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The B-type natriuretic peptide assay: A rapid test for heart failure

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.

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.

NEEDED: AN ACCURATE TEST FOR HEART FAILURE

We need an accurate diagnostic test for heart failure, as the signs, symptoms, and current diagnostic tests are unreliable, and many cases are misdiagnosed.

Symptoms are nonspecific; signs are not sensitive

Heart failure has historically been defined as a syndrome. As such, no single finding is pathognomonic. The symptoms are nonspecific, and the clinical signs, although reasonably specific, are not at all sensitive.¹ Chakko et al² found that clinical, radiographic, and hemodynamic evaluations yielded conflicting results in patients with chronic heart failure.

The physical examination has poor diagnostic efficacy in heart failure (TABLE 1).^{3–8} Lung sounds, peripheral edema, jugular venous distention, abdominal jugular reflex, and extra heart sounds all indicate fluid overload, but these signs are insensitive and nonspecific in patients at risk for heart failure.

Furthermore, the differential diagnosis for people at risk is long and complicated. Most patients with heart failure are elderly, and many have multiple concomitant conditions

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that tend to obscure the diagnosis. In individual cases, even experienced physicians often disagree on the diagnosis of heart failure, especially in the early stages of the disease.¹

Tests are unreliable

Easily available diagnostic tests for heart failure (laboratory measurements, echocardiography, radiography) are not accurate enough to always make a correct diagnosis.^{9,10}

Many physicians rely on chest radiographs to help diagnose heart failure, but chest radiography is a blunt instrument. For example, in chronic heart failure, radiographic signs of congestion have unreliable sensitivity, specificity, and predictive value for identifying those with high pulmonary capillary wedge pressure.¹¹

The ejection fraction, considered the single most important measurement in heart failure,¹ is the standard for noninvasive assessment of ventricular function, and it can define the cause and the type of heart failure.

However, the ejection fraction has no correlation with symptoms.¹² Furthermore, the ejection fraction is measured echocardiographically, and urgent echocardiographic assessment may be difficult to obtain in the outpatient clinic or primary care office. In a study in Scotland,¹³ where health care is tightly rationed, an experimental program that made echocardiography accessible to general practitioners led to a change in management in more than two thirds of patients referred.

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 systems^{17,18} 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 counterbalancing 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. Analyte and fluorescent antibody conjugates are captured in discrete zones along the column. Bound fluorescent material represents the serum BNP concentration.

TABLE 2

Conditions associated with increased BNP levels

Heart failure
Left ventricular hypertrophy
Cardiac inflammation (eg, myocarditis, cardiac allograft rejection)
Arrhythmogenic right ventricle with decreased ejection fraction
Kawasaki disease
Primary pulmonary hypertension
Renal failure
Ascitic cirrhosis
Endocrine disease (primary hyperaldosteronism, Cushing syndrome)
Geriatric age

After 15 minutes—but no later than 30 minutes—the device is placed in an immunofluorescent 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:

Only use EDTA as the anticoagulant in BNP samples

BNP levels increase with severity of heart failure

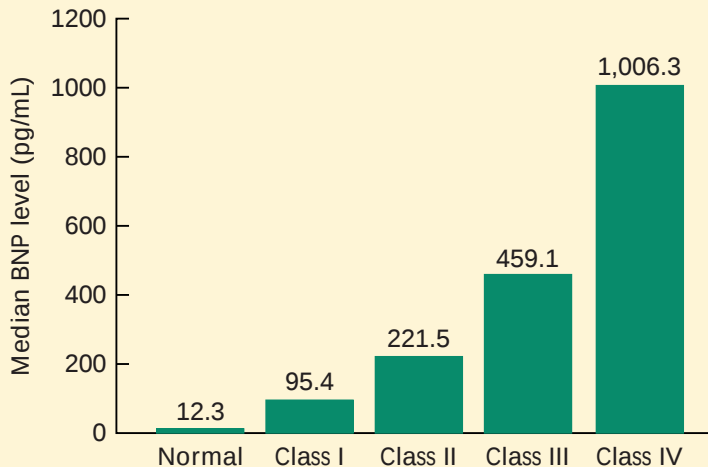


FIGURE 1. Brain natriuretic peptide (BNP) levels in normal subjects and in patients with heart failure.

DATA FROM BIOSITE PACKAGE INSERT

A BNP > 100 pg/mL suggests the diagnosis of heart failure

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



specificity 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 $1,076 \pm 138$ 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 con-

BNP levels beat physical examination in diagnosing heart failure

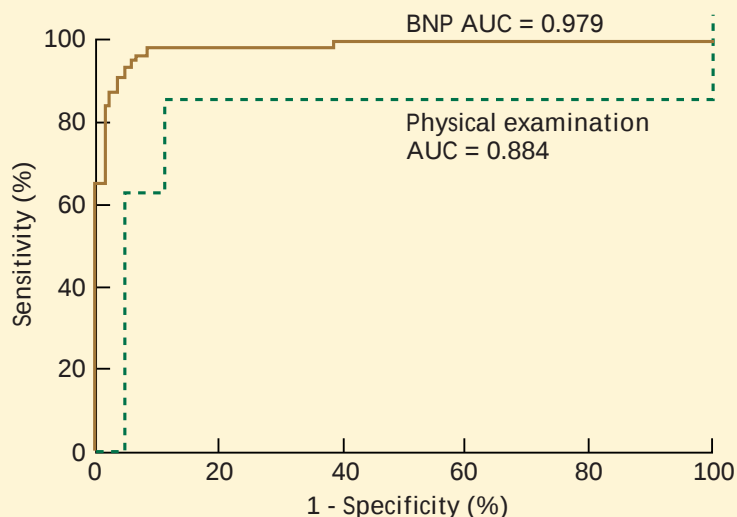


FIGURE 2. Receiver operating characteristic curves for the accuracy of elevated brain natriuretic peptide (BNP) levels and physical examination in the emergency department in 250 patients with suspected heart failure. AUC, area under the curve; the larger the AUC, the better the test.

FROM DAO Q, KRISHNASWAMY P, KAZANEGRA R, ET AL. UTILITY OF B-TYPE NATRIURETIC PEPTIDE IN THE DIAGNOSIS OF CONGESTIVE HEART FAILURE IN AN URGENT-CARE SETTING. J AM COLL CARDIOL 2001; 37:379-385.

centration 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

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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,³⁶ 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,³⁷ 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,³⁸ BNP measurement has been suggested as a way to screen candidates for echocardiography—which does measure the ejection fraction accurately.

In 1,252 patients,³¹ 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%.³⁹

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,⁴⁰ improving ejection fraction correlated well with declining BNP ($r = -0.698$, $P < .01$).

In a case report⁴¹ 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,⁴² 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,³⁹ 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.⁴³

In a report on 15 patients with decompensated heart failure⁴ 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.^{44,45} After myocardial infarction, BNP is a strong independent predictor of left ventricular function, heart failure, and long-term survival.^{43,45,46} 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,⁴⁶ 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,⁴⁷ 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),⁴⁸ BNP levels were 40 ± 30 pg/mL in unstable angina vs 15 ± 8 pg/mL with stable angina and 10 ± 6 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.⁴⁹ 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. An 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

If BNP is normal, consider a diagnosis other than heart failure

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,^{50,51} and

appropriate treatment and monitoring strategies should be considered for this group of patients.



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