B-Type Natriuretic Peptides: A Diagnostic Breakthrough for Clinicians

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B-type natriuretic peptide (BNP), a neurohormone synthesized in the cardiac ventricles, is released as preproBNP and then enzymatically cleaved to the N-terminal-proBNP (NT-proBNP) and BNP upon ventricular myocyte stretch. Blood measurements of BNP and NT-proBNP have been used to identify patients with congestive heart failure (CHF). Important considerations for these tests include their half-lives in plasma, dependence on renal function for clearance, and the interpretation of their units of measure. The BNP assay currently available in North American markets, approved for use as a diagnostic aid in CHF and a prognostic marker in acute coronary syndromes (ACS), has particular advantages because it is available at the point of care and has had considerable use in clinical studies. In general, a BNP level less than 100 pg/mL has strong negative predictive value for CHF. In addition, BNP levels can be used to gauge the effect of short-term treatment of acutely decompensated CHF. BNP has been shown to be a reliable and independent predictor of sudden cardiac death. In the absence of renal dysfunction, NT-proBNP has also been shown to be of diagnostic value in CHF, related to CHF severity, predictive of sudden death, and prognostic for death in ACS. This article reviews the literature concerning the use of these peptides in a variety of clinical scenarios.
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The prevalence of congestive heart failure (CHF) grew rapidly during the 1990s owing to the use of disease-modifying agents, including angiotensin-converting enzyme (ACE) inhibitors and β-blockers.[1] In addition, more patients are surviving acute myocardial infarction (AMI) and are left at risk for the development of CHF. On average, the 5-year mortality rate for CHF is 50%, with 90% dead at 10 years.[1] Many aspects of CHF remain

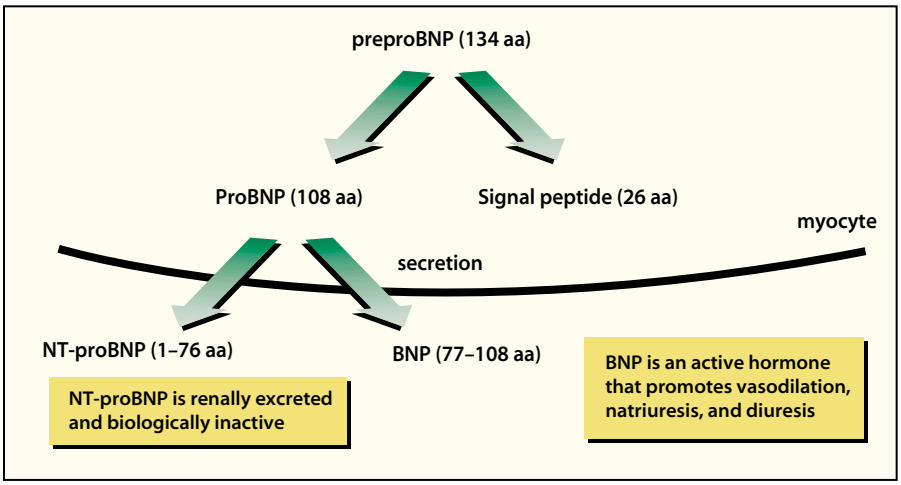

Figure 1. *The cardiac natriuretic peptide family. BNP, B-type natriuretic peptide; NT, N-terminal; aa, amino acid.*

clinical challenges. We not only have difficulty diagnosing CHF, we have difficulty assessing the results of treatment, both in hospital and outpatient settings.[2] Although patients admitted to the hospital with decompensated heart failure frequently improve with treatment, traditionally there has been no practical way to evaluate the long-term effects of such treatment. Indeed, in-hospital mortality and readmission rates for CHF patients are extremely high.[1–3] Conventional cardiac function tests are time consuming and often do not correlate well with symptomatic changes in a patient's condition. Therefore, most patients are discharged when they "feel better," which may preclude further titration of medical therapy. The recognition of B-type natriuretic peptide (BNP) and N-terminal-proBNP (NT-proBNP) as markers for the diagnosis, severity, and prognosis of CHF is truly a breakthrough for clinicians and patients faced with CHF.

The Natriuretic Peptide Family as Important Cardiac Neurohumoral Markers

Heart failure is characterized by complicated cardiorenal, hemodynamic, and neurohormonal alterations.[4,5] The fact that increased levels of vasoconstrictor neurohumoral factors, such as norepinephrine, renin, endothelin-1, interleukin (IL)-6, and tumor necrosis factor α (TNF-α), have been found to have significant prognostic value in CHF suggests that these vasoconstrictors play an important role in the pathogenesis of the disorder.[4–9] Although pharmacologic modulation of these factors has led to improvements in cardiac function in some cases, relying on these factors to monitor therapy has proved impractical.[10,11] Levels of neurohormones and cytokines, such as TNF-α and IL-6, have wide ranges, assay stability issues, and may vary considerably over time.[12]

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The vasodilator natriuretic peptide family may be best suited for neurohumoral profiling in CHF.[13,14] Three major natriuretic peptides, all sharing a common 17-amino-acid ring structure, are under investigation: atrial (A-type) natriuretic peptide (ANP) and BNP, which are of myocardial cell origin, and C-type natriuretic peptide, which is of endothelial origin.[15–17] All three peptides are cleared by the natriuretic peptide C-receptor and degraded by neutral endopeptidase.[15,16] Unlike ANP, whose major storage sites include both the atria and ventricles, the major source of plasma BNP is the cardiac ventricles, where it is synthesized as preproBNP (132 amino acids) (Figure 1). This suggests that BNP and NT-proBNP may be more sensitive and specific indicators of ventricular disorders than other natriuretic peptides.[18,19]

BNP levels accurately reflect the decompensated state of circulatory congestion.[20,21] The atrial myocytes synthesize ANP, which is stored in granules and released episodically in response to atrial wall tension (Figure 2). A minor stimulus, such as exercise, can trigger release of significant amounts of ANP into the bloodstream.[22] In contrast, the nucleic acid sequence of the preproBNP gene suggests that turnover of messenger RNA is high and that the peptide is synthesized in bursts.[18,22] Release appears to be in direct proportion to ventricular volume expansion and pressure overload.[19,20] Both BNP and NT-proBNP are independent predictors of high left ventricular (LV) end-diastolic pressure and are more useful than ANP or other neurohormones for assessing mortality in patients with chronic CHF.[21] The half-life of NT-proBNP is 120 minutes, suggesting that meaningful changes in hemodynamics could be reflected by this test approximately every 12 hours.[23] The half-life of BNP is 22

minutes, and prior studies have established that BNP can accurately reflect pulmonary capillary wedge pressure changes every 2 hours.[24,25] Hence, the biologic differences in these peptides may leverage specific clinical applications for each.

Comparing BNP and NT-proBNP

Table 1 lists the important differences between BNP and NT-proBNP, the two currently approved assays for use in North America. As the table indicates, there are many important differences between these two blood tests. The strengths of the BNP assay are as follows: 1) it is available at the point of care for rapid diagnosis; 2) it is less influenced by age and renal function; and 3) it has a single approved cut-point for the diagnosis of CHF. In addition, with an established track record on the North American market for over 2 years, a knowledge base regarding BNP has amassed that validates its use in multiple clinical settings.[24] BNP is approved as a diagnostic aid in CHF and as a prognostic indicator in acute coronary syndromes (ACS).[24] As of 2003, BNP should be considered the gold-standard natriuretic peptide for clinical application.

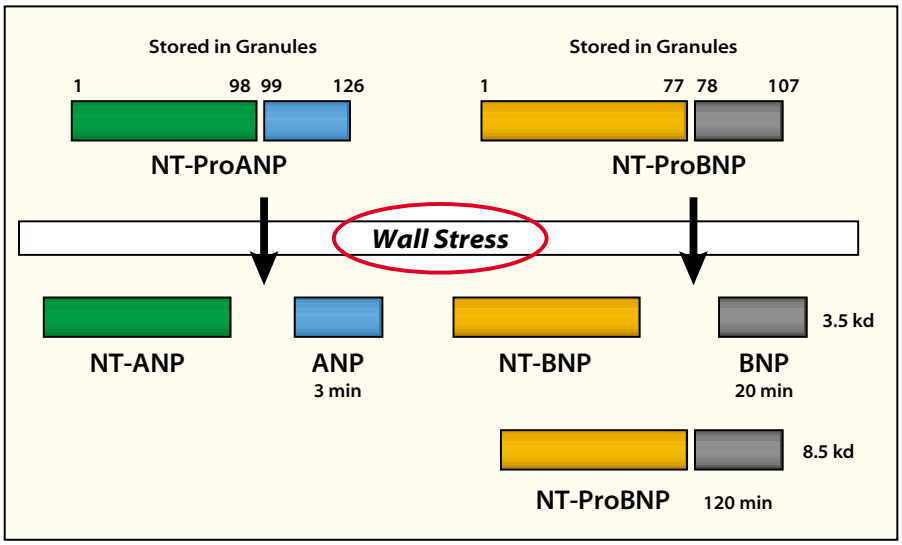

Figure 2. *Structure of the natriuretic peptides and their activation sites. NT, N-terminal; ANP, atrial (A-type) natriuretic peptide; BNP, B-type natriuretic peptide.*

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The strengths of NT-proBNP include its use on large laboratory platforms for economies of scale.[23] Its tight relationship to renal function has led some investigators to suggest that NT-proBNP may be an overall marker of cardiorenal function. Importantly, the diagnostic cutoff for NT-proBNP depends on the patient's age. Because the normal decline in glomerular filtration rate that occurs with age influences NT-proBNP, the cutoff for detecting CHF jumps from 125 pg/mL to 450 pg/mL after 75 years of age.[23] In patients between 65 and 85 years of age, in whom the peak incidence of CHF occurs, there is expected to be a considerable "gray zone" for NT-proBNP, in which the test will be of little value or potentially confusing to clinicians and patients. Future research using NT-proBNP will help determine in what settings it may have clinically useful applications—especially in the area of chronic kidney disease.

Putting BNP and NT-proBNP into Practice

Evaluating dyspnea can be challenging. In the urgent-care setting, it is often difficult to distinguish between cardiac and pulmonary causes of dyspnea.[2] A misdiagnosis can place the patient at risk for both morbidity and mortality, especially if treatment is inappropriate. Pulmonary diseases, including asthma and emphysema, are common in the elderly and often overlap or are confused with one another.[26] Sympathomimetic amines and β-agonists, for instance, can induce angina and arrhythmias in patients with dyspnea related to CHF. Therefore, although CHF needs to be diagnosed rapidly and accurately, a helpful history often is not obtainable in the acutely ill patient, and dyspnea, a key symptom of CHF, may be nonspecific. The symptom may be observed in elderly or obese patients in whom such comorbidities as respiratory disease and physical deconditioning are common.[2] Physical signs, such as elevated jugular venous pressure, a third heart sound, pulmonary rales, and edema, are often absent in patients with CHF.[2] Routine laboratory tests, electrocardiograms, and chest films also are not consistently diagnostic, given their lack of individual positive predictive value.[27] The availability of echocardiography in acute-care set-

Table 1
Key Distinguishing Features of the Ventricular Natriuretic Peptides

Characteristic	BNP	NT-proBNP
Components	BNP molecule	NT fragment (1–76) NT-proBNP (1–108)
Molecular weight	3.5 kd	8.5 kd
Hormonally active	Yes	No, inactive peptide
Genesis	Cleavage from NT-proBNP	Release from ventricular myocytes
Half-life	20 minutes	120 minutes
Clearance mechanism	Neutral endopeptidase clearance receptors	Renal clearance
Increases with normal aging	+	++++
Correlation with estimated glomerular filtration rate	−0.20	−0.60
Approved cutoff(s) for CHF diagnosis	100 pg/mL	Age < 75 years: 125 pg/mL Age ≥ 75 years: 450 pg/mL
Approved for assessment of CHF severity	Yes	No
Approved for prognosis in ACS	Yes	No
Prospective ED studies completed	Yes	No
Community screening studies completed	Yes	Yes
Available at the point of care	Yes	No
No. studies completed	1370	39
Date of entry on U.S. market	November 2000	December 2002

BNP, B-type natriuretic peptide; NT, N-terminal; CHF, congestive heart failure; ACS, acute coronary syndromes; ED, emergency department.

tings is also limited. Dyspneic patients may be unable to be still long enough for an echocardiographic study, and yet others may be difficult to image secondary to comorbid factors such as obesity or lung disease. Therefore, the need for a blood test to assist in the diagnosis of CHF is evident.

Although the reason is unknown, it is speculated that ventricular stiffening is more pronounced in women and in the elderly; hence, in all populations, women have slightly higher BNP and NT-proBNP levels than men.[28,29] In addition, normal levels of BNP and NT-proBNP rise with age. There appears to be no difference in BNP levels between Caucasian and African American patients.[29] There have been insufficient studies with NT-proBNP to determine racial differences at this time. There are no significant differences in BNP levels between normal patients with hypertension or diabetes and age-matched controls.[30,31] Importantly, both BNP and NT-proBNP levels can be elevated in the setting of renal dysfunction due to volume overload.[32,33] However, BNP is thought to be the superior test in diagnosing CHF in patients with elevations in serum creatinine, given the wide separation, more than 500 pg/mL, between those with and without CHF.[33] Patients with lung disease may have somewhat higher levels of BNP and NT-proBNP than patients without lung disease, in part because many patients with end-stage pulmonary disorders have concomitant right ventricular (RV) dysfunction. Nagaya and coworkers[34] measured hemodynamics and BNP levels in 44 patients with RV overload from pulmonary hypertension. The mean BNP level was 294 pg/mL and correlated with indices of pulmonary artery and RV end-diastolic pressures, as well as with long-term changes in hemodynamics. Hence, B-type natriuretic peptides must be viewed in conjunction with the clinical scenario and patient characteristics, including age, sex, and presence or absence of renal and pulmonary disease.

BNP and NT-proBNP Reflect Heart Failure Severity

The New York Heart Association (NYHA) functional system of classification correlates well with symptoms and mortality in patients with CHF but is inherently a subjective system, depending on patient self-report and physician assignment. Both BNP and NT-proBNP levels have been shown to accurately reflect heart failure severity; hence, these blood tests have inherent, objective contributions to patient assessment (Figure 3).[29]

Because BNP levels correlate to elevated end-diastolic pressure and LV wall tension, and because end-

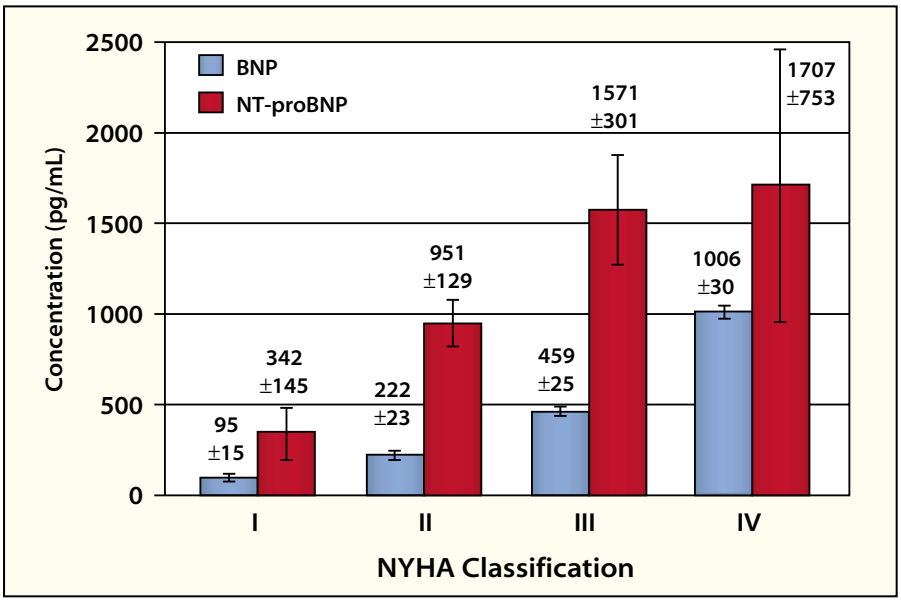


Figure 3. *Relationship between B-type natriuretic peptide (BNP) and N-terminal (NT)-proBNP and New York Heart Association (NYHA) functional classification. Data from Roche Diagnostics[23] and Biosite Inc.[24]*

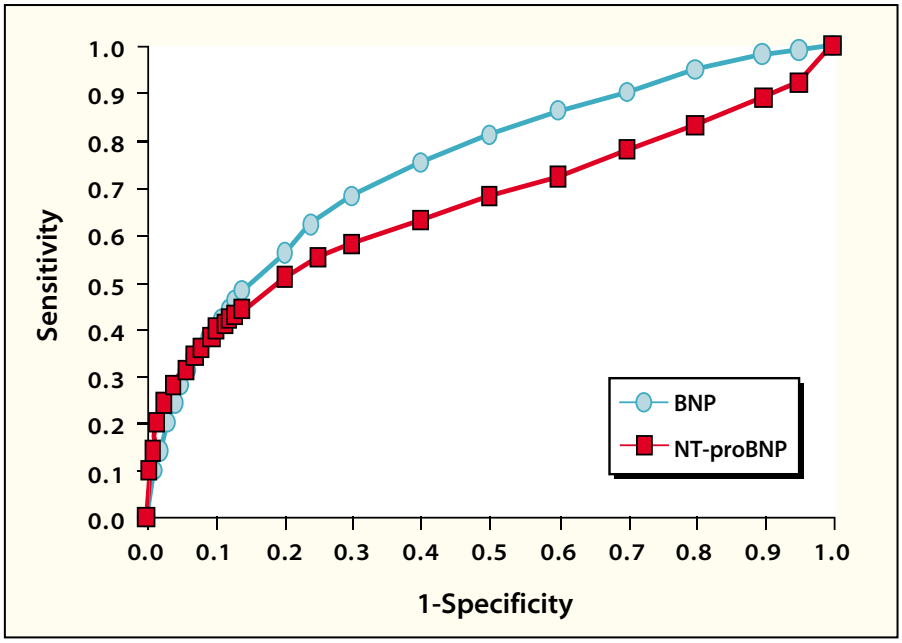
diastolic pressure is linked closely with dyspnea, it is not surprising that BNP levels correlate well with the NYHA classification scheme.[35] Given the known half-lives of BNP and NT-proBNP, the BNP level at the time it is drawn is thought to be most reflective of CHF severity at that moment. Levels of NT-proBNP lag behind the clinical picture, given its longer time for clearance from the blood pool. Importantly, when BNP and NT-proBNP levels have been compared head to head, BNP level has been found to be more accurate in identifying patients with reduced LV systolic function (Figure 4).[36]

Community Screening

Use of B-type natriuretic peptides as population screening tools for LV systolic dysfunction has been shown to be of value in comparison with a gold standard, such as echocardiography.[37–39] In a community-based study of 1653 persons who underwent cardiac screening, the negative predictive value of BNP levels < 18 pg/mL was 97% for asymptomatic LV systolic dysfunction.[39] In the urgent-care setting, Dao and coworkers[40] found BNP to have a sensitivity of 97%, a specificity of 84%, and a positive predictive value of 70% for the detection of LV dysfunction. BNP has been shown to be of lesser value in the detection of LV hypertrophy—especially in very low prevalence populations.[41] Another potential use of B-type natriuretic peptides may be in the screening process of young persons for hypertrophic obstructive cardiomyopathy—an area in which blinded screening studies are needed.

The main issue to consider in community screening is the prevalence and severity of disease in the population of interest. In general, when B-type natriuretic peptides are used for screening asymptomatic populations, a much lower cutoff value should be used (approximately 20 pg/mL for BNP) for the detection of LV dysfunction. In the acutely dyspneic patient, because BNP and NT-proBNP release is very rapid in response to increased LV wall ten-

Figure 4. *A comparison of area under the receiver operating characteristic curve (AUC) for B-type natriuretic peptide (BNP) and N-terminal (NT)-proBNP in the diagnosis of reduced left ventricular ejection fraction (LVEF). For the detection of resting LVEF < 40%, BNP was numerically the best marker, with an AUC of 0.83 ± 0.06 compared with NT-proBNP, with a slightly smaller AUC of 0.79 ± 0.07* (P = *ns*). *Data from Hammerer-Lercher et al.[36]*



sion, much higher cutoff values (BNP > 100 pg/mL) should be used to detect the presence of acute CHF.

Use in Emergency and Critical Care

Point-of-care testing allows diagnostic assays to be performed in locations such as the emergency department (ED) or intensive care unit, so that treatment based on the results can be administered immediately. Davis and colleagues[42] measured levels of ANP and BNP in 52 patients presenting with acute dyspnea. In this study, admission BNP concentrations more accurately reflected the final diagnosis than did LV ejection fraction (LVEF) or ANP level.

A multinational, prospective study using BNP levels to evaluate the cause of dyspnea (The BNP Multinational Study) was recently completed.[30] In this study of 1586 patients who presented to the ED with acute dyspnea, BNP levels were measured upon arrival, and the ED physicians (blinded to BNP) were asked to assess the probability of patients having CHF. Two independent cardiologists, also blinded to the BNP levels, later reviewed all clinical data and standardized scores to produce a "gold standard" clinical diagnosis. A BNP cutoff value of 100 pg/mL had a sensitivity of 90% and a specificity of 76% for differentiating CHF from other causes of dyspnea. A cutoff level of 50 pg/mL had a negative predictive value of 96%.[30] Importantly, a single, point-of-care test of BNP level performed immediately upon arrival to the ED had more diagnostic accuracy than did the clinician with all the tools available, including history, physical examination, conventional laboratory tests, chest x-rays, and review of old records.[43]

In an intensive care unit study, hemodynamic measurements and BNP levels were recorded every 4 hours for 48 hours in patients admitted for decompensated CHF.[27] Pulmonary capillary wedge pressure dropped from 33 ± 2 mm Hg to 25 ± 2 mm Hg over the first 24 hours, whereas BNP level dropped from 1472 ± 156 pg/mL to 670 ± 109 pg/mL. These reductions were apparent within the first 2–4 hours of treatment. The percent change in pulmonary capillary wedge pressure from baseline correlated significantly with the percent change of BNP from baseline ($r = 0.73$; $P < .05$), with an average BNP decline of 33 ± 5 pg/mL per hour. The correlation between BNP levels and other indices of cardiac function, including cardiac output, mixed venous oxygen saturation, and systemic vascular resistance, was not significant, suggesting that BNP values are complementary to the parameters derived from right heart catheterization.

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Of importance, BNP has been demonstrated to be useful in establishing the diagnosis of diastolic CHF.[44,45] Although levels tend to be lower for diastolic compared with systolic CHF, they are sufficiently elevated to detect CHF.[45] In addition, the elevation in BNP parallels the severity of diastolic dysfunction according to the filling patterns seen on the mitral inflow and left atrial pulmonary venous flow Doppler examination.[44] There have been no extensive studies of NT-proBNP in the detection of diastolic CHF.

BNP has proven useful in hospitalized patients with both systolic and diastolic CHF. A study of hospitalized patients (N = 72) admitted with decompensated NYHA class III–IV CHF reported on BNP levels daily.[46] In 22 patients, BNP levels increased during hospitalization (mean increase, 232 pg/mL; $P < .001$); these patients ultimately died or were readmitted. In the remaining patients, BNP levels decreased during treatment (mean decrease, 216 pg/mL), and these patients had favorable outcomes. In general, it is prudent to measure BNP or NT-proBNP as soon as possible after arrival to the ED and on the day of planned discharge.[47] Failure of these levels to drop over time, or an absolute BNP level > 500 pg/mL, predicts readmission and death. In such patients, a careful review of medications and intensification of therapy, if possible, are indicated.

Prognostic Markers for Sudden Death

A study of 452 ambulatory patients with an LVEF < 35% found that, in patients with mild to moderate CHF (NYHA class I/II), BNP levels were independent predictors of sudden death.[48] A cutoff BNP level of 130 pg/mL differentiated well between patients with high and low survival rates from sudden death. Only 1% (1 of 110) of patients with BNP levels below the cutoff point died suddenly, compared with a sudden death rate of 19% (43 of 227) among patients with BNP levels above the cutoff point. In this study, when BNP and NT-proBNP were considered together as prognostic markers, only BNP was found to independently predict sudden death.[48] Other studies support the notion that BNP

level can help predict death, especially in the elderly with CHF.[49]

Prognostic Markers in Acute Coronary Syndromes

A relationship between plasma levels of ANP and N-terminal atrial natriuretic peptide (NT-ANP) and survival after AMI was first demonstrated in 1992 and 1993.[50,51] These early studies convincingly showed that ANP and NT-ANP were predictive of mortality independently of conventional clinical risk markers.[52] In 1996, three separate reports were published demonstrating that BNP levels obtained in the acute or subacute phase were strongly related to both short-term and long-term mortality after AMI.[53–55] In contrast to ANP and NT-ANP, BNP provided additional prognostic information to LVEF.[53] In 1998, a relation between NT-proBNP levels and prognosis after AMI was reported by Richards and coworkers.[56] Both BNP and NT-proBNP obtained in the subacute phase were predictive of long-term, all-cause mortality, as well as readmission for CHF after AMI.[56]

Until recently, sparse information has been available regarding the natriuretic peptide system in patients with non-ST segment elevation myocardial infarction (NSTEMI) ACS. Cross-sectional data from two small-scale studies have suggested that circulating BNP and NT-proBNP, but not ANP levels, are higher in patients with unstable angina than in patients with stable coronary artery disease.[57,58] In one of these studies, BNP levels were increased in patients with echocardiographic evidence of regional wall-motion abnormalities, suggesting that BNP production may increase in proportion to coronary artery disease severity and the extent of myocardium at risk.[57] The prognostic value of NT-proBNP in patients with unstable angina or NSTEMI has recently been evaluated. Circulating NT-proBNP levels were significantly associated with death within 43 days and provided complementary prognostic information to conventional risk markers, including troponin I.[59] The prognostic value of BNP was recently evaluated in 2525 patients with ACS, including large subgroups with unstable angina and NSTEMI.[60] This important investigation confirmed and extended the results of previous studies by showing that the predictive power with regard to survival and heart failure hospitalizations was equally strong across the spectrum of ACS.[60] Moreover, the study demonstrated for the first time that BNP was predictive of recurrent ischemic events when the level was > 80 pg/mL.

The prognostic value of NT-proBNP across the spectrum of ACS has also been evaluated in a large cohort of patients.[61] NT-proBNP levels were strongly related to long-term mortality in patients with all forms of ACS. The relationship remained significant after adjustment for conventional risk markers, including LVEF. Of importance, NT-proBNP level was prognostic in the subgroup of patients with no signs of CHF (Killip class I) during the index hospitalization. These studies suggest that the B-type natriuretic peptides are akin to an early window for the Killip classifi-

Main Points

- In a patient presenting with dyspnea, congestive heart failure (CHF) is usually absent at B-type natriuretic peptide (BNP) levels less than 100 pg/mL, possible between 100 and 500 pg/mL, and probable at levels greater than 500 pg/mL. BNP levels between 100 and 500 pg/mL may also be seen in patients with known left ventricular (LV) dysfunction, lung disease (BNP produced from the right ventricle), renal failure, myocardial infarction, or pulmonary embolism.
- N-terminal proBNP (NT-proBNP) levels > 125 pg/mL in patients younger than 75 years and > 450 pg/mL in patients older than 75 years reflect the presence of CHF. Because NT-proBNP is influenced considerably by age and age-related normal decline in glomerular filtration rate, these two cutoff points must be used. NT-proBNP levels between 125 and 450 pg/mL in the elderly should be considered nondiagnostic until more data are available.
- In patients hospitalized with CHF, failure of the BNP to drop over the hospitalization or a discharge BNP > 500 pg/mL predicts high rates of readmission and death.
- In acute coronary syndromes, elevations in BNP or NT-proBNP predict higher rates of recurrent ischemic events, readmission for CHF, and death, even in Killip class I patients.
- When used in community practice to screen for systolic or diastolic dysfunction, a lower cutoff of BNP, >20 pg/mL, should trigger additional evaluation.
- There are important differences between these tests, especially with respect to the influence of age and renal function, which gives an edge to BNP as the diagnostic test of choice.

cation, identifying patients with large infarctions and impending LV dysfunction.

Conclusions

The natriuretic peptides are a major diagnostic breakthrough in cardiology. Both BNP and NT-proBNP are tests available to clinicians. There are important differences between these tests, especially with respect to the influence of age and renal function, which gives an edge to BNP as the diagnostic test of choice. Taken in aggregate, there is a considerable knowledge base for BNP and, to a lesser extent, for NT-proBNP, making these peptides an important component of future cardiac care. ■

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