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Brain Natriuretic Peptide in Diagnosis and Treatment of Heart Failure

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Abstract:
Currently we are in the midst of a chronic disease epidemic of congestive heart failure (CHF) worldwide. This epidemic is marked by a rapid rise in prevalent cases over the past decade that is due in part to the aging population and improved survival in patients with other cardiovascular conditions. At present there are 5 million Americans with congestive heart failure, with nearly 500,000 new cases every year. To provide cost-effective treatment for patients with congestive heart failure, rapid and accurate differentiation of congestive heart failure from other causes of dyspnea must be accomplished. Although echocardiography is considered the gold standard for the detection of left ventricular dysfunction, it is expensive, is not always easily accessible, and may not always reflect an acute condition.

B-type natriuretic peptide (BNP) is a cardiac neurohormone specifically secreted from the cardiac ventricles as a response to ventricular volume expansion, pressure overload, and resultant increased wall tension. BNP can be used in the diagnosis of CHF. However, the present American College of Cardiology/American Heart Association practice guidelines (2001) for the evaluation and management of CHF state that the role of blood BNP in the identification of patients with CHF remains to be fully clarified. We have discussed the role of BNP in the diagnosis and management of CHF.

(Key Words: Natriuretic peptides, nesiritide, congestive cardiac failure)

With increasing life expectancy, congestive heart failure is reaching epidemic proportions. A variety of different conditions can mimic congestive heart failure clinically. Despite the availability of a wide array of laboratory and radiological tests, clinicians sometimes fail to diagnose CHF initially. Accurate diagnosis of CHF can help in an early and appropriate therapeutic intervention. Estimation of BNP levels in serum has been recently introduced as a diagnostic test for CHF. It has also been shown to have value in guiding the therapy of CHF. Recombinant BNP (Nesiritide) has exciting prospects in therapy of CHF.

Natriuretic Peptides
Atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP), and C-type natriuretic peptide (CNP) are a family of structurally related peptides that participate in the integrated control of renal and cardiovascular function. C-terminal and N-terminal atrial natriuretic peptides (CT-ANP and NT-ANP) are mainly secreted by the atria in response to the stretch that occurs with the increased left-atrial pressure associated with CHF. Plasma NT - ANP levels rise early in the course of myocardial failure and have been used as a marker for the diagnosis of asymptomatic left ventricular dysfunction with a sensitivity and specificity of more than 90%. Most subsequent studies have focused on the plasma BNP concentration, which is more specific for myocardial failure, since it is not expressed in normal myocardium.

Brain natriuretic peptide (BNP) is a natriuretic hormone that is similar to ANP. It was initially identified in the brain but is also present in the heart, particularly the ventricles. The circulating concentration of BNP is less than 20 percent of that of ANP in normal subjects, but can equal or exceed that of ANP in patients with heart failure. It is synthesized in bursts, so with chronic and more advanced heart failure, ventricular cells are recruited to secrete both ANP and BNP in response to the high ventricular filling pressures.

Diagnosis of Heart Failure
The plasma concentrations of both ANP and BNP are increased in patients with asymptomatic and symptomatic left ventricular dysfunction, permitting their use in diagnosis. The value of rapid bedside measurement of plasma BNP for distinguishing between CHF and a pulmonary cause of dyspnea has been best evaluated in a seven-center, multinational study of 1586 patients presenting to the emergency room with a major complaint of acute dyspnea. Plasma concentrations of BNP were markedly higher in patients with clinically diagnosed CHF (in-
Brain natriuretic peptide (BNP) levels correlate with NYHA functional class of congestive heart failure.

including patients with right heart failure due to cor pulmonale) compared to those without CHF (mean 675 versus 110 pg/mL). Intermediate values were found in the patients with baseline left ventricular dysfunction without an acute exacerbation (346 pg/mL). A plasma BNP >100 pg/mL diagnosed CHF with a sensitivity, specificity, and predictive accuracy of 90, 76, and 83 percent respectively. Lower values were associated with more accurate negative predictive values (for a value of 50 pg per milliliter, the negative predictive value was 96 percent). Choosing values >125 or >150 pg/mL decreased sensitivity, increased specificity, and did not change overall predictive accuracy. The predictive accuracy of plasma BNP for heart failure was equivalent to or better than other parameters such as cardiomegaly on chest x-ray, a history of CHF, or rales on physical examination. Also it was found that plasma concentrations of BNP correlated with NYHA functional class, ranging from 244 to 817 pg/mL for class I to IV. Another analysis from Breathing Not Properly (BNP) Multinational Study compared plasma BNP to initial clinical judgment. This was the first large-scale prospective study of BNP as a diagnostic test that incorporates the ED physician’s pretest probability of CHF when blinded to the BNP result. Among patients judged on clinical grounds to have 80 percent probability of CHF, a plasma BNP >100 pg/mL was more sensitive (90 versus 49 percent) but less specific (73 versus 96 percent) than clinical judgment. Adding BNP to clinical judgment increased diagnostic accuracy (CHF versus no CHF) from 74 to 81 percent. More importantly, in those participants with an intermediate (21% to 79%) probability of CHF, BNP at a cutoff of 100 pg/mL correctly classified 74% of the cases. Plasma BNP correctly diagnosed 90 percent of the patients originally thought to have less than a 21 percent clinical probability of CHF. Similarly other studies also found a high positive and negative predictive value of plasma BNP in the diagnosis of CHF. BNP level of 75 pg/mL was 98% specific for detecting the presence or absence of LV dysfunction by echocardiography in a study. Elevations in plasma BNP can establish the presence of CHF due to diastolic dysfunction with similar accuracy to systolic dysfunction. However, the values do not differentiate between systolic and diastolic dysfunction. Based upon these data, BNP was approved by the FDA as an aid for CHF diagnosis. Plasma BNP concentrations are also elevated in patients with pulmonary hypertension and right ventricular dysfunction. In such patients, they correlate positively with mean pulmonary artery pressure, total pulmonary resistance and right ventricular mass. A high level of plasma BNP, and in particular, a further increase in plasma BNP during follow-up may have a strong, independent association with increased mortality in patients with primary pulmonary hypertension. The cost for a BNP test is about $20 and it has been suggested that measurement of BNP levels should be part of the diagnostic approach to patients with CHF. The value of BNP has already been recognized by their inclusion in the recent European guidelines for the diagnosis of chronic heart failure.

Prognostication and Response to Therapy

Plasma BNP measured at initial presentation, provides prognostic information in patients with chronic CHF, including those receiving therapy with a beta blocker and an ACE inhibitor and those with asymptomatic or minimally symptomatic left ventricular dysfunction. A high level of plasma BNP is an independent predictor of mortality in these patients. Sustained high plasma levels of BNP and IL-6 after additional standard treatment are independent risk factors for mortality in patients with CHF despite improvements in left ventricular ejection fraction (LVEF) and symptoms. The plasma BNP concentration may also predict the response to carvedilol and the prognosis after insertion of a left ventricular assist device (LVAD). In the Australian-New Zealand Heart Failure study, carvedilol appeared to reduce mortality only in patients with supramedian baseline values of BNP. This can help in the selection of the patient subgroup that can benefit from carvedilol therapy and can help in predicting the benefit from such therapy.

Guide to Therapy

The plasma concentrations of BNP fall after effective pharmacologic therapy of CHF. The magnitude of this effect was illustrated in a report of 102 patients with severe CHF who were studied at baseline and three months after optimized medical therapy including ACE inhibitors, beta blockers, and digoxin. Optimized medical therapy was associated with significant reductions in plasma BNP (917 at baseline to 285 pg/mL) levels. These findings suggest that measurement of plasma BNP may be helpful in titrating therapy. This issue was addressed in another trial of 69 patients with impaired left ventricular function and clinical CHF who were randomly assigned to medical treatment guided by plasma N-BNP concentrations (goal <200 pmol/L) or standard clinical assessment. At six months, a first cardiovascular event occurred less frequently in those undergoing N-BNP guided therapy (27 versus 53 percent for clinical assessment).
Another potential use of plasma BNP to guide therapy may be in patients who may require heart transplantation. As noted above, a fall in plasma BNP within the first week after initiation of an LVAD may be indicative of recovery of cardiac function without the need for transplantation.19

**Nesiritide in Decompensated Heart Failure**

Nesiritide (recombinant human BNP) appears to have a role in the treatment of decompensated heart failure. Nesiritide produces significant reductions in pulmonary capillary wedge pressure, right atrial pressure, and systemic vascular resistance; and significant increases in cardiac index and stroke volume index.20 These benefits are evident at one hour and are sustained throughout the infusion period. Creatinine clearance and urinary potassium excretion do not change but norepinephrine and aldosterone levels are decreased during human recombinant BNP (hBNP) infusion.21 Sodium excretion may also be modestly increased.22 The efficacy of nesiritide in the short-term treatment of decompensated heart failure was evaluated in a study of 432 patients.23 A six-hour infusion of nesiritide (0.015 and 0.03 µg/kg per min) decreased pulmonary capillary wedge pressure (6 and 9.6 mmHg versus an increase of 2 mmHg for placebo) and improved the clinical status in a greater number of patients (60 and 67 percent versus 14 percent). In the group of patients without hemodynamic monitoring, nesiritide produced significant improvement in clinical status and reduction in dyspnea and fatigue persisting during the entire infusion period and comparable to standard treatment with a single vasoactive agent (e.g., dobutamine, milrinone, nitroglycerin or nitroprusside). Since nesiritide exerts no direct positive inotropic action on the myocardium, the increase in cardiac output presumably reflects a reduction in left ventricular afterload. The decrease in blood pressure was not associated with reflex tachycardia or an increase in plasma norepinephrine levels in either of these groups. The potential for hypotension may be increased when nesiritide is used concurrently with other vasodilators, such as an ACE inhibitor.24 **PRECEDENT** study showed that among patients with decompensated heart failure requiring acute therapy, nesiritide is less likely than dobutamine to increase heart rate and provoke ventricular arrhythmias.25 So compared with dobutamine, nesiritide may be safer as a short term treatment for patients with decompensated CHF, especially in patients with tachycardia, a history of serious atrial or ventricular arrhythmias, or evidence of ventricular irritability. In the recently completed Measurement of BNP levels is an inexpensive rapid bedside test that can diagnose heart failure with high sensitivity and predictive accuracy.

Based on this discussion, it is clear that BNP is an inexpensive and reliable tool available for the rapid bedside diagnosis of heart failure. The use of this test should be encouraged among the emergency department physicians. Nesiritide (recombinant human BNP) is a new addition to the drugs available for the treatment of CHF. It has unique vasodilator, natriuretic and indirect inotropic properties but unlike pressors, doesn’t have the proarrhythmic effect. This makes it an attractive drug for the management of CHF once the subset of patients benefiting most has been defined more clearly.

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