.[2] The initial response to decreased systolic performance is an increase in myocardial preload and afterload, which serves to maintain systemic arterial pressures. Systolic performance, however, is not enhanced but is actually further compromised by the persistent increase in loading conditions, because atrioventricular valve regurgitation increases out of proportion to any total increase in stroke volume.[2] The sustained increases in cardiac volume and pressure lead to increased wall stress and myocardial oxygen demands, which can adversely affect left ventricular performance and can result in acute decompensation.[3] These hemodynamic alterations contribute to patients' symptoms, exercise intolerance, and clinical decompensations that result in hospitalizations.

The traditional goals of acute heart failure therapy have been to reduce extracellular fluid volume excess and improve hemodynamics by increasing cardiac output, reducing vascular resistance, and reducing ventricular filling pressures. Patients with decompensated heart failure may be classified clinically into four groups according to whether or not they have congestion (wet or dry) and whether or not they have low perfusion (warm or cold) (Figure 1).[4] In patients monitored with a pulmonary artery catheter, congestion corresponds to pulmonary capillary wedge pressure (PCWP) and low perfusion to cardiac index. Over 90% of patients hospitalized with decompensated heart failure have clinical congestion (ie, are classified as wet) and would show elevated PCWP if right heart catheterization were performed. These patients may have adequate or reduced perfusion or may be in cardiogenic shock. Patients with adequate perfusion are candidates for diuretics and oral angiotensin-converting enzyme (ACE) inhibitors. Patients in cardiogenic shock require intravenous inotropic agents and/or mechanical support.

The majority of patients hospitalized with acute decompensated heart failure have congestion and reduced perfusion, in the absence of cardiogenic shock. These patients have traditionally been treated with intravenous diuretics with or without intravenous vasodilators and/or intravenous inotropic agents. The most effective strategy for these patients has not been fully defined, in part because there has not been a consensus as to what, if any, is the most important hemodynamic treatment target for improving outcome in acute heart failure. Intravenous inotropic agents increase cardiac index and decrease systemic vascular resistance as a result of their primary mechanisms and decrease ventricular filling pressures indirectly. If the most important hemodynamic target in decompensated heart failure is cardiac index, these agents should be preferred. Intravenous

Figure 1. *Profiles and therapies of advanced heart failure. Clinical or hemodynamic assessment can be used to classify patients into four hemodynamic profiles. Patients hospitalized with acute decompensated heart failure usually have congestion at rest. PCWP, pulmonary capillary wedge pressure; CI, cardiac index; SVR, systemic vascular resistance.*



vasodilators decrease ventricular filling pressures and decrease systemic vascular resistance as a result of their primary mechanisms and increase cardiac index indirectly. If the most important hemodynamic target in decompensated heart failure is ventricular filling pressures, these agents should be preferred.

Left Ventricular Filling Pressures and Mortality

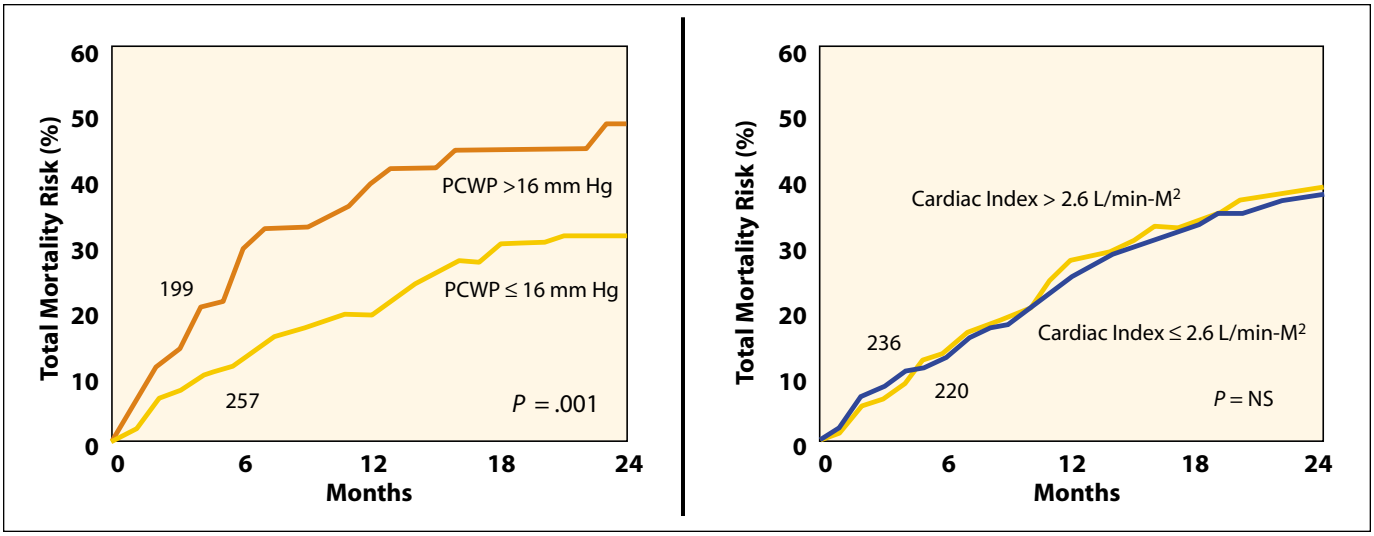
It is well recognized that in acute heart failure patients the decrease in symptoms of dyspnea at rest corresponds most closely with reduction in left ventricular filling pressure.[4] More controversial has been whether hemodynamic treatment targets are associated with improved clinical outcomes beyond symptoms in acute heart failure.

Persistent elevation in left ventricular filling pressures has been associated with an increased risk of progressive heart failure death, sudden death, and overall mortality in patients hospitalized with decompensated heart failure. In a study of 456 patients hospitalized with heart failure due to systolic dysfunction (mean left ventricular ejection fraction [LVEF] 0.20) and treated with intravenous vasodilators and diuretics, the achievement of near-normal left ventricular filling pressures (PCWP < 16 mm Hg) resulted in a 1-year survival rate of 80.8%, compared to only 64.1% in patients with persistently elevated ventricular filling pressures (P = .001) (Figure 2).[5] Hemodynamic measures at baseline, such as right atrial pressure, pulmonary arterial pressure, systemic arterial pressure, cardiac index, and systemic vascular resistance were not predictive of mortality in this patient population. Multivariate analysis showed high PCWP (P = .01), low serum sodium (P = .02), increased left ventricular end-diastolic dimension (P = .01), and low peak oxygen consumption on cardiopulmonary exercise testing (P = .01) to be the only independent predictors of total mortality at 1 year. It has also been shown that even at levels below symptom threshold, elevated PCWP predicts worse outcome in heart failure patients.[6] Other studies have also failed to find resting cardiac index to be associated with subsequent clinical outcome.[7]

There is additional evidence supporting a relationship between elevated filling pressures and clinical outcomes in heart failure. Persistence of orthopnea 4 to 6 weeks after hospitalization with Class IV heart failure symptoms predicted a 38% 2-year survival rate without urgent transplantation, compared to a 77% survival rate in patients without persistence of orthopnea.[8] B-type natriuretic peptide (BNP) is elevated in heart failure patients; elevated BNP closely correlates with elevated PCWP. Levels of BNP have also been shown to be an independent predictor of rehospitalization or death in patients hospitalized with heart failure.[9] Whether determined by direct hemodynamic measurement, inferred by symptoms of orthopnea, or assessed with a biologic assay, elevated left ventricular filling pressures are associated with adverse clinical outcomes and increased mortality.

As acute reduction in filling pressure with intravenous vasodilators

Figure 2. *Relationship between hemodynamic response and mortality. Left: Kaplan-Meier survival curves for the 257 patients with near-normal left ventricular filling pressure (PCWP ≤ 16 mm Hg) and the 199 patients with persistently elevated filling pressure (PCWP > 16 mm Hg) after receiving intravenous vasodilators. Right: Kaplan-Meier survival curves for the 220 patients with cardiac index ≤ 2.6 L/min/m² and the 236 patients with cardiac index > 2.6 L/min/m² after intravenous vasodilators.*



has been shown to be the only significant hemodynamic predictor of subsequent mortality, the use of oral direct vasodilators can be predicted to have a favorable effect on clinical outcome. Direct vasodilators have been shown to cause sustained reductions in left ventricular filling pressures, with resulting clinical improvement and reduced mortality, in the absence of favorable neurohumoral effects.[10] Although studies comparing ACE inhibitors to direct vasodilators clearly show that ACE inhibitors result in better overall survival, this was due to a reduction in sudden death; progressive heart failure death rates were equivalent with both drug types.[11] The results of these trials have been interpreted as indicating that the mechanism of benefit of ACE inhibitors in heart failure may be entirely independent of that of their hemodynamic effects. An alternative interpretation is that both the neurohormonal and the hemodynamic effects of these therapies influence the natural history of heart failure. Reduction in filling pressures with the use of intravenous vasodilators, besides bringing about rapid relief of symptoms of dyspnea, establishes a more favorable physiologic state.

Cardiac Index and Mortality

Despite the fact that decreased cardiac index is a central feature of decompensated heart failure, changes in cardiac index have not been shown to be predictive of subsequent outcome. As a result, inotropic therapy aimed at increasing cardiac index at rest would not be expected to improve patient outcome. Studies with acute or chronic intravenous or oral inotropic agents have shown these agents to be associated with increased risk of adverse events and in many trials to increase mortality.[12] The Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of Chronic Heart Failure (OPTIME-CHF) trial studied a 48-hour infusion of milrinone (0.5 μg/kg/min) in 949 patients hospitalized with decompensated heart failure.[13] The use of the inotropic agent milrinone did not reduce length of stay and was associated with a significant increase in adverse events compared to placebo (12.6% vs 2.1%, $P < .001$) and a trend for increased mortality (3.8% vs 2.3%). Trials with outpatient use of dobutamine, milrinone, vesnarinone, enoximone, and xamoterol have shown increased mortality with these drugs compared to placebo.[12] While the failure of inotropic agents to improve clinical outcome has been cited as evidence that improvement in "hemodynamics" is not associated with subsequent outcome, the hemodynamic parameter primarily targeted with these agents is increased cardiac index and stroke volume.

Pathophysiologic Mechanisms

There are a multitude of mechanisms by which persistent elevations in left ventricular filling pressures may directly contribute to sudden death, progressive ventricular dysfunction, and overall mortality in advanced heart failure (Table 1). Elevated filling pressures have been shown to contribute to sympathetic nervous system activation, because plasma norepinephrine level and sympathetic nerve activity as measured by microneurography strongly correlate with left ventricular filling pressure but not with left ventricular ejection fraction, cardiac index, or heart rate.[14] When myocytes are stretched as a consequence of elevated filling pressure, angiotensin II induces myocyte apoptosis directly and indirectly though gene modulation.[15] Persistently elevated filling pressures through increased wall stress and increased myocardial oxygen requirements can induce ischemia and ischemia-related ventricular arrhythmias. Sustained increases in cardiac volume and pressure in heart failure can contribute to progressive structural remodeling, as has been shown after myocardial infarction. It has been also shown that mechanical stretch of Purkinje fibers will cause partial depolarization, resulting in substantially slowed conduction velocity of a propagated impulse and increasing the proba-

Table 1

Potential Mechanisms by Which Elevated Left Ventricular Filling Pressure Could Contribute to Mortality in Heart Failure

- Mechanically induced neurohumoral activation and cellular apoptosis
- Mechanically induced myocardial structural remodeling
- Progressive atrioventricular valvular regurgitation
- Myocardial stretch–induced increase in intracellular cAMP and calcium
- Mechanically induced partial depolarization of myocytes and Purkinje fibers, leading to slowed conduction and abnormal automaticity
- Desensitization of low-pressure ventricular mechanoreceptors

Table 2
Sustained Improvement in Hemodynamics After Intravenous Vasodilators

	Baseline	24–72 hrs	8 months
RAP (mm Hg)	11 ± 6*	6 ± 3	4 ± 4
PCWP (mm Hg)	24 ± 9*	15 ± 5	12 ± 6
MAP (mm Hg)	87 ± 9*	74 ± 10	75 ± 15
HR bpm	93 ± 16*	86 ± 14†	74 ± 11
CI ($L/min^{-1}/m^{-2}$)	1.9 ± 0.4*	2.4 ± 0.6†	2.9 ± 0.6
SVR ($dynes/s/m^{-5}$)	1651 ± 369*	1207 ± 281	1003 ± 193

CI, cardiac index; HR, heart rate; MAP, mean arterial pressure; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; SVR systemic vascular resistance.
*$P < .05$, baseline vs 24–72 hours.
†$P < .05$, 24–72 h vs 8 months.

bility of reentrant ventricular arrhythmias.[16] Depolarized Purkinje fibers may also exhibit abnormal automaticity and triggered automaticity. Myocardial stretch has been shown to increase both myocardial cellular calcium and cyclic AMP concentration.[17] Thus, sustained increases in ventricular filling pressures due to increased intracellular calcium may contribute to an increased risk of sudden death and of progressive heart failure death.

Persistent elevated filling pressures may contribute to desensitization of baroreceptors and, by leading to prolonged atrial distention, may exacerbate the degree of secondary baroreceptor dysfunction, which may predispose patients to vasodepressor syncope and potentially fatal bradyarrhythmic events. Stretch of cardiac mechanoreceptors decreases cardiac vagal activity after myocardial infarction, and this correlates with the risk of sudden death.[18] Likewise, persistent mechanical stretch in heart failure, by causing such a decrease in cardiac vagal activity, may contribute to the high risk of sudden death from this disorder. Abnormal and potentially lethal reflexes may be more easily triggered when the wall tension in dilated ventricles is persistently increased by high filling pressures.

Treatment Strategies

The strategy of using intravenous inotropic therapy to reverse decompensation in patients hospitalized with acute heart failure primarily targets a physiologic parameter that is not associated with improved clinical outcome. The use of positive inotropic agents also carries with it a risk of aggravating ischemia and arrhythmias. Weaning from inotropic support is frequently done slowly, potentially contributing to a more prolonged hospitalization.

A strategy of using intravenous vasodilators to reverse decompensation is more physiologically rational, in that it primarily targets elevated filling pressures. The use of intravenous vasodilators has not been associated with worsening myocardial ischemia or with precipitation of ventricular arrhythmias. It also allows easier and more rapid transition to an oral ACE inhibitor and diuretic regimen.

The early hemodynamic effects achieved with intravenous vasodilators and diuretics can be maintained over the long term by using an oral heart failure medical regimen. The significant reduction (and near normalization) in filling pressures achieved with intravenous vasodilators and diuretics within 24 to 72 hours in patients with severe decompensated heart failure has been shown to be an effect that can be maintained over the next 8 months with an oral regimen of ACE inhibitors and diuretics, as shown in Table 2.[19] Thus, intravenous vasodilators can promote the rapid reversal of the decompensated state, with normalization or near normalization of resting hemodynamics that can then be maintained long term with an oral heart failure medical regimen. When combined with a heart failure disease management program, this approach has been associated with an 85% reduction in hospitalization and improved functional capacity compared with conventional management.[20] The vasodilator strategy can also facilitate the more rapid initiation and titration of other survival-enhancing heart failure medications, such as beta-blockers, by promoting the rapid resolution of volume overload.

The intravenous vasodilator strategy can be guided either by clinical assessment or by invasive hemodynamic monitoring. Currently, the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) is evaluating whether therapy guided by pulmonary catheter measurements and clinical assessment will yield better clinical outcomes (more days alive out of hospital) than therapy guided by clinical assessment alone.

Clinical Implications

In patients hospitalized with acute decompensated heart failure, persist-

ently elevated left ventricular filling pressure has been shown to be highly predictive of increased mortality, whereas measures of systemic perfusion, arterial pressure, and vascular resistance have not. Hemodynamic optimization with reduction in left ventricular filling pressures appears to be the most important target for therapy to reduce the long-term risk of fatal decompensation and sudden death in advanced heart failure. Neurohumoral mechanisms can interact with a hemodynamically stressed myocardium to precipitate arrhythmias and/or lead to heart failure disease progression. This interaction lends support to the concept that both hemodynamic abnormalities and neurohormonal activation play primary roles in the ventricular dysfunction, decompensation, and death associated with heart failure.

There is more compelling evidence supporting the use of vasodilators than of inotropic agents in the acutely decompensated heart failure patient, in the absence of cardiogenic shock. An ideal agent for acute decompensated heart failure would be one that rapidly reduces PCWP, results in balanced arterial and venous dilation, promotes naturiesis, lacks direct positive inotropic effects, and does not result in reflex neuroendocrine activation. After rapid reversal of decompensation, comprehensive neurohumoral blockade with ACE inhibitors, beta blockers, and aldosterone antagonists can then be initiated to further reduce disability, hospitalizations, and death from heart failure. ■

References

1. American Heart Association. *2001 Heart and Stroke Statistical Update*. Dallas: American Heart Association; 2000.
2. Stevenson LW, Bellil D, Grover-McKay M, et al. Effects of afterload reduction (diuretics and vasodilators) on left ventricular volume and mitral regurgitation in severe congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol*. 1987;60:654–658.
3. Chatterjee K, Parmley WW. Vasodilator therapy for acute myocardial infarction and chronic congestive heart failure. *J Am Coll Cardiol*. 1983;1:133–153.
4. Stevenson LW. Tailored therapy to hemodynamic goals for advanced heart failure. *Eur J Heart Failure*. 1999;1:251–257.
5. Fonarow GC, Stevenson LW, Steimle AE, et al. Persistently high left ventricular filling pressures predict mortality despite angiotensin converting enzyme inhibition in advanced heart failure. *Circulation*. 1994;90:I-488.
6. Campana C, Gavazii A, Berzuini C, et al. Predictors of prognosis in patients awaiting heart transplantation. *J Heart Lung Trans*. 1993;12:756–785.
7. Myers J, Gullestad L, Vagelos R, et al. Clinical, hemodynamic, and cardiopulmonary exercise test determinants of survival in patients referred for evaluation of heart failure. *Ann Intern Med*. 1998;129:286–293.
8. Lucas C, Johnson W, Hamilton MA, et al. Freedom from congestion predicts good survival despite previous class IV symptoms of heart failure. *Am Heart J*. 2000;140:840–847.
9. Cheng VL, Krishnaswamy P, Kazanegra R, et al. B-type natriuretic peptide predicts treatment outcomes in patients admitted with decompensated heart failure. *J Am Coll Cardiol*. 2001;37:386–391.
10. Cohn JN, Archibald DG, Ziesche S, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure: results of a Veterans Administration Cooperative Study. *N Engl J Med*. 1986;314:1547–1552.
11. Fonarow GC, Chelimsky-Fallick C, Stevenson LW, et al. Effect of direct vasodilation with hydralazine versus angiotensin-converting enzyme inhibition with captopril on mortality in advanced heart failure: the Hy-C trial. *J Am Coll Cardiol*. 1992;19:842–850.
12. Ewy GA. Inotropic infusions for chronic congestive heart failure: medical miracles or misguided medicinals? *J Am Coll Cardiol*. 1999;33:572–575.
13. Gheorghiade M. Outcomes of a prospective trial of intravenous (IV) milrinone for exacerbations of chronic heart failure (OPTIME-CHF). *J Am Coll Cardiol*. 2000;36:321–322.
14. Ferguson DW, Berg WJ, Sanders JS. Clinical and hemodynamic correlates of sympathetic nerve activity in normal humans and patients with heart failure: evidence from direct microneurographic recordings. *J Am Coll Cardiol*. 1990;16:1125–1134.
15. Leri A, Claudio PP, Li Q, et al. Stretch-mediated release of angiotensin II induces myocyte apoptosis by activating p53 that enhances the local renin-angiotensin system and decreases the Bcl2-to-Bax protein ratio in the cell. *J Clin Invest*. 1998;101:1326–1342.
16. Franz MR, Cima R, Wang D, et al. Electrophysiological effects of myocardial stretch and mechanical determinants of stretch-activated arrhythmias. *Circulation*. 1992;86:968–978.
17. Gordon AM, Ridgway EB. Stretch of active muscle during the declining phase of the calcium transient produces biphasic changes in calcium binding to the activating sites. *J Gen Physiol*. 1990;96:1013–1035.
18. Cerati D, Schwartz PJ. Single cardiac vagal fiber activity, acute myocardial ischemia, and risk for sudden death. *Circ Res*. 1991;69:1389–1401.
19. Steimle AE, Stevenson LW, Chelimsky-Fallick C, et al. Sustained hemodynamic efficacy of therapy tailored to reduce filling pressures in survivors with advanced heart failure. *Circulation*. 1997;96:1165–1172.
20. Fonarow GC, Stevenson LW, Walden JA, et al. Impact of a comprehensive heart failure management program on hospital readmission and functional status of patients with advanced heart failure. J *Am Coll Cardiol*. 1997;30:725–733.

Main Points

- Heart failure patients still have a 5-year mortality rate estimated at 50%, and half of all patients hospitalized with acute decompensated heart failure are rehospitalized within 6 months.
- Decompensated heart failure may be classified as wet or dry (with or without congestion) and cold or warm (low or normal perfusion); most patients hospitalized for decompensated heart failure have the cold, wet form.
- High left ventricular filling pressures are associated with adverse clinical outcomes and increased mortality.
- Acute reduction in filling pressure with intravenous vasodilators in heart failure has been shown to be the only significant hemodynamic predictor of subsequent mortality.
- Changes in cardiac index have not been shown to predict subsequent outcome in decompensated heart failure.
- Intravenous vasodilators, which primarily target elevated filling pressures, are more suitable for reversing decompensation in acute heart failure than intravenous inotropic agents, which primarily target elevated cardiac index.