B-Type Natriuretic Peptide Measurements in Diagnosing Congestive Heart Failure in the Dyspneic Emergency Department Patient

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For the acutely ill patient presenting to the emergency department with dyspnea, an incorrect diagnosis could place the patient at risk for both morbidity and mortality. The stimulus for B-type natriuretic peptide (BNP) release is a change in left-ventricular wall stretch and volume overload. A rapid, whole-blood BNP assay (Triage BNP Test, Biosite Inc, San Diego, CA) that allows quick evaluation of the dyspneic patient has recently been approved by the U.S. Food and Drug Administration. Preliminary research with this test set the stage for the recently completed "Breathing Not Properly" BNP Multinational Study, a seven-center, prospective study of 1586 patients who presented to the emergency department with acute dyspnea and had BNP measured with a point-of-care assay upon arrival. BNP was accurate in making the diagnosis of congestive heart failure (CHF), and levels correlated to severity of disease. Knowledge of BNP levels could have reduced clinical indecision by 74%. Algorithms are being developed for use in the emergency department that take into account other illnesses that might raise BNP levels. BNP levels should be extremely important in ruling out and diagnosing decompensated CHF, as long as baseline "euvolemic" BNP values are known. Finally, in addition to helping assess whether a dyspneic patient has heart failure, BNP levels may also be useful in making both triage and management decisions.
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Key words: Congestive heart failure • Dyspnea • Natriuretic peptide

Acute Heart Failure: The Problem

Despite the recent advances in our understanding of the complex pathophysiology of heart failure, both its diagnosis and the assessment of therapeutic approaches remain difficult. For the acutely ill patient presenting to the emergency department with dyspnea, an incorrect diagnosis could place the patient at risk for both morbidity and mortality.[1] Therefore, the emergency department diagnosis of congestive heart failure (CHF) needs to be rapid and accurate.

Unfortunately, the signs and symptoms of CHF are nonspecific.[2] A helpful history is not often obtainable in an acutely ill patient, and dyspnea, a key symptom of CHF, may also be a nonspecific finding in the elderly or obese patient in whom comorbidity with respiratory disease and physical deconditioning are common.[3] Routine lab values, electrocardiograms, and x-rays are also not accurate enough to always make the appropriate diagnosis.[2-4] Thus, it is difficult for clinicians to differentiate patients with CHF from those with other conditions such as pulmonary disease on the basis of routinely available laboratory tests.

Echocardiography has limited availability in acute-care settings. Furthermore, dyspneic patients may be unable to hold still long enough for an echocardiographic study, and others may be difficult to image secondary to coexisting diseases such as obesity or lung disease. Therefore, even in emergency departments where echocardiography is available, an accurate, sensitive, and specific blood test for heart failure would be a useful addition to the currently existing tools available to the physician.

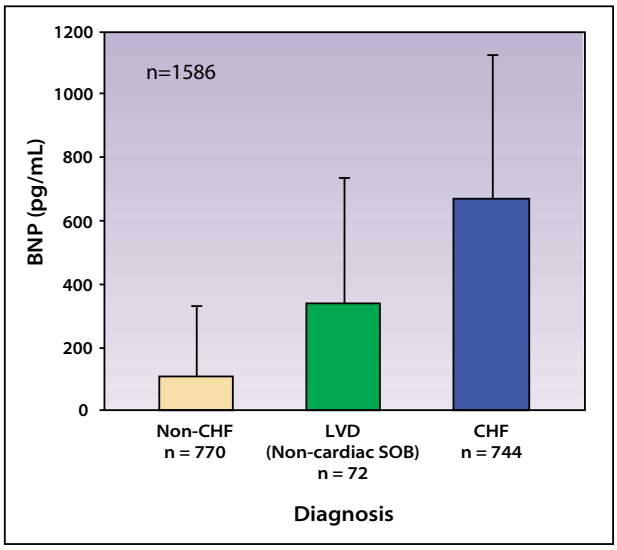

Figure 1. *Mean B-type natriuretic peptide (BNP) levels and final diagnosis. CHF, congestive heart failure; LVD, left ventricular dysfunction; SOB, shortness of breath. Error bars represent standard deviations.*

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B-Type Natriuretic Peptide

B-type natriuretic peptide (BNP) is a 32-aa polypeptide containing a 17-aa ring structure common to all natriuretic peptides.[5,6] BNP is a potent natriuretic, diuretic, and vasorelaxant peptide. It coordinates fluid and electrolyte homeostasis through its activity in the central nervous system (CNS) and peripheral tissue. BNP promotes vascular relaxation and lowers blood pressure, particularly in states of hypervolemia. It inhibits sympathetic tone, the renin-angiotensin axis, and synthesis of vasoconstrictor molecules such as catecholamines, angiotensin II, aldosterone, and endothelin-1.[7] Its renal effects include increasing glomerular filtration rate and enhancing sodium excretion.[7,8]

Unlike atrial natriuretic peptide (ANP), whose major storage sites include the atria and ventricles, the major source of plasma BNP is cardiac ventricles. This suggests that BNP may be a more sensitive and specific indicator of ventricular disorders than are other natriuretic peptides.[9,10] Because ANP is contained in storage granules, even a minor stimulus such as exercise can trigger a significant release of this peptide into the bloodstream. On the other hand, BNP has minimal presence in storage granules. Instead, the nucleic acid sequence of the BNP gene contains the destabilizing sequence *tatttat*, which suggests that turnover of BNP messenger RNA is high and that BNP is synthesized in bursts.[11,12]

The stimulus for BNP release is a change in left-ventricular (LV) wall stretch and volume overload, suggesting that BNP may be a "distress hormone," more specific for ventricular disorders than are other members of the natriuretic peptide family.[13,14] BNP is removed from plasma through two distinct mechanisms, endocytosis and enzymatic degradation by endopeptidases.[8] Natriuretic peptide receptor–C binds to all members of the natriuretic peptide family with equal affinity. When a ligand-receptor complex forms, the complex undergoes receptor-mediated endocytosis. The second mechanism to remove

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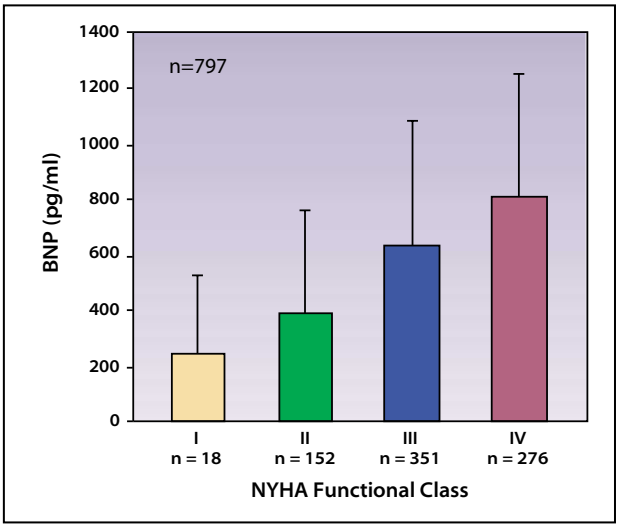
natriuretic peptides from plasma involves zinc-containing endopeptidases.[8,13,14] These enzymes are present in renal tubules and vascular endothelial cells.

A rapid, whole-blood BNP assay (Triage BNP Test, Biosite Inc, San Diego, CA) has recently been approved by the U.S. Food and Drug Administration (FDA). Since the assay is point-of-care, it can be used in clinical settings such as the emergency department as well as in the regular laboratory.

Figure 2. *B-type natriuretic peptide (BNP) and New York Heart Association (NYHA) functional class. Error bars represent standard deviations.*



BNP Use in Diagnosis of Patients Presenting with Dyspnea

For a diagnostic screening test to be useful in an acute-care setting, it should have a high negative predictive value, allowing clinicians to rapidly rule out serious disorders,[15] while also facilitating efficient use of resources available in an urgent care setting. BNP was first used in the evaluation of dyspnea by Davis and colleagues, who measured the natriuretic hormones ANP and BNP in 52 patients presenting with acute dyspnea. They found that admission plasma BNP concentrations more accurately reflected the final diagnosis than did ejection fraction or concentration of plasma ANP.[16] As intriguing as those results were, it was not until a rapid assay became available that BNP testing could be applied in the urgent-care or clinic setting.

Dao and colleagues were the first to use the rapid assay in evaluating 250 patients presenting to the San Diego VA Healthcare Urgent Care Center with dyspnea as their chief complaint.[17] Emergency department physicians blinded to the results of BNP measurements were asked to assess the probability of the patient having CHF as the cause of his or her symptoms. Patients with the final diagnosis of CHF (n=97) had a mean BNP concentration of 1076 ± 138 pg/mL, while the non-CHF group (n=139) had a mean BNP concentration of 38 ± 4 pg/mL. Of crucial importance was that patients with the final diagnosis of pulmonary disease had lower BNP values (86 ± 39 pg/mL) than those with a final diagnosis of CHF ($P < .001$). This distinction is perhaps the key element in the differential diagnosis of patients who present with acute dyspnea.

The above study set the stage for the recently completed "Breathing

Figure 3. *B-type natriuretic peptide (BNP) versus National Health and Nutrition Examination Survey (NHANES) and Framingham criteria: comparative accuracy.*

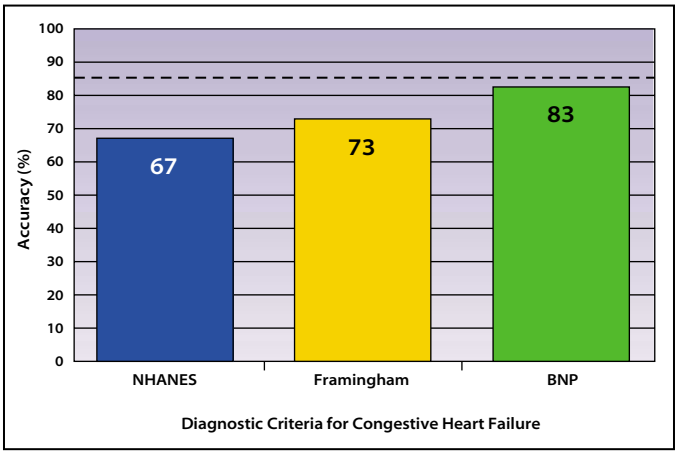
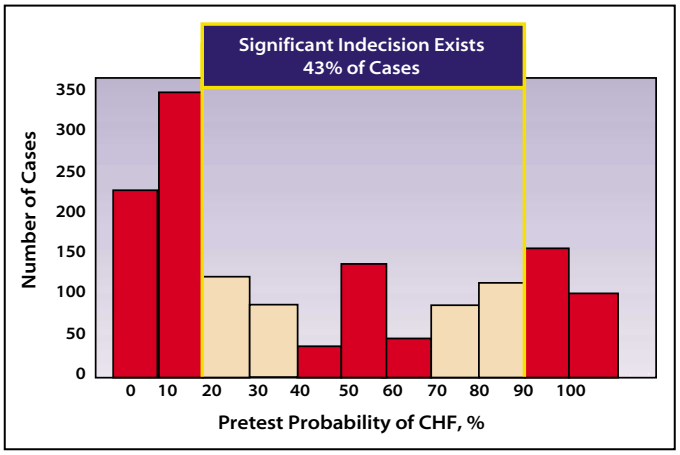


Figure 4. *Clinical probability of congestive heart failure (CHF) as assessed by emergency department physicians blinded to B-type natriuretic peptide (BNP) levels.*



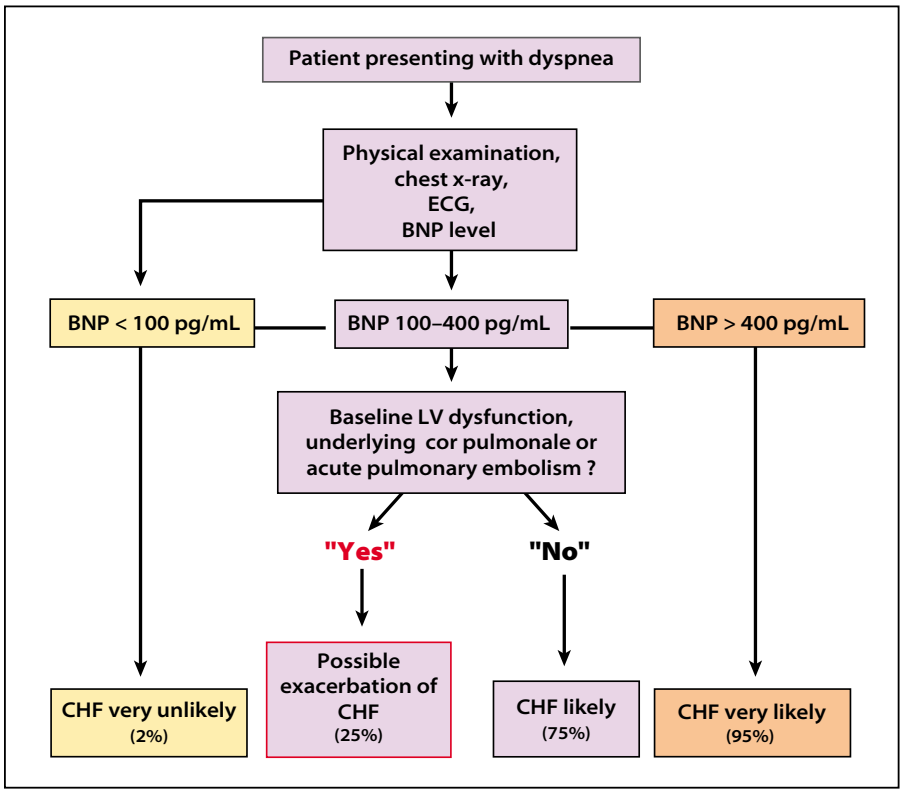


Figure 5. *Algorithm for using B-type natriuretic peptide (BNP) levels in the emergency department to diagnose congestive heart failure (CHF). ECG, electrocardiogram; LV, left ventricular.*

Not Properly" BNP Multinational study,[18] a seven-center, prospective study of 1586 patients who presented to the emergency department with acute dyspnea and had BNP measured with a point-of-care assay upon arrival. The gold standard for CHF was adjudicated by two independent cardiologists, blinded to BNP results, who reviewed all clinical data and standardized scores. Figure 1 shows BNP levels for patients in the study. Patients diagnosed with acute CHF had BNP levels of 675 ± 450 pg/mL (mean ± SD), while the non–congestive heart failure group had BNP levels of 110 ± 225 pg/mL. The group of 72 patients identified as baseline ventricular dysfunction without an acute exacerbation had a mean concentration of 346 ± 390 pg/mL.

Figure 2 shows BNP values in relation to New York Heart Association functional class as agreed on by both cardiologists. BNP levels differed significantly as a function of severity of CHF ($P < .001$). BNP levels by themselves were more accurate than any historical or physical findings or laboratory values in delineating the cause of dyspnea. The area under the receiver operating characteristic curve for BNP in the determination of CHF was 0.91 (95% CI, 0.90–0.93), $P < .001$). The diagnostic accuracy of BNP at a cutoff of 100 pg/mL was 83.4%, which was more accurate than the standard National Health and Nutrition Examination Survey (67%) or Framingham (73%) criteria (Figure 3). The negative predictive value of BNP at levels less than 50 pg/mL was 96%. In multivariate analysis, BNP measurements added significant, independent predictive power to other clinical variables in models predicting which patients had CHF. In this trial, the physicians, who were blinded to BNP levels, were required to give a probability from 0% to 100% that the patient had CHF. Clinical indecision, that is, probability assessed at between 20% and 80%, existed for 43% of cases (Figure 4). In this setting, a BNP level of over 100 pg/mL would have reduced the clinical indecision from 43% to 11% (74% reduction).

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Algorithms for Using BNP to Diagnose CHF

The measurement of the BNP concentration in blood is likely to be a potent, cost-effective addition to the diagnostic armamentarium of acute-care physicians. Based on his experience, the author has developed an algorithm for CHF diagnosis in the emergency department. This algorithm is presented in Figure 5. When a patient comes to the emergency department with acute shortness of breath, an electrocardiogram, a chest x-ray, and a BNP level are obtained. CHF is usually absent at BNP levels under 100 pg/mL and usually present at BNP levels over 400 pg/mL. Those patients with BNP levels between 100 and 400 pg/mL have several other diagnostic possibilities that need to be considered. First, patients may have baseline LV dysfunction. BNP levels are often greater than 100 pg/mL in these cases, but if the cause of dyspnea is something other than

acute exacerbation, the levels are usually under 400 pg/mL. Morrison and colleagues were recently able to show that rapid testing of BNP could help differentiate pulmonary from cardiac etiologies of dyspnea.[19] Some types of pulmonary disease, however, such as cor pulmonale, lung cancer, and pulmonary embolism have elevated BNP levels, but not usually to the same extent as in patients with acute LV dysfunction. Thus, clinical judgment needs to be used in these cases. Often, patients present with both pulmonary and cardiac disease, as one frequently begets the other, again calling for clinical judgment and further testing. Finally, a pulmonary embolism large enough to raise the pulmonary artery pressure due to right ventricular strain may raise BNP levels. If the above conditions can be ruled out, then it is much more likely that BNP levels between 100 and 400 pg/mL represent CHF.

Table 1
Special Circumstances in Interpreting BNP Levels

Factors other than CHF that can account for high BNP levels
Advanced age
Renal failure
Myocardial infarction
Acute coronary syndrome
Lung disease with right-sided failure
Acute, large pulmonary embolism
High-output states like cirrhosis
Factors that can account for lower-than-expected BNP levels when CHF is present
Flash pulmonary edema
CHF secondary to causes upstream from the left ventricle
Acute mitral regurgitation
Mitral stenosis
Atrial myxoma
Stable NYHA class I patients with low ejection fractions

BNP, B-type natriuretic peptide; CHF, congestive heart failure; NYHA, New York Heart Association.

Special Circumstances in Interpreting BNP Values

Table 1 lists (1) those factors other than CHF that can account for elevated BNP values and (2) circumstances in which BNP levels may be normal or lower than expected despite the presence of CHF. Some of the conditions that can account for elevated levels in the absence of CHF are mentioned above. In addition, BNP is elevated in late (predialysis) stages of renal failure and is elevated in virtually every patient on dialysis.[20] This elevation is in part related to the decreased renal clearance secondary to downregulation of the natriuretic peptide clearance receptor, as well as the accompanying increased intravascular volume. Some of this elevation may be secondary to fluid overload, borne out by the fact that following dialysis, though still elevated, BNP levels show significant drops.[20]

Heart failure can occur is several settings where BNP is normal.

Both BNP and N-terminal BNP are elevated early in the course of acute myocardial infarction (MI). A second peak of BNP measured 2 to 4 days after MI is associated with remodeling of the heart and is a strong predictor of subsequent LV dysfunction and mortality.[21,22]

In a trial of more than 2000 patients presenting with acute coronary syndrome, a BNP level over 80 pg/mL was an independent predictor of death, CHF, and recurrent MI.[23] While the cause is not known, BNP levels in this situation may represent acute diastolic dysfunction from increased area of myocardium at risk.

Heart failure can occur in several settings where the BNP level is normal. It is estimated that in the setting of flash pulmonary edema, at least 1 hour is necessary to see elevations in BNP levels. It is speculated that this early release may be preformed BNP located in the atrium. CHF occurring upstream from the left ventricle is most commonly seen with acute mitral regurgitation. These patients often present with acute CHF, yet LV function is not yet compromised.

BNP Levels in Diagnosing Decompensated Heart Failure

Patients with known CHF, even on effective treatment, will sometimes present with symptoms suggesting decompensation. Determining whether these symptoms represent true worsening of CHF is important,

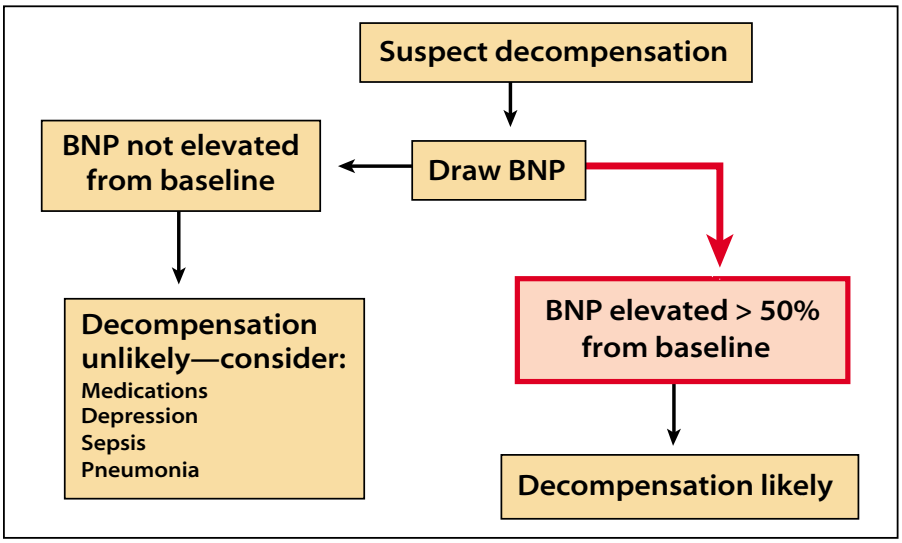


Figure 6. *Algorithm to detect decompensation in patients with established heart failure and baseline B-type natriuretic peptide (BNP) values. BNP levels can confirm whether patient's congestive heart failure has truly decompensated.*

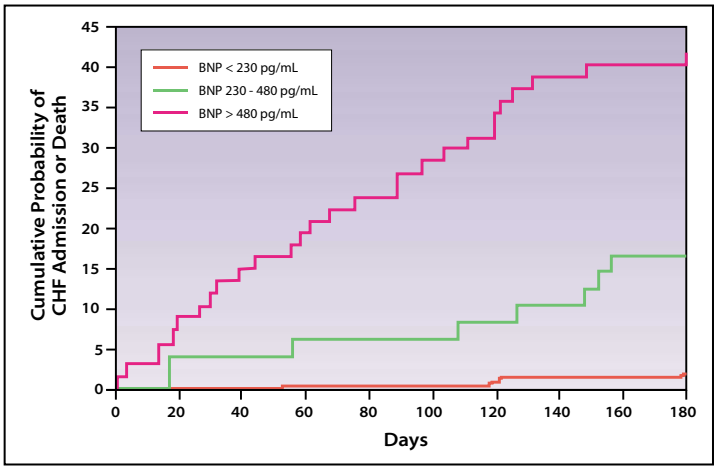
as truly decompensated patients often require hospitalization. Yet worsening CHF can be difficult to diagnose. For instance, CHF patients commonly experience depression, whose symptoms of lethargy, fatigue, and shortness of breath may mimic CHF. Patients have been brought into the hospital for a presumed decompensated state, only to be found later to have wedge pressures that are low instead of high. A subsequent diagnosis of sepsis or pneumonia is then made.

At our hospital, an algorithm similar to that shown in Figure 6 is sometimes followed. This algorithm is based on patients with known LV dysfunction having baseline "dry weight" BNP levels, that is, levels determined after excess volume has been diuresed and the patient is euvolemic. When such a patient presents to the clinic or emergency department with symptoms that might represent decompensation, a BNP level is measured. In the author's experience, if the BNP level has not increased over baseline, the diagnosis is usually something other than CHF exacerbation. This determination is important as it can allow one to avoid a potentially harmful, wrong treatment and lessen delays in determining the real cause for the dyspnea. On the other hand, if the BNP level has increased by 50% or more over baseline (eg, BNP increasing from 400 to 600 pg/mL), true decompensation is likely. However, the absolute level of BNP increase that insures the correct diagnosis of CHF decompensation is not yet known. Since the Biosite BNP assay has a coefficient of variation in the range of 10%, a baseline value of 300 pg/mL has a true range of 240 to 360 pg/mL.

Implications of BNP Levels in Emergency Department Management of CHF

Correctly diagnosing CHF, whether it is of new onset or decompensation, is only the first step, as appropriate triaging of the patient along with maximal treatment is extremely important in insuring the well-being of the patient. BNP level has been shown to be a powerful tool for assessing prognosis and risk stratification in the setting of heart failure. In a recent study of 78 patients referred to a heart failure clinic, BNP showed a significant correlation to the heart failure survival score.[24] In addition, changes in plasma BNP levels were significantly related to changes in limitations of physical activities and were a powerful predictor of functional status deterioration. Harrison and colleagues followed 325 patients for 6 months after an index visit to the emergency department for dyspnea.[25] Higher BNP levels were associated with a progressively worse prognosis (Figure 7).

Figure 7. *Reverse Kaplan-Meier plot showing cumulative risk of any hospitalization or death from congestive heart failure (CHF), stratified by B-type natriuretic peptide (BNP) levels at the time of initial visit to the emergency department. Higher BNP levels are associated with progressively worse prognosis. Patients with BNP levels more than 480 pg/mL had a 6-month cumulative probability of CHF admission or death of 42%. Patients with BNP levels less than 230 pg/mL had only a 2% cumulative probability of an event.*



The cumulative risk at 6 months of CHF admission or death in patients with BNP levels more than 480 pg/mL was 24 times the risk in patients with levels less than 230 pg/mL.

Thus, use of BNP levels might ultimately be helpful not only in assessing whether or not a dyspneic patient has heart failure, but also in making both triage and management decisions. In some emergency departments, the diagnosis of CHF leads to immediate admission to the hospital. Yet there are many patients who come in with only mild CHF, often precipitated by dietary indiscretions or noncompliance with medications. In the author's experience, many of these patients have BNP levels less than 400 pg/mL and do well after one injection of a loop diuretic. On the other hand, there are patients who come in with significant CHF symptomatology and who have BNP levels in excess of 1000 pg/mL. These patients might be better off being directly admitted to the hospital where they could receive aggressive inpatient treatment.

A study called REDHOT (Rapid Emergency Department Heart Failure Outpatient Trial) is currently under way to assess an algorithm for using BNP levels in the triage and management of patients (Figure 8). In this protocol, BNP levels will be ascertained during a run-in period and then patients will be stratified to light treatment, aggressive treatment, or immediate admission on the basis of BNP levels.

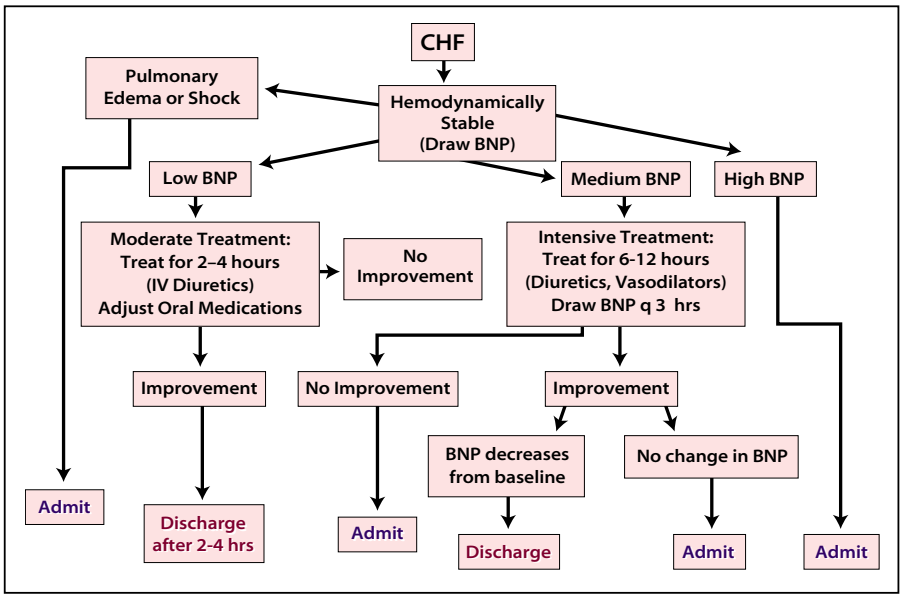


Figure 8. *Algorithm for using B-type natriuretic peptide (BNP) levels in the triage and treatment of emergency department patients presenting with heart failure, from the Rapid Emergency Department Heart Failure Outpatient Trial (REDHOT). CHF, congestive heart failure; IV, intravenous.*

Since BNP is a volume-sensitive hormone with a short half-life (18–22 minutes), there may be a future for BNP levels in guiding diuretic and vasodilator therapy in patients presenting to the emergency department with decompensated CHF. Cheng and colleagues found that patients who were not readmitted in the following 30 days after discharge could be characterized by dropping BNP levels during hospitalization.[26] On the other hand, patients who were readmitted or died in the following 30 days had no such decrease in BNP levels on their index hospitalization, despite their overall "clinical" improvement. In a study by Kazanagra and colleagues, patients undergoing hemodynamic monitoring had changes in wedge pressures that were strongly correlated with dropping BNP levels and clinical improvement.[27] Thus, in the future it may be possible that titration of vasodilators will no longer require Swan-Ganz catheterization, but rather the use of a BNP level as a surrogate for wedge pressure.

There may be a future for BNP levels in guiding diuretic and vasodilator therapy in patients presenting to the emergency department with decompensated CHF.

A new vasodilator, nesiritide, was recently approved by the FDA for treatment of decompensated heart failure. The drug is human BNP and possesses many of the characteristics of an ideal agent for treating acute decompensated heart failure. It causes vasodilation and natriuresis without any of the side effects of an inotropic agent, such as arrhythmias. Also, it blunts the sympathetic nervous system as well as aldosterone. The question of why administering exogenous BNP is helpful when endogenous levels are already high has not been fully explained. It is probably analogous to giving insulin for insulin resistance. As stated previously, endogenous BNP may be released as a "distress hormone," and exogenously provided BNP may overwhelm the dampened system, perhaps upregulating the renal natriuretic peptide clearance receptor

and clearing BNP. In preliminary studies by the author, it appears that within 6 hours after cessation of nesiritide infusion, endogenous BNP levels are 20%–30% lower than baseline.

Conclusions

BNP testing may be the biggest advancement in diagnosing heart failure since the advent of echocardiography 20 years ago. While it is not a stand-alone test, it clearly adds to any information the physician can gather through history, physical examination, chest x-ray, and ancillary testing. Its high sensitivity and negative predictive value make it a reliable test to rule out heart failure with a high degree of certainty. The higher the BNP value, the greater the specificity and positive predictive value. Since the degree of BNP elevation correlates to severity of heart failure and prognosis, levels may ultimately be used to triage patients with CHF to the appropriate treatment setting and to help guide therapy of CHF in the emergency department. ■

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Main Points

- Diagnosis of heart failure in patients presenting to the emergency department with dyspnea is difficult, and incorrect diagnosis places patients at risk for morbidity and mortality.
- B-type natriuretic peptide (BNP) release is stimulated by change in left-ventricular wall stretch and volume overload, suggesting that BNP may be a "distress hormone," more specific for ventricular disorders than are other members of the natriuretic peptide family.
- BNP levels correlate to severity of heart failure and prognosis.
- BNP testing can be used to diagnose and rule out congestive heart failure (CHF) with a high degree of certainty.
- BNP testing may also aid in the triage and management of patients with CHF.