

The Role of BNP Testing in Heart Failure

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Brain natriuretic peptide (BNP) levels are simple and objective measures of cardiac function. These measurements can be used to diagnose heart failure, including diastolic dysfunction, and using them has been shown to save money in the emergency department setting. The high negative predictive value of BNP tests is particularly helpful for ruling out heart failure. Treatment with angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers, spironolactone, and diuretics reduces BNP levels, suggesting that BNP testing may have a role in monitoring patients with heart failure. However, patients with treated chronic stable heart failure may have levels in the normal range (i.e., BNP less than 100 pg per mL and N-terminal proBNP less than 125 pg per mL in patients younger than 75 years). Increases in BNP levels may be caused by intrinsic cardiac dysfunction or may be secondary to other causes such as pulmonary or renal diseases (e.g., chronic hypoxia). BNP tests are correlated with other measures of cardiac status such as New York Heart Association classification. BNP level is a strong predictor of risk of death and cardiovascular events in patients previously diagnosed with heart failure or cardiac dysfunction. (*Am Fam Physician* 2006;74:1893-8. Copyright © 2006 American Academy of Family Physicians.)

Until recently, no simple blood test could detect heart failure or monitor its progression or guide its treatment. With the increasing availability of assays for the measurement of brain natriuretic peptide (BNP), a cardiac hormone, this test may have a role in detecting, monitoring, and perhaps preventing chronic heart failure.

Pathophysiology

The heart secretes natriuretic peptides as a homeostatic signal to maintain stable blood pressure and plasma volume and to prevent excess salt and water retention. Atrial natriuretic peptide (ANP) initially was identified in the atrial myocardium of rats.¹ BNP subsequently was isolated in porcine brains.² Natriuretic peptides have several actions: (1) down-regulating the sympathetic nervous system and the renin-angiotensin-aldosterone system, (2) facilitating natriuresis and diuresis through the afferent and efferent hemodynamic mechanisms of the kidney and distal tubules, (3) decreasing peripheral vascular resistance, and (4) increasing smooth muscle relaxation. Natriuretic peptides also may inhibit cardiac growth and hypertrophy, counteracting the mitogenesis that causes ventricular remodeling.³⁻⁵

BNP primarily is secreted by the ventricles in the heart as a response to left ventricular stretching or wall tension.⁶ It may be a backup hormone that is activated only after a prolonged period of volume overload.⁷ Cardiac myocytes secrete a BNP precursor that is synthesized into proBNP, which consists of 108 amino acids. After it is secreted into the ventricles, proBNP is cleaved into the biologically active C-terminal portion and the biologically inactive N-terminal (NT-proBNP) portion.

Influences on BNP Levels

Many medications used to treat heart failure (e.g., diuretics such as spironolactone [Aldactone], angiotensin-converting enzyme inhibitors, angiotensin-II receptor blockers) reduce natriuretic peptide concentrations.⁸⁻¹³ Therefore, many patients with chronic stable heart failure will have BNP levels in the normal diagnostic range (i.e., BNP level less than 100 pg per mL [100 ng per L]). However, digoxin and some beta blockers appear to increase natriuretic peptide concentrations.¹⁴⁻¹⁶ Exercise causes a short-term increase in BNP levels,¹⁷ although only small changes (i.e., increase of 0.9 percent in patients without heart failure, 3.8 percent in patients with New York Heart Association [NYHA] class I or II heart failure, and

SORT: KEY RECOMMENDATIONS FOR PRACTICE

<i>Clinical recommendation</i>	<i>Evidence rating</i>	<i>References</i>
BNP testing is recommended to detect or rule out heart failure, including diastolic heart failure. The test has a high negative predictive value—a negative result rules out disease more effectively than a positive result rules in disease.	C	24
BNP testing is a useful tool in predicting prognoses in patients with heart failure and appears to be a stronger predictor than some traditional indicators (e.g., left ventricular ejection fraction, ischemic etiology, serum levels, New York Heart Association classification).	C	33
BNP is a predictor of death and cardiovascular events in persons without a previous cardiac dysfunction diagnosis.	C	33
It is premature to use BNP for treatment monitoring in patients with heart failure until further randomized controlled trials are completed.	C	32

BNP = brain natriuretic peptide.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, see page 1821 or <http://www.aafp.org/afpsort.xml>.

15 percent in patients with NYHA class III to IV heart failure) are detectable one hour after exercise.¹⁸ No circadian variation has been reported when BNP is measured every three hours for 24 hours,¹⁹ and there is less hourly variation with BNP than with ANP.²⁰

BNP to Diagnose Heart Failure

There is no agreed-upon first-line test for the diagnosis of heart failure and no simple method of measuring the adequacy of cardiac output in relation to normal levels of activity. Heart failure usually is diagnosed in persons with known heart disease who present with nonspecific symptoms (e.g., breathlessness, ankle swelling) and signs (e.g., basal lung crackles). To confirm clinically suspected heart failure, physicians rely on surrogate measures of cardiac function such as left ventricular ejection fraction. However, it is clear that a large proportion of patients with heart failure, particularly older patients and women, have preserved systolic function (i.e., diastolic heart failure). The best way to diagnose and treat these patients is unclear. BNP increases when cardiac myocytes are strained; therefore, BNP is an effective method for detecting heart failure with or without systolic dysfunction.

Elevated BNP levels also have been associated with renal failure (because of reduced clearance),²¹ pulmonary embolism, pulmonary hypertension,^{22,23} and chronic hypoxia.

A systematic review included 20 studies

evaluating BNP testing in the diagnosis of heart failure.²⁴ The eight studies that measured BNP against a reference standard of reduced left ventricular ejection fraction (i.e., 40 percent or lower or the equivalent) had a pooled diagnostic odds ratio of 12 (95% confidence interval [CI], 8 to 16).²⁴ This result is consistent with a moderately accurate diagnostic test. The seven studies that measured BNP against clinical criteria (i.e., a consensus view using all other clinical information and often using a panel of two or three cardiologists) had a pooled diagnostic odds ratio of 31 (95% CI, 27 to 35).²⁴ The two studies that measured BNP against echocardiographic criteria for systolic and diastolic heart failure had a pooled diagnostic odds ratio of 38 (95% CI, 6 to 237).²⁴ Therefore, the review showed a greater agreement with a heart failure measure that included diastolic heart failure than one that included systolic heart failure alone (assuming there were no other differences between the studies).²⁴

Results from significant studies of the diagnostic accuracy of BNP and NT-proBNP measurements are shown in *Table 1*.²⁵⁻²⁹ The largest of these studies enrolled 1,586 patients presenting with dyspnea to seven emergency departments.²⁵ Using a cutoff BNP level of 50 pg per mL (50 ng per L), the positive likelihood ratio was 2.6 (95% CI, 2.3 to 2.8), and the negative likelihood ratio was 0.05 (95% CI, 0.03 to 0.07). This indicates that a low BNP value is highly effective at ruling out

heart failure, whereas a value more than 50 pg per mL is only a fair indicator of disease.

The number of studies conducted in the primary care setting is approximately equal to the number set in hospitals, and little difference in diagnostic odds ratio has been shown between the two settings. Although the sensitivity and specificity of BNP testing in primary care and hospital settings are similar, interpretation of the test varies between asymptomatic and symptomatic patients and between primary and acute care settings (Table 2^{25,27,29}).

The optimal cutoff value for a heart failure diagnosis and whether reference levels should vary with age and sex remain unclear. There is a trade-off, because lowering the cutoff decreases the false-negative

rate (i.e., increased sensitivity and fewer missed diagnoses) but increases the false-positive rate (i.e., decreased specificity and more incorrect diagnoses). In addition, the average levels of BNP and NT-proBNP are greater in women than in men and increase with age.^{19,30} However, these higher levels in women may reflect an increasing prevalence of undetected and possibly asymptomatic cardiac dysfunction in this group.

A trial that included patients presenting with dyspnea to a Swiss emergency department assessed health outcomes and cost of treatment associated with BNP-assisted diagnoses.³¹ The trial showed that, compared with no BNP test, the test reduced the median length of hospitalization (eight versus 11 days) and the mean total cost of

TABLE 1
Summary of Studies Evaluating the Diagnostic Accuracy of BNP and NT-ProBNP Measurements in Heart Failure

<i>Study setting</i>	<i>Number of patients</i>	<i>Cutoff value</i>	<i>Reference test</i>	<i>Overall probability of heart failure (%)</i>	<i>LR+ (95% CI)*</i>	<i>LR- (95% CI)†</i>
BNP						
Patients presenting with dyspnea to emergency departments (United States, France, Norway) ²⁵	1,586	50 pg per mL (50 ng per L)	Consensus of two cardiologists	47	2.6 (2.34 to 2.79)	0.05 (0.03 to 0.07)
Patients without a previous heart failure diagnosis randomly selected from 21 general practices (United Kingdom) ²⁶	1,331	66 pg per mL (66 ng per L)	LVEF of 40 percent or lower	1	1.8 (1.8 to 1.9)	0.0 (0.0 to 0.4)
Patients with suspected heart failure in general practice (United Kingdom) ²⁷	106	77 pg per mL (77 ng per L)	Consensus of three cardiologists using ESC criteria	27	6.2 (3.8 to 10.6)	0.04 (0.01 to 0.20)
NT-proBNP						
Patients selected from general practices (Denmark) ²⁸	672	366 pg per mL (366 ng per L)	LVEF of 40 percent or lower	6	2.3 (1.8 to 2.8)	0.35 (0.19 to 0.59)
General population older than 45 years (United Kingdom) ²⁹	307	304 pg per mL (304 ng per L)	Consensus of three cardiologists using ESC criteria	2	3.3 (3.2 to 4.0)	0.0 (0.0 to 0.5)

BNP = brain natriuretic peptide; NT-proBNP = N-terminal pro-brain natriuretic peptide; LR+ = positive likelihood ratio; CI = confidence interval; LR- = negative likelihood ratio; LVEF = left ventricular ejection fraction; ESC = European Society of Cardiologists.

*—Values from 2 to 5 weakly to moderately increase the likelihood of heart failure.

†—Values of 0.1 or less greatly decrease the likelihood of heart failure.

Information from references 25 through 29.

treatment (\$5,410 versus \$7,264).³¹ These results are attributable to the test's ability to rule out heart failure, allowing the physician to initiate treatment for an alternative diagnosis such as chronic obstructive pulmonary disease or pneumonia. According to an updated guideline from the American College of Cardiology (ACC) and the American Heart Association (AHA), BNP measurements can be useful in patients presenting in the urgent care setting when the clinical diagnosis of heart failure is uncertain.³²

Determining Prognoses

Nineteen studies showed that elevated BNP levels in patients with heart failure are associated with an increased risk of death or cardiovascular events.³³ Pooled results from five studies showed that a BNP increase of 100 pg per mL caused a 35 percent increase in risk of death.³³ BNP was the only statistically significant independent predictor of mortality in nine studies, indicating that BNP tests potentially are more useful than traditional predictors of mortality (e.g., age, ischemic etiology, left ventricular ejection fraction, NYHA classification, serum creatinine levels).³³

Screening and Prevention

Because BNP tests can predict death and cardiovascular events in patients without a previous heart disease diagnosis, they are being studied as a possible tool for heart failure screening. Although BNP tests may help detect patients at high risk of overt heart failure and may prevent its progression, randomized controlled trials are needed to determine who should be tested and whether or not treating asymptomatic patients is beneficial.

Several studies (some of which excluded persons previously diagnosed with heart failure) have measured the prognostic value of BNP in asymptomatic populations. In the two largest studies, the relative risk of death during the four to five years of follow-up approximately doubled in patients with a BNP value higher than relatively low cutoff levels (17.9 to 23.3 pg per mL [17.9 to 23.3 ng per L]).^{34,35}

Monitoring Patients with Heart Failure

BNP measurement is a potential tool for monitoring treatment response in patients with heart failure because of the test's ability to diagnose heart failure, predict prognosis, and correlate with more invasive clinical

TABLE 2
Interpreting BNP Measurements for Heart Failure in Different Clinical Settings

Clinical setting	Pretest probability of heart failure (%)†	Posttest probability of heart failure (%)*		
		BNP < 50 pg per mL (50 ng per L)	BNP 50 to 150 pg per mL (50 to 150 ng per L)	BNP > 150 pg per mL
Patients presenting in the primary care setting (screening) ²⁹	2	0.2	1	9
Patients presenting in the primary care setting who have at least one risk factor for heart failure (e.g., history of myocardial infarction, angina, hypertension, or diabetes) ²⁹	7	0.6	4	27
Patients with suspected heart failure in the primary care setting ²⁷	27	3	17	65
Patients presenting with dyspnea to the emergency department ²⁵	50	7	36	83

BNP = brain natriuretic peptide; LR+ = positive likelihood ratio; LR- = negative likelihood ratio.

*—Based on an assumed LR+ of 5.0 for > 150 pg per mL, LR+ of 0.57 for 50 to 150 pg per mL, and LR- of 0.08 for < 50 pg per mL.

†—Overall prevalence of heart failure.

Information from references 25, 27, and 29.

measures (e.g., pulmonary capillary wedge pressure).³⁶ Prognostic studies have shown that BNP levels measured after treatment took effect were more predictive of the risk of death or further cardiovascular events than those initiated at first presentation.^{37,38}

Ideally, randomized trials would offer definitive evidence; however, only two small trials (including 69 and 21 patients) have evaluated BNP-guided treatment.^{39,40} The first trial showed a nearly twofold decrease in cardiovascular events,³⁹ and the second trial showed a decrease in BNP levels with BNP-guided treatment.⁴⁰ However, according to the ACC/AHA guideline on the management of heart failure, the value of serial BNP measurements in guiding therapy for patients with heart failure is not well established.³² Larger randomized controlled trials are needed before routine BNP monitoring of heart failure can be recommended.

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