B-type natriuretic peptide. A biomarker for all the right reasons

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(Ital Heart J 2004; 5 (6): 417-420)

Received April 6, 2004;
accepted April 8, 2004.

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Owing 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 congestive heart failure), there has been an immense increase in incidence and prevalence of heart failure. In the United States alone heart failure with the prevalence of 4.9 million and an incidence of 550 000 cases per year is a major and increasing cause of death and disability and its extremely high readmission rates account for significant resource use[1-4].

Seventy percent of the congestive heart failure patients present at the emergency department and until recently determining the cause of dyspnea has been difficult especially in the urgent-care setting because traditional, subjective methods of distinguishing heart failure from pulmonary conditions leave a high level of uncertainty. Maisel et al. in 2002 demonstrated that measurements of neurohormones, in particular B-type natriuretic peptide (BNP), can not only significantly increase diagnostic accuracy (Fig. 1)[5-7], but also correlate with long-term morbidity and mortality in patients with chronic heart failure presenting to the emergency department[8].

Natriuretic peptides such as BNP are secreted by cardiac ventricle mainly in response to wall stress and the neurohormonal imbalance caused by vasoconstrictive factors like the sympathetic nervous system, endothelins, and the renin-angiotensin-aldosterone system in heart failure (Fig. 2)[9-11]. BNP is initially secreted as preproBNP (132 amino acids) in response to wall stress and then it is sequentially broken down to a 76 amino acid N-terminal fragment (NT-BNP) and a 32 amino acid active hormone (BNP) (Fig. 3). Natriuretic

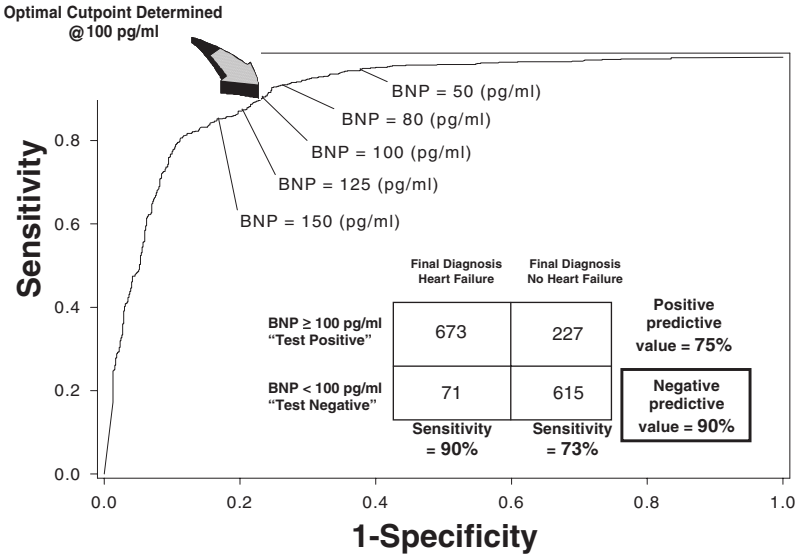

Figure 1. *Sensitivity vs specificity for heart failure by B-type natriuretic peptide (BNP) levels. Data from Maisel et al.[6].*

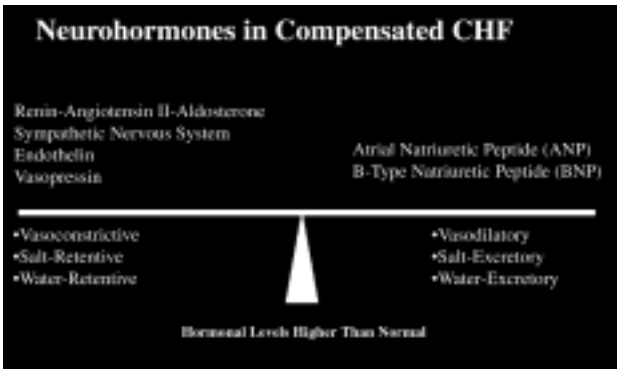

Figure 2. *The figure shows the complex balance between vasodilatory and vasoconstrictive systems in heart failure. CHF = congestive heart failure. Data from Weber[9], Chen and Burnett[10], and Dzau[11].*

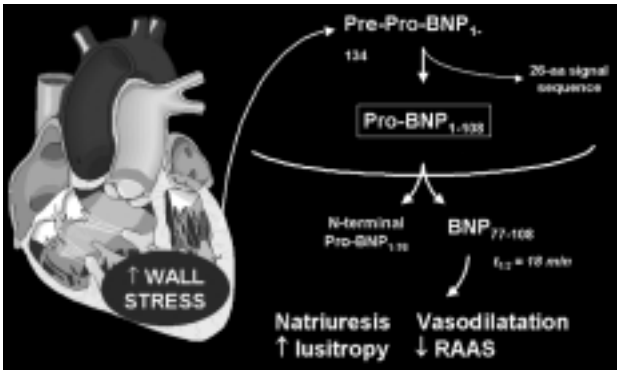

Figure 3. *The figure shows the secretion of preproB-type natriuretic peptide (BNP) (132 amino acids) in response to wall stress and then its sequential break down to a 76 amino acid N-terminal fragment (NT-BNP) and a 32 amino acid active hormone (BNP). RAAS = renin-angiotensin-aldosterone system.*

peptides in general increase myocardial relaxation and oppose the vasoconstrictive, sodium retaining, and antidiuretic effect caused by the above-mentioned vasoconstrictive factors. Table I[12-21] shows the history of development of BNP point-of-care test.

Recently Wang et al.[22], the investigators from the Framingham Offspring Study, examined the long-term prognostic importance of the levels of atrial natriuretic peptide and BNP in asymptomatic middle-aged persons. After adjusting for traditional risk factors, Wang et al. found that the level of BNP was independently predictive of the risk of death, heart failure, atrial fibrillation, and stroke over a mean follow-up period of about 5 years. Levels of BNP > 80th percentile in this cohort (i.e., > 20 pg/ml) were associated with an increase by > 60% in the long-term risk of death. Furthermore, there was a significant prognostic gradient with respect to the risk of heart failure, atrial fibrillation, and stroke among the three levels of BNP (low, intermediate, and high) examined. This remarkable finding suggests that, in the asymptomatic community based cohort, there are important prognostic data even in the range of BNP levels < 100 pg/ml, the level used to rule out heart failure in 90% of acutely dyspneic patients. Echocardiographic measurements of left ventricular mass, left atrial diameter, and left ventricular systolic function did statistically explain the association between the level of BNP and the risk of death. These associations persisted even after adjustment for standard risk factors and echocardiographic measurements, suggesting that slight elevations of BNP may reflect very early stages of patho-

Table I. The B-type natriuretic peptide (BNP) story.

1956	Henry and Pearce[12] described natriuretic response in balloon stretch of the atrium
1981	de Bold et al.[13] injected homogenized atrial tissue into rats and noted a potent natriuretic response
1984	Kangawa et al.[14] identified structure of ANP
1988	Sudoh et al.[15] isolated BNP from porcine brain tissue
1988	Early work began to synthesize recombinant ANP and BNP
1991	Mukoyama et al.[16] demonstrated that BNP is a novel cardiac hormone secreted primarily by the ventricles
1992	Kohno et al.[17] found hypertensive patients with LVH had higher BNP levels
1993	Multiple reports of elevated BNP levels in CHF
1996	Yamamoto et al.[18] found BNP had superior performance compared with the other natriuretic peptides when measured in systolic dysfunction, LVH, and diastolic dysfunction
1997	Cowie et al.[19] confirmed BNP could be used to diagnose CHF in the primary care setting
1998	McDonagh et al.[20] demonstrated BNP was superior to the other natriuretic peptides in the clinical diagnosis of CHF (n=1653)
2000	Bosite, Inc. introduced BNP (point-of-care) test
2001	Nesiritide (Natrecor) was introduced in the US market as an intravenous treatment for decompensated CHF
2002	Wieczorek et al.[21], in Breathing Not Properly study, demonstrated utility of BNP point-of-care assay in diagnosis of CHF
2003	Bayer Diagnostics introduced laboratory-based BNP assay
2004	Bayer Diagnostics introduces BNP on their ACS:180 immunoassay system analyzer for lower volume laboratories

ANP = A-type natriuretic peptide; CHF = congestive heart failure; LVH = left ventricular hypertrophy.

logic processes that precede the development of apparent cardiac manifestations (such as measurable left ventricular hypertrophy).

In this community cohort only 2.2% of the participating men and 1.5% of the women had levels > 80 pg/ml, which is expected as these are asymptomatic patients without any signs of overt heart failure.

The other study reported in the February 12th issue of the *New England Journal of Medicine* by Mueller et al.[23], extends the value ascertained from the Breathing Not Properly trial in terms of cost-effectiveness of using BNP levels throughout the diagnostic and hospitalization phases of heart failure. In the study, the investigators studied patients presenting to the emergency department with acute dyspnea who were randomly assigned to undergo either a single measurement of BNP or no such measurement. Participating clinicians were advised that a level of BNP < 100 pg/ml made the diagnosis of congestive heart failure unlikely, whereas a level > 500 pg/ml made it highly likely. For intermediate levels, use of clinical judgment and adjunctive testing were encouraged. In this single-blind trial of 452 patients, rapid measurement of BNP in the emergency department was associated with decreases in the rate of hospital admission by 10% points, the median length of stay by 3 days, and the mean total cost of treatment by about $1,800, with no adverse effects on mortality or the rate of subsequent hospitalization. This carefully performed trial suggests that the use of an inexpensive blood test for BNP in the emergency evaluation of acute dyspnea can significantly improve both the efficiency and the quality of care. These results are consistent with the Breathing Not Properly study and showed that the use of an improved diagnostic test in the emergency department can reduce the use of hospital resources and associated costs by eliminating the need for other, more expensive tests; or by establishing an alternative diagnosis that does not require hospitalization. This finding is similar to our REDHOT study presented in Heart Failure Society of America in Las Vegas in September 2003 which showed that use of BNP would have decreased unnecessary hospitalization by approximately 10% which if extrapolated according to DRG would result in saving of $400 million per year in the United States alone. Not only does BNP useful in diagnosis and prognostication, recently a cut-off BNP level of 20 pg/ml has been shown to be useful by Atisha et al.[24] in screening and in forming a pre-test probability in patients undergoing echocardiography with its high sensitivity and negative predictive value especially in systolic and combined systolic and diastolic heart failure. Recently Heidenreich et al.[25] also found that screening with BNP using a cut-off BNP level of 24 pg/ml followed by echocardiography in those with an abnormal test was economically attractive for 60-year-old men and possibly for women for patient groups with at least a 1% prevalence of moderate or greater left ventricular systolic dysfunction (ejection fraction < 40%). Screening all patients with echocardiography was expensive, but sequential BNP echocardiography screening strategy was economically attractive.

To conclude, 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[26] and titrating therapy[27], d) providing objectivity in assessing discharge and admission criteria[28], and e) predicting and decreasing adverse cardiac events and readmissions in heart failure in patients[29]. The rapid, inexpensive, point-of-care tests are simple to administer in a variety of clinical settings, which enable care providers to facilitate and optimize care of heart failure patients. Emerging clinical data will help further refine biomarker-guided therapeutic and monitoring strategies involving BNP.

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