Although major advances in our understanding of the pathophysiology of congestive heart failure (CHF) have resulted in treatments that lead to symptomatic improvement and longer life, CHF still remains a major clinical challenge, especially in the areas of diagnosis, prognosis, and risk stratification. For the first time since the introduction of echocardiography some 20 years ago, a simple blood test appears to offer a significant advance in these areas.

See p 2392

B-type natriuretic peptide (BNP) is a neurohormone secreted mainly in the cardiac ventricles in response to volume expansion and pressure overload. Activation of BNP in patients with left ventricular (LV) dysfunction has generated considerable interest in both its diagnostic and prognostic properties. Although data have shown that BNP levels correlate with the severity and prognosis of heart failure, it was not until the development of a rapid, inexpensive assay that BNP could be used in the active clinical setting. In fact, present data, including the article in this issue of Circulation by Berger et al., suggest that BNP has finally cemented its role in these areas.

BNP in the Diagnosis of Dyspnea

For diagnostic screening tests to be useful in acute care, a test should have a high negative predictive value by itself and, along with clinical findings, should aid in the identification of patients whose dyspnea is a result of CHF. Davis et al. who measured the natriuretic hormones atrial natriuretic peptide and BNP in 52 patients presenting with acute dyspnea, found that admission plasma BNP concentrations more accurately reflected the final diagnosis than did ejection fraction or concentration of plasma atrial natriuretic peptide. Dao et al. used the newly available point-of-care rapid assay for BNP (Triage Assay, Biosite Inc) in 250 patients presenting to the San Diego VA Healthcare Urgent Care Center. 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. BNP at a cut point of 80 pg/mL was found to be highly sensitive and highly specific 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 emergency department physician, BNP levels continued to provide meaningful diagnostic information not available from other clinical variables.

More recently, Morrison et al were able to show that rapid testing of BNP could help differentiate between pulmonary and cardiac causes of dyspnea. Some types of pulmonary disease, such as cor pulmonale, lung cancer, and pulmonary embolism, had elevated BNP levels, but these were not usually elevated to the same extent as in patients with acute LV dysfunction.

The above studies set the stage for the recently completed multinational Breathing Not Properly (BNP) study. In this unique large-scale study, 1586 patients with acute shortness of breath were examined. Not only was BNP able to differentiate CHF from non-CHF causes of dyspnea (area under receiver operating characteristic curve=0.91) with good specificity and high negative predictive values, but a single BNP level was more accurate than both the National Health and Nutrition Examination Score and Framingham, arguably the two criteria most commonly used to diagnose CHF (Figure 1).

BNP as a Prognostic Marker in CHF

Several algorithms incorporating various hemodynamic variables or symptomatic indexes have been developed in an attempt to assess an individual heart failure patient’s prognosis. However, most single-variable markers are characterized by unsatisfactory discrimination of patients with and without increased heart failure mortality risk. BNP has been shown to be a powerful marker for prognosis and risk stratification in the setting of heart failure. In a recent study of 78 patients referred to a heart failure clinic, BNP showed a significant correlation to the heart failure survival score. In addition, changes in plasma BNP levels were significantly related to changes in limitations of physical activities and were a powerful predictor of the functional status deterioration. Harrison et al. monitored 325 patients for 6 months after an index visit to the emergency department for dyspnea. Higher BNP levels were associated with progressively worse prognoses (Figure 2). The relative risk of 6-month CHF death in patients with BNP levels >230 pg/mL was 24.
Risk stratification of CHF is confounded by the fact that CHF is a multi-system disease involving altered regulation of neurohormonal systems and altered function of other systems, such as renal and skeletal muscle. Yet CHF trials have suggested that up to 50% of deaths may be due to an arrhythmia rather than deterioration of pump function. Although other markers of hemodynamic status might help assess severity of disease, BNP may be the first marker that also reflects the physiological attempt to compensate for the pathophysiological alterations and restore circulatory homeostasis. Hence, BNP might be expected to influence both mechanical dysfunction and arrhythmic instability as the mechanisms most commonly involved in heart failure mortality. Berger and his colleagues have done a commendable job in cementing the role of BNP as a prognostic marker for sudden, presumably arrhythmic death in CHF. Following 452 patients with ejection fractions <35% for up to 3 years, they found that the BNP level was the only independent predictor of sudden death. Their cutoff value of 130 pg/mL is similar to the 80 pg/mL used by Dao and the 100 pg/mL cutoff of the rapid assay.

The significance of the findings of Berger et al is underscored by the renewed interest in preventing sudden cardiac death by use of implantable cardiac defibrillators (ICDs). To achieve the maximum benefit of these costly devices, one needs to be able to prognosticate which patients will do better with an ICD. Their article underscores that BNP allowed specification of a patient group with a much higher risk of sudden death, suggesting that it is an additional simple method to help identify patients who might benefit from ICD implantation.

Future Use of BNP Levels: A Marker for Therapy of Heart Failure

Inpatient Modulation of Treatment
Readmission after hospitalization for heart failure is surprisingly common, estimated at 44% at 6 months within the Medicare population. Considering that hospitalization is the principal component of the cost for patient care (70% to 75% of the total direct costs), a reduction in heart failure...
hospitalizations is an appropriate goal, regardless of which treatment modalities are in place.

Because BNP is a volume-sensitive hormone with a short half-life (18 to 22 minutes), there may be a future for BNP levels in guiding diuretic and vasodilator therapy on presentation with decompensated CHF. Cheng et al.19 found that patients who were not readmitting in the 30 days after discharge could be characterized by falling BNP levels during hospitalization. On the other hand, patients who were readmitted or died in the 30 days after discharge had no such decrease in BNP levels on their index hospitalization, despite their overall “clinical” improvement. In a study by Kazenegra et al.,20 patients undergoing hemodynamic monitoring had changes in wedge pressures that strongly correlated with dropping BNP levels and clinical improvement. Thus, in the future it may be possible that titration of vasodilators will no longer require Swan-Ganz catheterization, but rather the use of a BNP level as a surrogate for wedge pressure and perhaps noninvasive cardiac output measurements (Bio-Z, Cardiodynamics) as a measure of cardiac output. Interestingly, patients receiving the drug Natrecor (exogenous BNP; Scios Inc) have lower endogenous levels of BNP 6 hours after Natrecor cessation than at the time of admission (author’s own unpublished data).

Outpatient Treatment

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 care or cardiology clinic. The Australia–New Zealand Heart Failure Group analyzed plasma neurohormones for prediction of adverse outcomes and response to treatment in 415 patients with left ventricular dysfunction who were randomly assigned to receive carvedilol or a placebo.21 They found that BNP was the best prognostic predictor of the success or failure of carvedilol. Recently, Troughton et al.22 randomized 69 patients to N-terminal BNP (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.

Although BNP levels may be helpful in guiding therapy in the outpatient setting, the magnitude of fluctuations of BNP levels in an individual patient over time needs to be ascertained before BNP levels can be used to titrate drug therapy. Perhaps patients with high BNP levels who do not respond to treatment should be considered for other types of therapies, such as cardiac transplantation or ventricular assist devices. In a recent trial of patients who received ventricular assist devices for end-stage heart failure, BNP levels appeared to fall as remodeling of the heart occurred, and an early decrease in BNP plasma concentration was indicative of recovery of cardiac function during mechanical circulatory support.23

Conclusion: A Cautionary Note

Like other tests of its generation in which the initial excitement was followed by some disappointment as reality set in, much work still needs to be done with regard to BNP levels. Although BNP clearly improves diagnostic accuracy of patients presenting with dyspnea, it is not a stand-alone test. The physician must bring to the table adequate history and physical examination skills, as well as abilities to interpret other laboratory tests such as chest x-rays. In our own institution, we have found that the negative predictive value of BNP levels under 100 pg/mL is the strongest feature of this peptide. Although the positive predictive value in a given patient at a cutoff of 100 pg/mL is 80%, most patients with significant CHF as a cause of their dyspnea will have levels of >400 pg/mL. Thus, in patients presenting with levels between 100 and 400 pg/mL, one needs to exclude baseline LV dysfunction without exacerbation, pulmonary embolism, and cor pulmonale.

The future for BNP testing looks promising. We must continue to help it find its identity for patients with heart failure.

References


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B-Type Natriuretic Peptide Levels: Diagnostic and Prognostic in Congestive Heart Failure: What's Next?

Alan Maisel

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