

## B-Type Natriuretic Peptide and the Diagnosis of Acute Heart Failure

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*Heart failure is a major public health problem and despite significant advances in treatment remains the only cardiovascular disease still on the rise. Because this patient population often has a number of other concomitant diseases, including hypertension, coronary artery disease, arrhythmias, diabetes, chronic obstructive pulmonary disease, and renal insufficiency, diagnosis can be difficult. Currently, diagnosis of acute decompensated heart failure (ADHF) relies largely on patient history, signs, and symptoms. Rapid and accurate diagnosis of ADHF in the emergency department (ED) is essential for timely initiation of treatment. Thus, any means for improving the speed and accuracy of ADHF diagnosis in the ED can contribute to better clinical and economic outcomes. Measurement of circulating endogenous B-type natriuretic peptide (BNP) has proven to be a sensitive and specific test for heart failure that can easily be used in the ED. Used in conjunction with standard diagnostic procedures, measurement of BNP levels can improve the accuracy of ADHF diagnosis during the critical window for optimal care.*

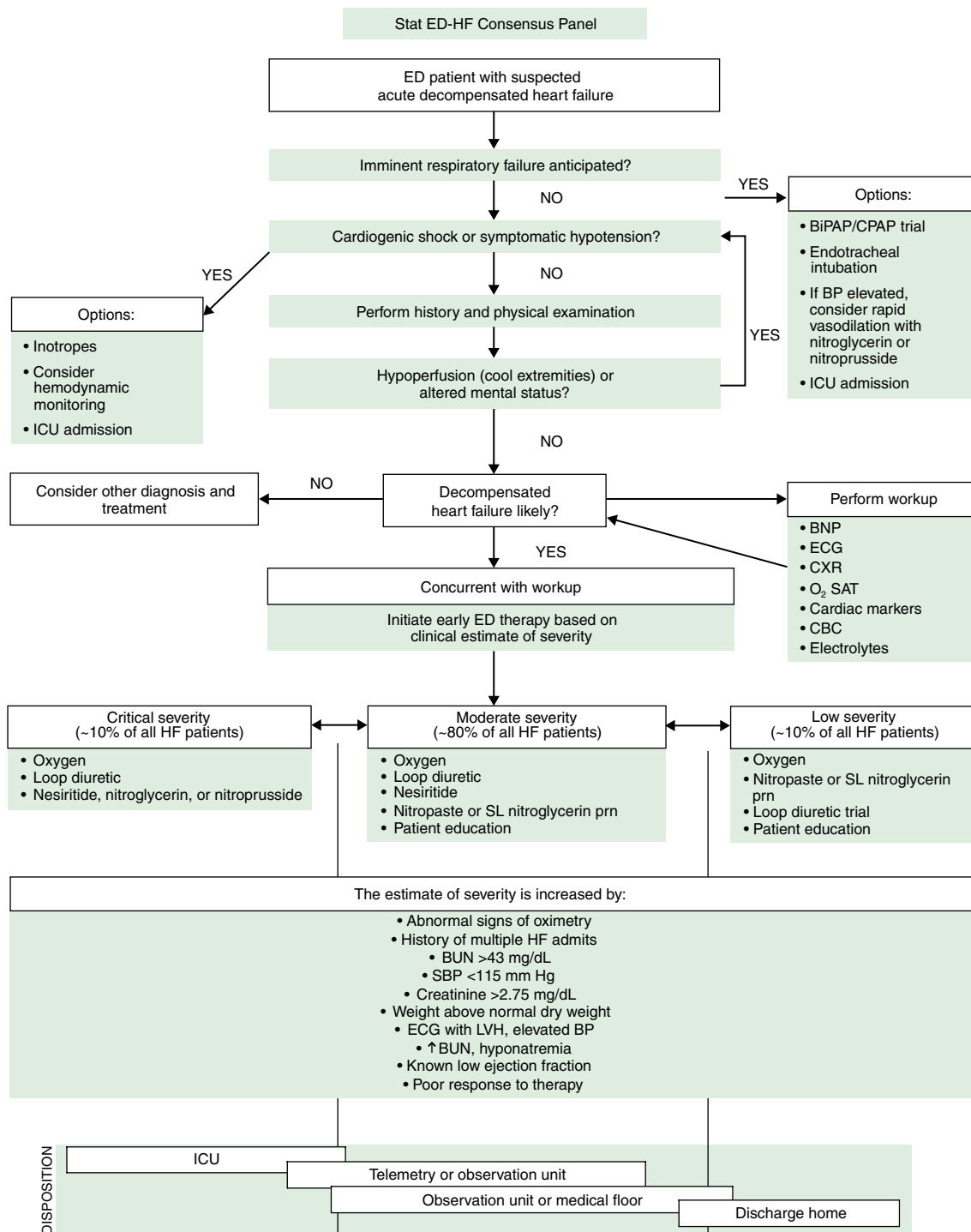
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**Key words:** B-Type natriuretic peptide • Heart failure • Nesiritide

**H**ear failure is a major public health problem and despite significant advances in treatment remains the only cardiovascular disease still on the rise.<sup>1</sup> Acute decompensated heart failure (ADHF) is responsible for nearly 1 million hospitalizations annually in the United States.<sup>2</sup> Over the past decade, the rate of hospitalization in the United States has increased by greater than 150%, and it is estimated that almost \$24 billion is spent annually on direct costs attributable to hospital care.<sup>1</sup> Predominantly a disease of the elderly,



This treatment algorithm represents only one approach to the management of patients with heart failure. It is provided solely as a guide, and the decision regarding the specific care of a particular patient must be made by, and is the responsibility of, the physician and patient in light of all the circumstances presented by that patient.

**Figure 1.** Guidelines for the early stabilization and disposition of acute decompensated heart failure in the emergency department (ED). BiPAP, bilevel positive airway pressure; BNP, B-type natriuretic peptide; BP, blood pressure; BUN, blood urea nitrogen; CBC, complete blood cell count; CPAP, continuous positive airway pressure; CXR, chest x-ray; ECG, electrocardiography; HF, heart failure; ICU, intensive care unit; LVH, left ventricular hypertrophy; O<sub>2</sub> SAT, oxygen saturation; prn, as needed; SBP, systolic blood pressure; SL, sublingual. Adapted with permission from Emerman.<sup>6</sup>

ADHF is the most common cause of hospitalization for individuals more than 65 years of age.<sup>2</sup> Because this patient population often has a number of other concomitant diseases, including hypertension, coronary artery disease, arrhythmias, diabetes, chronic obstructive pulmonary disease (COPD), and renal insufficiency,<sup>3,4</sup> diagnosis can be difficult.

Currently, diagnosis of ADHF relies largely on patient history, signs, and symptoms. At least in part because of the potential for multiple comorbidities, the misdiagnosis rate is 12% in the emergency department (ED), where most patients with ADHF first present. Overdiagnosis and underdiagnosis occur with equal frequency.<sup>5</sup>

Rapid and accurate diagnosis of ADHF in the ED is essential for timely initiation of treatment. Initiation of early treatment in the ED has been proven to decrease the need for hospitalization, improve clinical outcomes, and reduce costs.<sup>3,6</sup> Thus, any means for improving the speed and accuracy of ADHF diagnosis in the ED can contribute to better clinical and economic outcomes. Measurement of circulating endogenous B-type natriuretic peptide (BNP) has proven to be a sensitive and specific test for heart failure that can easily be used in the ED. Used in conjunction with standard diagnostic procedures, measurement of BNP levels can improve the accuracy of ADHF diagnosis during the critical window for optimal care.

### Diagnosis of ADHF in the ED: Clinical Assessment

The first step in assessing patients in the ED who are suspected of having ADHF is to identify those with imminent respiratory failure and cardiogenic shock. Inotropic therapy, hemodynamic monitoring, and admission to the intensive care unit should be considered for patients with cardiogenic shock.<sup>6</sup> For patients without imminent respiratory failure or cardiogenic shock, a diagnostic workup, which includes a review of past medical history, clinical assessment, laboratory evaluations (ie, BNP level, electrolytes, blood urea nitrogen [BUN], and serum creatinine), electrocardiogram (ECG), and chest x-ray, should be performed and therapy initiated in the ED whenever possible (Figure 1).<sup>6</sup> Determination of the need for hospitalization can be based on severity of decompensation and response to initial treatment.

A number of criteria sets are widely used to diagnose heart failure. These include the Framingham, National Health and Nutrition Examination Study (NHANES), and Boston criteria.<sup>7</sup> The Boston criteria are

the urgent-care center of the San Diego Veterans Healthcare system, prior diagnosis of heart failure was the best clinical predictor of ADHF.<sup>5</sup> However, in this analysis, diagnosis based solely on a history of heart failure resulted in a correct diagnosis of heart failure for only 80% of cases.<sup>5</sup> Similar results were obtained in a prospective study of 1586 patients who presented to the ED with acute dyspnea. In this population, the accuracy rate was 75% for history of chronic heart failure. A history of paroxysmal dyspnea was also predictive of heart failure in 60% of cases.<sup>8</sup> Patient history of myocardial infarction, chest pain, hypertension, and recent weight gain resulting from fluid retention also might have predictive value. However, reliance on patient history might be limited by the inability of acutely ill patients to provide accurate information.<sup>9,10</sup>

### Symptoms

The symptoms of ADHF are nonspecific. However, dyspnea on exertion is a hallmark of ADHF, occurring in 70% of patients who present to the ED.<sup>5</sup> Among patients without a his-

*Reliance on patient history might be limited by the inability of acutely ill patients to provide accurate information.*

based on a combination of patient history, findings on physical examination, and chest radiography. Of these three sets, the Boston criteria are considered to have the best combined sensitivity (50%) and specificity (78%).<sup>7</sup> To improve the accuracy of the diagnostic criteria, the predictive strength of the individual components has been analyzed.

### Patient History

Patient history is critical to the accurate diagnosis of ADHF. In one study of 250 patients presenting to

tory of heart failure, dyspnea on exertion was found to have a diagnostic accuracy rate of 90%.<sup>5</sup> Typically, cough and rapid fatigue accompany dyspnea. As the severity of heart failure increases, patients might develop abdominal bloating and altered mental status. Dyspnea on exertion frequently progresses to paroxysmal dyspnea, orthopnea, and dyspnea at rest. The Boston criteria heavily weight the latter two symptoms as predictive of heart failure.<sup>7</sup> In one study, ADHF was correctly diagnosed on the basis of dyspnea on exertion

in only 55% of cases in the overall population. In the same study, the presence of orthopnea had a diagnostic accuracy rate of 72% on univariate analysis and 86% after multivariate analysis.<sup>5</sup> These findings suggest that symptoms in patients with less severe disease, who might be good candidates for outpatient treatment, are less reliable diagnostic indicators of ADHF than in more seriously ill patients.

Dyspnea at rest or on exertion, a new cough, and altered mental status associated with hypoxia are often associated with left ventricular failure. Acute or progressive gastrointestinal symptoms, including tenderness over the right upper quadrant (hepatomegaly), increasing abdominal girth (ascites), bloating and diarrhea (bowel edema), and lower extremity edema, reflect predominant right ventricular failure.

#### *Physical Examination*

Findings on physical examination of patients with ADHF might include high or low blood pressure, rales, wheezing, peripheral edema, ascites, and abnormal heart sounds.<sup>5</sup> Because patients with heart failure might have high, low, or normal blood pressure, abnormal blood pressure is not indicative of heart failure. On univariate anal-

ysis, elevated systolic blood pressure (>149 mm Hg) and low systolic blood pressure (<100 mm Hg) had diagnostic accuracy rates of 54% and 60%, respectively.<sup>5</sup> However, patients with heart failure and with systolic blood pressure less than 90 to 100 mm Hg who are not taking antihypertensive medication have the poorest prognosis. Oxygen saturation of less than 90% is also indicative of poor outcome and a need for hospital admission.<sup>7,11</sup> The presence of rales was one of the best predictors of ADHF, with an accuracy rate of 70%.<sup>5</sup> Other signs of heart failure, including jugular venous distention in patients weighing more than 180 pounds with S3 gallop, might be useful in substantiating a diagnosis but are of little predictive value alone because they are associated with a number of other comorbidities.<sup>5</sup>

#### *Diagnostic Tests*

An ECG is recommended for all patients suspected of having ADHF. Although findings on an ECG are not diagnostic for heart failure, the presence of atrial and ventricular arrhythmias is common and can be indicative of poor prognosis. Moreover, a wide QRS complex in a patient shown to have a low ejection fraction (EF) might be an indication for possible treatment with a biventricular implantable cardiac defibrillator.

Chest x-rays allow for analysis of heart size, which has a diagnostic accuracy rate of 75% to 80%, a rate similar to that of history of heart failure.<sup>5</sup> Evidence of increased pulmonary venous pressure and pleural effusion secondary to heart failure

#### *Laboratory Evaluation*

Similar to other aspects of routine diagnosis in the ED, no single laboratory test or combination of routine tests is specific for ADHF diagnosis. In addition, results of laboratory tests are important for managing comorbidities. Electrolyte levels are typically within the normal range in patients with heart failure. However, perturbations of sodium and potassium levels can result from the use of diuretics and inhibitors of the renin-angiotensin-aldosterone system (RAAS).<sup>7</sup> Elevations in BUN and serum creatinine levels occur, and azotemia might be found in patients with advanced disease.<sup>7</sup>

Practical tools to identify prognostic indicators for patients hospitalized with ADHF have recently been identified.<sup>12</sup> Data from the Acute Decompensated Heart Failure National Registry (ADHERE) identified two routine laboratory values (BUN and serum creatinine) that can be used to risk stratify ADHF patients. The best predictor for mortality was high BUN ( $\geq 43$  mg/dL) on admission followed by low systolic blood pressure (<115 mm Hg) on admission and then by high serum creatinine ( $\geq 2.75$  mg/dL).<sup>12</sup>

To achieve early and accurate diagnosis of ADHF, a rapid, sensitive, and specific test is needed. Rapid measurement of endogenous BNP levels is now possible and adds significant predictive power to standard diagnostic procedures.<sup>13</sup>

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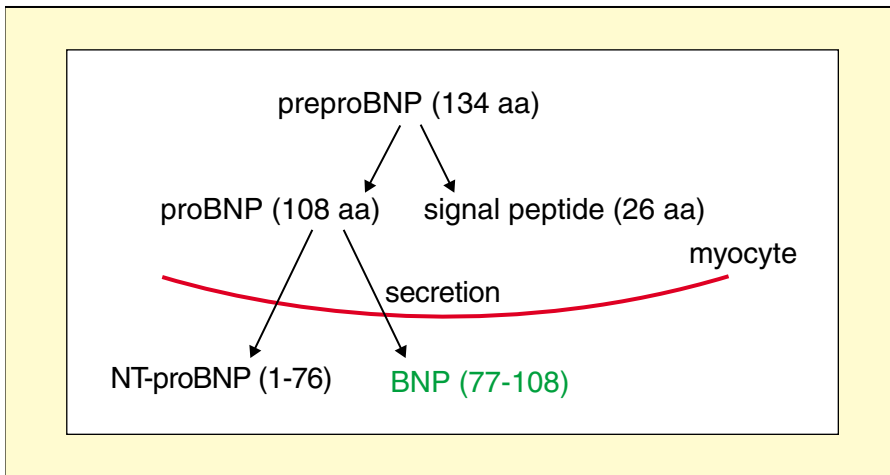
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also might be visualized on a chest x-ray.<sup>7</sup>

Echocardiography can be used to assess ventricular size, mass, and function and is currently the gold standard for diagnosing left ventricular dysfunction.<sup>5,7</sup> However, this technique is expensive and might be difficult to perform on patients with heart failure.<sup>5</sup>

#### **B-Type Natriuretic Peptide**

BNP is a counter-regulatory neurohormone with pluripotent properties. Synthesized and released by the cardiac ventricles, BNP is upregulated in response to volume expansion and increased wall tension resulting from pressure overload.<sup>5,14</sup> BNP facilitates natriuresis and diuresis while enhancing glomerular fil-



**Figure 2.** Release of B-type natriuretic peptide (BNP) from cardiac myocytes. aa, amino acid; NT-proBNP, N-terminal pro-BNP.

tration rate (GFR)<sup>15-18</sup>; produces vasorelaxation<sup>15,19,20</sup>; suppresses neurohormonal activation of angiotensin II, aldosterone, and endothelin-I<sup>16,18,21,22</sup>; and regulates fluid and electrolyte homeostasis, contributing to volume and blood pressure regulation.<sup>15,16</sup> In addition, BNP is sympathoinhibitory with respect to adrenergic discharge. Finally, BNP has lusitropic (diastolic-relaxing), antifibrotic, and antiremodeling capabilities.<sup>23</sup>

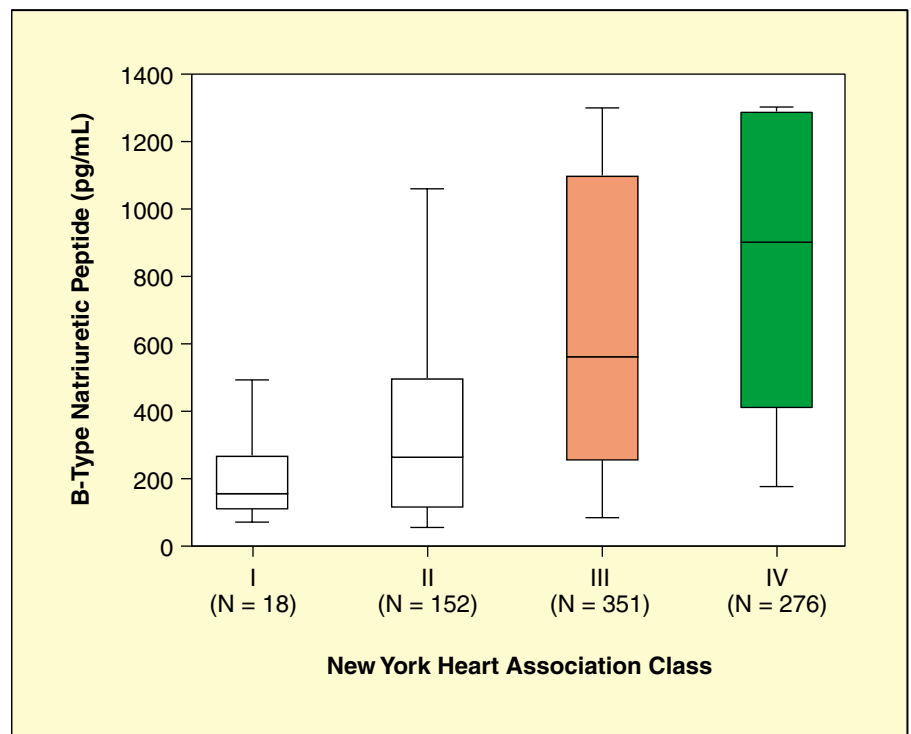
Two bioassays are available to measure BNP levels.<sup>24</sup> The endogenous cardiac hormone BNP has been more commonly investigated as a predictable marker for heart failure progression and improvement. Recently, the aminoterminal portion of pro-BNP (NT-proBNP) has been introduced as a second biomarker with prognostic potential (Figure 2).<sup>25</sup>

As would be expected, levels of circulating BNP are elevated in heart failure and are highly correlated with severity as defined by New York Heart Association classification (Figure 3).<sup>8</sup> Caution is needed, however, in interpreting test results because levels of BNP increase with age, in COPD, and in end-stage renal disease. These elevations with age

might be related to an increase in diastolic dysfunction with a decrease in creatinine clearance, COPD with fluid overload and right ventricular dysfunction, and in end-stage renal disease, a decrease in renal clearance

of BNP secondary to downregulation of the NP clearance receptor as well as the accompanying increase in intravascular volume.<sup>26,27</sup> No differences in BNP levels have been measured in patients with hypertension or diabetes and age-matched controls.<sup>10</sup>

In an initial evaluation, the optimal diagnostic cutoff for blood BNP levels was 80 pg/mL.<sup>5</sup> The 80-pg/mL cutoff had a sensitivity of 98% and a specificity of 92%. The positive predictive value was 90%, and the negative predictive value was 98%. The accuracy rate of 94% exceeds that of any of the other variables tested.<sup>5</sup> In multivariate analyses, the addition of BNP concentrations to the regression substantially increased the explanatory power of the model. The diagnostic accuracy of BNP levels was 97% for the overall population and 98% for those without a history of



**Figure 3.** Box plots depicting the median, interquartile range, and minimum and maximum levels of B-type natriuretic peptide by New York Heart Association functional class in the Breathing Not Properly Multinational Study. Reprinted with permission from Maisel et al.<sup>8</sup>

Table 1  
Multiple Logistic-Regression Analysis of Factors Used for Differentiating  
Between Patients With and Without CHF

Predictor	P	Odds Ratio (95% CI)*
Age	.4	1.02 (1.00–1.03)
History of heart failure	<.001	11.08 (6.55–18.77)
History of myocardial infarction	<.001	2.72 (1.41–4.54)
Rales	<.001	2.23 (1.41–3.58)
Cephalization of vessels	<.001	10.69 (5.32–21.47)
Edema	<.001	2.88 (1.81–4.57)
Jugular venous distention	.04	1.87 (1.04–3.36)
B-type natriuretic peptide	<.001	29.60 (17.75–49.37)

CHF, congestive heart failure; CI, confidence interval.  
\*The odds ratio reflects the odds for patients with the characteristic in question, as compared with those without the characteristic. The odds ratio for age represents the exponent for each year of age in the logistic equation.  
Reprinted with permission from Maisel AS et al.<sup>8</sup>

heart failure. This finding indicates that BNP levels contribute meaningful diagnostic information not provided by history, symptoms, signs, or radiologic and laboratory findings. Had a cutoff of 80 pg/mL been used in diagnosing the patients in this analysis, 29 of the 30 erroneous diagnoses could have been avoided.<sup>5</sup>

These results were confirmed in a second study that used a blood BNP cutoff level of 100 pg/mL. This cutoff level discriminated between ADHF and other causes of dyspnea with a sensitivity of 90%, a specificity of 76%, and an accuracy of 83% (Figure 4).<sup>8</sup> These results were more accurate than those obtained with either the Framingham (73%) or the NHANES (67%) criteria.<sup>8,28,29</sup>

In this study, multiple logistic regression analysis demonstrated that although a history of heart failure and cephalization of vessels on chest x-ray were strong independent predictors of heart failure, a BNP level greater than 100 pg/mL was the strongest predictor measured.<sup>8</sup> The odds ratios for history of heart failure and cephalization of vessels were 11.08 (95% confidence interval [CI]

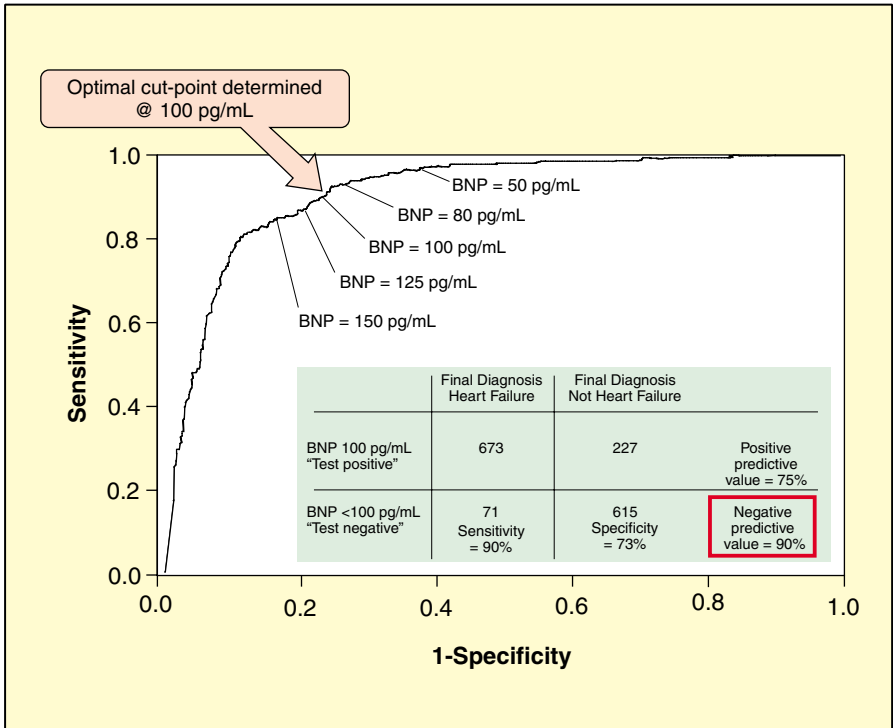
6.55–18.77) and 10.69 (95% CI 5.32–21.47), respectively. For BNP levels greater than 100 pg/mL, the odds ratio was almost tripled at 29.60

(95% CI 17.75–49.37) (Table 1).<sup>8</sup> Although BNP levels greater than 100 pg/mL are likely to be due to heart failure, clinical correlations are always necessary.

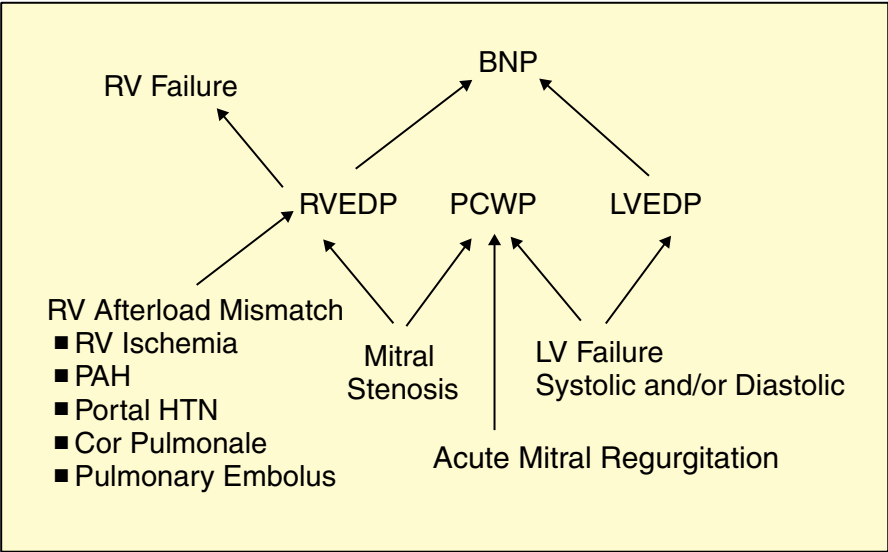
**Interpreting BNP Levels: Hemodynamic Determinants and Special Considerations**  
When making a diagnosis of ADHF, a correct interpretation of the BNP level is essential to its correct application. A variety of hemodynamic conditions affect BNP levels (Figure 5).

**Elevated Pulmonary Capillary Wedge Pressure**  
BNP is often thought of as a verisimilitude of the pulmonary capillary wedge pressure (PCWP); however, BNP is not made in the pulmonary capillary tissue but rather is of ventricular origin.<sup>5,14</sup> With left

Figure 4. Specificity, sensitivity, and accuracy of a B-type natriuretic peptide (BNP) cutoff value of 100 pg/mL for differentiating heart failure from other causes of dyspnea. Adapted with permission from Maisel et al.<sup>8</sup>







**Figure 5.** Hemodynamic determinants of B-type natriuretic peptide (BNP). HTN, hypertension; LV, left ventricular; LVEDP, left ventricular end diastolic pressure; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; RV, right ventricular; RVEDP, right ventricular end diastolic pressure.

ventricular dysfunction, an increase in filling pressure (eg, left ventricular end diastolic pressure [LVEDP]) occurs; and in straightforward left ventricular heart failure, there is

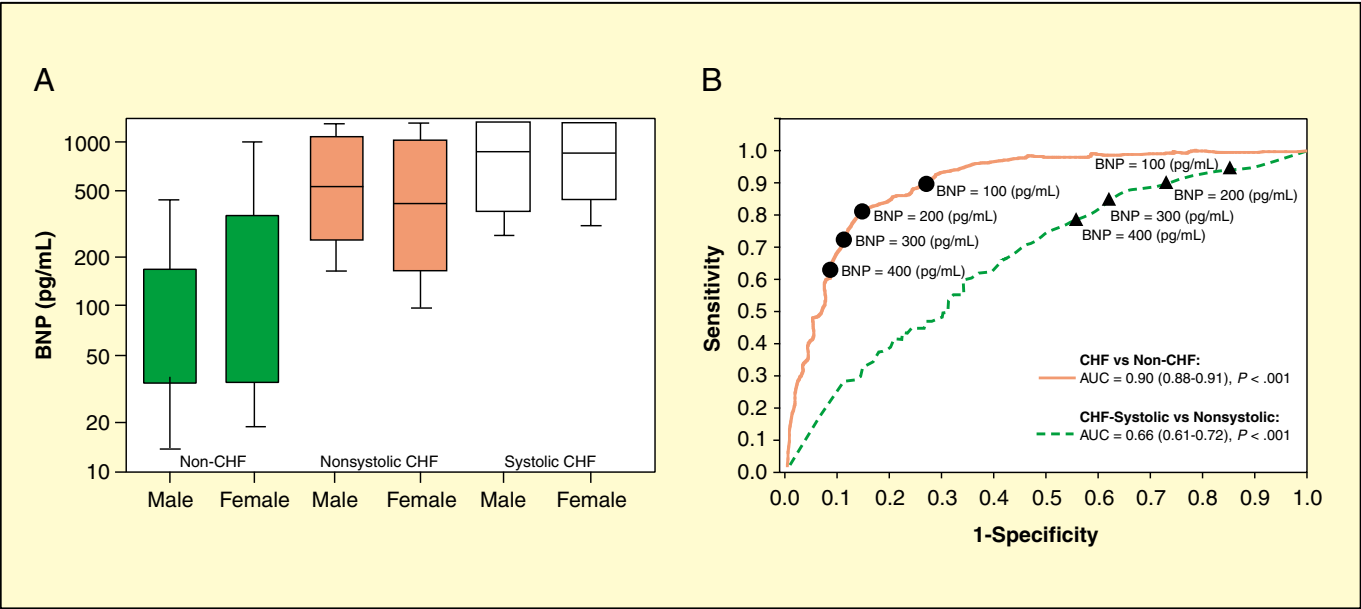
equilibration of the LVEDP and the PCWP. In contrast, in heart failure secondary to causes upstream from the left ventricle, including acute mitral regurgitation (MR), the

PCWP will increase where there is no initial effect on the LVEDP. In this context, BNP levels are lower than expected. With chronic MR, once again the LVEDP and PCWP equilibrate, and BNP is secreted in expected amounts compatible with volume overload.

With chronic decompensated heart failure in patients at the more severe end of the heart failure spectrum, BNP might correlate poorly with PCWP, leading to the concept of “dry” or euvolemic BNP versus “wet” or volume overload BNP.<sup>30</sup> In most cases of chronic heart failure, euvolemic (or baseline) BNP levels are extremely important during ADHF evaluation and workup. In the absence of preexisting euvolemic BNP levels, rapid BNP levels, along with clinical assessments, guide ADHF diagnosis.

**Systolic Versus Diastolic Heart Failure**  
The prevalence of systolic and diastolic heart failure is approximately equal in acute and chronic disease.<sup>31</sup>

**Figure 6. (A)** Box-plot results from the Breathing Not Properly Multinational Study, showing median levels of B-type natriuretic peptide (BNP) measured in men and women more than 70 years of age with dyspnea not due to congestive heart failure (CHF) with an adjunct final diagnosis of heart failure. Patients are subdivided by those with systolic CHF versus nonsystolic CHF. **(B)** Receiver-operating characteristic curve for BNP for differentiating between CHF and non-CHF cases and between systolic versus nonsystolic dysfunction (non-CHF patients excluded). AUC, area under the curve. Both panels adapted with permission from Maisel et al.<sup>32</sup>



Although Doppler echocardiography can facilitate diagnosis, diastolic heart failure is often diagnosed on the basis of typical signs and symptoms of heart failure, with preserved left ventricular function and no valvular abnormalities on echocardiogram.<sup>9</sup> Elevated BNP levels have been described for both systolic and diastolic heart failure. However, patients with diastolic heart failure have been found to have significantly lower levels at presentation. In the Breathing Not Properly study, the mean BNP level for patients with diastolic heart failure was 413 pg/mL, compared with 821 pg/mL ( $P < .001$ ) for those with systolic dysfunction.<sup>32</sup> Despite the disparity in mean BNP levels in ADHF with preserved EF, BNP elevations significantly overlap acute low EF BNP elevations, indicating significant neurohormonal activation by both types of acute heart failure (Figure 6A).<sup>32</sup> The receiver operating characteristic (ROC) for heart failure with preserved EF as compared with that for low EF is less reliable (Figure 6B). However, Angeja and Grossman suggested that "the simplest definition of a diastolic CHF may be an elevated BNP with normal systolic function."<sup>33</sup> Because BNP increases during exercise along with left ventricular filling pressure in heart failure patients, exercise measurements of BNP might even be a provocative test to identify chronic diastolic heart failure.<sup>34</sup>

Although BNP levels might add modest discriminatory value in differentiating diastolic from systolic heart failure, initial treatment in the acute setting might be similar for both conditions, obviating with the use of vasodilator and diuretic therapy the need for early differential diagnosis. Therefore, the major role for BNP assessment is to distinguish patients with heart failure from those without heart failure (Table 2).<sup>32</sup>

#### *Right Ventricular Pulmonary Disease*

Another instance in which BNP levels are elevated is in right ventricular failure, especially in association with pulmonary hypertension. Right ventricular ischemia, pulmonary hypertension, lung disease with right heart failure, a large pulmonary embolus, and right ventricular afterload mismatch (eg, Mustard procedure with uncorrected transposition of the great vessels) are among the conditions that lead to an elevation in the right ventricular end diastolic pressure (RVEDP). In the case of a massive pulmonary embolus, BNP

levels can approach 1000 pg/mL, reflecting maximal right ventricular production of BNP. With persistent elevation of the RVEDP, right ventricular failure with dilation might occur, with a significant decrease in right ventricular systolic function followed by declining pulmonary artery pressures, which result in a decrease in the RVEDP. In this case, BNP levels decline presumably as a result of severely diminished myocyte functional integrity. If reverse remodeling is obtained through appropriate therapy, a paradoxical rise in BNP is observed, reflecting improved

Table 2  
Causes of Elevated or Reduced B-Type Natriuretic Peptide

	Relationship
<b>Elevated BNP*</b>	↑ RVEDP
Precapillary pulmonary HTN	
Pulmonary arterial HTN	
Pulmonary embolus	
COPD with cor pulmonale	
Portal pulmonary HTN	
Transposition of the great vessels with Mustard procedure	
Acute coronary syndrome	Transient rise in LVEDP
Arrhythmia-induced LV dysfunction	Transient rise in LVEDP
Renal failure	Related to clearance receptor down-regulation; increase in effective volume overload
Aging	Increasing diastolic dysfunction (modest); decreasing creatinine clearance
<b>Lower-Than-Expected BNP</b>	
Obesity (BMI $\geq 30$ kg/m <sup>2</sup> )	Related to the natriuretic clearance receptor in adipose tissue
Flash pulmonary edema	Delay in synthesis of BNP
Acute mitral regurgitation	Heart failure upstream from LV
Mitral stenosis†	Heart failure upstream from LV
Atrial myxoma	Heart failure upstream from LV
Severe RV failure	Inability to synthesize BNP associated with loss of functional integrity of myocytes, which may reverse with improvement in RV systolic function

BMI, body mass index; BNP, B-type natriuretic peptide; COPD, chronic obstructive pulmonary disease; HTN, hypertension; LV, left ventricle; LVEDP, left ventricular end diastolic pressure; RV, right ventricular; RVEDP, right ventricular end diastolic pressure.

\*Other than congestive heart failure. In general, RV maximum BNP levels are  $\leq 1000$  pg/mL. LV BNP maximal levels might be significantly greater (ie,  $>5000$  pg/mL).

†BNP elevation secondary to ↑ RVEDP.



right ventricular systolic function (unpublished data, Berkowitz).

#### Acute Ischemia

Acute ischemia leads to a transient increase in BNP levels regardless of the presence of heart failure. Two studies have shown that this ischemia-related rise in BNP is prognostic but not necessarily correlated with hemodynamic status. The increase in BNP level in this setting without the presence of heart failure might be treated with heparin and antiplatelet agents; diuretic therapy would be inappropriate. De Lemos and colleagues<sup>35</sup> reported a significant, stepwise increase in the unadjusted death rate among patients with acute coronary syndromes in increasing quartiles of BNP values ( $P < .001$ ). BNP levels were also associated with the risk of new or recurrent myocardial infarction ( $P < .001$ ) and new or worsening heart failure ( $P < .001$ ) at 10 months.<sup>35</sup> A second analysis of baseline BNP levels of 1676 patients with non-ST-elevation acute coronary syndromes revealed that baseline values were predictive of clinical outcomes.<sup>36</sup> Individuals with BNP levels greater than 80 pg/mL had a more than threefold greater risk of mortality at 7 days (2.5% vs 0.7% with BNP < 80 pg/mL,  $P = .006$ ) and at 6 months (8.4% vs 1.8% with BNP < 80 pg/mL,  $P < .0001$ ). These same patients were five times more likely to develop new heart failure within 30 days (5.9% vs 1% with BNP < 80 pg/mL,  $P < .0001$ ). However, in this study, BNP levels were not predictive of response to early invasive evaluation.<sup>36</sup>

In the special case of flash pulmonary edema, it is estimated that at least 1 hour is necessary to see significant BNP elevations.

#### Renal Disease

The neurohormonal factors that contribute to cardiovascular disease

can also contribute to renal dysfunction. It is not surprising, therefore, that approximately half of all patients with heart failure have a serum creatinine level of at least 1.5 mg/dL, and an estimated 40% of individuals with chronic kidney disease (CKD) have heart failure.<sup>37</sup> Approximately 20% of patients admitted to the hospital with ADHF have a serum creatinine level greater than 2 mg/dL, and 30% have a history of CKD.<sup>3</sup> These findings are consistent with data from NHANES III. In this cross-sectional sample of adults in the United States, patients with CKD (serum creatinine >1.7 mg/dL for women and >2.0 mg/dL for men) were 15 times more likely to have CHF than were those with normal renal function. As renal function deteriorates, the prevalence of CHF increases.<sup>37</sup>

The mean BNP levels for patients with GFRs less than 60 mL/min/1.73 m<sup>2</sup> are typically above normal, raising the question of whether BNP contributes to renal dysfunction (Table 3).<sup>38</sup> However, the correlation between GFR and BNP levels in patients without heart failure is weak.<sup>38,39</sup> Furthermore, BNP levels do not stabilize after dialysis.<sup>39,40</sup> Rather, BNP levels are significantly correlated with left ventricular mass in-

dex ( $P < .001$ ).<sup>39</sup> These results suggest that elevated BNP is not the result of CKD alone.

Although ADHF does not typically result in electrolyte imbalances, diuretics and inhibitors of the RAAS can lead to severe electrolyte abnormalities.<sup>7,41</sup> Serum creatinine levels and BUN values can be used to distinguish between patients with drug-related electrolyte disturbances and those who actually have CKD. Making this distinction is important because morbidity and mortality are significantly increased in cardiorenal failure compared with either disorder in isolation.<sup>12,42-47</sup> Data from ADHERE revealed that levels of BUN greater than 43 mg/dL and serum creatinine greater than 2.75 mg/dL on admission for ADHF were highly predictive of in-hospital mortality.<sup>12</sup> In a multivariate Cox regression model, the risk of all-cause mortality in patients admitted with ADHF increased with each quartile of BUN. Patients admitted for ADHF whose BUN values were in the highest quartiles had a 2.3-fold greater risk of death than those with BUN levels in the lowest quartiles (95% CI 1.3-4.1,  $P = .005$ ).<sup>48</sup> Furthermore, even minor worsening of renal function during hospitalization for ADHF is associated with worsening outcomes.<sup>47</sup>

Table 3  
Mean B-Type Natriuretic Peptide Levels at Different GFRs in  
Patients With and Without CHF

GFR (mL/min/1.73 m <sup>2</sup> )	BNP level (pg/mL)	
	With CHF	Without CHF
≥90	561.6	85.4
60-89	647.5	131.7
30-59	745.6	297.2
<30	850.7	285.0

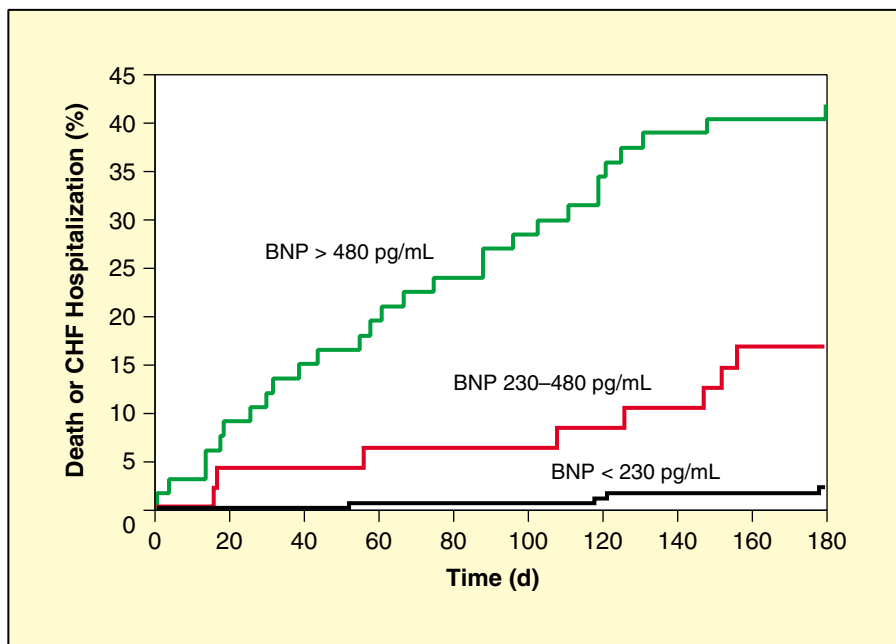
BNP, B-type natriuretic peptide; CHF, congestive heart failure; GFR, glomerular filtration rate. Adapted with permission from McCullough et al.<sup>38</sup>

### BNP Levels Predict Clinical Outcomes

In addition to increasing the accuracy of the diagnosis of ADHF, BNP levels are predictive of clinical outcomes and therefore might be useful in making decisions with regard to the treatment of ADHF. Baseline (at admission) BNP levels are correlated with in-hospital mortality.<sup>49</sup> In an analysis of data from 642 consecutive patients admitted with suspected heart failure, baseline BNP values were significantly higher among patients who died during the index hospitalization than among those who were discharged alive ( $763 \pm 473$  pg/mL vs  $368 \pm 412$  pg/mL;  $P < .0001$ ).<sup>49</sup>

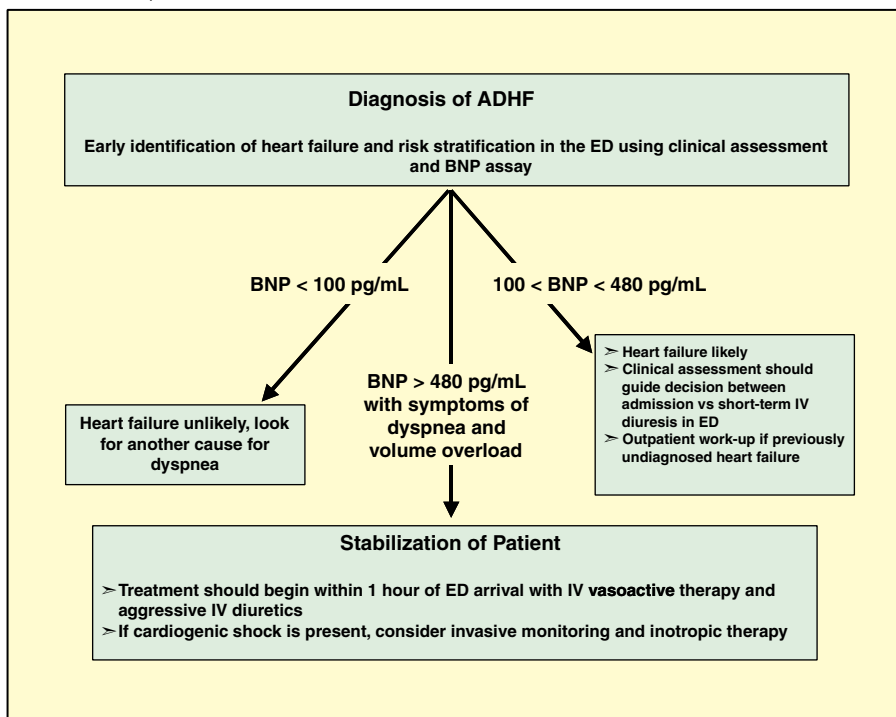
In one study of 325 patients who presented with dyspnea to the ED, the relationship between BNP levels at presentation and the incidence of heart failure–related death, hospital admission, or repeat ED visit was analyzed over a 6-month follow-up.<sup>50</sup> The higher the BNP at presentation, the greater was the risk of a negative heart failure–related outcome during follow-up. A BNP value of 480 pg/mL had a sensitivity of 68%, a specificity of 88%, and an accuracy rate of 85% for predicting a subsequent heart failure–related event. Individuals with BNP values greater than 480 pg/mL at presentation had a 51% 6-month cumulative probability of a heart failure event. Thirty-five percent of the patients in this group died of heart failure within 6 months. In contrast, patients whose baseline BNP levels were less than 230 pg/mL had a 2.5% cumulative probability of heart failure end points (Figure 7).<sup>50</sup>

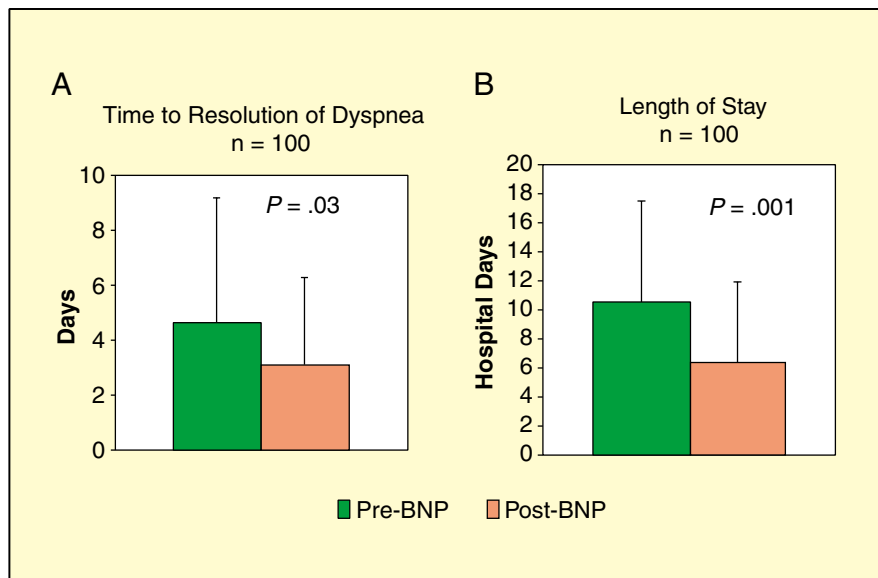
An algorithm using BNP levels and guiding diuretic and vasodilator therapy in patients presenting to the ED with dyspnea was developed at our hospital to facilitate the early treatment of ADHF, ideally within the first hour of arrival (Figure 8).



**Figure 7.** B-type natriuretic peptide (BNP) concentration for the prediction of clinical events. CHF, congestive heart failure. Adapted with permission from Harrison et al.<sup>50</sup>

**Figure 8.** Algorithm for using B-type natriuretic peptide (BNP) levels in the emergency department (ED) to diagnose acute decompensated heart failure (ADHF). IV, intravenous.





**Figure 9.** Time to resolution of symptoms (**A**) and reduction in length of stay (**B**) of heart failure admissions ( $n = 100$ ) using B-type natriuretic peptide (BNP) assay in the emergency department to facilitate early identification. Adapted with permission from Berkowitz et al.<sup>51</sup>

When BNP levels were required of all patients presenting with dyspnea and added to clinical judgment to facilitate early identification and stratification, there was a 40% decrease in length of stay and a 33% reduction in time to resolution of symptoms (Figure 9).<sup>51</sup>

An interesting feature of the algorithm is that it allows for rapid initiation of therapy because the need for an initial echocardiogram is precluded by the fact that neurohormonal activation of BNP occurs in both systolic and diastolic heart failure. The treatment with both acute presentations seems to be the same (intravenous diuretic and vasodilator therapy). An echocardiogram on the following day will differentiate systolic from diastolic heart failure because diuretic therapy in the case of the diastolic patient with the smaller left ventricular cavity might require a diminution in the amount of diuretic therapy to avoid overdiuresis that could lead to hypotension and prerenal azotemia.

### BNP Levels Guide ADHF Treatment

Monitoring of BNP levels also can be used to guide treatment for heart failure. In a pilot study of 72 patients, Cheng and associates<sup>52</sup> found that patients whose BNP levels fell during hospitalization for heart failure had lower rates of readmission and death in the 30 days following discharge. At discharge, patients who were to be event-free for the next 30 days had mean BNP level decreases of 215 pg/mL. In contrast, BNP levels significantly increased by a mean of 233 pg/mL for indi-

viduals who were readmitted or died within 30 days.<sup>52</sup> These results suggest that response to inpatient treatment is reflected in BNP levels and in subsequent clinical outcomes.

the rapid BNP test correlated with decreases in PCWP.<sup>53</sup> BNP levels dropped significantly (55%) among patients who responded to treatment in the first 24 hours compared with those who did not respond (8%). The percentage change in BNP levels correlated significantly with percentage change in wedge pressure from baseline ( $r = 0.79$ ,  $P < .05$ ).<sup>53</sup> These findings indicate that monitoring BNP levels might be useful in guiding treatment and warrant further investigation.

Periodic monitoring of BNP levels might potentially be useful in the outpatient setting to assess response to treatment as well. Blood levels of a number of neurohormonal factors increase in heart failure, including BNP, A-type natriuretic peptide, and norepinephrine. Of these markers of cardiac damage, BNP levels have been shown to be the best prognostic indicator of response to carvedilol in heart failure patients.<sup>54</sup> Also, Morimoto and colleagues<sup>55</sup> demonstrated that BNP testing every 3 months to assess treatment response has the potential to be cost-effective. Their assessment of quality-adjusted life-years found that over 1 year of follow-up, the costs of testing were offset by reductions in other treatment costs.<sup>55</sup>

Nesiritide, a human recombinant form of BNP, is an intravenous vasoactive agent with natriuretic, diuretic, and lusitropic properties

*Periodic monitoring of BNP levels might potentially be useful in the outpatient setting to assess response to treatment.*

viduals who were readmitted or died within 30 days.<sup>52</sup> These results suggest that response to inpatient treatment is reflected in BNP levels and in subsequent clinical outcomes.

In another pilot study, results from

that is safe and effective in the treatment of ADHF.<sup>56–58</sup> During nesiritide infusion, BNP levels should not be measured; BNP can be measured after exogenous BNP has been cleared (4–6 hours after discontinuation of the infusion).

## Conclusions

Clinical outcomes are improved by early, accurate diagnosis of ADHF. Predominantly a disease of the elderly, heart failure shares many signs and symptoms with other chronic illnesses common to this population. Endogenous BNP levels are elevated in patients with ADHF, and the extent of BNP elevation correlates with the severity of heart failure. Measurement of BNP levels offers a rapid test that can improve the accuracy of ADHF diagnosis when used in conjunction with history, physical examination, and chest x-ray and other standard diagnostic tests. Because BNP levels correlate with severity of heart failure and risk of morbidity and mortality, these values can contribute to treatment decisions, including the need for hospitalization.

Besides acute and chronic heart failure, BNP levels are elevated in cardiac ischemia, arrhythmias, pulmonary disorders, and indirectly in CKD. Thus, patients with elevated BNP levels should be evaluated for the presence of these other conditions. Treatment in response to a BNP perturbation should be directed at the underlying cause of the eleva-

tion. The case, for example, of arrhythmia-induced transient left ventricular dysfunction with correlative elevation of BNP might be treated most effectively with amiodarone; once again, treatment with a diuretic would be of little use. Once the diagnosis of heart failure is made, common comorbidities that might contribute to morbidity and mortality need to be ruled out. Treatment of underlying causes of heart failure is critical whenever possible. ■

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## Main Points

- Rapid and accurate diagnosis of acute decompensated heart failure (ADHF) in the emergency department (ED) is essential for timely initiation of treatment; thus, any means for improving the speed and accuracy of ADHF diagnosis in the ED can contribute to better clinical and economic outcomes.
- Measurement of circulating endogenous B-type natriuretic peptide (BNP) has proven to be a sensitive and specific test for heart failure that can easily be used in the ED.
- BNP facilitates natriuresis and diuresis while enhancing glomerular filtration rate; produces vasorelaxation; suppresses neurohormonal activation of angiotensin II, aldosterone, and endothelin-I; and regulates fluid and electrolyte homeostasis, contributing to volume and blood pressure regulation.
- Besides acute and chronic heart failure, BNP levels are elevated in cardiac ischemia, arrhythmias, pulmonary disorders, and indirectly in CKD; thus, patients with elevated BNP levels should be evaluated for the presence of these other conditions.
- In addition to increasing the accuracy of the diagnosis of ADHF, BNP levels are predictive of clinical outcomes and therefore might be useful in making decisions with regard to the treatment of ADHF.

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