B-Type Natriuretic Peptide (BNP) Levels: Diagnostic and Therapeutic Potential

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Finding a simple blood test that would aid in the diagnosis and management of patients with CHF would clearly have a favorable impact on the staggering costs associated with the disease. B-type natriuretic peptide (BNP) may be the first potential "white count" for heart failure. The fact that a point-of-care, rapid assay for BNP has recently been approved by the FDA gives the clinician an opportunity to explore its potential usefulness. Data suggest that serial point-of-care testing of BNP will be of immense help in patients presenting to urgent care clinics with dyspnea. Additionally, BNP might serve as a screen for patients referred for echocardiography, and might also be an effective way to improve the in-hospital management of patients admitted with decompensated CHF. Finally, the role of BNP in the outpatient cardiac or primary care clinic may be one of critical importance in titration of therapies as well as assessment of the state of the patient's neurohormonal compensation.
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A simple blood test that would aid in the diagnosis and management of patients with congestive heart failure (CHF) would clearly have a favorable impact on the staggering costs associated with the disease. Imagine the problems associated with the diagnosis and treatment of prostate cancer without the benefit of a prostate-specific antigen level, or the difficulty of diagnosing and then managing a life-threatening infection without the use of a white blood cell count—and so forth. However, there is no currently accepted blood test to aid in the diagnosis and management of patients with CHF.

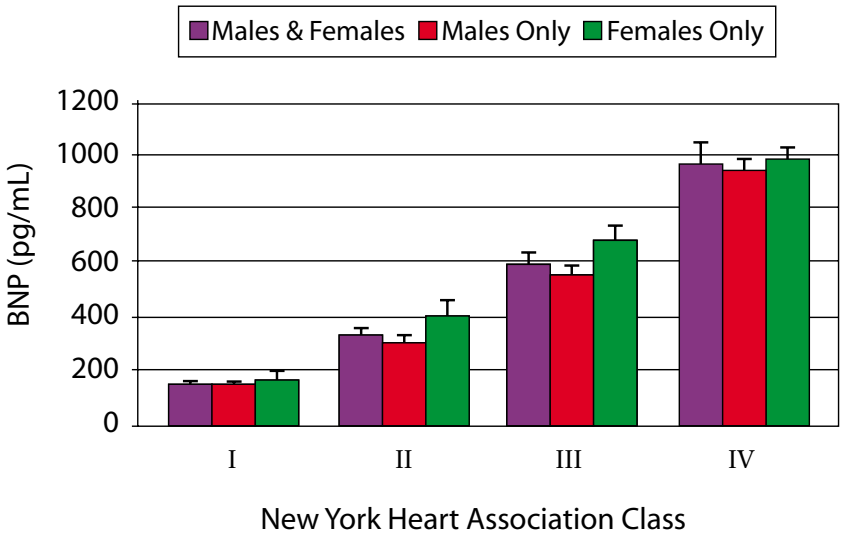

Figure 1. *B-type natriuretic peptide (BNP) levels in patients with congestive heart failure (CHF).*

B-Type Natriuretic Peptide

B-type natriuretic peptide (BNP) is a 32-amino acid polypeptide containing a 17-amino acid ring structure common to all natriuretic peptides.[1] Unlike the A-type (ANP), whose major storage sites include the atria and ventricles, the major source of plasma BNP is cardiac ventricles, suggesting that BNP may be a more sensitive and specific indicator of ventricular disorders than other natriuretic peptides.[2] BNP release appears to be in direct proportion to ventricular volume expansion and pressure overload.[3] BNP is an independent predictor of high left-ventricular end-diastolic pressure and is more useful than ANP or norepinephrine for assessing mortality in patients with chronic CHF.[4]

BNP levels in normals and in patients with CHF. BNP levels rise with age. Mean BNP levels are 26.2 ± 1.8 pg/mL in the group aged 55 to 64 years, 31. 0 ± 2.4 pg/mL for the group aged 65 to 74 years, and 63.7 ± 6 pg/mL for patients aged 75 years and older ($P < .001$; data on file with the U.S. Food and Drug Administration [FDA], Biosite Diagnostics). Additionally, women without CHF tend to have somewhat higher BNP values than do men of the same age group, with women 75 years and older having a mean BNP level of 76.5 ± 3.5 pg/mL. Although the reason is unknown, it is possible that aging women have stiffer left ventricles than age-matched men.

BNP and NYHA classification. Although the New York Heart Association (NYHA) classification correlates with symptoms as well as mortality in patients with heart failure, the fact that such a subjective classification is still the major means we use to describe the clinical condition of patients with heart failure underlies the need for more objective surrogates. Because BNP levels correlate with elevated end-diastolic pressure and because end-diastolic pressure correlates closely with the chief symptoms of CHF (dyspnea), it is not surprising that BNP correlates closely with the NYHA classification (Figure 1).

What should the cut-off for BNP be to diagnose CHF? Receiver operating characteristic (ROC) curves (data on file, Biosite Diagnostics) suggest that a BNP cut-off point of 100 pg/mL allows for the increased levels seen with advancing age and provides an excellent ability to discriminate CHF from non-CHF subjects. This level shows a sensitivity from 82.4% for CHF in general up to over 99% for NYHA class IV. The BNP test specificity exceeds 95% when comparing non-CHF with all CHF patients and is 93% in all subsets studied. A level of 100 pg/mL is high enough to avoid "BNP disease," that is, a group of patients who are mistakenly said to have heart failure because of falsely elevated BNP levels. In practice, though, it is likely that both a high and a low cut-off will be used, a high one (probably around 100 pg/mL) for its specificity and positive predictive value and a low one (40 to 60 pg/mL) for its high sensitivity and negative predictive value.

Point-of-Care Testing of BNP in the Emergency Department Setting

Point-of-care testing allows diagnostic assays to be performed in locations such as the emergency department (ED) or intensive care unit where treatment decisions are made and care is delivered based on the results of the assays. We completed a pilot study using a recently approved rapid BNP immunoassay (Triage Cardiac, Biosite Diagnostics, San Diego, CA) to assess 250 patients presenting to the San Diego VA Healthcare System urgent care area with the chief complaint of dyspnea.[5]

Patients diagnosed with CHF (n = 97) had a mean BNP concentration of 1076 ± 138 pg/mL, whereas the non-CHF group (n = 139) had a mean BNP concentration of 38 ± 4 pg/mL (Figure 2). The sicker the patient was (severity and admission

to the hospital), the higher the BNP level. Of crucial importance was that patients with the final diagnosis of pulmonary disease had lower BNP values (86 ± 39 pg/mL) than those with a final diagnosis of CHF (1076 ± 138 pg/mL, $P < .001$).

BNP at a cut-point of 80 pg/mL was found to be highly sensitive (98%) and specific (92%) for the diagnosis of CHF. The negative predictive value of BNP values under 80 pg/mL was 98% for the diagnosis of CHF. Multivariate analysis revealed that after all useful tools for making the diagnosis were taken into account by the ED physician (history, symptoms, signs, radiologic studies, and lab findings), BNP levels continued to provide meaningful diagnostic information not available from other clinical variables. Thus, the measurement of the BNP concentration in blood appears to be a sensitive and specific test for identification of patients with CHF in acute care settings. At the very minimum, it is likely to be a potent, cost-effective addition to the diagnostic armamentarium of acute care physicians.

BNP as a Screen of Left Ventricular Dysfunction

Although echocardiography, the most commonly utilized method to diagnose left ventricular dysfunction, is one of the fastest growing procedures in cardiology, its expense and limited access in community settings (where it may be needed most) may not make it the best screening test for patients, especially in those with low probability of left ventricular dysfunction.

We recently characterized patients in whom echocardiography was performed and BNP levels were assessed.[6] Among the patients with no documented history of CHF and no past determination of left ventricular function, 51% had abnormal echocardiographic findings. In this group BNP levels were significantly higher (328 ± 29 pg/mL) than the 49% of patients with no history of CHF and a normal echocardiogram (30 ± 3 pg/mL, $P < .001$). In patients with a known history of CHF, with preciously documented left ventricular dysfunction, all had abnormal findings (n = 102), with elevated BNP levels (545 ± 45 pg/mL). BNP levels were elevated in both systolic and diastolic dysfunction, with the highest values being reported in patients with systolic dysfunction plus a decreased mitral valve deceleration time.

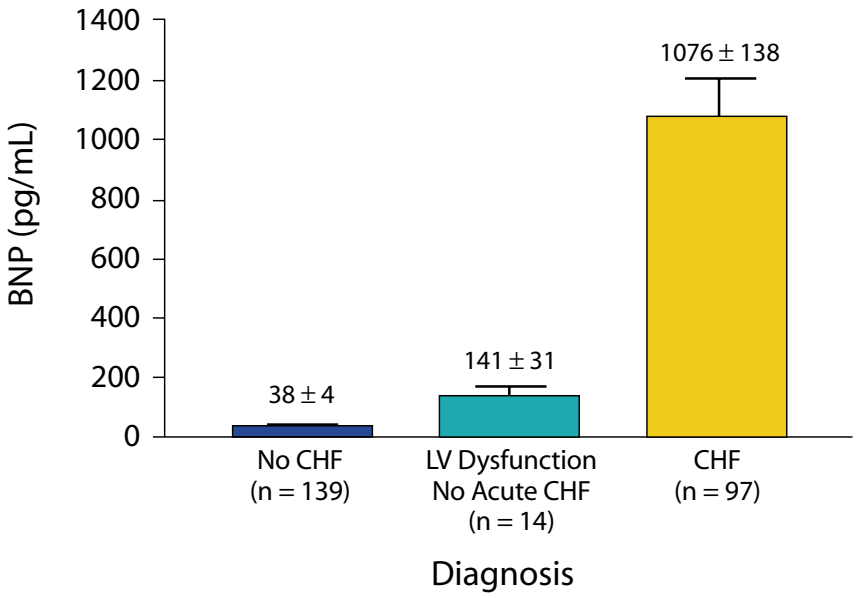

Figure 2. *B-type natriuretic peptide (BNP) levels in patients whose dyspnea was due to congestive heart failure (CHF), non-CHF causes, or baseline left ventricular (LV) dysfunction but non-CHF causes.*

Among patients with diastolic dysfunction, those with a restrictive filling pattern had higher BNP levels (428 pg/mL) than patients with impaired relaxation (230 pg/mL). The area under the ROC curve for BNP to detect diastolic dysfunction by echocardiography in patients with CHF and normal systolic function was 0.958. A BNP value of 71 pg/mL was 96% accurate in the prediction of diastolic dysfunction in this setting. BNP levels below 57 pg/mL gave a negative predictive value of 100% for the detection of clinically significant diastolic dysfunction. Additionally, multivariate analysis showed that in patients with clinical CHF and normal left ventricular function, BNP was the strongest predictor of diastolic abnormalities seen on echocardiography.

Elevated BNP levels … clearly indicate the presence of left ventricular dysfunction, whether the patient has symptoms or not, warranting further cardiac workup.

Thus, BNP may be an excellent screening tool for left ventricular dysfunction. Low BNP levels may preclude the need for echocardiog-

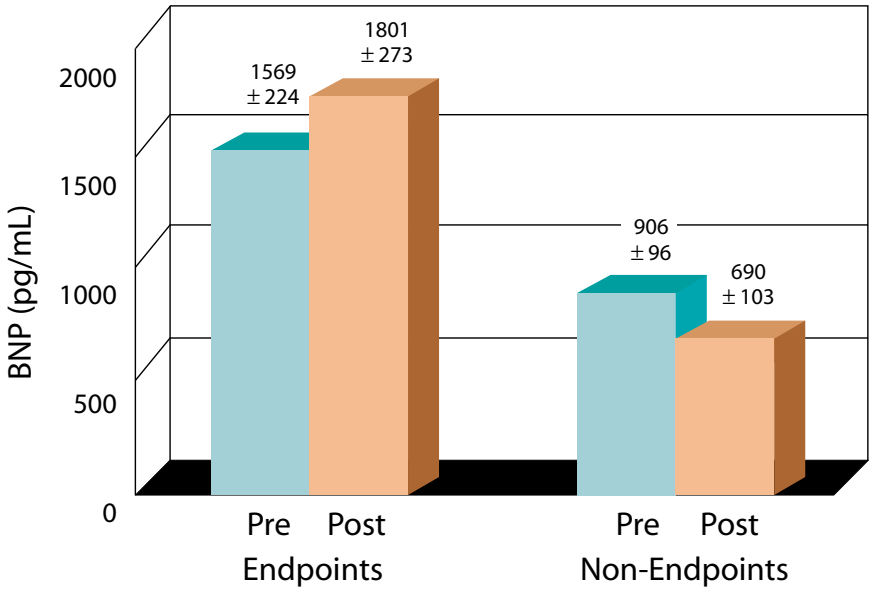

Figure 3. *B-type natriuretic peptide (BNP) levels before and after treatment for decompensated congestive heart failure based on whether or not the patient had a subsequent endpoint (death or readmission within 30 days).*

raphy in some patients, especially those who, even though at high risk, have no symptoms of heart failure. Elevated BNP levels, on the other hand, clearly indicate the presence of left ventricular dysfunction, whether the patient has symptoms or not, warranting further cardiac workup. It is clear that BNP should not replace imaging techniques in the diagnosis of CHF because these methods provide complementary information.

Can BNP Serve as a Surrogate Endpoint for the Treatment of Heart Failure?

Affecting 2% of the population, CHF is the fourth leading cause of adult hospitalizations in the United States and the most frequent cause of hospitalization in patients over the age of 65 years.[7] Although patients who are admitted to the hospital with decompensated heart failure often have improvement in symptoms with the various treatment modalities available, there has been no good way to evaluate the long-term effects of the short-term treatment. Indeed, in-hospital mortality and readmission rates for CHF patients are extremely high. The conventional tests for cardiac function take time and often do not correlate well with symptomatic changes in the patient's conditions. Therefore, most patients are discharged when they "feel better," which might then preclude further titration of medical therapy.

BNP in patients admitted for decompensated CHF. In a pilot study, we followed the course of 72 patients admitted with decompensated NYHA class III to IV CHF, measuring BNP levels on a daily basis.[8] We then determined the association between initial BNP measurement and the predischarge or premoribund BNP measurement and subsequent adverse outcomes (defined as death and 30-day readmission).

Of the 72 patients admitted with decompensated CHF, 22 endpoints occurred (death: n = 13, readmission: n = 9). In these 22 patients, BNP levels increased during hospitalization (mean increase, 233 pg/mL; $P < .001$; Figure 3). In patients without endpoints, BNP decreased during treatment (mean decrease 215 pg/mL). Patients who had good outcomes were characterized by decreases in both their NYHA class and BNP levels during hospitalization, whereas in those patients who were readmitted within 30 days of discharge had only minimal decreases in their BNP levels during hospitalization, despite improvement in NYHA classification. Finally, subjects who died in the hospital had rising BNP levels and little change in symptoms.

Although both admission BNP levels and the change in BNP levels over the period of hospitalization were significant predictors of outcomes, the last measured BNP level was the single variable most strongly associated with patients experiencing one of the prespecified endpoints. The mean BNP concentration was significantly greater in patients experiencing endpoints (1801 ± 273 pg/mL vs 690 ± 103 pg/mL) in patients with successful treatment of CHF ($P < .001$). Patients whose discharge BNP level fell below 430 pg/mL with treatment had a reasonable likelihood of leaving the hospital in good condition and not being readmitted within the following 30 days.

BNP Correlations with Falling Wedge Pressures in Patients Being Treated for CHF

In a pilot study, hemodynamic measurements (pulmonary capillary wedge pressure, cardiac output, right atrial pressure, and systemic vascular resistance) along with BNP levels were recorded every 2 to 4 hours for the first 24 hours and

every four hours for the next 24 to 48 hours in patients admitted for decompensated CHF.[9] Patients were treated at the discretion of the intensive care unit physicians in standard fashion with combinations of intravenous diuretics, vasodilators, and inotropic drug agents. The initial BNP level in the 15 responders (patients with a decrease in wedge pressure of less than 20 mmHg over the first 24 hours) was 1472 ± 156 pg/ mL. Twenty-four hours after treatment, BNP levels had dropped 55% to 670 ± 109 pg/mL. We found a significant correlation between percent change in wedge pressure from baseline per hour and the percent change of BNP from baseline per hour ($r = .73$, $P < .05$), with an average fall of BNP of 33 ± 5 pg mL per hour. The correlation between BNP levels and other indices of cardiac function-cardiac output (thermodilution), mixed venous oxygen saturation, and systemic vascular resistance was not significant. In the five nonresponders, there was little change in wedge pressure and only an 8% drop in BNP levels.

Diagnostic versus Therapeutic BNP

Diagnostically, as mentioned earlier in this article, studies have clearly shown that high levels of BNP are correlated with poor prognosis. An important question regarding the therapeutic use of nesiritide, which is exogenous BNP, is what happens to endogenous BNP levels? Because it takes 4 to 5 half-lives for 98% of the drug to be excreted from the body, nesiritide (which has a half-life of 18 minutes) should be excreted from the body within 2 hours after infusion. It seems reasonable, therefore, that measurement of endogenous BNP levels should not be performed until after this time.

Diagnostically, … studies have clearly shown that high levels of BNP are correlated with poor prognosis.

Regarding the therapeutic use of nesiritide, it is hypothesized that higher endogenous BNP levels will result in a better response to exogenous BNP administration, not because BNP receptors are affected, but because nesiritide has both vasodilator and diuretic properties, which appear to lower BNP by upregulating clearance mechanisms once more blood flow is restored to the kidneys. Thus BNP levels should be lower once the nesiritide infusion has stopped. Milrinone as well as nitroprusside will also lower BNP levels. However, the BNP levels frequently increase again as the patient's diuretics and vasodilators are adjusted prior to discharge. Frequently, patient medications are titrated according to hemodynamics in the cardiac care unit, and BNP levels decrease. Patients are then sent to the floor, where their diuretics and vasodilators are adjusted. By the time these patients are discharged from the hospital, their BNPs have increased from 400 pg/mL back to about 800 pg/mL. The use of nesiritide to lower BNP and the longer-term implications of how nesiritide will affect patient outcomes are currently being evaluated.

Tailored Treatment of Heart Failure—Is There a Role for BNP in the Clinic?

The correlation between the drop in BNP level and the patient's improvement in symptoms (and subsequent outcome) during hospitalization suggests that BNP-guided treatment might make "tailored therapy" more effective in an outpatient setting such as a primary

Main Points

- A blood marker for CHF would be of enormous value, considering the staggering costs associated with heart disease.
- Plasma B-type natriuretic peptide (BNP), found in the cardiac ventricles, is a promising new objective indicator of ventricular disorders.
- BNP levels have been shown to correlate closely with the NYHA symptom classification.
- A pilot study with a recently approved rapid BNP assay found that a cut-off point of 80 pg/mL was highly sensitive and specific for CHF diagnosis.
- BNP assay may prove to be an excellent screening tool for echocardiography, which is expensive and not always available in the community.
- In another pilot study, BNP assay proved to be a significant predictor of outcome, and in yet another study, BNP levels had a significant correlation with percent change in wedge pressure.
- BNP levels may also be helpful in tailoring therapy for outpatients, and more research is needed in this area.

care or cardiology clinic. Recently, Troughton and colleagues[10] randomized 69 patients to plasma amino terminal brain (N)-BNP-guided treatment versus symptom-guided therapy. Patients receiving N-BNP-guided therapy had lower N-BNP levels along with reduced incidence of cardiovascular death, readmission, and new episodes of decompensated CHF.

Thus, although studies have been limited, it appears that BNP levels may be helpful in guiding therapy in the outpatient setting. Further research is needed in this area.

Conclusions

Finding a simple blood test that would aid in the diagnosis and management of patients with CHF would clearly have a favorable impact on the staggering costs associated with the disease. BNP, which is synthesized in the cardiac ventricles and correlates with the left ventricular pressure, the amount of dyspnea, and the state of neurohormonal modulation, may be the first potential "white count" for heart failure. The fact that a point-of-care rapid assay for BNP has recently been approved by the FDA gives the clinician an opportunity to explore its potential usefulness. Our data, and data from others, suggest that serial point-of-care testing of BNP will be of immense help in patients presenting to urgent care clinics with dyspnea. Additionally, BNP might serve as a screen for patients referred for echocardiography. A low BNP level makes echocardiographic indices of left ventricular dysfunction (both systolic and diastolic) highly unlikely. BNP assay might also be an effective way to improve the in-hospital management of patients admitted with decompensated CHF. In some instances, BNP levels may obviate the need for invasive hemodynamic monitoring, and when such monitoring is used, they may help in tailoring treatment of the decompensated patient. Finally, the role of BNP in the outpatient cardiac or primary care clinic may be one of critical importance in titration of therapies as well as assessment of the state of the patient's neurohormonal compensation. ■

BNP, which is synthesized in the cardiac ventricles and correlates with left ventricular pressure, amount of dyspnea, and the state of neurohormonal modulation, makes this peptide the first potential "white count" for heart failure.

References

1. Grantham JA, Burnett JC Jr. BNP: increasing importance in the pathophysiology and diagnosis of congestive heart failure. *Circulation*. 1997;96:388–390.
2. Yandle TG. Biochemistry of natriuretic peptides. *J Intern Med*. 1994;235:561–576.
3. Maeda K, Takayoshi T, Wada A, et al. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. *Am Heart J*. 1998;135:825–832.
4. Tsutamoto T, Wada A, Maeda K, et al. Attenuation of compensation of endogenous cardiac natriuretic peptide system in chronic heart failure: prognostic role of plasma brain natriuretic peptide concentration in patients with chronic symptomatic left ventricular dysfunction. *Circulation*. 1997;96:509–516.
5. Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide (BNP) in the diagnosis of CHF in an urgent care setting. *J Am Coll Cardiol*. 2001;37:379–385.
6. Maisel AS, Koon J, Hope J, et al. A rapid bedside test for brain natriuretic peptide accurately predicts cardiac function in patients referred for echocardiography. *Am Heart J*. 2001;141:374–379.
7. Stevenson LW, Braunwald E. *Recognition and Management of Patients with Heart Failure. Primary Cardiology*. Philadelphia: WB Saunders Company; 1998:310–329.
8. Cheng VL, Krishnaswamy P, Kazanegra R, et al. A rapid bedside test for B-type natriuretic peptide predicts treatment outcomes in patients admitted with decompensated heart failure. *J Am Coll Cardiol*. 2001;37:386–391.
9. Kazanagra R, Cheng V, Garcia A, et al. A rapid test for B-type natriuretic peptide (BNP) correlates with falling wedge pressures in patients treated for decompensated heart failure: a pilot study. *J Card Failure*. 2001;7:21–22.
10. Troughton RW, Frampton CM, Yandle TG, et al. Treatment of heart failure guided by plasma amino terminal brain natriuretic peptide (N-BNP) concentrations. *Lancet*. 2000;355:1126–1130.