

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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