

B-Type Natriuretic Peptide and Congestive Heart Failure

DEBORAH A FAUBION

ABBREVIATIONS: ADL = activities of daily living; AMI = acute myocardial infarction; ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; CHF = congestive heart failure.

INDEX TERMS: B-type natriuretic peptide; congestive heart failure.

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Deborah A Faubion MA CLS(NCA), Implementation Specialist, Biosite, Inc.

Address for correspondence: Deborah A Faubion MA CLS (NCA), Implementation Specialist, Biosite Inc, 6610 Stewart, PMB 233, Galveston TX 77551. (409)741-8722 (fax). faubion4801@msn.com.

Eileen Carreiro-Lewandowski MS CLS(NCA) is the Focus: Cardiac Markers guest editor.

Focus Continuing Education Credit: see pages 57 to 60 for learning objectives, test questions, and application form.

LEARNING OBJECTIVES

1. Describe the impact of congestive heart failure (CHF) on the healthcare system.
2. List the New York Heart Association Classes for CHF.
3. List the three natriuretic peptides and their origin and stimulus of release.
4. Describe what makes B-type natriuretic peptide (BNP) a unique neurohormonal marker.

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5. Describe the utility of using BNP in the urgent care setting.
6. Describe the multinational trial evaluating the use of a rapid BNP test to diagnosis CHF in the emergency room setting.

Congestive heart failure (CHF) is the most frequent cause of hospitalization of those age 65 and older and is the cause of 5% to 10% of all hospital admissions.¹ As our population continues to live longer, CHF will add to hospitalization costs worldwide. In heart failure, regardless of the underlying etiology, fluids accumulate in the blood vessels of organs, causing congestion.

Heart failure is associated with impaired ventricular function and can be either systolic or diastolic in nature. It may also be considered right-sided or left-sided. Patients who experience impaired left ventricular function typically have shortness of breath (dyspnea) because the lungs become congested.

U.S. data indicates that heart failure is either the primary or secondary diagnosis in three million hospitalizations per year. 'Frequent fliers', those patients that visit emergency departments with great frequency, incur many of these hospitalizations. Thus, heart failure is associated with high readmission rates. According to the Centers for Medicare and Medicaid Services (CMS) costs associated with CHF outweigh those associated with cancer and myocardial infarction.²

Table 1. NYHA classification of CHF patients

Class	Characteristics
I	Asymptomatic with ADL*
II	Symptomatic with ADL, relief by resting
III	Symptoms relieved by rest and appear with a small amount of activity
IV	Symptomatic while resting, unable to carry out physical activity w/o discomfort

*ADL = Activities of daily living

Clinicians commonly classify CHF patients according to the characteristics described by the New York Heart Association (NYHA) rubric for CHF. These classes are based on how much physical activity will cause limitations to the patient (Table 1).

NATRIURETIC PEPTIDES

The natriuretic peptide system consists of four structurally similar natriuretic peptides that compensate for changes in volume and pressure by promoting the removal of Na⁺ ions from the blood. The atrial natriuretic peptide (ANP) was the first to be identified in the late 1960s, it is a 28-amino acid hormone found in the atrium of the heart. ANP is increased in volume overload conditions in CHF and non-CHF patients.³

The B-type, or formerly called brain natriuretic peptide has been found to be a useful marker for CHF because the hormone is elevated in patients with CHF and is not elevated in non-CHF patients. BNP is secreted by the ventricles of the heart in response to ventricular stretch and volume overload.³

The C-type natriuretic peptide (CNP) is found in the endothelium of the heart. It has a very low concentration in plasma and elevations in CNP are

not associated with CHF. Other members of the natriuretic system such as urodilation are still being identified and characterized. This family of hormonally active peptides has a regulatory role in cardiovascular disease.

Table 2 lists the origin and stimulus for the release of the natriuretic peptides.

B-TYPE NATRIURETIC PEPTIDE

The B-type natriuretic peptide (BNP) is produced from the cardiac myocytes as a prepro hormone that consists of 134 amino acids, which is then clipped into a pro-hormone upon stimulus for secretion; BNP is further modified and released into the blood as the fragmented protein N-terminal proBNP (NT-proBNP) and the active BNP hormone. The 32 amino acid BNP molecule is the hormone primarily responsible for counteracting the rennin-angiotensin-aldosterone (RAA) system. Thus, BNP is the biologically active molecule that promotes natriuresis and diuresis in response to RAA-induced vasoconstriction.³ NT-proBNP is the inactive molecule resulting from the cleavage of the pro-hormone.³ Finally, BNP has a significantly shorter half-life than the NT-proBNP (20 minutes versus one to two hours), making it the more appropriate marker for assessing a patient's current ventricular status.

BNP AS A NEUROHORMONAL MARKER

Diagnosing CHF is difficult, especially in asymptomatic or mildly symptomatic patients. CHF is easily misdiagnosed because the symptoms (fatigue, shortness of breath, and fluid retention) are also associated with many other diseases. Incorrect diagnosis of CHF can lead to inappropriate treatment and referrals for unnecessary and often expensive testing. BNP has emerged as a biochemical marker for diagnosing CHF. Numerous studies have shown that using BNP levels can reduce the number of unnecessary referrals and help to identify and improve the quality of life for CHF patients.

In 1988, Sudoh discovered and characterized BNP in the porcine (pig) brain tissue. This study showed that BNP's biological actions were similar to those of ANP. Then two years later, other researchers found BNP in the human atria and determined its amino acid sequence. In 1991, Mukoyama developed a radioimmunoassay for human BNP and showed that in severe cases of CHF, plasma BNP levels were more elevated than levels of ANP, and the BNP concentration in plasma increased in patients with acute myocardial infarction (AMI).⁴

The short half-life of BNP supports the utility of using BNP in diagnosing and assessing heart failure severity. More recent studies have shown the utility of BNP in risk stratification in patients with acute coronary syndromes. The BNP assay also possesses other possible advantages that include the ability to use a single diagnostic cutoff, no changes in concentration associated with renal insufficiency and its ability to be tested rapidly on a point-of-care diagnostic platform.

Table 2. Natriuretic peptides: origin and stimulus of release

Peptide	Primary origin	Stimulus of release
ANP	Cardiac atria	Atrial distension
BNP	Ventricular myocardium	Ventricular stretch/ volume overload
CNP	Endothelium	Endothelial stress

Adapted from Burnett JC. *J Hypertens* 2000;17(Suppl 1):S37-S43.

BNP CLINICAL STUDIES

There are over 1400 studies on the relationship between BNP and cardiac status. Below are summaries of just two studies that in particular show the significance of BNP as a rapid test for assessment of cardiac status in the emergency and acute-care settings. The studies reviewed here were conducted using the Triage[®] BNP Test from Biosite[®] Incorporated. The Triage[®] BNP test is a fluorescence immunoassay for the quantitative determination of BNP in EDTA whole blood or plasma.⁵ The Triage[®] system is a rapid, point-of-care diagnostic platform.

SUMMARY: THE VALUE OF BNP

Since shortness of breath is a nonspecific symptom that could be indicative of many serious diseases an accurate diagnosis is key in situations where time is critical. Measuring the BNP level has been demonstrated to improve diagnostic accuracy for assessing patients with suspected CHF.^{6,7} The ability to test BNP levels rapidly and accurately will help prevent complications associated with incorrect treatment pathways. And with more appropriate resource utilization patients will be directed to the appropriate departments/specialists.

Dao Q, and others. Utility of B-type natriuretic peptide in the diagnosis of CHF in an urgent-care setting. J Am Coll Cardiol 2001;37.

The goal of this study was to evaluate the utility of a rapid bedside technique for measurement of BNP in the diagnosis of CHF in an urgent-care setting. The study included 250 patients presenting to the urgent-care and emergency departments of an academic Veterans Affairs hospital with dyspnea. Clinicians were blinded to BNP results. Patients diagnosed with CHF had a mean BNP concentration of 1076 ± 138 pg/mL, while the non-CHF patients had a mean BNP concentration of 38 ± 4 pg/mL. The BNP concentrations were found to be higher for patients admitted to the hospital versus those patients who were not admitted. This finding is consistent with the relationship between BNP concentrations and disease severity. A univariate analysis was performed for all variables pertinent to a diagnosis of CHF, along with BNP concentrations at 80, 100, 115, 120, and 150 pg/mL. BNP was shown to be an accurate predictor of patient diagnosis in all ranges. The sensitivity appeared to be optimal in this study at 80 pg/mL. The manufacturer of the Triage BNP Test (Biosite Incorporated) recommends 100 pg/mL for diagnostic use. Like many other trials that have been published, the negative predictive value for BNP approaches 100%. Thus, this has established BNP to be a standard of care to exclude CHF in patients being evaluated. The ED physicians who were blinded to the BNP level misdiagnosed a total of 30 patients. Fifteen of the 30 patients were believed not to have CHF (under diagnosed) but were later diagnosed with CHF. The other 15 patients were believed to have CHF but did not (over diagnosed). Using the BNP level of 80 pg/mL as the diagnostic cutoff, 97% (29 out of 30) of the patients would have been accurately diagnosed if the BNP results had been available to the clinician.

Maisel AS, and others. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002;347:161-7.

This study reported on the results of a seven-center, multinational trial evaluating the use of a rapid BNP test to diagnose CHF in the emergency department (ED) setting. This was a prospective study of 1586 patients entering the ED with acute dyspnea and the clinicians were blinded to BNP values. The study involved seven sites worldwide, five in the United States, one in France, and one in Norway. The physician in the ED who was blinded to the BNP levels assigned an ED pre-test probability. They assessed the probability that the cause for dyspnea was CHF. The probability was assigned on clinical certainty ranging from 0% to 100%. Following the evaluation by the ED physician, confirmation of the diagnosis was performed independently by two cardiologists based on a review of the patient's medical records, which included all tests, medical reports, and other information obtained during ED workup. Again the BNP results were blinded and the cardiologists completed a checklist of signs and symptoms so that Framingham and NHANES scores could be completed. They classified patients into three groups: group 1 included patients having a final diagnoses of dyspnea due to CHF, group 2 included patients with dyspnea due to other causes but having a history of CHF, and group 3 included patients with dyspnea not related to CHF. In all cases of CHF, the cardiologists were requested to agree on severity based on the New York Heart Association class. A ROC (Receiver Operating Characteristic) curve analysis was performed. The optimal diagnostic accuracy was at a BNP cutoff of 100 pg/mL. The BNP level was found to be the strongest independent variable for predicting CHF at 81.1% when compared to the use of clinical judgment alone (74%). BNP levels were found to be more accurate than any other finding, including physical, laboratory, or historical findings, in delineating CHF as the cause of dyspnea. And when the BNP level was combined with the clinical judgment the clinical findings was only marginally improved over BNP alone at 81.6%. The study demonstrated that rapid measurement of BNP improves the ability of clinicians to differentiate patients with dyspnea due to CHF and that utilizing BNP levels significantly improves diagnostic power to standard clinical findings.

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LETTER TO THE EDITOR

Modes of Transmission for West Nile Virus

The Winter 2003 *Clinical Laboratory Science* published article on **West Nile Virus (WNV): An Emerging Virus in North America**, was very informative, organized, and well written. Although the article clearly documents that the transmission of WNV to human occurs most commonly through the bite of an infected mosquito, I would like to comment that there have been a few reported cases whereby other modes of transmission have occurred.

There have been reports of WNV transmission to other patients due to blood product transfusions such as red blood cell, plasma, and platelet transfusion. This poses some complications due to the fact that the majority of individuals infected with WNV will show no symptoms.¹ It has been estimated that only about 1% of those infected with the virus will develop a severe form of the disease such as West Nile (WN) meningitis, WN encephalitis, or meningoencephalitis.² Thus it was recommended that all potential blood donors should be screen for the virus.¹

WNV meningoencephalitis was also diagnosed in a woman after receiving post-partum blood transfusion from a donor infected with WNV. Breast milk sample taken from her also showed WNV specific IgG and IgM antibodies.

The newborn that was reported to have little outdoor exposure was also positive for WNV specific IgM antibodies. Additionally, a previously pregnant woman was admitted to the hospital with symptoms common to WNV meningoencephalitis. Serum and cerebral spinal fluid samples taken from her showed evidence of WNV specific IgM antibodies. The infant who was later delivered also showed evidence of WNV infection.¹

It was traditionally thought that infected mosquitoes were the only mode of transmitting the WNV to human. However, there is increasing evidence that other modes of transmitting the virus also exist. Understanding the modes of transmission of WNV can in some cases help in early diagnosis and treatment. This can also prevent misdiagnosis and possible fatalities.

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Kendra Williams, MS student
 Medical and Research Technology Department
 University of Maryland, Baltimore MD.