Nearly 6 million Americans have heart failure and 550,000 new cases are diagnosed each year.\(^1\) The increasing incidence and prevalence of heart failure is attributed to the aging population and improved survival from other cardiovascular disorders such as coronary artery disease.\(^2\) Mortality rates for heart failure are high; one in five die within 1 year of diagnosis.\(^1,2\) Eighty percent of men and 70% of women under 65 years of age who have heart failure will die within 8 years of diagnosis. Survival is poorer in men than in women, but fewer than 15% of women survive longer than 8 to 12 years.\(^1,2\)

Early detection of disease or decompensation is dependent on a rapid, accurate diagnosis, which is often difficult based solely on clinical presentation and physical assessment.\(^2\) Delayed recognition of heart failure or decompensation will result in treatment delays, worsening of myocardial function, and potentially death. The use of a rapid, sensitive, and specific diagnostic test for heart failure would be an asset to the clinician and help improve patient outcome. Evaluating B-type natriuretic peptide (BNP) can be useful in determining the probability of heart failure decompensation.\(^3,4\)

BNP is a neurohormone released by the ventricles in response to fluid volume overload. BNP levels are consistently elevated with heart failure, but aren’t markedly elevated with some other noncardiac etiologies of dyspnea and fatigue like chronic obstructive pulmonary disease unless heart failure is a comorbidity.\(^4,5\) Studies have shown that BNP levels can be useful in differentiating heart failure from medical conditions in symptomatic patients, in medication management, and in predicting morbidity and mortality.\(^6,7\) Early detection of heart failure or decompensation can lead to lower healthcare costs by improving heart failure management and reducing hospital admissions. Most important, early detection will decrease morbidity and mortality and improve quality of life.

**Natriuretic peptides**

Natriuretic peptides are hormones integral to the regulation of fluid volume and BP homeostasis. The natriuretic peptides include atrial natriuretic peptide (ANP), BNP, C-type natriuretic peptide (CNP), and urodilatin. In general, natriuretic peptides exhibit natriuretic (inhibiting renal sodium reabsorption) and diuretic (augmentation of sodium and water excretion) action, suppress the renin-angiotensin-aldosterone system and sympathetic nervous system, and produce arterial and venous dilation.\(^4,9\) Natriuretic peptides are primarily inactivated by neutral endoproteases enzymatic degradation after receptor binding.\(^10\)

PreproANP, a precursor to active ANP, is produced in cardiac myocytes and stored primarily as granules. Release is stimulated by atrial stretch or increased atrial volume.\(^4,9\) Granular storage of this precursor molecule provides a rapid response to sudden increases in vascular volume. The precursor molecule is rapidly processed during release from the granules to form active ANP. Once activated, ANP has a short half-life and is rapidly removed from circulation. Thus, the effects, which are primarily natriuresis and diuresis, are rapid but short-lived, and volume and pressure homeostasis are maintained.

BNP also is produced as a precursor molecule (preproBNP) primarily in ventricular myocytes; however, minimal quantities are stored in granules.\(^8,9\) Following stimulation by an increase in ventricular volume or pressure, the myocyte initiates production and release of the precursor molecule that’s then split into an inactive molecule,
N-terminal proBNP (NT-proBNP), and BNP, the biologically active molecule. BNP and NT-proBNP are found in equal concentrations, but the half-life of NT-proBNP is longer, providing more stability in the concentration of this molecule. BNP levels increase more slowly than ANP and with a slightly longer half-life; natriuretic and diuretic effects persist for a longer time. Because of these characteristics, BNP has been identified as a "distress hormone" secreted in response to increased ventricular load or elevated intrachamber pressure.12

CNP and urodilatin are paracrine peptides that typically receive less attention. Paracrine substances influence adjacent cells. CNP is synthesized primarily by the endothelium and current evidence suggests that its actions focus on local vascular regulation.8,9,13 Specifically, CNP produces relaxation of vascular smooth muscle and inhibits the action of local angiotensin-converting enzyme (ACE). CNP also inhibits vascular growth, but has less diuretic or natriuretic effect. The stimulus for release of CNP hasn’t been clearly identified, but recently, researchers suggested that CNP release is stimulated by an increase in myocardial wall tension.13 Urodilatin is a natriuretic peptide produced by renal tubular cells. Its primary actions include natriuresis and diuresis. When synthesized and used pharmacologically, urodilatin has had a significant bronchodilator effect on central and peripheral airways that’s potentially useful in the management of asthma and dyspnea secondary to heart failure.8,14 Urodilatin also has been used to prevent or attenuate renal failure due to tubular ischemia and to manage renal failure after organ transplant (liver, cardiac, bone marrow) and decompensated heart failure.15-18

Synthetic forms of BNP [nesiritide] and urodilatin have been produced for pharmacologic use.

Using BNP as a diagnostic tool
Brain natriuretic peptide concentration may be evaluated in plasma or whole blood by fluorescent immunoassay.11 In 2000, the FDA approved the Triage BNP Test, a rapid, point-of-care BNP analysis system. The specimen should be analyzed within 4 hours of sampling; however, plasma may be separated by centrifugation and stored at –20°C (–4°F) if testing must be delayed. The blood specimen is transferred from the collection tube to the Triage BNP panel, which is inserted into the meter. Results are usually available within 15 to 20 minutes.

The Triage BNP Test assesses BNP levels within 5 to 5,000 pg/mL; measured values have been found to be linear throughout this range. Analytical sensitivity, the lowest detectable BNP concentration, is less than 5 pg/mL. The precision of the measure or coefficient of variation ranges between 8.8% and 12.2%. There is a near-perfect association between measures made testing whole blood and those made testing plasma.

Lab and point-of-care testing is now available for NT-proBNP.11 One assay can measure NT-proBNP concentrations from 60 to 3,000 pg/mL, and is highly correlated with the lab assay.19 Results are available in 12 minutes. Values above and below the stated range aren’t measured, but are indicated as being above or below the limits of the equipment.

BNP and NT-proBNP concentrations increase with age and are higher in women than in men, so age and gender must be considered in the interpretation of BNP values [see Normal ranges for plasma BNP and NT-proBNP].20,21

In a study of patients presenting with dyspnea or peripheral edema, the use of BNP values improved the diagnostic accuracy for heart failure by 21% when compared with practitioner diagnosis based solely on physical assessment.22 Studies

| Normal ranges for plasma BNP and NT-proBNP |
|----------------|----------------|----------------|
| **BNP**       | **Women**     | **Men**        |
| Age           | Women         | Men            |
| 45 to 54      | 8 to 73 pg/mL | 4 to 40 pg/mL  |
| 55 to 64      | 10 to 93 pg/mL| 5 to 52 pg/mL  |
| 65 to 74      | 13 to 120 pg/mL| 7 to 67 pg/mL |
| 75 to 83      | 16 to 155 pg/mL| 9 to 86 pg/mL |
| **NT-proBNP** | **Women**     | **Men**        |
| Age           | Women         | Men            |
| 45 to 59      | 61 to 164 pg/mL| 28 to 100 pg/mL|
| 60 and up     | 86 to 225 pg/mL| 53 to 172 pg/mL|
have measured BNP concentration in dyspneic patients presenting to the ED to determine whether dyspnea was due to pulmonary disease or heart failure.\(^\text{20,23-25}\) A BNP concentration cut-off value of 94 pg/mL provided a sensitivity of 86%, specificity of 98%, and accuracy of 91%; a BNP level of 300 pg/mL had a sensitivity of 88%, specificity of 87%, and accuracy of 88%.\(^\text{23-25}\) In the Breathing Not Properly Multinational Study, a BNP concentration of 100 pg/mL differentiated dyspnea due to heart failure with a sensitivity of 90%.\(^\text{24}\) This concentration of BNP was also able to differentiate systolic heart failure with a sensitivity of 95%, but sensitivity was only 66% when attempting to differentiate systolic from diastolic heart failure in this group. Based on studies that evaluated the efficacy of BNP assays in the diagnosis of heart failure, a cut-off value of 100 pg/mL is recommended by the manufacturer of the Triage BNP Test, so patients who present with dyspnea and a BNP level less than 100 pg/mL may be rapidly evaluated for diagnoses other than heart failure.

BNP analysis has also been used as a prognostic marker in cardiac patients.\(^\text{26-31}\) For example, at the time of diagnosis, BNP concentrations that exceed 480 pg/mL are predictive of death or hospitalization due to heart failure within the next 6 months.\(^\text{26}\) BNP concentrations have also been highly predictive of left ventricular ejection fraction and functional capacity in patients with heart failure.\(^\text{27,28}\) BNP concentration has been identified as a powerful, independent predictor of death or hospital readmission following hospitalization for decompensated heart failure.\(^\text{29}\) Additionally, BNP concentrations measured during acute coronary syndromes independently predict mortality, heart failure, and the occurrence of a new myocardial infarction.\(^\text{30}\) More recently, BNP values have been found to predict significant rejection in cardiac transplant recipients.\(^\text{31}\)

### Nursing implications

The use of BNP assays to evaluate patients with dyspnea may provide clinicians with an opportunity for early detection of heart failure. Using a rapid BNP test in the primary care clinic when a patient presents with symptoms potentially related to heart failure will speed diagnosis and treatment. A test showing an elevated BNP concentration might ensure that the patient receives timely additional diagnostic testing with echocardiography or cardiac catheterization. If heart failure is diagnosed in early stages, patients may begin making lifestyle changes that could affect the course of the disease, and early diagnosis will also equate to earlier pharmacologic intervention using heart failure guidelines.\(^\text{32}\) The high negative predictive value of the test indicates the chief use would be to rule out heart failure in suspected cases when normal BNP concentrations are measured.\(^\text{5}\)

BNP measures can also detect decompensation of chronic heart failure. Early recognition and timely management in the clinical setting may reduce the need for emergent care and hospital admission and may decrease the length of stay when hospitalization is needed.\(^\text{33}\)

### Monitoring status

Because BNP levels increase with heart failure progression and are strongly correlated to patient outcomes, BNP levels may serve as a guide to the severity of heart failure and the efficacy of management. Both baseline and change in BNP (increase or decrease) are important determinants of subsequent morbidity and mortality.\(^\text{34}\) Researchers evaluated the diagnostic and prognostic value of NT-proBNP in older adults with acute dyspnea, and found that plasma NT-proBNP levels were associated with disease severity and were an independent predictor of mortality.\(^\text{7}\) Another study found that a greater percentage reduction in BNP after treatment for decompensated heart failure was associated with longer event-free survival.\(^\text{34}\) In another study, serial measures of BNP every 2 to 4 hours were made over a 2- to 3-day time period in patients admitted with decompensated heart failure. Researchers found a strong correlation between decreasing pulmonary capillary wedge pressures and BNP level.\(^\text{35}\) Although this was an acute situation and these investigators followed BNP over the very short term, there are implications for use of BNP levels in evaluating the response to heart failure management.

In a study of 325 patients presenting to the ED with dyspnea, BNP was a predictive marker of future cardiac events—rising BNP levels were
associated with progressively worse prognosis. In fact, patients with BNP levels greater than 480 pg/mL had a 51% 6-month cumulative probability of a heart failure event (death, hospital admission, or repeat ED visit). Alternatively, patients with BNP levels less than 230 pg/mL had an excellent prognosis with only 2.5% incidence of heart failure endpoint. Increased concentrations of BNP have independently identified heart failure patients who had a poor prognosis, using death as the endpoint. These data suggest BNP should be routinely used to evaluate heart failure patients, with high BNP levels indicating the need for more aggressive treatment.

Evaluating BNP measures on hospital admission, on discharge, and a few weeks after discharge can provide important information about patient prognosis. Patients with low BNP levels on admission, discharge, and follow-up, or those with reduced BNP after therapy, were significantly less likely to be rehospitalized or die within 6 months.

Management of therapy
BNP levels may be followed over time. In a study using BNP measures to optimize medical management of patients admitted with decompensated heart failure, one patient group received standard clinician-guided therapy while another group received optimized pharmacologic regimens (including ACE inhibitor, diuretic, digoxin, additional diuretic, angiotensin receptor blocker, and vasodilator in a stepwise fashion) based on BNP concentration. After 6 months, the BNP-guided group had fewer total cardiovascular events (death, hospital admission, heart failure decompensation) than the clinician-guided group. Their data demonstrated that circulating BNP concentration, as well as total cardiovascular events, were reduced by intensification of drug therapy. Further research is needed to determine the BNP levels appropriate for initiating specific drugs at specific dosages.

The Valsartan Heart Failure Trial (Val-HeFT) study of about 4,300 patients showed that valsartan produced a sustained reduction in BNP in patients with heart failure. This study determined that not only was BNP a strong predictor of all-cause mortality and first morbidity event, but also that changes in BNP over time corresponded to changes in morbidity and mortality. Other researchers have found the use of a BNP-guided approach to medication titration targeted to reduce BNP levels to a predetermined level has been associated with a significant reduction in cardiovascular events compared with the clinically guided approach.

Similar outcomes have been found by researchers using ACE inhibitors and spironolactone in combination. Results from the Randomized Aldactone Evaluation Study indicate a place in the optimization of medication management for monitoring BNP. Heart failure patients who received spironolactone had decreased BNP levels, which the authors suggested may be due to changes in left ventricular filling pressures or improved ventricular compliance. Neurohormonal profiling may guide introduction of beta-receptor antagonists in heart failure treatment for patients with ischemic left ventricular dysfunction. For example, titration of carvedilol, a nonselective beta-receptor blocker, reduced mortality and improved heart failure in those patients who demonstrated higher pretreatment BNP levels. In contrast, another study concluded that BNP-guided therapy wasn’t superior to symptom-guided therapy for heart failure, although survival time free of hospitalization for heart failure (a secondary outcome) was greater in the BNP-guided group. More research is needed to clearly establish the efficacy of BNP-guided therapy.

An evolution
The use of BNP testing for the management of cardiac disease is evolving. Aside from using it as a diagnostic or prognostic tool, or in the pharmacologic management of heart failure, evaluation of BNP level could even assist healthcare providers when determining whether to discharge a patient.

Patients with heart failure generate significant healthcare costs caused by intensive outpatient management, frequent ED visits, and inpatient admissions. The recidivism rate is high, with one-third of patients readmitted each year. Hospital discharges for heart failure rose 171% between 1979 (400,000) and 2005 (1.08 million). In 2008, direct and indirect costs of heart failure for Americans was $34.8 billion; projected costs for 2009 are
Diagnostic Update

$37.2 billion.¹ A test that can quickly and accurately diagnose a disease and assist in monitoring patients’ treatment efficacy and disease stage, as well as reduce healthcare costs, clearly should be considered useful in caring for patients with heart failure. ♦

REFERENCES


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