REVIEW
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The Role of Brain Natriuretic Peptide in the Patients with Acute Dyspnea in the Emergency Department

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ABSTRACT

For the acutely ill patients who present to the emergency department (ED) with dyspnea, an incorrect or delayed diagnosis of congestive heart failure (CHF) could place the patient at an increased risk for both morbidity and mortality. Therefore, a rapid and accurate diagnosis of CHF is mandatory for administering appropriate and efficacious management. Unfortunately, the signs and symptoms, and readily available emergency diagnostics are neither sensitive nor specific enough for diagnosing CHF alone. Brain natriuretic peptide (BNP) is secreted by myocytes in response to ventricular stretch and it has long been thought that BNP could become a biochemical marker for CHF and could be a useful tool in the diagnosis and exclusion of CHF if it is applied appropriately.
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KEY WORDS: Dyspnea ; Heart failure, congestive ; B-type natriuretic peptide.

Introduction

Heart failure (HF) is a major public health problem and the prevalence and incidence of this malady is increasing. The prognosis of patients with HF primarily depends on the nature of the underlying heart disease and on the presence or absence of precipitating factor that can be treated. In a multicenter Korean study, the 2 year survival rate of patients with congestive heart failure (CHF) was 76.4% and the major cause of CHF was ischemic heart disease.[1)]

Despite the high incidence and prevalence of this disease, it can still be difficult to diagnose CHF in the patient presenting with acute dyspnea. A correct and updated diagnosis of heart failure is the cornerstone that leads to appropriate and efficacious management, especially in the emergency setting. Risk factors such as age, gender, race and a history of hypertension or coronary artery disease can heighten the clinical suspicion, and the signs and symptoms that are gleaned from a careful history and physical examination may point either towards or away from the diagnosis of CHF. However, many of the classic signs and symptoms of heart failure are non-specific and they can occur with other disease processes as well.[2-4)]

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Although electrocardiogram (EKG) and radiography may provide supporting evidence for the diagnosis of CHF, neither is specific nor sensitive enough to confirm the diagnosis alone.[5)]

Echocardiography, although it is currently the gold standard for diagnosing heart function, is costly and has limited availability in acute care settings. Therefore, even in the settings where emergency department (ED) echocardiography is available, an accurate, sensitive and specific blood test for heart failure would be a useful addition to the currently existing tools that are available to the physician.

Overview of Brain Natriuretic Peptide

The 'endocrine' role of the heart came to light in the mid-1950s when Kisch detected secretory granules in guinea-pig atria[6)]; these granules were determined in 1984 to be atrial natriuretic peptide (ANP).[7)] In 1988, brain natriuretic peptide (BNP) was isolated from porcine brain tissue.[8)]

The three main natriuretic peptides are ANP, BNP and C-type natriuretic peptide. ANP is a 28 amino-acid hormone that's produced in the atria. BNP is principally produced in the ventricles as prohormone pre-proBNP, which is then enzymatically cleaved into the biologically active BNP (32 amino acids in length) and the biologically inactive NT-proBNP (76 amino acids in length).[9)10)] C-type natriuretic peptide is structurally distinct and it is mainly expressed in the central nervous

system and vascular tissues. The stimulus for the release of ANP and BNP is the same, that is, myocyte stretch secondary to volume expansion and pressure overload of the chamber, and they have very similar physiological activities. Both ANP and BNP cause natriuresis and diuresis by increasing the glomerular filtration rate and inhibiting sodium reabsorption, and they both dilate the arterial and venous sides, leading to a decrease of both the preload and afterload.[11]

BNP is mainly eliminated by two mechanisms: receptor-mediated endocytosis and enzymatic degradation by endopeptidases that are found on endothelial cells, smooth muscle cells, cardiac myocytes, renal epithelium and fibroblasts.[12] These clearance mechanisms account for BNP's relatively short half-life of about 20 minutes. NT-proBNP is primarily cleared by the kidneys, resulting in a longer half-life of about 60-90 min.

The normal plasma BNP level is unknown. Data from the Framingham Offspring study (n=3,552 subjects) showed that BNP levels above 20 pg/mL in the study's men and 23.3 pg/mL in the study's women, both genders were without heart failure, put them at an increased risk for heart failure, a first major cardiovascular event, a first stroke, atrial fibrillation and death.[13] In a prospective multicenter trial by Wieczorek et al.[14] on 1,050 inpatients, outpatients and healthy controls, the median plasma BNP level was 5.47 pg/mL (range: 5.0-12.8 pg/mL) for men and 12.8 pg/mL (range: 5.82-30.6 pg/mL) for women. A systematic review by Doust et al.[15] of eight studies with more than 4,000 patients concluded that a BNP level less than 15 pg/mL was a good cut-off point to exclude heart failure.

Brain Natriuretic Peptide and Congestive Heart Failure

Natriuretic peptide is increased in both systolic and diastolic heart failure and the level correlates with the New York Heart Association function class (NYHA Fc) of heart failure and with the echocardiographic findings.[14][16-22]

Song et al.[20] evaluated the correlation between the NT-proBNP levels, the NYHA Fc and the echocardiographic findings of patients who visited a cardiology department. The NT-proBNP levels were positively correlated with the NYHA Fc of dyspnea and the systolic dysfunction, and a 300 pg/mL NT-proBNP level appears to be a sensitive level to differentiate dyspnea of a heart origin from other causes.

There are many previous trials that examined the BNP level of patients presenting with dyspnea at an ED. Despite the similar methodologies of the previous studies, the BNP values used to differentiate between dyspnea due to CHF and dyspnea due to other causes ranged from 50 to 295 pg/mL. The discrepancy between those values might be attributed to the differences in the patient populations that were used in the studies.

Dao et al.[4] evaluated the BNP level for the diagnosis of CHF in an urgent setting. The BNP levels were obtained from blood samples of 250 patients who presented with the chief complaint of acute dyspnea. Those patients diagnosed with CHF had higher BNP values compared to the non-CHF group (1,076±138 pg/mL vs 38±4 pg/mL, respectively) and those patients with the final diagnosis of pulmonary disease had lower BNP values than those patients with a final diagnosis of CHF (86±39 pg/mL vs 1,076±138 pg/mL, respectively, $p<0.001$). A level of 80 pg/mL was determined to be an accurate predictor of the presence of CHF, with a sensitivity, specificity and negative predictive value of 98%, 92% and 98%, respectively.

A related investigation by Morrison et al.[23] attempted to differentiate CHF from other causes of dyspnea in 321 patients who presented to an ED. The same as was noted in Dao's investigation, those patients determined to have the presence of CHF had significantly higher BNP levels than those patients who were determined to have an absence of CHF (a mean of 759 pg/mL vs. 61 pg/mL, respectively). A BNP value of 94 pg/mL had a sensitivity, specificity and accuracy of 86%, 98%, and 91%, respectively.

In the Breathing Not Properly Multinational Study (BNPMS), Maisel et al. performed a multicenter trial that analyzed 1586 patients who presented to the ED with acute dyspnea. Their BNP levels were measured at the bedside with a point-of-care assay; emergency physicians who were "blinded" to the BNP levels were asked to assign the likelihood of heart failure in the patients as a percentage (0-100%). A final diagnosis was determined by two independent cardiologists who were blinded to the BNP results, but they had full access to the patients' medical records. The BNP level was accurate for making the diagnosis of CHF and it was correlated with the severity of disease. It could reduce the clinical indecision by 74%. The BNP level was the single most accurate predictor of differentiating CHF from other etiologies of dyspnea (the area under the receiver operating characteristic curve was 0.91). A plasma BNP level of >100 pg/mL was more accurate for identifying heart failure as the cause of dyspnea than any other historical or laboratory finding, and it was the strongest independent predictor of CHF with an odds ratio of 29.6 [95% confidence interval (CI): 17.7-49.4]. The diagnostic accuracy of the BNP at a cutoff value of 100 pg/mL was 83.4% with a sensitivity of 90%, a specificity of 76%, a positive predictive value of 79% and a negative predictive value of 89%,[24-27] which was more accurate than the standard national health and nutrition examination survey (NHANES) (67%) or Framingham criteria (73%). In a subsequent review, McCullough

stated that CHF was unlikely to be present with BNP levels less than 100 pg/mL; CHF was possible with levels between 100 and 500 pg/mL and CHF was probable at levels greater than 500 pg/mL.[28]

In Korea, Yoo et al.[22] reported that the cut-off value of BNP that separated systolic heart failure (SHF) patients from the control patients was 108 pg/mL with 92.5% sensitivity and 86.1% specificity. However, Choi et al.[16] enrolled 1,040 Korean patients and who had visited an ED, with dyspnea and the reserachers reported that the optimal threshold of the BNP level for detecting heart failure was higher than the normal cut-off value of 100 pg/mL (296.5 pg/mL); this difference was probably the result of racial differences or the lesser obesity of Koreans.

Brain Natriuretic Peptide and Diastolic Heart Failure

As many as 40% to 55% of patients with the diagnosis of heart failure have preserved systolic function and it is difficult to distinguish diastolic heart failure (DHF) from systolic heart failure (SHF) by using the traditional parameters.[29][30]

Diastolic dysfunction is also associated with high BNP levels[18][31] and measuring the BNP may be helpful for differentiating DHF from SHF in the ED setting. Kang et al. studied a total of 69 consecutive patients who presented to the ED with suspected dyspnea of a cardiac origin. BNP sampling and Doppler echocardiography were performed at baseline and at 1 year after pharmacologic treatment for the patients (N=42) who were diagnosed with DHF in either the ED or the outpatient clinic. The mean BNP levels of the SHF and DHF groups were significantly higher than that of the control group (716±532 pg/mL, 390±446 pg/mL and 13±14 pg/mL, respectively, $p<0.01$).[18] Maisel et al.[25] evaluated 452 patients with a final diagnosis of CHF and they had undergone echocardiography within 30 days of their visit to the ED. An ejection fraction of greater than 45% was defined as non-systolic CHF. Of the 452 patients with a final diagnosis of CHF, slightly over one-third of the patients (36.5%) who presented to the ED had non-systolic dysfunction. The BNP levels were accurate for separating all the CHF patients from the non-CHF patients, but these levels were not very accurate for separating systolic CHF patients from the non-systolic CHF patients. Those authors concluded that BNP had a modest discriminatory value for differentiating DHF from SHF and its major role was still to separate patients with CHF from those without CHF.[25] Although the BNP levels could not by themselves differentiate between SHF and DHF, a low BNP level in the setting of normal systolic function, as determined via echocardiography, was able to rule out the clinically significant diastolic abnormalities seen on echocardiography. On the other hand, elevated BNP levels in patients with normal systolic function, and especially those in older patients with a history of CHF, correlated with the ventricular filling abnormalities seen on Doppler studies.[32]

Using the Brain Natriuretic Peptide Levels for the Prognosis

Natriuretic peptide testing is useful not only for the diagnosis or excluding CHF, but also for stratifying the long-term risk of mortality in community-based populations without CHF[13] and also in those populations with chronic CHF.[33-35] It is also useful to predict the prognosis of individuals with non-CHF disease such as coronary artery disease, pulmonary embolism (PE) and critical illness, and also following cardiac transplantation.

Higher initial BNP levels at the time of presentation to the ED have been correlated with both the mortality and early readmission for CHF.[36-40]

Harrison et al.[40] followed 325 patients for six months after an index visit to the ED for dyspnea; they found that the relative risk of CHF death within six months after the ED visit for patients with BNP levels more than 230 pg/ml was 24.

Januzzi et al.[41] prospectively enrolled a total of 599 breathless patients who were treated in the ED and their NT-proBNP levels were measured. After 1 year, the vital status of each patient was ascertained, and the association between the NT-proBNP values at presentation and their mortality was assessed. At 1 year, 91 patients (15.2%) had died. The median NT-proBNP concentrations at presentation among those patients who died were significantly higher than those of the survivors (3,277 vs 299 pg/mL, respectively, $p<0.001$). The optimal NT-proBNP cut point for predicting the 1-year mortality was 986 pg/mL. In a multivariable model, a NT-proBNP concentration greater than 986 pg/mL at presentation was the single strongest predictor of death at 1 year [hazard ratio (HR): 2.88, 95% confidence interval: 1.64-5.06, $p<0.001$], and this was independent of a diagnosis of heart failure.

Changes in the BNP levels over time may also provide useful prognostic information for those patients who are treated for CHF.[36][38][42] Anand et al.[35] demonstrated that patients with decreasing BNP levels over time had lower morbidity and mortality, whereas patients with rising BNP levels over time had increased morbidity and mortality.

The prognostic information from the BNP values may assist the emergency physician for deciding on the disposition of patients. In fact, there may be a disconnection between the clinical status as assessed by a physician and the prognosis as predicted by BNP level.[36][39]

Accordingly, the BNP levels may assist physicians in determining those patients who can be safely discharged or those patients who would benefit from more intensive care.

Discordant Brain Natriuretic Peptide Values

Although BNP has been mainly studied for the diagnosis and treatment of left ventricular systolic dysfunction, it is also equally important to note that other processes can have an influence on the BNP levels (Table 1).

It is often a challenge to interpret the BNP levels in the setting of acute or chronic renal failure. The BNP levels are increased in patients with severe renal disease. It may be unclear if an elevated BNP is secondary to heart failure, renal failure or both. There is a discrepancy between the BNP levels and the degree of renal failure. Cataliotti et al.[43] reported that the BNP levels were not significantly increased by renal dysfunction alone, and elevated BNP levels have been shown to be useful for predicting left ventricular hypertrophy. In study by Jun et al.[44] the BNP levels were increased in patients with chronic kidney disease (CKD) and the BNP level was higher in CKD patients with heart failure as compared to that of those patients without heart failure. Yet the BNP levels showed no difference according to the degree of renal failure in patients with CKD.

In the study by McCullough et al.[45] the renal function was weakly correlated with the BNP level and the renal function influences the optimal cut point for the BNP, particularly in those patients with an estimated GFR less than 60 mL/min/1.73 m^2. Similar to patients with normal renal function, the BNP level in patients with renal failure also had diagnostic and prognostic value for cardiac disease, but higher cutoff values need to be identified.[43][46][47]

Table 1. Discordant BNP levels

Other factors that can account for high BNP levels
Advanced age
Renal failure, esp. in patients on dialysis
Acute myocardial infarction
Lung disease with right-sided failure
Pulmonary embolic disease
Ischemic heart disease without infarction
Asymptomatic hypertrophic cardiomyopathy
High output states like cirrhosis
Factors other than CHF that account for lower than expected BNP levels
Flash pulmonary edema (one hour or less)
CHF secondary to causes upstream from the left ventricle
Acute mitral regurgitation
Mitral stenosis
Stable NYHA class I patients with a low ejection fraction
Obesity

BNP: B-natriuretic peptide, CHF: congestive heart failure, NYHA: New York Heart Association

The limitations of BNP testing include the possible delayed production of BNP. A Japanese study concerned with rat ventricular cardiocytes examined the gene expression of BNP and that study found maximal activity at 1 h.[9] In the Logeart study, the sensitivity of using the BNP level declined from 96% to 71% for patients presenting with less than a 4 h duration of symptoms.[48] Therefore, one should remember that it takes time to produce BNP, and that patients who present with "flash" pulmonary edema may have a low initial BNP level. The other confounding factors are age, gender and obesity since the levels of BNP are higher in the elderly and females and the BNP levels are inversely related to the body mass index.[14][49][50]

Conclusion

Determining the BNP levels can be a useful tool for the diagnosis and exclusion of CHF if it is applied appropriately. Those patients who are clinically determined to have either a very high likelihood of CHF or those with a very low likelihood of CHF may not need a BNP test, but the measurement of BNP levels may provide additional information for the patients with an indeterminate clinical likelihood of CHF or lung disease. A BNP level of less than 80 pg/dL indicates a low probability of CHF, levels greater than 400 pg/dL have a moderate probability of CHF and levels greater than 1,000 pg/dL have a very high probability of CHF. Since differentiation between SHF and DHF is difficult using only the BNP levels themselves, the BNP levels clearly cannot be a substitute for measuring the LV function and they should not be considered as a surrogate for echocardiography.[25]

The best utility of BNP is to exclude CHF in a setting where the diagnosis is unclear, but it is a misuse of BNF testing to assume that all the patients with elevated BNP levels (>100 pg/mL) are secondary to CHF, and also that all the patients with low BNP levels (<100 pg/mL) do not have CHF. When used in conjunction with other clinical information, rapid measurement of the BNP in the ED reduces the time to start the most appropriate therapy; it also reduces the need for hospitalization and intensive care, the time to discharge and the total cost of treatment.[51]

Finally, using the BNP levels might not only be helpful for assessing whether or not a dyspneic patient has heart failure, but it may also be useful for making both triage and management decisions.

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