

Acute Decompensated Heart Failure: Formulating an Evidence-Based Approach to Diagnosis and Treatment (Part II)

FRANCESCO BUCCELLETTI, M.D.¹, AND LUKE HERMANN, M.D.²

Abstract

Acute decompensated heart failure (ADHF) is a disease of enormous scope and impact. Despite significant advances in our understanding of the pathophysiology of the disease, the initial treatment of ADHF has changed little in the past 40 years. This article, the second in a two-part series, will examine the emergency department approach to ADHF, including the issues of risk stratification and goal-directed therapy. It will also review therapeutic interventions, including available medications and the role of non-invasive ventilation devices for the stabilization and treatment of ADHF.

Key Words: Heart failure, natriuretic peptides, vasodilator therapy, neurohormones.

Introduction

AS NOTED IN PART I, heart failure (HF) is a disease of enormous scope and impact. Since most patients with acute decompensated heart failure (ADHF) present to the emergency department (ED), emergency physicians are in a unique position to improve both short- and long-term outcomes. This article will focus on the initial evaluation and treatment of the ADHF patient, including issues of risk stratification and goal-directed therapy, and a review of the medications available to treat the disease.

Initial Evaluation and Risk Stratification

Although heart failure represents a complex interplay between cardiac deficits and compensatory responses, the common issue across the spectrum of the disease is a primary deficit in cardiac performance. The clinical presentation of this deficit

varies widely, from the patient who is asymptomatic except during periods of exertion to the patient who presents in overt shock when cardiac output is no longer able to meet end-organ metabolic requirements. Since the therapeutic requirements of these patients are significantly different, the initial assessment of the ADHF patient should be directed at determining the degree of cardiac dysfunction.

In 1976, Forrester et al. demonstrated that by using clinical findings, hemodynamic profiles reflective of cardiac function could accurately be identified in the post-myocardial infarction setting (1). Recently, this classification was evaluated for HF patients referred for evaluation in a tertiary care center (2). The results demonstrate that, based on clinical evidence of elevated filling pressures (evaluated by the presence of jugular venous distention, pulmonary crackles, or peripheral edema), and the grade of peripheral perfusion (evaluated by mental status, blood pressure, skin temperature, peripheral cyanosis, and capillary refill time), HF patients can be rapidly classified into one of four groups according to whether congestion is present (wet or dry) and perfusion is adequate (warm or cold). This classification scheme is not only helpful in directing initial therapy but has also recently been shown to correlate with six-month mortality with patients in the wet-cold profile (i.e., cardiogenic shock), not surprisingly demonstrating an increased risk of death (2).

¹Research Fellow and ²Assistant Professor, Director, Chest Pain Unit, Department of Emergency Medicine, Mount Sinai Medical Center, Mount Sinai School of Medicine, New York, NY.

Address all correspondence to Luke Hermann, M.D., Director, Chest Pain Unit, Department of Emergency Medicine, Box 1149, Mount Sinai School of Medicine, One East 100th Street, New York, NY 10029-6574; e-mail: luke.hermann@mssm.edu

Dr. Hermann receives grant support from Scios, Inc.
Accepted for publication October 2005.

Glossary

ACE = angiotensin-converting enzyme	HF = heart failure
ADHERE = Acute Decompensated Heart Failure National Registry	K-ATPase = potassium adenosine triphosphatase
ADHF = acute decompensated heart failure	LMWH = low-molecular-weight heparin
BiPAP = bilevel positive airway pressure	LOS = length of stay
BNP = B-type natriuretic peptide	NIPPV = non-invasive positive pressure ventilation
BP = blood pressure	NTG = nitroglycerin
BUN = blood urea nitrogen	PCWP = pulmonary capillary wedge pressure
CCU = coronary care unit	PSV = pressure support ventilation
CPAP = continuous positive airway pressure	RAAS = renin-angiotensin-aldosterone system
DVT = deep vein thrombosis	RCT = random clinical trial
ED = emergency department	SVR = systemic vascular resistance
ED-1 = endothelin-1	VMAC = Vasodilation in the Management of Acute Congestive Heart Failure
ETI = endotracheal intubation	VTE = venous thromboembolism
GMP = guanosine monophosphate	

Effective use of risk stratification tools to direct therapeutic and disposition decisions for ED patients is becoming increasingly important (3, 4). Though studies have attempted to quantify the risk of mortality and adverse events for patients hospitalized for decompensated heart failure (5–7), they are generally limited by their retrospective nature, small number of subjects, and inability to identify or evaluate low risk groups for whom ED discharge might be appropriate.

Recently, an analysis of data obtained from 65,275 patients in the Acute Decompensated Heart Failure National Registry (ADHERE) has allowed for development of a simple risk stratification scheme based on data that are easily obtained in the ED setting (8). Using recursive partitioning techniques, the authors developed a model to predict in-hospital mortality using the first 33,046 patients enrolled in the registry. This model was then tested prospectively, using data from 32,229 subsequent hospitalizations. The results demonstrate that using initial systolic blood pressure and serum levels of blood urea nitrogen (BUN) and creatinine, patients can be divided into low, intermediate, and high risk groups based on in-hospital mortality (Table 1). This tool, by enabling clinicians to

classify patients based on short-term mortality risk, may be helpful in determining aggressiveness of care. The applicability of the tool to patients who could be treated and discharged from the ED is limited, however, by the inclusion of only hospitalized patients in the study.

Several trials have recently evaluated the utility of B-type natriuretic peptide (BNP) levels in predicting adverse events in patients presenting with dyspnea (9–11). One trial, which analyzed data from 464 patients diagnosed with ADHF, showed that patients with BNP < 200 pg/mL have significantly fewer adverse events at 90 days compared to patients with BNP levels above this level (9). Although 11% of patients admitted with ADHF in this study had BNP < 200 pg/mL, this degree of elevation is generally considered indeterminate for diagnostic purposes. Similarly, in a prospective trial that evaluated the predictive value of BNP levels in 325 patients presenting to the ED with undifferentiated dyspnea, patients with levels < 230 pg/mL had a 6-month end point (HF-related death, hospital admission, or repeat ED visit) of only 2.5%. On the other hand, BNP levels > 480 pg/mL in this study correlated with a 51% 6-month event rate (10).

TABLE 1
Risk Stratification for In-Hospital Mortality of Acute Decompensated Heart Failure

Clinical Feature	Mortality
Both BUN < 43 mg/dL and systolic BP > 115 mm Hg	2% (low risk)
Either BUN > 43 mg/dL or systolic BP < 115 mm Hg	5–6% (intermediate risk)
Both BUN > 43 mg/dL and systolic BP < 115 mm Hg	12–22% (high risk)

BUN = blood urea nitrogen; BP = blood pressure.

Goal-Directed Therapy

The concept of early goal-directed therapy is familiar to ED physicians. In cases of sepsis, the practice of goal-directed therapy involves targeting specific hemodynamic parameters to optimize patient outcomes. In a more general sense, the goal of aggressive reperfusion in acute myocardial infarction reflects a similar concept, with dissolution of the arterial thrombus identified as the initial therapeutic target. Traditionally, the approach to ADHF has focused primarily on reduction of symptoms as the initial goal of therapy. Given the role of vascular tone on cardiac performance and the issues of neurohormonal activation discussed in Part I, the critical question is whether an approach based purely on reduction of symptoms is too simplistic to provide optimal short- and long-term outcomes.

To answer this question it is helpful to clearly define what parameters might represent legitimate therapeutic targets in ADHF. In basic terms, HF patients typically share three physiologic abnormalities: a decline in cardiac performance, an increase in vascular tone, and varying degrees of volume retention. As pharmacologic interventions can be directed at any of these parameters, a discussion of the merits of targeting each is provided below.

Targeting Cardiac Performance with Inotropic Agents

Historically, the argument for using inotropic agents in ADHF has been based on the assumption that HF is a result of progressive volume overload in the setting of impaired contractility (systolic dysfunction). Recently, it has been noted that for up to 50% of patients admitted for decompensated heart failure, no contractility issue exists (12). In this group, decompensation develops as a result of impaired ventricular filling, commonly referred to as "diastolic dysfunction." Although differentiating systolic from diastolic dysfunction is an important issue for prognosis and management of chronic disease, in the ED setting the end result of both processes is typically the same, i.e., elevated filling pressures which are transmitted backward to the pulmonary vasculature, resulting in transudation of fluid into the alveoli. Clearly, in patients presenting with ADHF as a result of diastolic dysfunction, targeting improved contractility as a goal of initial therapy is unlikely to improve outcomes. In fact, even among patients with known systolic dysfunction, the use of inotropic agents is somewhat controversial, since they have been shown to increase both adverse events and mortality, pre-

sumably as a result of their arrhythmogenic effects (13). Because of this, the ED use of inotropic agents in ADHF should generally be limited to the patient who presents in cardiogenic shock.

Targeting Volume Reduction with Diuretics

As reflected by registry data, volume reduction via diuresis is the most commonly accepted goal of initial therapy for the ADHF patient (14). However, this approach makes sense only if volume overload is accepted as the primary issue in ADHF. In reality, with the exception of dialysis-dependent patients, volume overload in HF is a result of falling cardiac output, not the primary cause. Although removal of fluid via diuresis will eventually improve cardiac performance, it is an inefficient mechanism to do so, particularly in advanced HF, where issues of renal insufficiency and diuretic resistance may complicate the picture (15). Furthermore, the indirect effects of loop diuretics may be counterproductive to attempts to return the patient to a compensated state, for the following reasons.

Loop diuretics have long been known to cause an increase in serum norepinephrine, renin and vasopressin levels, an effect that can result in reflex vasoconstriction and a subsequent decrease in cardiac output (16, 17). Given the prominent role of neurohormonal activation in the expression and progression of heart failure as a disease, this effect is troubling.

From a hemodynamic standpoint, it is common teaching that the administration of loop diuretics produces a vasodilatory effect that precedes any diuresis. In truth, the vasoactive effects of loop diuretics are prostaglandin mediated and have been shown to be blunted in patients receiving aspirin (18). Since many patients with heart failure have concomitant ischemic heart disease and will therefore be on chronic aspirin therapy, a vasodilatory response in this group is unlikely to occur.

Furthermore, attempts at diuresis may be initially ineffective, particularly in advanced HF. As cardiac output falls and neurohormonal activity increases, renal blood flow declines, leading to decreases in the glomerular filtration rate, limiting both diuretic delivery and efficacy (19). Additionally, chronic diuretic use leads to hypertrophy of the distal nephron with a subsequent increase in sodium resorption that manifests clinically as diuretic resistance (20). As a result, patients with advanced disease often require escalating doses of loop diuretic to obtain an adequate clinical response (15).

Finally, there is growing evidence that the high doses of diuretics often required in advanced HF

may lead to worsening of renal function in the setting of ADHF (21, 22). In one case control study of 382 patients hospitalized for decompensated heart failure, high-dose diuretics were independently associated with the development of worsening renal function (21). Overall diuresis was not significantly different between either study group suggesting that the effect was not related to the development of pre-renal azotemia as a result of overdiuresis. Worsening renal function is clinically significant in the treatment of ADHF, since it has been linked to both prolonged hospital length of stay (LOS) and increased mortality after discharge (22).

Filling Pressure Reduction as the Goal of Therapy

The vast majority of patients presenting with ADHF do so with symptoms of dyspnea, the result of elevated filling pressures transmitted from the left ventricle to the pulmonary vasculature. As described in Part I, filling pressures are a function of cardiac loading conditions, suggesting that the most efficient mechanism for lowering filling pressures acutely is to target cardiac loading conditions via the use of vasodilator agents.

Elevated filling pressures have long been known to correlate with mortality in heart failure patients. In a 1994 study of 465 patients hospitalized for ADHF, the lowering of filling pressures to near-normal levels increased the 1-year survival from 64% to 81% (23). In a more recent prospective trial of 59 patients admitted for ADHF, similar results were noted (24). In this group of patients with advanced HF, aggressive filling pressure reduction was attempted with a combination of IV vasodilator therapy and diuresis. In the 68% of patients who demonstrated significant reduction in filling pressures, the cardiac death rate was reduced from 47% to 27% and rehospitalization for cardiac causes decreased from 58% to 8% during the 19-month follow-up period. Of note, a lack of adequate response in this study was linked to renal dysfunction, underscoring the importance of maintaining adequate renal function in HF patients.

Similarly, targeting filling pressure reduction with vasodilator therapy in the ED has been shown to improve short-term outcomes (25). In a 1998 study, Cotter et al. randomized 110 patients presenting with acute pulmonary edema to an initial treatment approach that emphasized either vasodilator therapy (with high-dose IV nitrates and low-dose diuretics) or aggressive diuresis (with high-dose diuretics and low-dose IV nitrates). Significantly fewer patients in the high-dose IV nitrate

arm required endotracheal intubation (13%) when compared to those in the high-dose diuretic group (43%).

The Proaction Trial, a double-blinded, ED observation-unit-based study, compared standard therapy to standard therapy plus the IV vasodilator nesiritide for patients presenting with ADHF (26). In this study of 237 patients, those who received nesiritide were significantly less likely to require hospital admission after ED observation-unit treatment. Furthermore, there was a trend toward reduction of 30-day readmission rate among the nesiritide group when compared to standard therapy. This reduction was more pronounced for New York Heart Association (NYHA) class III and IV patients (29%), and for those who failed observation unit therapy and had to be hospitalized (57%), suggesting that sicker patients received more benefit from the addition of an IV vasodilator.

Finally, data from the ADHERE registry suggest that early initiation of IV vasodilator therapy results in decreased hospital length of stay (27). In this retrospective study of over 3,600 patients, those who received IV vasodilators in the ED showed a reduction in LOS of nearly 30%, from 9.5 to 6.4 days, compared to patients who received IV vasodilators after hospitalization. Although subject to the inherent limitations of retrospective data, these results support the idea that targeting filling pressure reduction as the goal of initial therapy with vasodilator therapy may result in more rapid return to a compensated state.

Treatment of ADHF

Airway Issues / The Role of Noninvasive Ventilation

As with every high acuity patient who presents to the ED, initial treatment in ADHF is directed at ensuring the adequacy of the patient's airway, breathing, and circulation. Many patients with ADHF present in respiratory distress, and common indications for endotracheal intubation (ETI) apply, with the caveat that the respiratory symptoms that accompany decompensated heart failure reflect cardiovascular rather than pulmonary pathology and are therefore often rapidly reversible. This point is important because, in many cases, aggressive lowering of filling pressures with vasodilator agents may avert the need for ETI (25).

Patients with moderate-to-severe ADHF incapable of maintaining a peripheral oxygen saturation greater than 90% despite the use of a non-rebreather mask, may be appropriate for mechanical support by non-invasive positive pressure ventila-

tion (NIPPV). NIPPV consists of continuous positive airway pressure (CPAP), bilevel positive pressure ventilation (BiPAP) or pressure support ventilation (PSV). CPAP is typically provided by a device that generates high flow oxygen with a unidirectional preset valve capable of maintaining a constant positive pressure throughout the respiratory cycle. The associated positive intrathoracic pressure recruits collapsed alveoli, counteracts capillary transudation of fluid and reduces the ventricular filling pressure by acting directly on ventricular and atrial walls (28).

BiPAP and PSV require a device capable of switching between different levels of pressure during the respiratory cycle. In the former technique, the ventilator cycles are based on preset times and there is no synchronization with patient breath. In PSV, the ventilator is capable of sensing a patient's inspiratory effort (which causes a rapid decline of pressure and negative flow in the circuit) and delivers the higher level of pressure to coincide with inspiration. By optimizing patient-ventilator synchronization, this system reduces the work of breathing. Regardless of the technique employed, the aim of NIPPV is to ventilate and oxygenate patients without ETI, until symptomatic improvement occurs as a result of pharmacologic therapy (29).

Multiple studies suggest that NIPPV is effective at improving gas exchange and reducing the need for ETI in ADHF patients (28, 30–33). CPAP has been shown to be safe and effective for selected patients and is often considered the technique of choice when NIPPV is considered (28, 30). Data regarding BiPAP remains somewhat controversial, as an early, randomized trial comparing CPAP to BiPAP demonstrated higher rates of myocardial infarction in the BiPAP group (31). This finding, perhaps related to the inclusion of more patients with complaints of chest pain in the BiPAP group, may reflect inadequate randomization rather than risks inherent in the technique itself (33).

In a recent ED-based prospective trial that randomized 80 patients presenting with cardiogenic pulmonary edema to CPAP, BiPAP, or oxygen via face mask in addition to standard therapy, no cardiac ischemic complications were noted with either NIPPV group (33). Endotracheal intubation rates were dramatically reduced with both types of NIPPV (7%) when compared to the oxygen-by-face-mask group (42%), suggesting that either CPAP or BiPAP provides a safe, effective means to avoid ETI during the time interval required for medication-related improvement. For successful application of NIPPV, close monitoring, hemodynamic stability and patient cooperation are re-

quired. Indications and contraindications for NIPPV are presented in Table 2.

Circulatory Issues / Cardiogenic Shock

Once immediate airway issues are addressed, a rapid assessment of circulatory function should be performed, since this will guide initial pharmacologic therapy. As described above, the hemodynamic profile of the ADHF patient can be determined at the bedside, based on the presence or absence of congestion (reflective of filling pressures) and the adequacy of perfusion (indicative of pump function) (1). For patients presenting with clinical evidence of cardiogenic shock, initial therapy should be directed toward improving end-organ perfusion via inotropic and vasopressor agents.

Inotropic agents are drugs that improve cardiac contractility by increasing the amount of intracellular calcium available to the myocardium (34). As perfusion pressure is a direct reflection of cardiac output and systemic vascular resistance, augmenting contractility provides a potentially effective mechanism for blood pressure support in this setting. Because the benefit of inotropic agents is predicated on improving systolic function, indications for ED use should include patients with known or suspected systolic dysfunction, clinical evidence of shock, and signs of pulmonary congestion (wet-cold profile). In the absence of congestion (dry-cold profile), an initial small fluid challenge (normal saline: 100–250 mL bolus) may be appropriate, since low cardiac output in this setting may be a reflection of hypovolemia secondary to overdiuresis or other volume loss rather than contractility related.

There is little evidence to guide clinicians regarding choice of individual inotropic agents. Available studies are not easily applied to many acute patients, since they involved patients in the post-myocardial-infarction setting, a situation where inadequate cardiac output may not be a direct result of systolic dysfunction (i.e. papillary muscle or ventricular wall rupture) (35, 36). Agents are typically classified according to their primary mechanism of action, with individual drugs showing significantly variable inotropic and peripheral vascular effects.

TABLE 2

Contraindications to Noninvasive Positive Pressure Ventilation

1. Respiratory or cardiac arrest
2. Altered mental status / inability to cooperate
3. Hemodynamic instability
4. Upper airway obstruction
5. Facial deformity that precludes adequate seal

Catecholamines. The actions of catecholamines depend on their affinity for specific adrenergic receptors, a phenomenon that is both medication and dose related. In general, catecholamines provide inotropic effect via activation of cardiac beta-adrenergic receptors and vasoconstriction via activation of peripheral vascular alpha-receptors.

Dopamine is a catecholamine that acts primarily on beta-receptors at low doses (2–5 micrograms/Kg/min) and on beta- and alpha-receptors at higher doses (> 10 micrograms/Kg/min). It has a dose-dependent positive inotropic, chronotropic, dromotropic and vasoconstrictor effect. The vasoconstrictor effect results in an increase in systemic vascular resistance that limits its utility in the setting of severe systolic dysfunction, where increases in afterload result in decreased cardiac output. Furthermore, the chronotropic effects of dopamine result in tachycardia and consequently an increase in myocardial oxygen demand, potentially worsening ventricular performance in this setting. Because of these issues, dopamine is generally used in combination with other, more potent inotropic agents for the treatment of cardiogenic shock (34).

Dobutamine is a synthetic catecholamine with relatively selective action on cardiac beta1 receptors. It also has a moderate beta2 and a mild alpha2 affinity at high doses. The result is an agent with primarily inotropic and mild vasodilatory effects. Although this combination makes it attractive for the management of refractory systolic heart failure, its vasodilatory properties make it unsuitable as a lone agent for the patient in frank shock. For patients presenting with mild hypotension (systolic blood pressure between 80 and 90 mm Hg), dobutamine can be initiated as a single agent; and if symptomatic hypotension persists, dopamine can then be added. Dobutamine is typically started at 2–7 micrograms/kg/min and titrated up to 20 micrograms/Kg/min based on the hemodynamic response.

Phosphodiesterase inhibitors. Amrinone and milrinone enhance the entry of calcium into myocardocytes via phosphodiesterase inhibition. Though potent inotropic agents, their prominent vasodilatory effects limit their utility in the hypotensive patient. Although interest has developed regarding the utility of adding milrinone to standard therapy for the treatment of refractory systolic HF, a recent trial found that milrinone provided no benefit compared to placebo and was associated with higher incidence of symptomatic hypotension and new atrial arrhythmias (37).

Calcium sensitizers. Levosimendan belongs to a promising new class of inotropic agents called

“calcium sensitizers,” which act by increasing sensitivity of troponin-C to intracellular ionized calcium, as well as causing peripheral vasodilation by opening potassium adenosine triphosphate (K-AT-Pase) channels in vascular smooth muscle cells. One randomized prospective study of 203 low-output HF patients suggests that levosimendan is more effective than dobutamine at improving hemodynamic parameters, as measured by cardiac output and pulmonary “capillary” wedge pressure (PCWP) (38). In this study, lower mortality through 180 days was also noted in the levosimendan group. Although these results are intriguing, further study is required and currently levosimendan remains an investigational drug.

Pharmacologic Options for the Hemodynamically Stable Patient

For most patients presenting with ADHF, adequate perfusion exists. In this group, as discussed above, a growing body of evidence suggests that the goal of therapy should be an early and sustained reduction in filling pressures. Vasodilator therapy, by favorably altering cardiac loading conditions, offers the most efficient mechanism to achieve this goal. There are several classes of vasodilators currently available for the treatment of ADHF. The choice of agent and route of delivery (oral vs. IV) should be based on the severity of the presentation and the likely disposition of the patient.

Vasodilator Drugs

Nitrates. Nitroglycerin (NTG) is the vasodilator most commonly used for the treatment of ADHF. It acts by increasing intracellular levels of cyclic guanosine monophosphate (GMP), resulting in venous and, for higher doses, arterial vasodilation. The advantages of NTG include low cost, patient comfort and a proven safety profile. Additionally, in patients requiring a rapid therapeutic effect or in those in whom IV access is being obtained, sublingual NTG has been shown to provide a rapid hemodynamic response (39, 40).

Interestingly, the hemodynamic efficacy of sublingual nitrate preparations may not be noted with intravenous preparations administered at usual doses. Data from a study of ADHF in which one group of patients underwent invasive hemodynamic monitoring found that significant reduction of PCWP did not occur until the intravenous NTG dose was well above 100 micrograms per minute (41). This was more than twice the mean dose received by patients treated without invasive monitoring, suggesting that physicians were unlikely to

achieve adequate dosage unless a PCWP was available to guide therapy.

Suboptimal dosing aside, there are two primary obstacles to the effective use of NTG, the phenomenon of tolerance and its effect on neurohormonal pathways. "Tolerance" refers to the progressive attenuation of pharmacologic effect that develops rapidly in high-dose nitrate therapy, limiting efficacy without continuous monitoring and upward dose titration (42). In the study referenced in the previous paragraph, investigators found that maximal wedge pressure reduction with NTG occurred within the first 3 hours of therapy but gradually normalized over the following 21 hours despite intervening diuresis and upward nitrate dose titration, presumably a reflection of the effect of tolerance (41).

Though the phenomenon of tolerance is complex and poorly understood, there is evidence that nitrate-induced neurohormonal activation may play a significant role (43). Several studies have demonstrated an increase in plasma concentrations of catecholamines, renin and endothelin with continuous nitrate therapy (44–46). As the vasoconstrictive effects of neurohormonal pathways progressively overshadow the vasodilatory effect of nitrate therapy, the clinical manifestation of tolerance may become apparent. Given the importance of neurohormonal activation in the development and progression of heart failure, this potential etiologic mechanism for the phenomenon of tolerance raises questions about the suitability of continuous nitrate therapy in ADHF patients.

As with any vasodilator, nitrates must be avoided in the presence of hypertrophic cardiomyopathies or severe aortic stenosis, since they will increase the obstructive gradient and reduce cardiac output. Furthermore, vasodilators must be used with caution in patients with hypoperfusion or evidence of right ventricular myocardial infarction, since both of these conditions are pre-load dependent. When patients become acutely hypotensive during nitrate infusions, these conditions must be ruled out and the etiology of ADHF re-considered.

Sodium nitroprusside. Nitroprusside is perhaps the most potent arterial vasodilator available. Although its short half-life and rapid effect make it an appealing agent for the treatment of ADHF, its monitoring requirements limit its applicability to most ED patients. Furthermore, nitroprusside is metabolized to thiocyanate—a potential source of toxicity for infusions lasting more than 24 hours.

ACE Inhibitors. Angiotensin-converting enzyme (ACE) inhibitors have been shown in multiple studies to decrease mortality in chronic HF. Although there is less data regarding their use in

ADHF, ACE inhibitors have been shown to be effective vasodilators in this setting (40, 47, 48). In one study of 24 ADHF patients randomized to receive either nitroglycerin or captopril sublingually, captopril was shown to be as effective at decreasing preload and afterload as nitroglycerin. One noted benefit of captopril was its longer duration of action, with return to baseline hemodynamics not occurring for 2–3 hours after administration of the medication. Though this duration of action is an improvement over sublingual NTG, the 8-hour recommended dosing interval means that captopril is unlikely to provide the sustained reduction in filling pressures desired in ADHF.

Regarding their effect on neurohormonal activation, ACE inhibitors clearly inhibit activation of the renin-angiotensin-aldosterone system (RAAS) system, but their effect on adrenergic tone and endothelin activity is less clear (47). Interestingly, ACE inhibitors have been shown to decrease the diuretic and natriuretic effect of loop diuretics. In two prospective studies with a total of 37 HF patients, the diuretic effect of furosemide was compared after pretreatment with captopril or placebo (49, 50). In the groups that received captopril, diuresis decreased 41–43%. Given the small size of these studies, the clinical relevance of this issue is not clear. Because ACE inhibitors have been clearly shown to decrease mortality in chronic heart failure, they should be started in every patient within the first 24 hours of admission and in any case before hospital discharge if no contraindications are present (51).

Nesiritide. Nesiritide is a synthetic form of b-type natriuretic peptide (BNP) that was approved by the Food and Drug Administration (FDA) for use in ADHF in 2001. As an analog of the body's own counter-regulatory hormone, it embodies many of the characteristics desired of an ideal agent for the treatment of ADHF. The beneficial hemodynamic effects of BNP in ADHF have been demonstrated in multiple studies, with early work focusing on the vasodilatory effect of escalating doses of BNP given either as a bolus or an infusion.

In one early study, nesiritide was found to provide a dose-related decrease in PCWP, systemic vascular resistance (SVR), mean pulmonary artery pressure and mean arterial pressure when given as a bolus to HF patients (52). At the highest doses, PCWP and SVR were reduced by 73% and 53%, respectively. A similar effect was noted in a subsequent study in which patients were given a 90-minute infusion of BNP (53). In this trial of 20 patients with "severe" HF, the infusion resulted in a mean decrease of PCWP from 25.1 mm Hg to 13.2 mm Hg.

In a 1999 multicenter random clinical trial (RCT) with 103 heart HF, a 24-hour infusion of nesiritide was found to produce significant reductions in PCWP (27–39%) that were dose dependent (54). Additionally, increases in cardiac index and stroke volume index were noted, with no concomitant change in heart rate, suggesting that the improvement in cardiac performance did not come at the expense of increased myocardial oxygen demand. The beneficial hemodynamic effects of BNP in this study were noted within 1 hour of initiating the infusion and were maintained through the duration of treatment. These results were replicated in a subsequent RCT of 127 HF patients (55). In this study, nesiritide use resulted in a 6-hour reduction of PCWP of 6 and 9 mm Hg (dependent on dose) and improvements in global clinical status in 60–67% of patients.

In the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) trial, 489 patients with ADHF were randomized to receive either nesiritide, IV NTG, or placebo (56). The placebo group was subsequently randomized into one of the active treatment arms after 3 hours. The primary end points included change in PCWP (catheterized group only) and change in dyspnea symptoms at 3 hours. Significant change in the PCWP at 3 hours was noted in the nesiritide group but not the NTG group when compared with placebo. A recently published subgroup analysis of patients from the VMAC trial who all underwent invasive hemodynamic monitoring demonstrated that patients treated with nesiritide had a mean reduction of PCWP of 6.5 mm Hg at 1 hour and 12.2 mm Hg at 24 hours. The available evidence suggests that nesiritide is a potent vasodilator that provides both early and sustained reduction in filling pressures in the ADHF patient.

The potential benefits of nesiritide extend beyond its efficacy as a vasodilator. Natriuretic peptides have long been known to attenuate neurohormonal activity, and not surprisingly, nesiritide has been shown to decrease sympathetic tone as well as inhibit production of renin, aldosterone and endothelin (57–59). These effects presumably not only help speed return to a compensated state in the acute setting but may also slow disease progression, a process that appears to be largely mediated via neurohormonal pathways.

Additionally, BNP promotes natriuresis and diuresis at the level of the kidney while maintaining glomerular filtration rate and renal blood flow (57, 60). Although clinically this effect appears to be limited, nesiritide use has been noted to lessen diuretic requirements in coronary care unit (CCU) patients and in patients with renal insufficiency when compared to NTG (61, 62).

A recent article has raised concerns about the effect of nesiritide on renal function in decompensated heart failure (63). This meta-analysis of 5 randomized controlled trials found that compared to controls, patients treated with nesiritide had an increased risk of developing worsening renal function, defined as an increase in serum creatinine of > 0.5 mg/dL (relative risk 1.54; 95% CI 1.20–1.99; $p=0.001$). However, the results of this study are limited by the authors' lack of access to primary data and the inclusion of many patients who received drug infusion rates well above the approved dosing range. The latter point is important, since symptomatic hypotension, and thus the potential for renal hypoperfusion, becomes much more common as the dose of nesiritide increases. Regardless of the etiology, these results contradict the commonly held belief that nesiritide provides a degree of renal protection during treatment of ADHF. This belief is based on several potentially beneficial renal actions, including effects on efferent and afferent vascular tone and inhibition of renin synthesis. In the near future, the effect of nesiritide on renal function in ADHF will be more definitively addressed by a multicenter prospective trial of approximately 1,900 patients, currently underway in Europe (64).

A more frequently voiced concern about widespread use of nesiritide is its cost. Interestingly, there is evidence that the use of nesiritide may decrease the overall cost of care. This is likely a reflection of the fact that the bulk of costs associated with treatment of any disease are not a function of the price of medications as much as hospital LOS. For heart failure patients, medications have been shown to represent approximately 10% of the total cost of care (65). Of more importance in overall cost of care for HF is patient recidivism and frequent hospital readmission. The six-month readmission rate for patients with ADHF is approximately 25%, but it increases to over 45% in high-risk groups (66). Successful treatment of ADHF from a financial perspective, therefore, should presumably focus on decreasing hospital LOS and readmission rates.

In one study, nesiritide was shown to decrease health care resource utilization and LOS for patients admitted to the CCU (63). In this retrospective, case-controlled evaluation of 216 heart failure patients admitted to the CCU, patients who received nesiritide showed a significant decrease in CCU LOS and decrease in health care resource costs, even when the price of the drug was included. The PROACTION study demonstrated a reduction in costs for patients treated with nesiritide compared to standard therapy in an ED obser-

vation unit (26). Cost reduction was apparently secondary to a decrease in admission rate, readmission rate, and shorter LOS on readmission. Although further study in the form of large prospective trials is needed, the available evidence suggests that the added expense of using nesiritide for the treatment of ADHF may be offset by the benefits, specifically by decreases in hospital LOS and readmission rates.

Many of the potential benefits offered by nesiritide for the treatment of ADHF are a result of both its efficacy as a vasodilator and its ability to provide neurohormonal blockade, actions that are intimately related. The impact of these effects on important outcomes (hospital LOS, readmission rates, and mortality) has yet to be delineated by large, randomized, controlled trials.

Diuretics. Clearly, effective management of ADHF cannot be accomplished without the use of diuretics. Yet given their known neurohormonal effects and their potential link to worsening renal function at high doses, the frequent use of loop diuretics as the primary therapeutic agent for ADHF needs to be questioned. Increasingly, it would appear that ideal therapy during episodes of decompensation should include diuretics as one part of an approach that places primary emphasis on the early and sustained control of filling pressures with vasodilator therapy. For patients who present with mild decompensation, particularly in the setting of known dietary indiscretion or medication noncompliance, an initial trial of diuresis without the addition of an IV vasodilator may allow for resolution of symptoms and avoidance of hospital admission.

When treating ADHF, loop diuretics should be administered intravenously, as bowel wall edema can delay absorption (34). Furosemide, the most commonly used diuretic, should initially be administered at a dose equal to twice the patient's usual dose. If ineffective, repeat dosing at double the initial amount can be attempted. All loop diuretics cause potassium and magnesium depletion and at high doses can lead to ototoxicity. Data from the SOLVD trial, in fact, suggest a higher mortality for chronic heart failure patients treated with loop diuretics, probably a result of hypokalemic-related arrhythmias (67). Adequacy of response to therapy should be based on improvement of symptoms and urinary output, which generally should exceed 500 mL after two hours.

Diuretic resistance, which often accompanies advanced HF, necessitates escalating diuretic doses, a situation that has been linked to worsening renal function and prolonged hospitalization (21, 22). In this setting, the use of continuous diuretic

infusions has been shown more effective than bolus therapy in achieving an adequate response (68). In one prospective case control study of elderly, class IV ADHF patients, delivering furosemide as a constant infusion resulted in a mean diuresis of 5.0 liters in the first 24 hours of therapy and 14 liters over the duration of treatment (69). This group had an average hospital LOS that was 2.3 days shorter than matched controls, resulting in a cost savings of \$5,249 per patient as calculated by the authors of the study. Additionally, renal function in the infusion group remained relatively stable, with an average change in serum creatinine of 0.2 mg/dL during the treatment period. Although more study is required to determine the applicability of this approach to all ADHF patients, it would appear that continuous furosemide infusion offers an efficacious alternative to high-dose bolus therapy in patients with advanced disease.

Anticoagulant therapy. The importance of venous thromboembolism (VTE) as a frequent contributor to morbidity and mortality among patients hospitalized for medical conditions has been noted in multiple studies (70–72). Consistently, admission for ADHF is noted as an independent risk factor for the development of VTE, particularly among patients with significant left ventricular dysfunction (73). For patients hospitalized with high-risk medical conditions (ADHF, chronic obstructive pulmonary disease, systemic infections) the risk of deep vein thrombosis (DVT) has been reported at approximately 16% (72). A recent review of two RCTs that evaluated the efficacy of different low-molecular-weight heparin (LMWH) formulations compared to placebo for prevention of VTE in 4,783 medical patients found a 50% reduction in VTE with a non-significant increase in major bleeding in the LMWH groups (73). These and similar results have led expert panels to recommend consideration of thromboprophylaxis for all patients admitted for ADHF, particularly those over the age of 60 (72, 73). Prophylaxis can be provided with either LMWH (i.e., enoxaparin 40 mg or dalteparin 5000 IU) or unfractionated heparin (5000 IU) although a recent meta-analysis of 9 trials comparing LMWH to unfractionated heparin found a trend toward greater reduction of DVT in the LMWH group (74).

Newly Emerging Drugs

A number of investigational drugs are currently under development for the treatment of ADHF, several targeting neurohormonal blockade, specifically endothelin and vasopressin pathways. Endothelin-1 (ET-1) is a potent vasoconstrictor

that is increased in ADHF, and tezosentan, an ET receptor blocker, has recently emerged as a promising therapeutic agent. Four studies have been done focusing on the safety and efficacy of tezosentan. One study, in which 292 ADHF patients were randomly assigned to tezosentan or placebo in addition to standard therapy, found that tezosentan decreased both symptoms and PCWP more than placebo, with a positive trend in patient outcomes in the tezosentan group (75). These results are encouraging but preliminary.

Vasopressin acts through peripheral receptors mediating both vasoconstriction (V1 receptor) and water retention in the renal tubules (V2 receptor) (76). After experimental observations indicated that vasopressin levels are elevated in ADHF, interest developed in the role of vasopressin receptor blockade as a mechanism for treatment for the disease. Tolvaptan, a V2 receptor antagonist, has been shown in preliminary studies to increase urine output in HF patients, decreasing edema and body weight during hospitalization while increasing serum sodium in hyponatremic patients. Although potentially beneficial, tolvaptan has yet to demonstrate clinical benefit over standard therapy (76).

Summary

Heart failure is a disease whose incidence and impact are expected to rise in the coming decades, mandating development and application of evidence-based treatment strategies. Although ultimately this will require large, ED-based prospective trials, the evidence currently available underscores the importance of filling pressure reduction as both the initial and long-term goal of heart failure care. To this end, the use of IV vasodilator therapy, with attention to issues of neurohormonal activation, appears to provide the most efficient mechanism for rapid resolution of symptoms and slowing of disease progression.

References

- Forrester JS, Diamond G, Chatterjee K, Swan HJ. Medical therapy of acute myocardial infarction by application of hemodynamic subsets (second of two parts). *N Engl J Med* 1976; 295:1404–1413.
- Nohria A, Tsang SW, Fang JC, et al. Clinical assessment identifies hemodynamic profiles that predict outcomes in patients admitted with heart failure. *J Am Coll Cardiol* 2003; 41:1797–1804.
- Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000; 284(7):835–842.
- Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med* 1997; 336(4):243–350.
- Selker HP, Griffith JL, D'Agostino RB. A time-insensitive predictive instrument for acute hospital mortality due to congestive heart failure: development, testing, and use for comparing hospitals: a multicenter study. *Med Care* 1994; 32(10):1040–1052.
- Chin MH, Goldman L. Correlates of major complications or death in patients admitted to the hospital with congestive heart failure. *Arch Intern Med* 1996; 156:1814–1820.
- Katz MH, Nicholson BW, Singer DE, et al. The triage decision in pulmonary edema. *J Gen Intern Med* 1988; 3:533–539.
- Fonarow GC, Adams KF, Abraham WT, et al. Risk stratification for in-hospital mortality in acutely decompensated heart failure. *JAMA* 2005; 293:572–580.
- Maisel A, Hollander JE, Guss D, et al. Primary results of the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT). A multicenter study of B-type natriuretic peptide levels, emergency department decision making, and outcomes in patients presenting with shortness of breath. *J Am Coll Cardiol* 2004; 44(6):1328–1333.
- Harrison A, Morrison LK, Krishnaswamy P, et al. B-type natriuretic peptide predicts future cardiac events in patients presenting to the emergency department with dyspnea. *Ann Emerg Med* 2002; 39(2):131–138.
- Mueller C, Scholer A, Laule-Kilian K, et al. Use of B-type natriuretic peptide in the evaluation and management of acute dyspnea. *N Engl J Med* 2004; 350:647–654.
- Vasan RS, Larsen MG, Benjamin EJ, et al. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *J Am Coll Cardiol* 1999; 33(7):1948–1955.
- Ewy GA. Inotropic infusions for chronic congestive heart failure: medical miracles or misguided medicinals? *J Am Coll Cardiol* 1999; 33(2):572–575.
- ADHERE™ Registry [database]. First Quarter 2003 Benchmark Report. Sunnyvale, CA: Scios, Inc.; January 2003.
- Kramer BK, Schweda F, Riegger GA. Diuretic treatment and diuretic resistance in heart failure. *Am J Med* 1999; 106(1):90–96.
- Francis GS, Siegel RM, Goldsmith SR, et al. Acute vasoconstrictor response to intravenous furosemide in chronic congestive heart failure. Activation of the neurohumoral axis. *Ann Intern Med* 1985; 103(1):1–6.
- Bayliss J, Norell M, Canepa-Anson R, et al. Untreated heart failure: clinical and neuroendocrine effects of introducing diuretics. *Br Heart J* 1987; 57:17–22.
- Jhund PS, Davie AP, McMurray JJ. Aspirin inhibits the acute venodilator response to furosemide in patients with chronic heart failure. *J Am Coll Cardiol* 2001; 37(5):1234–1238.
- Gottlieb SS, Brater DC, Thomas I, et al. BG9719(CVT-124), an A1 adenosine receptor antagonist, protects against the decline in renal function observed with diuretic therapy. *Circulation* 2002; 105:1348–1353.
- De Bruyne LK. Mechanisms and management of diuretic resistance in congestive heart failure. *Postgrad Med* 2003; 79(931): 268–271.
- Butler J, Forman DE, Abraham WT, et al. Relationship between heart failure treatment and development of worsening renal function among hospitalized patients. *Am Heart J* 2004; 147(2):331–338.
- Wenfeld MS, Chertow GM, Stevenson LW. Aggravated renal dysfunction during intensive therapy for advanced chronic heart failure. *Am Heart J* 1999; 138(2 Pt 1):285–290.
- 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 [abstract]. *Circulation* 1994; 90:I–488.

24. Cioffi G, Stefanelli C, Tarantini L, et al. Hemodynamic response to intensive unloading therapy (furosemide and nitropruside) in patients >70 years of age with left ventricular systolic dysfunction and decompensated chronic heart failure. *Am J Cardiol* 2003; 92(9):1050–1056.
25. Cotter G, Metzko E, Kaluski E. Randomised trial of high-dose isosorbide dinitrate plus low-dose furosemide versus high-dose furosemide plus low-dose isosorbide dinitrate in severe pulmonary oedema. *Lancet* 1998; 351(9100):389–393.
26. Peacock WF 4th, Holland R, Gyarmathy R, et al. Observation unit treatment of heart failure with nesiritide: results from the proaction trial. *J Emerg Med* 2005; 29(3):243-252.
27. Emerman CL, Peacock WF, Fonarow GC. Effect of emergency department initiation of vasoactive infusion therapy on heart failure length of stay. *Ann Emerg Med* 2002; 40(Suppl 4):S46.
28. Bersten AD, Holt AW, Vedig AE, et al: Treatment of severe cardiogenic pulmonary edema with continuous positive airway pressure delivered by face mask. *N Engl J Med* 1991; 325:1825–1830.
29. Mehta S. Continuous versus bilevel positive airway pressure in acute cardiogenic pulmonary edema? A good question! *Crit Care Med* 2004; 32(12):2546–2548.
30. Lin M, Yang YF, Chiang HT, et al: Reappraisal of continuous positive airway pressure therapy in acute cardiogenic pulmonary edema. Short-term results and long-term follow-up. *Chest* 1995; 107:1379–1386.
31. Mehta S, Jay GD, Woolard RH, et al: Randomized, prospective trial of bilevel versus continuous positive airway pressure in acute pulmonary edema. *Crit Care Med* 1997; 25 620–628.
32. Masip J, Betbesé AJ, Páez J, et al: Noninvasive pressure support ventilation versus conventional oxygen therapy in acute cardiogenic pulmonary oedema: A randomized trial. *Lancet* 2000; 356:2126–2132.
33. Park M, Sangean MC, Volpe Mde S, et al. Randomized, prospective trial of oxygen, continuous positive airway pressure, and bilevel positive airway pressure by face mask in acute cardiogenic pulmonary edema. *Crit Care Med* 2004; 32(12):2407–2415.
34. Braunwald, E. Pathophysiology of heart failure. In: Braunwald E, editor. *Heart disease*, 4th ed. Philadelphia: Saunders; 1992.
35. Cotter G, Kaluski E, Blatt A, et al. L-NMMA (a nitric oxide synthase inhibitor) is effective in the treatment of cardiogenic shock. *Circulation* 2000; 101:1358–1361.
36. Cotter G, Kaluski E, Milo O, et al. LINCOS: L-NAME (a NO synthase inhibitor) in the treatment of refractory cardiogenic shock: a prospective randomized study. *Eur Heart J* 2003; 24:1287–1295.
37. Gheorghiadu M. Outcomes of a prospective trial of intravenous milrinone for exacerbations of chronic heart failure (OPTIME-CHF). *J Am Coll Cardiol* 1999; 33:572–575.
38. Follath F, Cleland JG, Just H, et al. Efficacy and safety of intravenous levosimendan compared with dobutamine in severe low-output heart failure (the LIDO study): a randomised double-blind trial. *Lancet* 2002; 360(9328):196–202.
39. Bussman W-D, Schupp D. Effect of sublingual nitroglycerin in emergency-treatment of severe pulmonary edema. *Am J Cardiol* 1978;41:931–936.
40. Haude M, Steffen W, Erbel R, Meyer J. Sublingual administration of captopril versus nitroglycerin in patients with severe congestive heart failure. *Int J Cardiol* 1990; 27(3): 351–359.
41. Elkayam U, Akhter M, Singh H, et al. Comparison of effects on left ventricular filling pressure of intravenous nesiritide and high-dose nitroglycerin in patients with decompensated heart failure. *Am J Cardiol* 2004; 93:237–240.
42. Elkayam U, Roth A, Henriquez B, et al. Hemodynamic and hormonal effects of high-dose transdermal nitroglycerin in patients with chronic congestive heart failure. *Am J Cardiol* 1985; 56:555–559.
43. Gori T, Parker J. The puzzle of nitrate tolerance, pieces smaller than we thought. *Circulation* 2002; 106(8):2404–2408.
44. Parker J.D., Farrel B, Fenton T, et al. Counter-regulatory responses to continuous and intermittent therapy with nitroglycerin. *Circulation* 1991; 84(6): 2336–2345.
45. Dupuis J, Lalonde G, Lemieux R, et al. Tolerance to intravenous nitroglycerin in patients with congestive heart failure: role of increased intravascular volume, neurohormonal activation and lack of prevention with N-acetylcysteine. *J Am Coll Cardiol* 1990; 16(4):923–931.
46. Munzel T, Giaid A, Kurz S, et al. Evidence for a role of endothelin 1 and protein kinase C in nitroglycerin tolerance. *Proc Natl Acad Sci U S A* 1995; 92(11):5244–5248.
47. Annane D, Bellissant E, Pussard E, et al. Placebo-controlled, randomized, double blind study of intravenous enalaprilat efficacy and safety in acute cardiogenic pulmonary edema. *Circulation* 1996; 94(6):1316–1324.
48. Podbregar M, Voga G, Horvat M, et al. Bolus versus continuous low dose of enalaprilat in congestive heart failure with acute refractory decompensation. *Cardiology* 1999; 91(1):41–49.
49. McLay JS, McMurray JJ, Bridges AB, et al. Acute effects of captopril on the renal actions of furosemide in patients with chronic heart failure. *Am Heart J* 1993; 126:879–886.
50. Flapan AD, Davies E, Waugh C, et al. Acute administration of captopril lowers the natriuretic and diuretic response to a loop diuretic in patients with chronic cardiac failure. *Eur Heart J* 1991; 12:924–927.
51. Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients. ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* 2000; 355(9215):1575–1581.
52. Hobbs RE, Miller LW, Bott-Silverman C, et al. Hemodynamic effects of a single intravenous injection of synthetic human brain natriuretic peptide in patients with heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1996; 78(8):896–901.
53. Marcus LS, Hart D, Packer M, et al. Hemodynamic and renal excretory effects of human brain natriuretic peptide infusion in patients with congestive heart failure. *Circulation* 1996; 94:3184–3189.
54. Mills RM, LeJemtel TH, Horton DP, et al. Sustained hemodynamic effects of an infusion of nesiritide (human b-type natriuretic peptide) in heart failure: a randomized, double-blind, placebo-controlled clinical trial. *J Am Coll Cardiol* 1999; 34(1):155–162.
55. Colucci WS, Elkayam U, Horton DP, et al. Intravenous nesiritide, a natriuretic peptide, in the treatment of decompensated heart failure. *N Engl J Med* 2000; 343:246–253.
56. The VMAC Publication Committee. Intravenous nesiritide vs nitroglycerin for treatment of decompensated congestive heart failure: a randomized controlled trial. *JAMA* 2002; 287:1531–1540.
57. Abraham WT, Lowes BD, Ferguson DA, et al. Systemic, hemodynamic, neurohormonal and renal effects of a steady-state infusion of human brain natriuretic peptide in patients with hemodynamically decompensated heart failure. *J. Card Fail* 1998; 4:37–44.
58. Brunner-La Rocca HP, Kaye DM, Woods RL, et al. Effects of intravenous brain natriuretic peptide on regional sympathetic activity in patients with chronic heart failure as compared with healthy control subjects. *J Am Coll Cardiol* 2001; 37(5):1221–1227.

59. Aronson D, Burger A. Intravenous nesiritide (human B-type natriuretic peptide) reduces plasma endothelin-1 levels in patients with decompensated congestive heart failure. *Am J Cardiol* 2002; 90(4):435–438.
60. Jensen Kt, Carstens J, Pederson EB. Effect of BNP on renal hemodynamics, tubular function and vasoconstrictive hormones in humans. *Am J Physiol* 1998; 274(Suppl):F63–F72.
61. Emerman CL, Peacock WF. Efficacy and safety of nesiritide (B-type natriuretic peptide) vs. nitroglycerin in patients with renal insufficiency. Presented at: American College of Emergency Physicians (ACEP) Scientific Assembly 2002. October 2002, Seattle, WA.
62. Lenz TL, Floral PA, Malesker MA, et al. Impact of nesiritide on health care resource utilization and complications in patients with decompensated heart failure. *Pharmacotherapy* 2004; 24:1137–1146.
63. Sackner-Bernstein JD, Skopicki HA, Aaronson KD. Risk of worsening renal function with nesiritide in patients with acutely decompensated heart failure. *Circulation* 2005; 111(12):1487–1491.
64. Teerlink JR, Massie BM. Nesiritide and worsening renal function, the emperor's new clothes? *Circulation* 2005; 111:1459–1461.
65. American Heart Association. Heart disease and stroke statistics—2004 update. Dallas, TX: American Heart Association; 2004.
66. Philbin EF, Dec GW, Jenkins PL, DiSalvo TG. Socioeconomic status as an independent risk factor for hospital readmission for heart failure. *Am J Cardiol* 2001; 87(12):1367–1371.
67. Domanski M, Norman J, Pitt B, et al. Diuretic use, progressive heart failure, and death in patients in the studies of left ventricular dysfunction (SOLVD). *J Am Coll Cardiol* 2003; 42:705–708.
68. Dornans TP, van Meyel JJ, Gerlag PG, et al. Diuretic efficacy of high dose furosemide in severe heart failure: bolus injection versus continuous infusion. *J Am Coll Cardiol* 1996; 28:376–382.
69. Howard PA, Dunn MI. Aggressive diuresis for severe heart failure in the elderly. *Chest* 2001; 119:807–810.
70. Silverstein MD, Heit JA, Mohr DN, et al. Trends in the incidence of deep vein thrombosis and pulmonary embolism: a 25-year population-based study. *Arch Intern Med* 1998; 158:585–593.
71. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. *N Engl J Med* 1999; 341(11):793–800.
72. Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. *Chest* 2001; 119(Suppl 1):132S–175S.
73. Leizorovicz A, Mismetti P. Preventing venous thromboembolism in medical patients. *Circulation* 2004; 110(Suppl IV):IV-13–IV-19.
74. Mismetti P, Laporte-Simitsidis S, Tardy B, et al. Prevention of venous thromboembolism in internal medicine with unfractionated or low-molecular-weight heparins: a meta-analysis of randomised clinical trials. *Thromb Haemost* 2000; 83(1):14–19.
75. Torre-Amione G, Young JB, Colucci WS, et al. Hemodynamic and clinical effects of tezosentan, an intravenous dual endothelin receptor antagonist, in patients hospitalized for acute decompensated heart failure. *J Am Coll Cardiol* 2003; 42(1):140–147.
76. Gheorghiane M, Gattis WA, O'Connor CM, et al. Effects of tolvaptan, a vasopressin antagonist, in patients hospitalized with worsening heart failure: a randomized controlled trial. *JAMA* 2004; 291(16):1963–1971.