The B-type or brain natriuretic peptide (BNP) assay is a quick blood test that can help in situations when heart failure is suspected: if BNP levels are low, we can be confident that heart failure is absent.

This article reviews data accumulated since the BNP assay was introduced and summarizes the present and potential future clinical uses of BNP measurement in patients with heart failure and myocardial infarction.

**ABSTRACT**

The B-type or brain natriuretic peptide (BNP) assay, a 15-minute bedside blood test, is highly sensitive and fairly specific for diagnosing heart failure and is useful in evaluating suspected heart failure in outpatients and in emergency care. Other uses include screening for left ventricular dysfunction and predicting outcome in patients with an established diagnosis of heart failure or myocardial infarction.

**KEY POINTS**

BNP, a cardiac neurohormone, first discovered in the brain of pigs, is secreted in response to increased ventricular volume and pressure.

Circulating BNP levels increase in proportion to the severity of heart failure, and BNP is detectable even with minimal clinical symptoms.

With a negative predictive value of greater than 95%, a normal BNP level can help exclude heart failure and other causes of neurohormone activation from the differential diagnosis.
Heart failure often misdiagnosed

Even though heart failure is common, it is often misdiagnosed, particularly in primary care, where symptoms can be less acute than in the hospital.14,15

Since the mortality rate in heart failure correlates with its stage at presentation, the earlier the diagnosis is made and treatment is begun, the greater the potential benefit.16 Unfortunately, because current diagnostic tests are not sensitive, many patients without symptoms are not identified.

Various strategies have been devised to improve diagnostic accuracy. Point schemes such as the Boston and Framingham heart failure score systems17,18 can simplify the problem, but they rely heavily on patient complaints and are insensitive when the patient has no symptoms.

**WHAT IS BNP?**

The natriuretic peptides, which include atrial natriuretic peptide and BNP, help regulate blood pressure and fluid balance by countering the renin-angiotensin system: whereas renin and angiotensin raise blood pressure, decrease urine output, and cause vasoconstriction, the natriuretic peptides have the opposite effects. Both atrial natriuretic peptide and BNP increase excretion of sodium and water by increasing glomerular filtration and inhibiting renal sodium resorption.19 They also decrease secretion of aldosterone and renin and cause vasodilation,
reducing blood pressure and extracellular fluid volume.19

“Brain natriuretic peptide” was so named because it was first identified in the brains of pigs. In humans, however, the main source of BNP is the ventricles of the heart,20 although it can also be demonstrated in the atria of the failing heart.21

BNP is continuously released in response to increases in ventricular volume and pressure.1 Physiologically, BNP levels correlate with:

- Left ventricular end-diastolic pressure
- Pulmonary artery wedge pressure and atrial pressure
- Ventricular systolic and diastolic dysfunction
- Left ventricular hypertrophy.

Clearance is rapid
Once released, BNP undergoes initial degradation by neutral endopeptidases and endothelial clearance receptors. When neutral endopeptidase inhibitors are given, BNP clearance declines and BNP’s effects increase.22 BNP clearance also occurs in the kidney.23 Clearance is rapid: the half-life of exogenously administered BNP is only 22 minutes.

**HOW THE ASSAY WORKS**

The only currently approved BNP assay (Triage BNP, Biosite Diagnostics, San Diego, CA) is a fluorescent immunoassay that quantitatively measures BNP levels in whole blood or plasma specimens. EDTA must be used as the anticoagulant.

The test kit comes in a sealed pouch requiring refrigeration, but it must be at room temperature for use. Once opened, it is stable for 14 days.

The test can be performed at the bedside. A sample is placed in the device, and plasma moves by capillary action into a reaction chamber containing murine fluorescent antibodies. The reaction mixture then flows through an elution column. A nalyte and fluorescent antibody conjugates are captured in discrete zones along the column. Bound fluorescent material represents the serum BNP concentration.

Afer 15 minutes— but no later than 30 minutes—the device is placed in an immuno-fluorescent reader, which reports the BNP concentration.

The assay can detect levels as low as 5 pg/mL, up to a maximum of 1,300 pg/mL, according to the package insert. The package insert also states that no significant interference or cross-reactivity was seen when the assay was tested against more than 50 commonly used cardiac medications, including digoxin, warfarin, nitroglycerin, and furosemide; or cardiac neurohormones including renin, aldosterone, angiotensin I, II, and III, and atrial natriuretic peptide.

The test, which costs $26, is considered “moderately complex” by regulatory agencies; however, it is simple to perform, and the time required for training is minimal.

Other BNP tests and an assay for pro-BNP should be available in the near future.

**REFERENCE VALUES NOT WELL DEFINED**

The physiologically possible range of BNP is 0 to approximately 3,500 pg/mL. The upper limit of normal is not clearly defined, although a concentration higher than 100 pg/mL suggests the diagnosis of heart failure, and this is the upper limit of normal suggested by the test manufacturer.

Some caveats in interpreting BNP values:

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### TABLE 2

**Conditions associated with increased BNP levels**

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Heart failure</td>
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Left ventricular hypertrophy
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**Only use EDTA as the anticoagulant in BNP samples**
Assays differ
Because various immunoassays use different antibodies, they may not have the same performance characteristics. Consult the manufacturer’s reference values when using a specific immunoassay system.

Factors other than heart failure affect BNP
BNP values should be considered only in the context of the patient’s presentation, as factors other than heart failure can affect BNP levels (Table 2).

- **Age.** Older people have slightly higher BNP levels than younger people.24–26
- **Sex.** Women have slightly higher levels than men.24
- **Cirrhosis.** Patients with cirrhosis had BNP levels approximately three times higher than healthy subjects in one study.24
- **Renal failure.** Patients in renal failure had markedly elevated BNP levels in two studies.23,24 Their BNP levels declined somewhat after dialysis sessions.23 It is unclear whether the elevations are due to volume overload (leading to increased BNP secretion), decreased metabolism and clearance of BNP, or decreased cardiac function.

- **Left ventricular hypertrophy.** BNP levels correlate well with age and with the left ventricular mass index.25 This observation may explain the higher BNP levels in older people: BNP is synthesized in the ventricles, and the elderly have more ventricular mass than younger adults.26

- **Other conditions** associated with increased BNP levels include cardiac inflammation (eg, myocarditis, cardiac allograft rejection), arrhythmogenic right ventricle with decreased ejection fraction, Kawasaki disease, primary pulmonary hypertension, primary hyperaldosteronism, and Cushing syndrome.

While some studies found higher BNP levels in people with hypertension,27 others did not unless the patients also had left ventricular hypertrophy.26

BNP levels do not seem to rise and fall in any circadian rhythm.24

### STUDIES OF USE OF BNP ASSAYS

The BNP assay became available only recently, and clinical studies are gradually providing us the data we need to define its appropriate uses. Many studies were limited by small sample size. Nevertheless, from the available data, BNP measurement appears to have several important potential uses.

#### BNP as a test for heart failure
In heart failure, BNP levels are proportional to illness severity and may be as much as 25 times higher than in people without heart failure (Figure 1).28

The sensitivity and specificity of BNP as a test for heart failure depends on the upper limit of normal used: a lower cut point is more sensitive but less specific, whereas a higher cut point is less sensitive but more specific.

Several studies,1,28–31 using various assays and cut points, reported sensitivities ranging from 85% to 97% and specificities of 84% to 92%. The positive predictive values were 70% to 95%,1,28 while the negative predictive values were consistently higher than 95%.28,31

A Veterans Administration study,28 using a cut point of 100 pg/mL, found the Biosite BNP assay to have a sensitivity and
specification of 94% for diagnosing heart failure among 250 patients presenting to urgent care departments because of dyspnea. The positive predictive value was 92%, and the negative predictive value was 96%. The mean BNP level in patients with heart failure was 1,076 ± 138 pg/mL, vs 38 ± 4 pg/mL in patients without heart failure.

The investigators plotted the receiver operating characteristic (ROC) curves for diagnosis by BNP levels and diagnosis by the physician in the emergency department (FIGURE 2). Both performed well, but the BNP level performed better.

Thirty patients were misdiagnosed. Fifteen were initially diagnosed as having heart failure but were later proven to have another diagnosis. Their mean BNP level was 46 ± 13 pg/mL. In 15 patients initially given another diagnosis but later shown to have heart failure, the mean BNP level was 742 ± 337 pg/mL.

The investigators concluded that a normal BNP level is a good indication that dyspnea is due to a condition other than heart failure, eg, an acute exacerbation of chronic obstructive pulmonary disease. It was also good for excluding heart failure as the cause of edema: the mean BNP level in patients with edema without heart failure was 63 pg/mL, vs 1,036 in edematous patients with heart failure.

Using BNP to predict outcome in heart failure

Serial BNP measurement can predict outcomes in patients hospitalized for decompensated heart failure.

In one study,32 BNP levels increased in 52% of patients who died or required readmission within 30 days. In contrast, BNP levels declined in 84% of patients who had good outcomes.

BNP measurements are also a good indicator of heart failure severity and prognosis in outpatients.33 In 290 patients with New York Heart Association class I or II heart failure with a mean ejection fraction of 37% followed for a median of 812 days, an initial BNP concentration greater than 56 pg/mL was an independent predictor of progression of heart failure and death.34

In another study,35 an elevated BNP concentration was a better predictor of death from cardiovascular causes in the next 12 months than was age, atrial natriuretic peptide level, ejection fraction, pulmonary artery pressure, gender, heart failure etiology, or New York Heart Association class.

In general, an elevated BNP concentration portends a greater risk of death and morbidity for heart failure patients, independent of underlying coronary artery disease. In fact, in a study comparing normal subjects, patients with coronary artery disease, and patients with heart failure,33 coronary artery disease did not cause BNP elevation unless the patient had coexistent left ventricular dysfunction.

In the Veterans Administration study,28 BNP levels also predicted whether emergency patients would be hospitalized or sent
home. Those requiring hospitalization had a mean BNP level of 700 pg/mL, while those who were sent home had a mean BNP level of 254 pg/mL.

BNP in assessing right ventricular dysfunction
BNP appears to be elevated in right or left ventricular dysfunction, regardless of the cause of the dysfunction, although not to the same extent in right ventricular dysfunction as seen in left ventricular dysfunction.

In 60 patients with primary pulmonary hypertension, BNP levels independently predicted 24-month mortality. During follow-up, mortality was also markedly lower in patients whose BNP levels decreased than in those whose levels increased.

In patients with arrhythmogenic right ventricular dysplasia, increased BNP levels related to the severity of right ventricular dysfunction.

**BNP and echocardiography**
It is important to distinguish whether a patient with heart failure has systolic or diastolic failure by measuring the ejection fraction. Although BNP levels do not accurately predict the ejection fraction, BNP measurement has been suggested as a way to screen candidates for echocardiography—which does measure the ejection fraction accurately.

In 1,252 patients, elevated BNP had a sensitivity of 77%, specificity of 87%, and negative predictive value of 97.5% for predicting left ventricular dysfunction. In patients over age 55, the sensitivity was 92%, the specificity was 72%, and the negative predictive value was 99.2%. Therefore, although the specificity is not extremely high, the high negative predictive value makes this an appropriate method for selecting patients who need echocardiography.

Another evaluation found that elevated BNP predicted systolic dysfunction with a sensitivity of 83% and a specificity of 77%, and it predicted diastolic dysfunction with a sensitivity of 85% and a specificity of 70%.

**Monitoring response to heart failure therapy**
Once a baseline BNP level is established, serial measurements can evaluate the response of the ejection fraction to therapy.

In heart failure patients receiving carvedilol, improving ejection fraction correlated well with declining BNP (r = -0.698, P < .01).

In a case report of malignant hypertension and left ventricular hypertrophy, treatment resulting in regression of the hypertrophy was associated with declining BNP levels over the next month.

While these data are only suggestive, sequential BNP measurement may have a future application in monitoring the response to heart failure therapy.

**Predicting intracardiac pressures**
Several studies suggest that BNP levels are an indicator of elevated intracardiac pressures, and that they respond dynamically to changes in ventricular volumes and pressure.

In 72 patients with symptomatic left ventricular dysfunction, defined as an ejection...
fraction less than 50%, BNP was an independent predictor of increased left ventricular end-diastolic pressure, and BNP levels varied directly with changes in pressure.

In another study, the sensitivity for predicting left ventricular end-diastolic pressure greater than 18 mm Hg was 81% and the specificity was 85%. Others support that an elevated BNP predicts elevated end-diastolic pressures.

In a report on 15 patients with decompensated heart failure in which BNP levels were obtained every 2 hours during treatment, BNP levels declined in parallel with wedge pressures ($r = 0.79, P < .05$; Figure 3). Patients who died had higher final BNP levels. BNP levels seem to function as a serum measurement of pulmonary capillary wedge pressure.

**BNP in acute coronary syndromes**

BNP measurement provides information about acute coronary ischemia and prognosis after myocardial infarction and, therefore, may be a useful noninvasive method to identify patients at high risk for poor outcome.

Several studies found that BNP levels were elevated in acute myocardial infarction. After myocardial infarction, BNP is a strong independent predictor of left ventricular function, heart failure, and long-term survival.

In patients with acute myocardial infarction, an elevated BNP on the day of admission or on day 2 predicted a poor prognosis, possibly reflecting poor residual left ventricular function after myocardial infarction.

**BNP may be a marker of ventricular remodeling** within the first 30 days after myocardial infarction. In 30 patients, BNP levels 1 week after myocardial infarction correlated with cardiac remodeling ($r = 0.77, P < .001$). Higher BNP levels were associated with greater increases in left ventricular volume and less improvement in ejection fraction compared with those whose BNP stayed lower.

**Gauging the response to therapy after myocardial infarction.** In another report examining response to therapy, a rise in BNP was seen 16 hours after myocardial infarction, with a second peak at 2 to 3 days. However, the second peak did not occur if angiotensin-converting enzyme (ACE) inhibitor therapy was started.

Plasma BNP levels increase in unstable angina and decrease with medical treatment. In 73 patients (33 with unstable angina, 20 with stable angina, 20 controls), BNP levels were $40 \pm 30 \text{ pg/mL}$ in unstable angina vs $15 \pm 8 \text{ pg/mL}$ with stable angina and $10 \pm 6 \text{ pg/mL}$ in controls.

The precise application of BNP testing in acute coronary syndromes is as yet undefined, but it clearly offers good prognostic information after acute myocardial infarction. More research is needed to answer whether BNP measurement helps in the urgent diagnosis of acute coronary syndromes.

**GUIDELINES FOR THE PRACTITIONER**

Few published guidelines for the clinical use of BNP measurements are currently available. However, a review of the recent literature suggests the following.

- BNP is most useful for excluding the diagnosis of heart failure in cases in which the differential diagnosis would normally suggest it. For example, in a patient without a diagnosis of heart failure but with any of its classic signs or symptoms (eg, shortness of breath, dyspnea on exertion, orthopnea, dependent edema, an audible third cardiac sound, jugular venous distention, or basilar rales), a BNP level in the normal range should cause the clinician to strongly consider an alternative diagnosis.

- Because conditions other than heart failure can result in an elevated BNP, the clinical context of a patient with a positive BNP must be considered. A n elevated BNP level should prompt routine tests to confirm the diagnosis in addition to evaluating the cause and defining the type of heart failure (eg, electrocardiography, chest radiography, and echocardiography).

- As for using BNP levels to monitor patients with diagnosed chronic heart failure, levels correlate well with treatment efficacy. Following an exacerbation of heart failure, a declining BNP indicates a good response to therapy and portends a more favorable outcome. A rising BNP suggests a greater risk of
adverse outcome, warranting a more aggressive treatment strategy.

- An elevated BNP level 48 hours after myocardial infarction strongly predicts heart failure or death within the next year, and appropriate treatment and monitoring strategies should be considered for this group of patients.

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REFERENCES
39. Yamamoto K, Burnett JC, Jougasaki M, et al. Superiority of brain...
natriuretic peptide as a hormonal marker of ventricular systolic and diastolic dysfunction and ventricular hypertrophy.


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