B-type natriuretic peptide is a neurohormone secreted from the cardiac ventricles in response to ventricular stretch and pressure overload. It counteracts the vasoconstriction that occurs as a compensatory mechanism in heart failure. A new test for measuring plasma levels of B-type natriuretic peptide can help in the diagnosis and treatment of patients with congestive heart failure. Dyspnea associated with cardiac dysfunction is highly unlikely in patients with levels of the peptide less than 100 pg/mL. Whereas most patients with significant congestive heart failure have levels of the peptide greater than 400 pg/mL, in patients with levels of 100 to 400 pg/mL, left ventricular dysfunction without volume overload, pulmonary embolism, and cor pulmonale must be ruled out. Thus, incorporating measurement of B-type natriuretic peptide into clinical evaluation helps physicians and nurses diagnose heart failure more quickly, especially in patients who have multiple comorbid conditions. Elevated levels of B-type natriuretic peptide indicate a poor prognosis in terms of a higher mortality and more hospital readmissions. Levels of B-type natriuretic peptide could be used to guide therapy and discharge planning for patients admitted with decompensated heart failure. (American Journal of Critical Care. 2004;13:46-55)

Heart failure is a condition of impaired systemic perfusion resulting from a combination of cardiac pump dysfunction and abnormalities of the peripheral vascular system. An improved understanding of its pathophysiology has led to newer diagnostic and therapeutic options, which most likely will decrease the high morbidity and mortality rates associated with heart failure. In this article, we discuss the use of B-type natriuretic peptide (BNP) as a diagnostic and prognostic biomarker in the management of patients with heart failure. If validated, this application holds significant promise in improving treatment patterns and, ultimately, clinical outcomes of patients who have this common debilitating condition. Biomarkers may become increasingly relevant in the evaluation and care of patients with heart failure, as highlighted by the recent introduction of a point-of-care rapid assay for measuring BNP.

Pathophysiology of Chronic Heart Failure

Chronic heart failure is a clinical syndrome characterized by symptoms of exertional dyspnea and fatigue that gradually progress to marked limitation of functional capacity and, eventually, death.
common triggers of cardiac dysfunction include ischemic heart disease, chronic hypertension, valvular heart disease, and other primary cardiomyopathies. After an index event that can be either abrupt, such as an acute myocardial infarction, or insidious, such as hypertension, a complex set of compensatory mechanisms is initiated to counter the initial decline in the heart’s pumping function. The mechanisms involve components of the sympathetic nervous system (catecholamines), the renin-angiotensin-aldosterone system (angiotensin II and aldosterone), endothelin, vasopressin, and natriuretic peptides. Although cardiac output is initially maintained by the effect of these mediators on cardiac contractility, heart rate, and peripheral vascular resistance, persistent activation of the mediators eventually results in deteriorated cardiac function.

Components of the neurohormonal system contribute to the progression of heart failure by their direct effects on the heart itself and on the peripheral vasculature. The effects include the positive chronotropic and inotropic effects of catecholamines and the vasoconstrictor properties of catecholamines, angiotensin II, and endothelin. Aldosterone enhances renal tubular reabsorption of sodium and water. These neurohormones are not merely compensatory; over time they can cause direct cardiac damage and result in deleterious structural and mechanical changes.

**Natriuretic Peptides in Heart Failure**

Natriuretic peptides are a family of naturally occurring counterregulatory molecules that represent a relatively favorable aspect of neurohormonal activation. They are characterized by their vasodilatory and natriuretic properties, which counteract the vasoconstriction and salt and water retention caused by the action of other molecules such as catecholamines and components of the renin-angiotensin-aldosterone system. The family of natriuretic peptides includes atrial natriuretic peptide (ANP), BNP, and C-type natriuretic peptide. Different genes code for different peptides, which are synthesized in a precursor form known as propeptides. These propeptides are cleaved into fragments of different sizes, which circulate in the plasma and mediate their biological effects by binding to specific receptors in the cardiovascular system, the kidneys, and the central nervous system. The tissue distribution, synthesis, and storage mechanisms differ for the different peptides.

ANP is predominantly produced in the cardiac atria and its levels are elevated in patients with increased intravascular volume and congestive heart failure. In humans, a limited amount of ANP is produced by the normal heart; increased synthesis has been noted in hypertrophied hearts.

BNP was originally isolated from porcine brain, but in humans, its concentration is higher in the heart than in the brain. BNP is rapidly synthesized in response to ventricular stretch and pressure overload. Both ANP and BNP have a similar range of biological effects. They reduce cardiac preload by causing vasodilatation and increasing vascular capacitance. They reduce sympathetic nervous tone and induce natriuresis by their actions on the renal vasculature and tubules.

C-type natriuretic peptide has the lowest concentration of the circulating plasma natriuretic peptides. It is predominantly distributed in the central nervous system, kidneys, and endothelial cells. Although C-type natriuretic peptide lacks natriuretic action, it has marked vasodilatory and growth-inhibiting properties.

**BNP Versus ANP**

Although ANP and BNP have similar physiological effects, they differ greatly in their mechanism of synthesis, tissue distribution, and release. Unlike ANP, which is predominantly localized in atrial storage granules, BNP is primarily localized in cardiac ventricles. Significant amounts of ANP can be released in response to minor stimuli such as exercise. BNP is synthesized in bursts and is released predominantly in response to stretching of the ventricular wall and volume overload; it has a half-life of 22 minutes.

Compared with measurement of plasma levels of ANP and the N-terminal fragment of ANP, measurement of plasma levels of BNP is superior for diagnosis of left ventricular dysfunction. When circulating levels and tissue concentrations of BNP and of ANP were measured in samples obtained at autopsy of patients with heart failure, circulating levels correlated well with the actual tissue expression for BNP but not for ANP. Therefore, circulating levels reflect tissue production more accurately for BNP than for ANP and thus the physiological stimuli that cause the production of the peptides.

**Measurement of BNP**

Two commercial assays for measuring plasma levels of BNP are available. In the classic method, BNP is
BNP Levels in Normal and Pathological States

An important limitation in evaluating the clinical literature on BNP is the different assay methods used in different studies. Redfield et al. studied the relationship between plasma levels of BNP and age and sex in a subset of 746 normal subjects without cardiovascular, pulmonary, or renal disease. A unique strength of the study was the direct comparison of the 2 common BNP assays. The BNP values differed according to the assay used and also according to age and sex. BNP levels increased with increasing age. Compared with men, women without heart failure had higher BNP levels. This difference may be related to estrogen status, because women receiving hormonal replacement therapy had significantly higher BNP levels than did women not receiving such therapy.

Plasma levels of BNP are significantly elevated in patients with heart failure and left ventricular dysfunction. The results of previous clinical studies in which both methods of measurement were used suggested different cutoff values of plasma levels of BNP for diagnosing these conditions. For the point-of-care assay, a value of 100 pg/mL has been approved for differentiating patients with heart failure from patients without (specificity 95%, area under the curve 0.91). This cutoff value may not be sensitive enough for detecting patients with ventricular systolic dysfunction, who may have more modest elevations of BNP. Although BNP levels are elevated in patients with diastolic dysfunction, BNP values cannot be used to differentiate between systolic and diastolic heart failure.

BNP levels are also significantly increased in conditions such as right-sided heart failure associated with a pulmonary etiology, and acute pulmonary embolism. In patients with end-stage renal disease, BNP levels may be increased because of impaired clearance of circulating BNP. False-negative results of BNP assays in patients with clinical heart failure are possible in patients with acute “flash” pulmonary edema and heart failure due to mitral regurgitation. Patients with New York Heart Association (NYHA) class I heart failure whose condition is stable who have low left ventricular ejection fraction can also have BNP values in the normal range. The NYHA classification correlates with clinical signs and symptoms and is the most commonly used subjective assessment of functional status in heart failure. Although a significant correlation between BNP and NYHA class exists, the higher the BNP level, the greater is the severity of heart failure (Figure 1). When the point-of-care assay was used to measure BNP levels in 572 patients with heart failure, mean levels were 152 (SD 16), 332 (SD 25), 590 (SD 31), and 960 (SD 34) pg/mL for NYHA classes I, II, III, and IV, respectively (Figure 1).

Usefulness of BNP in the Diagnosis of Acute Dyspnea Due to Heart Failure

Acute dyspnea is a common clinical finding in the emergency department and other urgent care locations. Treatment of dyspnea can differ markedly depending on the initial clinical impression. An assay with high sensitivity and high negative predictive value would be useful both in detecting dyspnea due to heart failure and in ruling out the diagnosis in patients with confounding comorbid conditions. Dao et al. used the point-of-care assay to evaluate 250 urgent care patients who had dyspnea as their chief complaint. A BNP cutoff value of 80 pg/mL had high sensitivity (98%), specificity (92%), and negative predictive value (98%). Mean BNP values were 1076 (SD 138) pg/mL in patients with heart failure (n = 97) and 38 (SD 4) pg/mL in patients without heart failure (n = 139). This study was limited; the sample size was small, and the study population was predominantly elderly men (Table 1).
Morrison et al^3^ studied BNP levels in 321 emergency department patients who had dyspnea. Physicians blinded to BNP levels were asked to evaluate the probability that each patient had heart failure and the patient’s final diagnosis. Two independent cardiologists blinded to BNP levels reviewed the data and determined which patients had heart failure. Mean BNP levels were 758.5 (SD 798) pg/mL in patients with heart failure (n = 134) and 61 (SD 10) pg/mL in patients with a final diagnosis of pulmonary disease (n = 85); these differences were significant. In the patients with pulmonary disease, BNP levels ranged from 0 to 200 pg/mL. The highest BNP levels occurred in patients with acute pulmonary embolism and the lowest in patients with asthma^3^ (Table 2). An interesting finding of this study was that in a subgroup of patients who had a history of heart failure but currently had chronic obstructive pulmonary disease (n = 11), BNP levels were not elevated (mean 47 pg/mL, SD 23 pg/mL). A BNP value of 94 pg/mL had a sensitivity of 86%, a specificity of 98%, and an accuracy of 91% for differentiating heart failure from pulmonary disease. This study was limited by the fact that 95% of the patients were men at a Veterans Affairs medical center.

The Breathing Not Properly study^23^ was a multicenter prospective study in which the usefulness of plasma BNP levels was evaluated in 1586 emergency department patients who had acute dyspnea. The clinical likelihood of patients with heart failure determined by assessment of clinical findings by emergency department physicians was compared with assessment based on plasma BNP levels. Two independent cardiologists blinded to the results of BNP assays assessed the patients for heart failure. The final diagnosis was dyspnea due to heart failure in 47% of patients, dyspnea due to noncardiac causes in 5%, and no findings of heart failure in 49%. The diagnostic accuracy of BNP levels at a cutoff of 100 pg/mL was 83.4%. The negative predictive value of BNP at levels less than 50 pg/mL was 96%. Most significantly, a single BNP value was more accurate than other clinical diagnostic criteria for detecting congestive heart failure. This study was the largest of its kind to date with a population more representative of the community. Further analysis of data^24^ indicated that adding BNP point-of-care testing to clinical assessment increased the area under the receiver-operating-characteristic curve from 0.86 (95% CI 0.84-0.88) to 0.93 (95% CI 0.92-0.94). Because the usefulness of the rapid point-of-care assay was assessed in this study, the results have immediate clinical relevance and could be used to refine the emergency diagnosis of heart failure in patients who have an intermediate probability of congestive heart failure before any testing is done.

**BNP Levels as a Therapeutic Guide**

If lowering BNP levels during hospitalization improves patients’ signs and symptoms, treatment based on BNP values might be effective in an outpatient setting such as a cardiology or a primary care clinic. Increased levels would indicate decompensation, whereas decreas-
ing levels would indicate improvement. Murdoch et al. noted that BNP-based adjustments in doses of angiotensin-converting enzyme inhibitors led to a profound inhibition of the renin-angiotensin-aldosterone system in patients (n = 20) already receiving apparently optimal doses of the inhibitors as outpatients. This finding was determined by measuring plasma levels of angiotensin II and plasma renin activity, which reflected enhanced inhibition of angiotensin-converting enzyme.

In the Rapid Assessment of Bedside BNP in Treatment of Heart Failure clinical trial, 700 patients will be studied to determine the clinical usefulness of using the rapid point-of-care BNP assay to guide therapy in outpatients with heart failure. When the trial is completed, clinicians will have a larger data base in which all components of scientific variations have been considered to support or not support using BNP levels to guide therapy in an outpatient setting.

Increasing levels of BNP despite optimal medical therapy may also be indicative of patients at a higher risk of mortality associated with heart failure. Determining plasma levels of BNP may also be beneficial in patients who may require heart transplantation. In a small study of patients with nonischemic cardiomyopathy, an early reduction in the plasma BNP level after implantation of a left ventricular assist device was indicative of recovery of cardiac function without the need for transplantation.

### BNP as a Prognostic Marker in Heart Failure

Levels of neurohormones (norepinephrine, ANP, and BNP) are often used to determine prognosis and risk stratification in patients with heart failure. Tsutamoto et al. evaluated the usefulness of ANP, BNP, and norepinephrine as prognostic biomarkers in 85 patients with chronic congestive heart failure (left ventricular ejection fraction <0.45). They found that BNP but not ANP was an independent predictor of mortality. In a larger study of 452 patients with left ventricular ejection fraction less than 0.35, Berger et al. found that BNP levels measured by using the rapid assay were a strong independent predictor of sudden death. In another recent study, significant elevation of BNP levels was associated with increased rates of mortality due to all causes, cardiac causes, and pump failure. However, no correlation between sudden cardiac death and high BNP was found.

In a pilot study, 72 patients admitted for exacerbation of heart failure (NYHA class III-IV) had daily BNP monitoring. BNP levels increased (from 1500 to 2000 pg/mL) during hospitalization in the 13 patients who died and remained the same (1500 pg/mL) in the 9 patients who were readmitted within 30 days. In contrast, patients who did not die or have a readmission within 30 days had decreased (from 900 to 550 pg/mL) levels of BNP at the time of discharge. BNP levels of 430 pg/mL or less before discharge were predictive of the least likelihood for readmission. The investigators

### Table 1: Selected studies of a rapid assay for B-type natriuretic peptide (BNP) in the diagnosis of heart failure

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of patients</th>
<th>Design</th>
<th>Results</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dao et al.</td>
<td>250</td>
<td>Single-site urgent care study</td>
<td>BNP concentration was significantly higher (P &gt; .001) in patients with heart failure (mean 1076 pg/mL, SD 138 pg/mL) than in patients without heart failure (mean 38 pg/mL, SD 4 pg/mL). A BNP value of 80 pg/mL was an accurate predictor of congestive heart failure (95%); values &gt;80 pg/mL had a high negative predictive value (98%).</td>
<td>Study was done at a single site, and the patients in the sample were mostly men (94%).</td>
</tr>
<tr>
<td>Morrison et al.</td>
<td>321</td>
<td>Prospective, single-center emergency department study</td>
<td>BNP levels were significantly higher in patients who had dyspnea due to heart failure (mean 758.5 pg/mL, SD 798 pg/mL) than in patients who had dyspnea associated with a primary pulmonary etiology (mean 61 pg/mL, SD 10 pg/mL).</td>
<td>Study was limited to patients in the emergency department of a Veterans Affairs medical center, and 95% of the patients were men. Results may not be applicable in other populations of patients.</td>
</tr>
<tr>
<td>Maisel et al.</td>
<td>1586</td>
<td>Prospective, multicenter diagnostic study</td>
<td>BNP levels alone were adequate for diagnosing heart failure in 744 patients. BNP values &gt;100 pg/mL had a sensitivity of 90% and a specificity of 73%.</td>
<td>BNP measurement could have been confounded by other factors, including acute ischemia or renal insufficiency, in patients who were not excluded on these grounds.</td>
</tr>
</tbody>
</table>
concluded that BNP levels might be used successfully to assess prognosis of patients admitted because of decompensated heart failure.

In the Valsartan Heart Failure Trial, in which plasma levels of BNP and norepinephrine were measured in a large population of patients with NYHA class III and class IV heart failure (4300 patients who were treated with Valsartan) over a period of 12 months, both of these biomarkers were important predictors of morbidity and mortality due to heart failure. Among patients who continued to have high levels of BNP despite aggressive therapy, patients with the greatest percentage of decrease in BNP and norepinephrine from baseline to 12 months had the lowest mortality and morbidity.

BNP as a Therapeutic Agent in Acute Heart Failure

The potentially beneficial role of BNP in heart failure has been tested clinically by using an intravenous form of human BNP. Nesiritide (Natrecor), a recombinant form of human BNP, was approved by the Food and Drug Administration in August 2001 for the treatment of acute decompensated heart failure. Although the mechanism of action of nesiritide is similar to that of its endogenous counterpart, the hemodynamic effects of the recombinant drug are longer lasting than might be expected on the basis of its short half life of 18 minutes. The Nesiritide Study Group evaluated the efficacy of the drug and compared treatment with nesiritide with standard intravenous therapy in 432 patients hospitalized with symptomatic heart failure and a mean left ventricular ejection fraction of 0.22. Although compared with placebo, treatment with nesiritide reduced pulmonary capillary wedge pressure (PCWP) and improved global clinical status at 6 hours in the efficacy part of the trial, the improvement in clinical end points up to 7 days was not superior to standard therapy in the comparison part of the trial. Also, 17% of patients in the nesiritide group experienced symptomatic hypotension, whereas only 4% in the standard treatment group did.

Recently, investigators in the Vasodilation in the Management of Acute Congestive Heart Failure study compared the use of nesiritide, nitroglycerin, and placebo in addition to standard therapy in 489 patients with decompensated heart failure. Most patients had NYHA class III or IV heart failure, and the primary end points were the absolute change in PCWP at 3 hours and the patient’s evaluation of dyspnea.

Nesiritide had a marginally greater effect on PCWP at 3 hours than did nitroglycerin, and both agents were more effective than placebo (Figure 2). At 3 hours, nesiritide reduced dyspnea compared with placebo but did not differ compared with nitroglycerin. Symptomatic hypotension occurred in 5% of the nitroglycerin group and 4% of the nesiritide group. Differences in mortality between the nesiritide group and the nitroglycerin group at 7 days or 6 months and in rates of readmission because of all causes or because of acute decompensated heart failure at 30 days were not significant.

The current recommended dosage of nesiritide is an intravenous bolus of 0.01 µg/kg followed by a continuous infusion of 0.01 µg/kg per minute for no longer than 48 hours. The drug is primarily recommended as a short-term adjunctive therapy for acute decompensated heart failure along with intravenous diuretics. BNP levels will be falsely elevated in patients given nesiritide, because the assays cannot differentiate endogenous BNP from the recombinant drug form. Nesiritide is contraindicated in patients who are hypersensitive to any of its components and is not recommended for patients with cardiogenic shock, significant valvular stenosis, restrictive or obstructive cardiomyopathy, constrictive pericarditis, pericardial tamponade, or other conditions in which cardiac output depends on venous return. The dose of intravenous diuretics may be reduced during treatment with nesiritide to prevent hypotension and thus prevent loss of large volumes of fluid during a short period. Other inotropes are administered along with nesiritide as clinically indicated.

Patients receiving nesiritide should be monitored for hypotension and arrhythmias. If these occur, treatment should be discontinued. Treatment can be restarted without the initial bolus dose once the hypotension is

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of patients</th>
<th>B-type natriuretic protein, pg/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>42</td>
<td>54</td>
</tr>
<tr>
<td>Asthma</td>
<td>11</td>
<td>27</td>
</tr>
<tr>
<td>Acute bronchitis</td>
<td>14</td>
<td>44</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>8</td>
<td>55</td>
</tr>
<tr>
<td>Tuberculosis</td>
<td>2</td>
<td>93</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>4</td>
<td>120</td>
</tr>
<tr>
<td>Acute pulmonary embolism</td>
<td>3</td>
<td>207</td>
</tr>
</tbody>
</table>

![Table 2](http://ajcc.aacnjournals.org/Downloaded from http://ajcc.aacnjournals.org/ by AACN on September 5, 2017)
resolved. Along with blood pressure, fluid intake and output should be monitored to ensure adequate diuresis. In patients who have a pulmonary artery catheter in place, hemodynamic variables such as PCWP should be monitored. Other heart failure medications can be continued during treatment with nesiritide. Although initial studies indicated that vasodilatation induced by nesiritide is as effective as and comparable to that induced by nitroglycerin, further studies may be needed to justify the routine use of this newer but costlier ($300 per 48-hour infusion) option instead of conventional therapy.

**Conclusion**

BNP is released by the cardiac ventricles in response to ventricular stretch, and plasma levels of BNP correlate with elevated left ventricular pressure and clinical signs and symptoms such as dyspnea. With recent approval by the Food and Drug Administration of a point-of-care rapid assay for BNP, clinicians have an opportunity to explore the potential usefulness of the assay as a diagnostic aid. Left ventricular dysfunction is highly unlikely in patients with BNP levels less than 100 pg/mL. Most patients with
heart failure as the cause of dyspnea have levels greater than 400 pg/mL. In patients with BNP levels between 100 and 400 pg/mL, left ventricular dysfunction without volume overload, pulmonary embolism, and cor pulmonale must be excluded as possible causes of dyspnea.

Plasma levels of BNP may also be useful in evaluating the prognosis of patients with heart failure. However, clinical trials are ongoing to evaluate whether BNP levels should be used to adjust or guide therapy. Nevertheless, clinical trials are ongoing to evaluate whether plasma levels of BNP may be useful in evaluating the prognosis of patients with heart failure. Furthermore, a recombinant form of human BNP has been approved for acute treatment of compensated heart failure in combination with conventional therapy.

ACKNOWLEDGMENTS
We thank Dr. Anita Deswal, Dr. Debra K. Moser, Dr. Douglas L. Mann, and Dr. Arun Prakash for their contributions, guidance, and support. We also thank Dr. Bikidi Agoston for her encouragement in the incipient stages of this article.

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