Evolution of B-type natriuretic peptide in evaluation of intensive care unit shock*

Congestive heart failure (CHF) is a major and increasing cause of death and disability in United States. Its prevalence is attributable to the drastic increase in cardiovascular risk factors such as obesity and diabetes and improved survival rate after acute myocardial infarction (and subsequent development of CHF). CHF has a prevalence of 4.9 million and an incidence of 550,000 cases per year. The extremely high readmission rates for CHF patients account for significant resource use (1–4).

Until recently, owing to the subjectivity of methods used to distinguish heart failure from pulmonary conditions, determining the cause of dyspnea has been difficult especially in the urgent care setting. In 2002, the Breathing Not Properly as well as other studies demonstrated that B-type natriuretic peptide (BNP) not only significantly increases diagnostic accuracy (Fig. 1) (5–7) but also correlates with long-term morbidity and mortality in patients with chronic heart failure presenting to the emergency department (8).

Since elevations of BNP are related to presence and severity of CHF, it is no surprise that it is 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 (9). In addition, changes in plasma BNP concentrations were significantly related to changes in limitations of physical activities and were a powerful predictor of functional status deterioration. Hence, BNP concentrations may be able to accurately objectify New York Heart Association classification (6). Harrison et al. (8) followed 325 patients for 6 months after an index visit to the emergency department for dyspnea. Higher BNP concentrations were associated with a progressively worse prognosis. The relative risk of 6-month CHF admission or death in patients with BNP concentrations >230 pg/mL was 24 times the risk of concentrations less than this. Cheng et al. (10) followed the course of 72 patients admitted with decompensated CHF with daily BNP concentrations and their relationship to 30-day readmission rates or death. Patients who were most likely to have a cardiac event had higher BNP concentrations both at the time of admission and at discharge. Only 16% of patients with a decrease in BNP concentrations during hospitalization had a subsequent cardiac event, whereas 52% of those with increasing BNP concentrations during treatment had either readmission or cardiac death. Patients whose discharge BNP concentrations fell below 430 pg/mL had a reasonable likelihood of not being readmitted within the following 30 days. These data were supported by a recent study by Bettencourt et al. (11), who found that failure of BNP concentrations to decrease over the hospitalization period predicted death/rehospitalization and that discharge concentrations <250 pg/mL predicted event-free survival. In another study by Berger et al. (12), 452 high-risk cardiovascular patients with ejection fraction <35% were followed for 3 yrs. In this study, BNP with a cut-point of 130 pg/mL was the only independent predictor of sudden cardiac death in a multivariate analysis with standard variables like ejection fraction, New York Heart Association class, or antiarrhythmic medication. Recently, Wang et al. (13), the investigators from the Framingham Offspring Study, showed that the utility of BNP concentrations >20 pg/mL were associated with an increase by >60% in the long-term (5 yrs) risk of death even in asymptomatic middle-aged persons (Fig. 2).

In another important article, published in this issue of *Critical Care Medicine*, Dr. Tung and colleagues (14) demonstrate that BNP concentrations in intensive care unit shock might provide powerful information for use in mortality prediction. Median BNP concentrations were higher in those who died than those who survived (943 pg/mL vs. 378 pg/mL, $p < .001$). Also, using multivariate analysis, they showed that BNP concentration in the highest log-quartile was the strongest predictor of mortality (odds ratio = 4.50). Even though they showed no correlation between a single BNP value and pulmonary artery occlusion pressure in interpatient analysis (which could be explained by variation of individual patients, age, gender, ethnicity, baseline and dry BNP concentration, and to some extent by renal function), it is clear that a BNP <350 pg/mL had a very high negative predictive value (95%) for the diagnosis of cardiogenic shock. This study support the study published in 2001 by Kazanagra et al. (15), involving 20 patients with decompensated New York Heart Association class III–IV CHF undergoing tailored therapy, which showed a significant correlation between percent change in occlusion pressure from baseline per hour and the percent change of BNP from baseline per hour (Fig. 3). In this study, the authors also showed that the patients who died had higher final BNP concentrations (1078 ± 123 pg/mL vs. 701 ± 107 pg/mL). The authors concluded that although BNP concentrations will not obviate the need for invasive hemodynamic monitoring, these concentrations may be a useful adjunct in tailoring therapy to these patients and may improve the in-hospital management of patients admitted with decompensated CHF. Even though Dr. Tung and colleagues (14) could not differentiate cardiogenic from noncardiogenic shock using BNP, BNP concentrations have been a useful surrogate of occlusion

*See also p. 1643.

Key Words: congestive heart failure; cardiovascular risk factors; survival rate; acute myocardial infarction; resource use

DOI: 10.1097/01.CCM.0000135748.75590.54

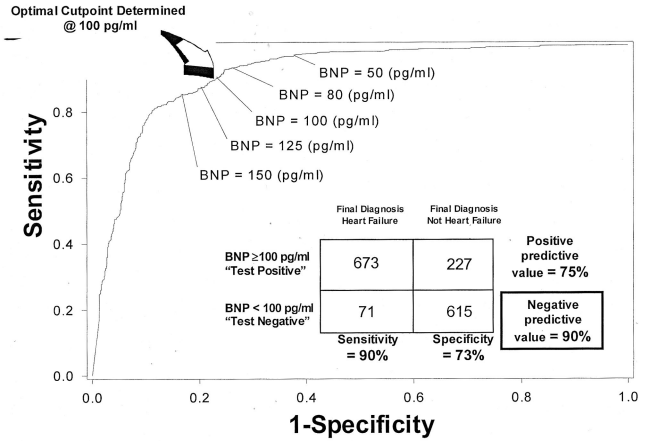

Figure 1. Sensitivity vs. specificity for heart failure by B-type natriuretic peptide concentrations. Data from the Breathing Not Properly Multinational Study; adapted with permission (6).

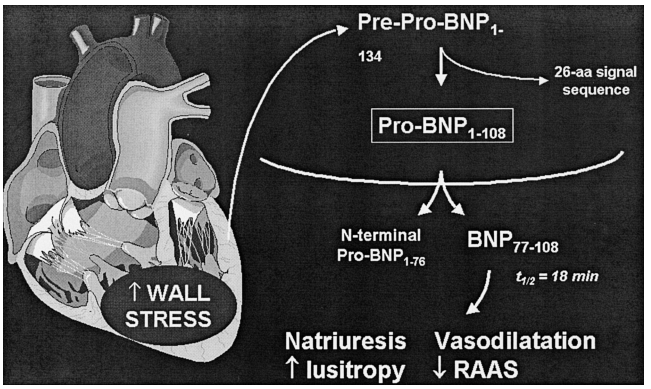

Figure 2. Shows the secretion of B-type natriuretic peptide (*BNP*; 132 amino acids) in response to wall stress and then its sequential breakdown to a 76-amino acid N-terminal fragment and a 32-amino acid active hormone.

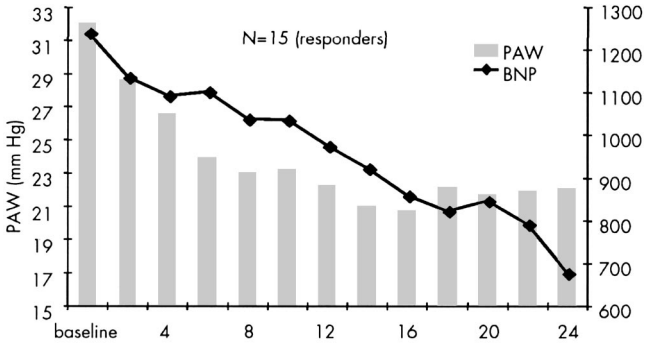

Figure 3. The correlation of treatment induced change in pulmonary artery occlusion pressure (*PAW*) with change in B-type natriuretic peptide (*BNP*) from baseline. Adapted with permission (15).

pressure and are useful in differentiating heart failure from lung disease, and BNP may be useful not only in excluding cardiogenic shock but also in differentiating cardiogenic from noncardiogenic pulmonary edema. In a study by Berman et al. (16), BNP concentrations were obtained in 35 patients with acute respiratory distress syndrome (ARDS) and from 42 patients hospitalized for severe dyspnea with a diagnosis of CHF. The median BNP concentration in patients with CHF of 773 pg/mL was significantly higher than patients with ARDS (123 pg/mL, $p < .001$, Fig. 4). The area under the receiver operator characteristic curve using BNP to differentiate CHF from ARDS was 0.90

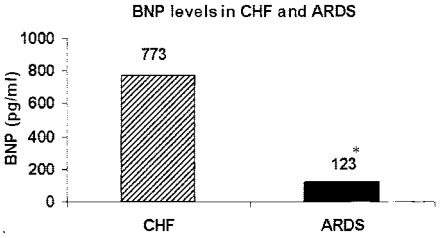

Figure 4. B-type natriuretic peptide (*BNP*) concentrations in coronary heart failure (*CHF*) and acute respiratory distress (*ARDS*) syndrome patients. Adapted with permission (16). *$p < .001$.

(0.83–0.98, $p < .001$). At a cut-point of 360 pg/mL, there was 90% sensitivity, 86% specificity, 89% positive predictive value, and a 94% negative predictive value (accuracy = 88%) for ARDS vs. CHF. Thus, BNP may be accurate enough to differentiate noncardiogenic from cardiogenic pulmonary edema such that invasive hemodynamic catheter placement may not always be necessary. Hence, BNP concentrations >360 pg/mL suggest CHF as the diagnosis of pulmonary edema.

There are very few limitations of the study by Dr. Tung and colleagues (14), including small sample size and single point BNP testing, but the utility of multiple BNP testing in monitoring the hemodynamic state of patients has been already addressed by Kazanagra et al. (15). The merit of this study is in that it shows that low BNP concentrations, tested by a single inexpensive point of care assay, can exclude cardiogenic shock (a high pulmonary artery occlusion pressure or low cardiac index) in the intensive care unit and may be useful to avoid pulmonary artery catheterization and the risks associated with pulmonary artery placement as well as the necessity of an intensive care unit bed. Also, elevated BNP concentrations may offer superior prognostic information to the critical care practitioner to help identify patients at highest risk for mortality.

BNP is the first biomarker to prove its value in a) screening for left ventricular dysfunction; b) assessing prognosis while monitoring patients; c) tailoring management and titrating therapy (17); d) providing objectivity in assessing discharge and admission criteria; e) predicting and decreasing adverse cardiac events and readmissions in heart failure patients (18); and f) characterization and prognostication of intensive care unit patients in shock.

To conclude, this rapid, inexpensive, point-of-care test, which is simple to administer in a variety of clinical settings, can enable care providers to facilitate and optimize care of heart failure patients. As with everything there are limitations to BNP testing, as it is not a standalone test; however, when used judiciously, it could be a powerful tool in the hands of clinicians. Emerging clinical data will help further refine biomarker-guided therapeutic and monitoring strategies involving BNP.

Vikas Bhalla, MD
Alan S. Maisel, MD
Department of Cardiology
Veterans Administration Medical Center
University of California
San Diego, CA
Meenakshi A. Bhalla, MD
University of Buffalo
Mercy Hospital
Buffalo, NY

REFERENCES

1. American Heart Association. Heart Disease and Stroke Statistics—2003 Update. Dallas, TX, American Heart Association, 2002
2. Cohn JN, Levine TB, Olivari MT, et al: Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. *N Engl J Med* 1984; 311:819–823
3. Vinson JM, Rich MW, Sperry JC, et al: Early readmission of elderly patients with heart failure. *J Am Geriatr Soc* 1990; 38: 1290–1295
4. Krumholz HM, Wang Y, Parent EM, et al: Readmission after hospitalization for congestive heart failure among Medicare beneficiaries. *Arch Intern Med* 1997; 157:99–104
5. Dao Q, Krishnaswamy P, Kazanegra R, et al: Utility of B-type natriuretic peptide (BNP) in the diagnosis of heart failure in an urgent care setting. *J Am Coll Cardiol* 2001; 37: 379–385
6. Maisel AS, Krishnaswamy P, Nowak RM, et al: Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. *N Engl J Med* 2002; 347:161–167
7. Morrison L, Harrison A, Krishnaswamy P, et al: Utility of rapid B-type natriuretic peptide in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. *J Am Coll Cardiol* 2002; 39:202–209
8. Harrison A, Morrison LK, Krishnaswamy P, et al: B-type natriuretic peptide (BNP) predicts future cardiac events in patients presenting to the emergency department with dyspnea. *Ann Emerg Med* 2002; 39:131–138
9. Koglin J, Pehlivanli S, Schwaiblamir M, et al: Role of brain natriuretic peptide in risk stratification of patients with congestive heart failure. *J Am Coll Cardiol* 2001; 38: 1934–1941
10. 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
11. Bettencourt P, Ferreira S, Azevedo A, et al: Preliminary data on the potential usefulness of B-type natriuretic peptide levels in predicting outcomes after hospital discharge in patients with heart failure. *Am J Med* 2002; 113:215–219
12. Berger R, Huelsman M, Strecker K, et al: B-type natriuretic peptide predicts sudden death in patients with chronic heart failure. *Circulation* 2002; 105:2392–2397
13. Wang TJ, Larson MG, Levy D, et al: Plasma natriuretic peptide levels and the risk of cardiovascular events and death. *N Engl J Med* 2004; 350:655–663
14. Tung RH, Garcia C, Morss AM, et al: Utility of B-type natriuretic peptide for the evaluation of intensive care unit shock. *Crit Care Med* 2004; 32:1643–1647
15. Kazanagra R, Cheng V, Garcia A, et al: A rapid test for B-type natriuretic peptide correlates with falling wedge pressures in patients treated for decompensated heart failure: A pilot study. *J Card Fail* 2001; 7:21–29
16. Berman B, Spragg R, Maisel A: B-type natriuretic peptide (BNP) levels in differentiating congestive heart failure from acute respiratory distress syndrome (ARDS). Abstracts from the 75th Annual Scientific Meeting of the American Heart Association. *Circulation* 2002; 106:S3191
17. 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
18. Lee S-C, Stevens TL, Sandberg SM, et al: The potential of brain natriuretic peptide as a biomarker for New York Heart Association class during the outpatient treatment of heart failure. *J Card Fail* 2002; 8:149–154

Nurse-assessed tool for evaluating death in the intensive care unit*

Over the last few decades, intensive care unit (ICU) care has evolved from a technical endeavor to a holistic approach that combines state-of-the-art life support and a strong focus on communication and empathy within the patient-family-staff triad (1–3). This second component, known as patient- and family-centered care, has been investigated in epidemiologic (4–12) and interventional studies (13–15), which have identified areas for improvement (16). Although patient- and family-centered care is initiated at ICU admission when the patient's outcome is still uncertain, specific needs of dying patients and their relatives have been identified (17–19), and considerable effort has been directed at providing patients and their families with a "good death" (20–23).

In 2002, Curtis et al. (24) provided clinicians with an easy-to-use instrument aimed at improving the care of dying patients. Using the perceptions of family members interviewed after the death of their relatives in the ICU, these authors developed a reliable and valid tool for assessing the dying experience (24). Their 31-item Quality of Dying and Death (QODD) questionnaire assesses symptoms, patient preferences, and satisfaction with care. Curtis and coworkers showed that symptom assessment and treatment, continuity of care, and good communication within the patient-family-staff triad were associated with a better quality of death. In this issue of *Critical Care Medicine*, the same group turned the spotlight onto nurses as a valuable source of information about the quality of dying in the ICU (25). Instead of asking physicians or family members how they perceived death in the ICU, Dr. Hodde and colleagues (25) asked nurses. The authors based this approach on data showing that nurses are both more critical about end-of-life care than physicians and less likely to be distressed by after-

*See also p. 1648.

Key Words: holistic care; life support; communication; patient-centered care; family-centered care; dying patients

DOI: 10.1097/01.CCM.0000135746.49065.72