The Use of B-type Natriuretic Peptide to Diagnose Congestive Heart Failure

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This paper explains the background and current use of B-type natriuretic peptide (BNP) assays to differentiate congestive heart failure (CHF) from other causes of dyspnea. With a large and growing elderly population, CHF is being diagnosed much more often in emergency rooms in the United States. Doctors need a way to quickly distinguish whether a patient with respiratory distress is suffering from cardiac insufficiency or another etiology. BNP is released from the ventricles in response cardiac overload from CHF or some other form of left ventricular systolic dysfunction. Therefore, the detection and measurement of BNP is a fast and accurate method of determining if CHF is the cause of a patient's breathing difficulties.

ABBREVIATIONS: ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; CHF = congestive heart failure; CNP = C-type natriuretic peptide; COPD = chronic obstructive pulmonary disease; ECG = electrocardiography; LVSD = left ventricular systolic dysfunction; POCT = point of care testing; RAAS = renin-angiotensin aldosterone system.

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

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The maturing of the large baby-boomer population is leading to an increase in the number of congestive heart failure (CHF) and left ventricular systolic dysfunction (LVSD) cases throughout the United States. Many of these individuals will not be diagnosed until they arrive at an emergency room seeking treatment for breathing difficulties. Although these patients suffer from respiratory distress caused by cardiac insufficiency, this symptom is common to many other conditions and diseases. Even when CHF is suspected, it is difficult to evaluate and the diagnostic tests are non-specific. Therefore, physicians need a way to quickly distinguish this disease from other causes of dyspnea. Tests used to measure plasma levels of B-type natriuretic peptide (BNP) are becoming the preferred method of identifying CHF in dyspneic patients.[1]

Normally found in the ventricles of the heart, the BNP precursor (proBNP) is cleaved and released into the blood stream when the myocardium is stretched due to cardiac overload. Both the biologically active BNP fragment and the inactive NT-proBNP portion are clinically useful in the detection of LVSD and CHF.[2] Tests to detect these markers are primarily used in acute care settings with patients exhibiting symptoms of heart failure.[3] Studies show that assays used to quantitatively measure this peptide are quite accurate in differentiating CHF from other dyspneic patients.[4] Additionally, BNP assays are faster and much less expensive than echocardiography – the current "gold standard" diagnostic tool for CHF. This means quicker treatment for those in distress due to heart failure while avoiding the expense, risk, and discomfort of additional testing for those who are not experiencing CHF. The results from the rapid implementation of BNP testing can be used to limit additional heart damage to the patient, allow better allocation of emergency room resources, and save heath care dollars used to diagnose this disease.

BACKGROUND

According to the 2005 statistics from the American Heart Association (AHA), CHF affects 4.9 million Americans with 550,000 new cases and 264,900 deaths annually. This report also notes that from 1979 to 2002 hospital discharges

for CHF rose from 377,000 to 970,000 – an increase of 157%. Furthermore, the death rate from this disease rose 35.3% from 1992 to 2002 while the overall death rate for the same time period saw only a 7.7% increase.[5] Moreover, readmissions for heart failure are very high. Some surveys show that 50% of all CHF patients return to the emergency room within six months; in addition, 16% of those queried returned to the hospital more than once in the same time period.[6] Although CHF can strike at any age, the AHA lists it as the leading cause of hospitalization among the elderly.[5] This fact is important when you consider that by the year 2010 the growth rate of older Americans is expected to be as much as 3.5 times greater than the general population.[7] Moreover, a US Census Bureau report on aging in the twenty-first century shows the number of Americans aged 60 or older growing from 16.5% in 1997 to a projected 24.6% in 2025. The overall costs of this disease were expected to top $27.9 billion in 2005.[5]

Congestive heart failure occurs when the heart muscle, weakened due to injury or disease, can no longer pump effectively. The loss of cardiac inotropy (contractility) results in a lower ventricular stroke volume and ejection fraction by decreasing end-systolic volume. This cardiac insufficiency means less blood is being pumped with every beat of the heart. With less oxygen-rich blood reaching and perfusing the tissues of the body, the patient is left feeling weak and easily fatigued. The kidneys respond to the lowered cardiac output by activating the renin-angiotensin aldosterone system (RAAS) in order to increase fluid volume by retaining sodium. Meanwhile, a compensatory rise in preload (the amount of blood returning to the heart) causes stretching of the myocardium. Also, the increased pressure in the ventricles, as well as direct oxidative damage from angiotensin II and aldosterone, causes left ventricular remodeling including myocyte hypertrophy, fibrosis, and necrosis.[8] Besides further hindering the ability of the heart to pump blood, this increased fluid volume also allows liquid to accumulate throughout the body leading to edema (swelling). Right ventricular failure results in edema that is especially noticeable in the lower extremities. Left ventricular failure causes fluid to build up in the lungs; thus, leading to pulmonary edema characterized by shortness of breath, the most common symptom of CHF.

Other signs and symptoms of CHF include: chest pain, cardiomegaly, tachycardia, tachypnea, rales, ascites, third heart sounds, hepatojugular reflex (distended jugular veins due to an enlarged liver), increased blood pressure (early stage of CHF), decreased blood pressure (resulting from cardiogenic shock in advanced CHF), and a decreased level of consciousness.[9] These signs, however, do not specifically indicate CHF nor differentiate it from other conditions that have dyspnea as their major symptom. To make the diagnosis even more difficult, as many as 50% of CHF patients may present with no symptoms at all.[10] Likewise, diagnostic tests such as electrocardiography (ECG) and chest radiography are helpful but by no means conclusive. Making the wrong diagnosis about CHF can lead to life-threatening consequences. While echocardiography has long been considered the "gold standard" diagnostic tool for CHF, it is not without its drawbacks. It is not a definitive test, but merely gives an indirect measure of left ventricular filling pressures.[11] Also, echocardiography requires an expert operator to both perform the test and interpret the results, thus making this a costly procedure that is often not readily available in an acute care setting. The advent of BNP assays, however, has given clinicians a rapid, accurate and easy to use method to either confirm or exclude the diagnosis of CHF.

ACTION OF BNP

BNP is produced and released by secretory granules of the heart in response to pressure overload and volume expansion.[12] It belongs to a family of natriuretic peptides that includes atrial natriuretic peptide (ANP) found in the atria of the heart, C-type natriuretic peptide (CNP) found in endothelial cells, and urodilatin found in the tubular cells of the kidney. Natriuretics are a class of neurohormone that allows the heart to take part in vascular fluid balance by increasing sodium (natrium) excretion to control the amount of fluid loss (uresis) from the body. Neurohormonal peptides were initially described by Henry and Pearce in 1956 after they noted uresis following the inflation of a balloon placed in a dog's atrium.[13] In 1981, a similar response was observed when de Bold and others injected atria homogenate into rats.[14] BNP, although first identified from the porcine brain in 1988, is found mainly in the ventricles of the heart.[15] It is made up of a 17-amino acid residue ring structure consisting of a disulfide bridge between two cysteine residues with a 9-residue N-terminal extension and 6-residue C-terminal extension. BNP is cleaved from a 108 amino acid residue precursor called proBNP to yield the active 77 to 108 amino acid C-terminal molecule and the inactive one to 76 amino acid N-terminal proBNP (NT-proBNP) molecule. Recent studies have shown that both BNP and NT-proBNP are equally effective as markers in the diagnosis of CHF.[16]

BNP, along with atrial natriuretic peptide, works to regulate fluid balance and blood pressure.[17] These molecules act to

counteract the vasoconstrictive, anti-diuretic, and sodium retentive properties of the renin-angiotensin aldosterone system of the kidneys. They do this by inhibiting the secretion of renin and aldosterone as well as increasing the glomerular filtration rate. This leads to vasodilation, diuresis, an increase in sodium excretion, and relaxation of the myocardium. Although the actions of this compensatory apparatus result in a decreased workload for the heart and reduced blood pressure, the event is short lived and eventually overcome by the sympathetic nervous system, RAAS, and endothelin-1.[18] The decompensated CHF patient suffers from progressively worse left ventricular systolic dysfunction with a corresponding increase in symptoms. The level of BNP found in the blood likewise increases as the disease advances.[12]

BNP ASSAYS

There are several types of assays and instruments to determine plasma BNP levels. For example, the Access 2 BNP (Biosite Diagnostics, San Diego, CA), ADVIA Centaur BNP (Bayer Diagnostics, Tarrytown, NY), and the AxSYM BNP (Abbott Diagnostics, Abbott Park, IL) are automated instruments that measure the biologically active C-terminal BNP fragment. The automated E170 NT-proBNP (Roche Diagnostics, Indianapolis, IN), on the other hand, measures the inactive N-terminal portion of BNP. Although there are differences in these molecules (such as half-life and renal clearance), both BNP and NT-proBNP are able to effectively assess CHF.[19]

The Biosite Triage® (Biosite Diagnostics, San Diego, CA) is an example of a point of care testing (POCT) device for BNP that meets the needs of an emergency room setting. It is highly portable, simple to use, and capable of providing results in as little as 15 minutes.[20] This test consists of a single-use fluorescence immunoassay "cartridge" and a meter used to read the device. It requires 250 µL of venous whole blood or plasma from an EDTA (purple top) collection tube. The specimen is added to the device using the included pipette and then placed in the meter. According to the manufacturer, the Triage meter has a reportable range of five pg/mL to 5000 pg/mL. BNP results of less than or equal to 100 pg/mL is considered normal (no CHF) while results of greater than 100 pg/mL are indicative of patients with CHF.[20] A study of 1586 patients that showed the Triage test has a sensitivity of 90%, a specificity of 76%, and an overall accuracy of 83% in discriminating CHF from other causes of dyspnea with a BNP cutoff level of 100 pg/mL.[21] When used to differentiate between CHF and other causes of dyspnea, BNP has an area under the receiver-operator curve (ROC) of 0.91 with a 95% confidence interval of 0.90 to 0.93 ($p<0.001$).[21]

Further studies show increasing concentrations of BNP correlate with the New York Heart Association's classification system for the progression of CHF.[13,20] In this system, Class I patients (with median BNP levels of 95.4 pg/mL) show no signs or symptoms of CHF with normal activity, Class II patients (221.5 pg/mL) display slight symptom of the disease with physical activity, Class III patients (459.1 pg/mL) have marked signs and limitations due to CHF, and Class IV patients (1006.3 pg/mL) are unable to perform any physical activity without distress. Additionally, elevated levels of BNP show a relationship with other physical signs of CHF including raised pulmonary wedge pressure, reduced ventricular systolic and diastolic function, myocardial infarction, and left ventricular hypertrophy.[22] In a separate study of 1286 people without CHF, the Triage assay demonstrated negative predictive value of 98% with BNP levels of less than or equal to 100 pg/mL.[20]

Calibration of the meter is accomplished via a coded chip that corresponds to the reagent lot in use. Low and high liquid controls are run as if they are patients with each new shipment or lot change of the BNP devices. A special quality control device, similar in appearance to the test device, is used at the initial meter setup, prior to daily testing and whenever the integrity of the test results is in question. Furthermore, each device has a set of built-in controls that ensure enough sample was added; that unbound antibodies were washed away; and that the device was correctly inserted to, and read by, the meter. The recovery of BNP is not interfered with by hemoglobin (up to 10,000 mg/dL), lipids (up to 1000 mg/dL), bilirubin (up to 20 mg/dL), all pharmaceuticals tested, and related proteins and peptides. However, grossly hemolyzed specimens should be avoided.[20] Samples should be well mixed and at room temperature before testing. If the specimen cannot be tested within four hours of collection then the plasma must be separated and stored at -20 °C until testing can be performed.

CONCLUSION

The incidence of CHF will continue to increase as the size of the elderly population grows. It is likely, however, that the many other causes of dyspnea will rise as well. With a finite number of emergency room beds and healthcare dollars, the ability to quickly distinguish heart failure from pulmonary etiologies will save money as well as patients. Modern BNP POCT analyzers such as the Biosite Triage assay offer a fast and accurate method to differentiate those patients suffering from cardiac insufficiency from those that are not in heart failure. A BNP level of greater than 100 pg/ml is indicative

of CHF; and, this level will increase with the severity of the disease. In addition, it appears that increased amounts of BNP may be a predictor of mortality among coronary heart disease patients.[23] Conversely, BNP levels of less than or equal to100 pg/ml have a negative predictive value of 98%; therefore, this test can be used to rule out cardiac causes of dyspnea. This means that inappropriate treatment and expensive follow-up testing (e.g., echocardiography) can be avoided. Although BNP alone cannot be used to solely diagnose CHF, it has become the most important marker of heart failure. This assay, along with echocardiography, chest x-rays, and ECG, has removed much of the guess work in the determination of CHF.

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