

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

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Abstract

Heart failure is a disease that affects approximately 5 million Americans, accounts for 1 million hospitalizations annually, and represents the most common hospital discharge diagnosis for patients over the age of 65. Despite the significant impact of this disease, the accepted approach to treatment of acute decompensated heart failure (ADHF) has changed little in over 40 years. Another potential problem is that differentiating ADHF from other causes of dyspnea can be difficult, as historical elements, physical examination findings, and radiographic results lack adequate sensitivities to accurately identify the disease. This article, the first of a two-part series, will explore the historically accepted disease models for heart failure and their relevance to developing a therapeutic approach to ADHF. Additionally, diagnostic issues in heart failure will be examined, particularly the emerging role of natriuretic peptide assays for the identification of ADHF.

Key Words: Acute decompensated heart failure, natriuretic peptides, vasodilator response, neurohormones.

Introduction / Epidemiology

HEART FAILURE is a widespread disease. An estimated 5 million Americans suffer from heart failure, with over 500,000 new cases diagnosed annually (1, 2). The disease accounts for approximately 1 million hospitalizations annually and represents the most common discharge diagnosis for patients over the age of 65 (1). The financial burden that heart failure places on our health care system is enormous. It represents Medicare's single largest expense, with direct costs estimated at \$25.3 billion in 2005 (3). By comparison, the combined direct cost of all cancers in the US was \$69 billion in 2004, and HIV cost an estimated \$13.6 billion in 1999 (3). In spite of advances in therapy, the diagnosis of heart failure carries an abysmal prognosis.

In one study of over 30,000 patients admitted with new onset heart failure, the 30-day and one-year mortality rates were an astounding 12% and 30%, respectively (4). Of concern for the future, the hospitalization rate for heart failure has increased 159% in the past 10 years (1). Given our success in treating cardiac ischemic disease and our aging national population, the incidence of the disease can be expected to continue to increase in the coming decades.

Despite the enormous impact of heart failure and significant changes in our understanding of the physiology of the disease, the therapeutic approach to acute decompensated heart failure (ADHF) has changed little in the past 40 years. Registry data demonstrate that for a majority of patients hospitalized for heart failure, the only intravenous medication they will receive is a diuretic (5). The static nature of this therapeutic approach, largely unchanged in over 4 decades, is undoubtedly a result of multiple factors that influence clinical decision making in ADHF, including: few randomized controlled trials on which to base treatment decisions, a lack of consensus guidelines from professional organizations, and an apparent underappreciation of disease severity. The last point is underscored by the fact that despite an in-hospital mortality rate

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Glossary

ACE = angiotensin-converting enzyme
 ADHF = acute decompensated heart failure
 ANP = atrial natriuretic peptide
 BNP = b-type natriuretic peptide
 CHF = congestive heart failure
 COPD = chronic obstructive lung disease
 CNP = c-type natriuretic peptide
 ECG = electrocardiogram

ED = emergency department
 EDTA = ethylenediaminetetraacetic acid
 JVD = jugular venous distension
 LV = left ventricular
 MR = mitral regurgitation
 NT-ANP = N-terminal ANP
 NT-BNP = N-terminal BNP

that is similar to that of non-ST-elevation myocardial infarction, the vast majority of patients hospitalized with ADHF receive relatively non-aggressive medical care (6–8).

Pathophysiology—Choosing the Right Disease Model

Our clinical approach to ADHF is a reflection of the conceptual model we choose to apply to the disease. Disease models are essential to the practice of medicine. From a research perspective, a conceptual model allows us to form the hypotheses that clinical trials are designed to test. From a clinical perspective, our understanding of a disease model always influences our therapeutic approach to that disease. As evidence accumulates, models change, which in turn leads to changes in the diagnostic and treatment process.

As an example, the evolution of treatment guidelines for myocardial infarction from an approach that favored bed-rest and nitrates 50 years ago, to the anti-platelet and anti-thrombin treatment regimens of today, is a reflection of changes in our conceptual model of cardiac ischemia. Similarly, we would expect the therapeutic approach to ADHF to mirror changes to the accepted model of the disease. Interestingly, this does not appear to have occurred. A brief discussion of the evolution of the conceptual model for heart failure is important, because it not only helps explain why prevailing practice patterns exist, but also helps identify opportunities to improve our care of heart failure patients.

Three distinct heart failure models have existed over the past 50 years (9). Though these models have been used primarily to understand chronic heart failure, they offer valuable insight into how we should approach periods of acute decompensation. Each begins with the premise that an index event (myocardial infarct, chronic hypertension, myocarditis, etc.) leads to a decline in cardiac function. The end result of this process, including

compensatory responses and therefore the ideal approach to treatment, varies with each model and will be described below.

The Cardiorenal Model

The cardiorenal model, first described in the 1940s, viewed heart failure as an acute process defined by the presence or absence of edema as a result of decreased renal blood flow secondary to cardiac dysfunction (9). As volume retention and contractility were believed to be the primary determinants of decompensation, treatment centered on volume reduction with diuretics and contractility support with digoxin. No controlled studies were done to assess the efficacy of this approach, and by the 1970s the validity of the cardiorenal model had come into question for several reasons. First, the model could not explain the progressive nature of the disease (9). Second, invasive hemodynamic monitoring in heart failure patients consistently demonstrated excessive peripheral vasoconstriction, which was found to contribute significantly to decreases in cardiac performance (10).

However, even though the cardiorenal model was largely abandoned as an acceptable model for heart failure over three decades ago, our current approach to ADHF still appears to be based on it. As previously noted, the only parenteral medication most heart failure patients receive during hospitalization is a diuretic (5). Targeting volume reduction as the primary goal of initial therapy makes intuitive sense only if we accept the premise that volume overload is the most important physiologic abnormality in ADHF. In fact, the central issue in heart failure is a decline in cardiac performance. Fluid retention develops as a compensatory response to that primary deficit and is only one part of the clinical picture of heart failure. While it is true that diuresis eventually improves cardiac function as volume status returns to baseline, diuretics alone have no direct beneficial effect on cardiac performance. In fact, because they can

cause a reflexive increase in sympathetic tone and serum renin activity, the initial response to diuretic therapy may be a transient worsening of ventricular output (11). Increasingly, there is data to suggest that an approach that emphasizes diuresis as the mainstay of initial therapy has potential shortcomings, the evidence of which will be more thoroughly explored in Part II of this article.

The Cardiocirculatory Model

The extreme peripheral vasoconstriction that is typical of heart failure significantly impacts cardiac performance, a concept first described in the 1970s as the cardiocirculatory model of heart failure (9). Venous constriction, leading to an increase in preload and ventricular wall stress, and arterial constriction, causing an increase in afterload, both combine to cause a decrease in cardiac output, which results in decreased renal perfusion, leading eventually to sodium retention and volume overload (9). This sequence of events, initially characterized as the cardiocirculatory model, presents heart failure as a derangement between the heart and circulatory system, suggesting that the focus of therapy should be shifted away from the kidney to the peripheral blood vessels, and the use of vasodilator agents. The use of vasodilator therapy in ADHF has been shown to have both short- and long-term benefits. These benefits are presumably a result of the so called "vasodilator response" and reflect changes in cardiac loading conditions that result in improvement of cardiac performance (12).

The vasodilator response. The potential benefits of the vasodilator response, reflective of accepted basic cardiac physiology, are listed in Table 1. Ventricular force of contraction and therefore cardiac output are partially dependent on sarcomere stretch, a result of end-diastolic volume (preload) (13). Generally, increasing preload increases the overlap between actin and myosin filaments in the sarcomere, which results in an increase in ventricular force of contraction (Frank-Starling relationship). During periods of volume overload, significant increases in preload result in overstretching of the sarcomere, leading to a decline in the force of contraction because of less overlap between actin and myosin filaments. In this setting, decreasing preload allows for shortening of the sarcomere, more overlap of actin and myosin filaments, and a greater contractile force, with a subsequent improvement in cardiac output.

Additionally, in the presence of systolic dysfunction, changes in afterload have a significant effect on cardiac output (13). As a result, decreas-

TABLE 1
Vasodilator Response

1. Venous dilation / decreased preload
↓ Ventricular wall stress
↑ actin/ myosin overlap = ↑ force of contraction
↓ Ventricular dilatation
↓ 2° mitral regurgitation
2. Arterial dilation / decreased afterload
↓ Outflow resistance
improved cardiac output
↓ 2° mitral regurgitation
3. Combination of decreased preload / afterload
↓ filling pressures
↓ pulmonary edema / dyspnea
↑ cardiac output
improve renal perfusion / diuresis

ing afterload with arterial vasodilation results in improved ventricular performance.

Finally, secondary mitral regurgitation (MR) is a common contributor to decreased cardiac output in ADHF. "Secondary MR" refers to valvular incompetence that develops as a result of structural changes that accompany ventricular dilation during periods of volume overload. The incidence of secondary MR in ADHF approaches 100% in some studies (14). Significantly, in patients with secondary MR, treatment with an IV vasodilator has been shown to increase forward stroke volume by 40–60% and decrease regurgitant volume by 44% (15, 16).

In summary, the vasodilator response, by altering loading conditions in the heart, provides a mechanism to dramatically improve cardiac performance during periods of decompensation.

The Neurohormonal Model

Because vasodilatory efficacy was never clearly linked to long-term mortality and the cardiocirculatory model did not offer an explanation for disease progression, the search for a unifying model for heart failure continued (10). Early work on the neurohormonal model in the 1990s developed as a result of observations that certain biologically active molecules were present in increased amounts in heart failure patients (11). These molecules, initially termed "neurohormones," were found to have significant effects on cardiac performance, vascular tone, and intravascular volume, and in essence provided an explanation for the hemodynamic abnormalities common to heart failure patients. Although their expression is initially a compensatory mechanism to a fall in

cardiac output, chronic overexpression of these molecules was found to contribute to disease progression and episodes of decompensation via several mechanisms. The most well established neurohormonal systems are listed in Table 2.

Physiologic effects of neurohormonal activation. As a syndrome, heart failure patients share three common physiologic abnormalities: a decline in cardiac performance (related to either systolic or diastolic dysfunction), an increase in vascular tone, and varying degrees of volume retention. Neurohormonal pathways have significant influence over each of these physiologic parameters (Table 2).

One of the body's first responses to a decline in cardiac output is a reflex increase in sympathetic tone, which increases heart rate and contractility via beta-receptor stimulation. This response initially allows for maintenance of cardiac output, but with chronic stimulation, "downregulation" of beta receptors occurs, eventually leading to a decrease in inotropic response (17). In addition, endothelin, produced in both the vascular endothelium and ventricular tissue, has been shown to have negative inotropic effects in the failing heart (18). Serum norepinephrine, angiotensin, vasopressin, and endothelin all have well-described vasoconstrictive properties. Neurohormonal activation results in an overexpression of each of these peptides, a reasonable explanation for the increase in vascular tone common to the syndrome of heart failure (11, 19, 20). Finally, neurohormonal pathways, via aldosterone and vasopressin (anti-diuretic hormone), directly result in volume retention (20–22).

Perhaps the most appealing feature of the neurohormonal model is its ability to explain the progressive nature of heart failure as a disease process. Even when identifiable variables are controlled (e.g., ongoing cardiac ischemia, dietary in-

cretion, and medication noncompliance) heart failure is a progressive disease. Disease progression, reflected by worsening ventricular function, is believed to occur as a result of cardiac remodeling, in which changes occur at the cellular level of the heart, including myocyte hypertrophy, cellular apoptosis, and fibroblast proliferation and fibrosis. Essentially, healthy ventricular myocardium that is compliant and fills easily with blood during diastole, and pumps well during systole, is replaced by stiff, fibrotic tissue that neither fills nor pumps well. As a result, ventricular function progressively worsens, and the clinical syndrome of heart failure becomes apparent. In both human and animal models, neurohormonal activation has been shown to directly promote cardiac remodeling via its toxic effects on myocardial tissue (23–25).

The importance of neurohormonal activation in heart failure is underscored by its clear link to short- and long-term outcomes. Serum norepinephrine, endothelin, and renin levels have all been strongly linked to mortality, as has hyponatremia, a reflection of vasopressin activity (26–28). Furthermore, every medication that has been shown to decrease mortality in heart failure attenuates neurohormonal activity: beta blockers, angiotensin-converting enzyme (ACE) inhibitors, and spironolactone (an aldosterone antagonist) all exhibit significant effects on neurohormonal pathways, and presumably this is the mechanism of their benefit (29–31).

Although the importance of neurohormonal activation in the development and progression of heart failure appears clear, its direct importance in ADHF has been less studied. Given the fact that neurohormonal activation is directly responsible for the physiologic derangements common to ADHF, it seems intuitive that neurohormonal blockade would help speed return to a compensated state. Additionally, since the expression of neurohormones is increased during periods of decompensation, and these molecules are known to promote cardiac remodeling, the question arises as to whether remodeling accelerates in this setting. If true, therapy that provides neurohormonal blockade in ADHF may help slow overall disease progression, a consideration that will become increasingly important in the future, since many of the heart failure medications currently being developed selectively target neurohormonal pathways.

Also, relevant to this discussion is the role of the natriuretic peptides in heart failure. Natriuretic peptides are a group of endogenously occurring proteins that are released in response to ventricular stretch (32). The release of atrial natriuretic peptide (ANP, synthesized primarily in the atria), and

TABLE 2
Neurohormonal Activation in Heart Failure

Neurohormonal System	Physiologic Effects
Sympathetic nervous system	PV, VR
Renin angiotensin aldosterone system	PV, FR, VR
Endothelin system	PV, VR, NI
Antidiuretic hormone (vasopressin)	PV, FR, VR
Natriuretic peptides	vasodilation, diuresis

PV = peripheral vasoconstriction, VR = ventricular remodeling, FR = fluid retention, NI = negative inotrope

b-type natriuretic peptide (BNP, synthesized in the ventricles) is increased in heart failure (33). Both ANP and BNP have diuretic, natriuretic, and vasodilatory effects and act in a compensatory manner upon the physiologic derangements present in heart failure (34, 35). Additionally, they inhibit aldosterone secretion in the adrenal cortex, renin secretion in the kidney, and endothelin and sympathetic activity (36–38). Because they attenuate neurohormonal activity, natriuretic peptides offer a potentially protective mechanism against pathologic cardiac remodeling in heart failure.

Although levels of ANP and BNP increase in heart failure, their physiologic effect in this setting is blunted, possibly as a result of down-regulation of peptide receptors. Since they are overexpressed during periods of decompensation, natriuretic peptides have additional utility as diagnostic markers of myocardial dysfunction and heart failure.

Choosing the Right Disease Model

Because the evidence regarding the ideal treatment approach to ADHF is limited, formulating a therapeutic approach based on an acceptable disease model makes intuitive sense. Each model described above offers legitimate, if incomplete, insight into the physiology of decompensated heart failure, suggesting that a combined approach may be appropriate.

The vast majority of patients presenting with ADHF do so because of dyspnea, a result of fluid redistribution to the lungs reflective of cardiac dysfunction, specifically an increase in ventricular filling pressures. Since resolution of symptoms and return to a compensated state depends on normalization of filling pressures, this appears to be the most logical target for initial therapy. From this perspective, an emphasis on diuresis as the mainstay of therapy, as directed by the cardiorenal model, provides at best an inefficient, and at worst an ineffective mechanism for treatment. In contrast, an approach that focuses on reduction of filling pressures via the vasodilator response provides a direct mechanism to rapidly improve cardiac loading conditions, thereby increasing cardiac output. Furthermore, increasing cardiac output improves end organ perfusion including renal blood flow, presumably allowing for more effective subsequent diuresis. Finally, since neurohormonal pathways are directly responsible for the hemodynamic abnormalities that define decompensated heart failure, medication classes that provide direct neurohormonal blockade presumably offer superior efficacy for the treatment of ADHF. This

knowledge should be incorporated into the design of any therapeutic approach.

Diagnostic Options in Acute Decompensated Heart Failure

Conventionally, the initial diagnosis of ADHF is made based on the patient's history and physical exam, with additional information provided by a chest radiograph and electrocardiogram (ECG). The diagnosis, once suspected, is later confirmed by cardiac catheterization, echocardiogram, or radionuclide studies. Unfortunately, clinical findings tend to be neither sensitive nor specific for the diagnosis of heart failure (39–42). For example, jugular venous distension (JVD) has a specificity of 90% but a sensitivity of only 30%. Also, because the correct measurement is highly dependent upon the practitioner, the reproducibility of JVD is low (43). An S3 gallop, representative of rapid ventricular filling, is a highly specific but insensitive indicator of heart failure and can be particularly difficult to identify in a noisy emergency department (ED) setting (41). Other physical findings, such as pulmonary crackles or effusion, wheezing, and pedal edema, also carry a low combination of sensitivity and specificity, so that isolated findings alone are not very helpful in identifying the presence or absence of disease (44).

Chest radiography has long been considered a useful modality for diagnosing ADHF. When visualized, redistribution of pulmonary blood flow and pulmonary edema are accurate indicators of increased pulmonary artery wedge pressures characteristic of ADHF (44). Several studies, however, demonstrate the diagnostic limitations of chest radiography. In one small study of 22 subjects, Mahdyoon et al. demonstrated that patients with end-stage heart failure may have only cardiac enlargement without any evidence of radiographic pulmonary congestion, despite a significant increase in pulmonary artery wedge pressure (45). In another review of 880 patients presenting to the ED with dyspnea, radiographic evidence of ADHF (cephalization or pulmonary edema) had a specificity of 96–99% but a sensitivity of only 6–41% (44). Clearly, while radiographic findings of heart failure are quite helpful in identifying the disease, their absence does not preclude the diagnosis of ADHF.

Several ECG findings, including left bundle branch block and left ventricular hypertrophy, increase the likelihood of systolic dysfunction and therefore may have utility in identifying patients with ADHF. A recent study of 128 patients referred for evaluation of possible heart failure found that

QRS duration was an independent predictor of left ventricular dysfunction (EF<50%) (46). A prolonged QRS of either > 0.11 s or > 0.12 s had a specificity and positive predictive value of 90% and 98%, respectively. Sensitivities, however, were significantly lower (75–81%).

Recognizing that commonly available information concerning individual alternatives lacks the sensitivity or specificity to accurately diagnose ADHF, many investigators have examined a combined approach to the diagnosis. For example, the Framingham, Boston, and Duke criteria require multiple data elements (47, 48). Yet none of these criteria have shown adequate sensitivities or specificities to accurately diagnose ADHF.

The need for a simple, objective test to identify ADHF has driven much of the recent interest in the utility of the natriuretic peptides as an indicator of acute decompensation (49–51). In response to myocardial stretch, natriuretic peptides are synthesized as prohormones, which after being processed to hormones, are split into an inactive N-terminal fragment (NT-proANP or NT-proBNP) and a biologically active peptide (ANP and BNP), either of which may be measured as an indicator of heart failure (52).

Although all three natriuretic peptides (ANP, BNP, and c-type natriuretic peptide [CNP]) have been studied as markers of ventricular dysfunction, BNP testing is generally the most readily available in the ED setting and appears to be the most useful in identifying ADHF. The utility of BNP to identify ADHF was first studied in 1994 with 52 patients hospitalized for evaluation of acute dyspnea (49). In this study, radionuclide ventriculography and pulmonary function test were performed on each patient, and a panel of cardiologists, blinded to BNP results, determined the final diagnosis. BNP was found to have a sensitivity of 93% and a specificity of 90% for the diagnosis of heart failure.

More recently, point-of-care BNP testing has been evaluated in multiple studies in the ED setting. An early pilot study, observing 250 patients presenting with dyspnea to a Veteran Administration Hospital, found that with a BNP cutoff of 80 pg/mL, the sensitivity and negative predictive value for ADHF was 98% while the specificity was 92% (50). The sensitivity and specificity demonstrated in this study, higher than previously reported, may have been related to the fact that the study included only men and the mean age (64 years) was somewhat younger than would be expected in the general heart failure population. As BNP levels are known to increase with age and are typically higher in women than men, these results may not be applicable to the general population (52).

To address this issue, the Breathing Not Properly multinational study evaluated 1,586 patients who presented to seven emergency departments with acute dyspnea (51). A BNP level was measured for each patient at the time of presentation, and ED physicians, blinded to the result of the BNP assay, assessed the likelihood of congestive heart failure being the cause of the patients' acute dyspnea. Subsequently, two cardiologists reviewed the medical records of each patient, including the official interpretation of the ED chest X-ray, medical records that were not available at the time of presentation, follow-up tests such as echocardiogram, radionuclide angiography or left ventriculography, and the hospital course, to confirm the ED diagnosis.

The results of this study suggest that when compared to other clinical features, a BNP level is the most accurate predictor of the presence or absence of ADHF, with a sensitivity of 90% at a cut-off value of 100 pg/mL. As an isolated test, BNP was found to more accurately diagnose ADHF (83%) than either the National Health and Nutrition Examination Survey criteria (67%) or the Framingham criteria (73%) (51). Among patients for whom the clinician was highly confident of the diagnosis of ADHF, the use of BNP levels in this study raised the diagnostic accuracy by 10%. Perhaps more important, in the one-third of patients whose diagnoses were uncertain, based on clinical findings, adding a BNP level correctly identified 74% with ADHF and reduced the number of false negative diagnoses (for ADHF) to 7% (51).

Although these results appear very encouraging, the limitations of the BNP assay as a diagnostic aid for clinicians should be noted. A systematic review of the six ED-based BNP studies published through 2003 resulted in the following recommendations (53). BNP levels less than 50–80 pg/mL essentially rule out ADHF, while levels between 400 and 1,000 pg/mL and greater than 1,000 pg/mL are moderately and highly predictive of ADHF, respectively; BNP levels between 80 and 400 pg/mL represent a so-called diagnostic "grey zone," an area where non-heart-failure conditions may result in BNP elevations. As noted above, both age and female gender can cause mild elevations of BNP (100–200 pg/mL) that are not indicative of LV dysfunction (52, 54). Additionally, any disease process that increases right heart pressures will lead to an elevation of BNP, including pulmonary emboli, chronic obstructive lung disease (COPD), and primary pulmonary hypertension (52, 55, 56). Recently, sepsis has been shown to increase circulating BNP levels (57).

Lastly, concerns exist over the accuracy of BNP assays in the setting of renal dysfunction.

Key Concepts

1. Despite the enormous impact of heart failure on our society, our approach to the treatment of ADHF has changed little in the past 4 decades.
 2. As with any disease, treatment strategies in ADHF should be based on the accepted model of disease.
 - a. Emphasis on diuresis as the primary therapeutic intervention has limitations, particularly in advanced disease.
 - b. The use of vasodilator therapy provides rapid improvement in cardiac performance by altering loading conditions in the failing heart.
 - c. Attention to neurohormonal pathways may help slow disease progression and speed return to a compensated state.
 3. Differentiating ADHF from other causes of dyspnea can be difficult, as historical elements, physical exam findings, and radiographic results lack adequate sensitivities to accurately identify the disease.
 4. Natriuretic peptide levels (BNP and NT-BNP) are often helpful in identifying or ruling out ADHF; however, given frequent “grey zone” results, they must be interpreted in the context of other clinical information.
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Several studies indicate that BNP levels increase in renal patients in the absence of overt heart failure (58, 59). Though the impact of renal dysfunction on circulating BNP levels has not been clearly defined, the role of nonrenal clearance mechanisms and underlying patient substrate should be considered. Since BNP is cleared primarily by intracellular endopeptidases and clearance receptors, with renal filtration playing a minor role, the elevated BNP levels noted in patients with renal dysfunction may be reflective of volume and cardiac issues commonly associated with this patient group rather than renal failure itself (52). This idea is supported by a study of end-stage renal patients that found that BNP levels were only elevated in those patients with concurrent left ventricular (LV) hypertrophy (58).

Regardless of the cause, indeterminate results are not uncommon with BNP testing. In the Multinational Study, 40% of all patients with acute dyspnea had BNP levels in the “grey zone” range, as did 50% of patients ultimately diagnosed with ADHF (51). As a result, BNP testing can be expected to provide inconclusive results approximately 40% of the time, indicating the importance of incorporating BNP levels into the larger clinical picture to confirm the presence or absence of ADHF (53). Despite these limitations, the excellent negative predictive value of a low BNP level (< 80 pg/mL) can be helpful in ruling out congestive heart failure (CHF) as a cause of a patient’s dyspnea (53).

Although not studied as extensively as BNP, N-terminal BNP (NT-BNP) does appear to be useful as a diagnostic tool for ADHF. In an early study of 95 patients with suspected LV dysfunction, Fischer et al. found that BNP and NT-BNP had similar sensitivities (93% and 90%, respectively) and specificities (79% and 66%, respectively) for iden-

tification of impaired ventricular function (60). Of more relevance to the emergency physician, Lainchbury et al. compared BNP to NT-BNP in 205 patients presenting with acute dyspnea (61). They found BNP to be somewhat more sensitive (94% vs. 80%), while NT-BNP was more specific (87% vs. 70%) for the identification of ADHF. In this study, the assays values for both tests were highly correlated ($r=0.902$, $p<0.0001$).

From a laboratory perspective, NT-BNP assays may offer several advantages. As noted in a multicenter comparison study of 327 patient blood samples, NT-BNP remains stable in EDTA or heparinized plasma samples for 3 days at room temperature, while plasma BNP levels decline significantly after 4 hours at room temperature (62). Although irrelevant if BNP is run as a point of care assay, this liability may impact centralized laboratory testing. Additionally, NT-BNP has less than 0.01% crossreactivity with the active BNP peptide and so potentially can be used to guide treatment during nesiritide infusions (63).

Although less studied, plasma levels of NT-BNP are likely to be subject to the confounding variables listed above (pulmonary embolism, COPD, etc.) and may be more influenced by renal dysfunction than BNP. Although not clearly delineated, NT-BNP does not appear to be cleared by endopeptidases or clearance receptors, leading to speculation of a renal clearance mechanism (52). If true, this would decrease the utility of NT-BNP testing of patients with renal insufficiency.

Ultimately, given their similar diagnostic performance, it would appear that both BNP and NT-BNP are helpful in the identification of ADHF and that the choice of one assay over another should be based on institutional needs.

The other two natriuretic peptides, atrial natriuretic peptide (ANP) and CNP, have also been well studied for their possible utility in the diagnosis of ADHF. ANP, first identified and sequenced in the 1980s, has been shown to be a sensitive indicator of ventricular dysfunction. A majority of studies that have examined ANP and its precursor NT-ANP (N-terminal ANP) as a diagnostic tool have compared their levels against a measured degree of left ventricular dysfunction, often in the postmyocardial infarction setting (64–66). In these studies, sensitivities for an ejection fraction less than 40% ranged from 64–89%, with NT-ANP generally providing superior results. While it appears that both ANP and NT-ANP effectively identify LV dysfunction, two issues limit the applicability of these studies to the ED setting. First, although identification of ventricular dysfunction is certainly helpful in identifying patients at risk for ADHF, the diagnostic value of ANP levels in patients presenting with undifferentiated dyspnea has not been evaluated. Second, many patients presenting with ADHF suffer from isolated diastolic dysfunction, and the role of ANP testing in this group has not been evaluated.

CNP, derived predominantly from the vascular endothelium, has shown disappointing results as a marker for ADHF. Because plasma CNP levels are not consistently elevated in heart failure but are elevated in unrelated disease processes, it has been largely abandoned as a diagnostic tool for ventricular dysfunction (67–69).

Summary

ADHF is a disease process notable for both its increasing incidence and the severity of its prognosis. Although identification of the ADHF patient can be clinically challenging, the use of specific tools, particularly BNP testing, can improve diagnostic accuracy. Treatment strategies for ADHF should be grounded in an up-to-date understanding of the pathophysiology of the disease, as reflected by currently accepted conceptual models. Specific approaches to treatment will be more thoroughly explored in Part II of this article.

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

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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).

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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 myocytes 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.

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