B-Type Natriuretic Peptide: A Universal Cardiac Biomarker?

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B-type (previously called brain) natriuretic peptide is probably the most popular cardiac biomarker in recent years, with thousands of publications related to its use. Initially it was used to discriminate between cardiac and non-cardiac causes of acute dyspnea (chronic heart failure exacerbation versus chronic obstructive pulmonary disease exacerbation) [1]. Later, BNP was shown to be a powerful diagnostic [2,3] but also a prognostic tool in systolic heart failure [4]. Several trials demonstrated the usefulness of BNP in guiding the treatment of CHF patients (mainly hospitalized) [5]. It should be noted that N-terminal proBNP level has been used for the same purposes. The role of BNP in heart failure has been the subject of several recent reviews [6-8], some of which, however, have questioned the overwhelming enthusiasm regarding the BNP role in heart failure, especially when there is little doubt about the clinical diagnosis [9].

BNP was found to be an effective marker for diagnosis and prognosis in various other cardiac diseases including, but not limited to, diastolic heart failure [10], stable coronary artery disease [11], non-ST segment elevation acute coronary syndromes [12], ST segment elevation myocardial infarction [13,14], hypertrophic cardiomyopathy [15], and more. Recent reports indicate that BNP has prognostic significance in still other cardiac conditions, for example high BNP level before percutaneous coronary intervention predicts the no-reflow phenomenon [16], elevated BNP levels signify a worse prognosis in infective endocarditis, among others.

Moreover, elevated BNP levels have been used as both a diagnostic and prognostic tool in semi-cardiac or non-cardiac conditions, including pulmonary embolism, right heart failure due to pulmonary diseases [17], primary pulmonary hypertension, and in a variety of patients hospitalized in the critical care unit due to non-cardiac causes (e.g., sepsis, trauma or after surgery). Still, BNP levels are expected to be higher in systolic heart failure than in these other conditions, but it should be emphasized that the current impact of BNP measurements in CHF is mainly in prognosis and risk stratification.

Much has been written about BNP levels and chronic heart failure (including guided therapy, as stated above), but most articles focus on hospitalized patients. Relatively few papers deal with BNP levels and the treatment of outpatients [18]. In this

BNP = B-type natriuretic peptide
CHF = chronic heart failure
NT = N-terminal
LVEF = left ventricular ejection fraction

issue of *IMAJ*, the study by Amir at al. [19] is important because it involves ambulatory patients. Most CHF patients are now treated outside of the hospital; unfortunately many of them do not visit a specialized CHF clinic (such as the one where the current study was performed), although it is now accepted that participation in a multidisciplinary heart failure program has been associated with an improved outcome.

Their study population comprised 70 patients, mostly male, about half having coronary artery disease as CHF etiology. Hypertension and diabetes were also present in about half of the patients; about 40% had atrial fibrillation. The authors divided their patients into three groups according to the baseline N-terminal proBNP levels. The patients in group 3 had a higher prevalence of renal failure, lower hemoglobin, lower ejection fraction, lower body mass index, and higher C-reactive protein levels. It would seem that those patients had very advanced heart failure; perhaps some already had cardiac cachexia and multi-organ disease.

As expected, patients with the highest NT-proBNP levels had the highest mortality. It is noteworthy that when multivariate analysis was performed (which was age-adjusted and included body mass index, left ventricular ejection fraction, New York Heart Association class, QRS width, ischemic etiology, presence of atrial fibrillation, blood urea level, serum creatinine level, hemoglobin level, high sensitive C-reactive protein, and serum NT-proBNP level in the upper tertile), only NT-proBNP level was a statistically significant predictor of mortality. Similar results (showing BNP as a better mortality predictor than LVEF or other variables) were demonstrated in other studies but most were performed in hospitalized patients.

The results of this study suggest that it may be useful to obtain BNP levels in every patient entering the heart failure clinic or health management organization CHF program. This will help to address several important issues, including frequency of visits, aggressiveness of treatment (pharmacological, resynchronization therapy, implantable cardiovertion defibrillator, etc.), and the continuation of necessary therapy despite side effects.

On the other hand, it can be argued that despite the impressive statistics, elevated NT-proBNP may simply reflect the severity of the underlying heart failure, and with good clinical assessment an astute clinician may be able to define the same high risk patients and treat them accordingly. Actually, current heart failure treatment guidelines do not address the BNP levels as a factor that may influence treatment decisions.

The authors did not determine the follow-up NT-proBNP levels

and we therefore do not know whether the decrease or increase in their level influenced mortality. Interestingly, a recent study by Miller and colleagues from the Mayo Clinic [20] showed that in a similar group of patients (190 NYHA class III-IV ambulatory patients), elevated BNP levels were associated with adverse outcome (death or cardiac transplantation), whereas subsequent changes in these levels did not. This observation is in conflict with several previous studies that used BNP levels as a guide to therapy (and demonstrated good results when BNP levels fell) but those studies mainly targeted inpatients. Moreover, there may be a difference between the long-term and short-term prognosis of heart failure patients in terms of their correlation with the BNP levels.

It should be noted that the patients in the highest NT-proBNP tertile group were less likely to be treated with renin-angiotensin-aldosterone system inhibitors (52% versus 83% and 85%). These differences were not included in the multivariate analysis. It is not clear why almost half of these patients did not receive optimal therapy. One would assume that this was due to hypotension, low cardiac output, or advanced renal failure with hyperkalemia often seen in such sick patients. A recent study by Jordain and team [21] described the efficacy of BNP-guided therapy of ambulatory CHF patients. BNP-guided patients were significantly less likely to reach the study endpoint (death or hospitalization for CHF). The authors of that study attributed this mainly to higher doses of beta-blockers and RAAS inhibitors in the BNP-guided group. Keeping this in mind, the suboptimal treatment of the patients with the highest NT-proBNP levels may be one of the main causes of the excess mortality. In all likelihood those are the patients who need the most intensive treatment.

In summary, natriuretic peptide has an important role in risk stratification in modern cardiology. Its usefulness in the ambulatory setting in patients with advanced CHF was demonstrated by Amir and co-authors [19]. Correctly interpreting the BNP levels in such patients can help the attending physician to provide better care, improve the quality of life and perhaps even prolong life. However, the cost-effectiveness of such an approach should be carefully evaluated.

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NYHA = New York Heart Association
RAAS = renin-angiotensin-aldosterone system

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