Brain Natriuretic Peptide Measurement in Acute Coronary Syndromes
Ready for Clinical Application?

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Brain (B-type) natriuretic peptide (BNP) is a 32 amino acid peptide that is synthesized and released predominantly from ventricular myocardium in response to myocyte stretch. Like atrial natriuretic peptide (ANP), BNP seems to have almost exclusively beneficial physiological properties, including balanced vasodilation, natriuresis, and inhibition of both the sympathetic nervous system and the renin-angiotensin-aldosterone axis. Attempts to exploit these properties for therapeutic benefit has led to the development of recombinant human BNP (nesiritide) for the acute treatment of decompensated heart failure, and also of novel compounds that inhibit neutral endopeptidase, an enzyme that is partially responsible for BNP degradation.

Measurement of BNP in Patients With Suspected Heart Failure

In patients with heart failure, the cardiac neurohormonal system is activated, and circulating plasma levels of ANP, BNP, and the N-terminal fragments of their prohormones (N-proANP and N-proBNP) are elevated. Compared with ANP and N-proANP, BNP and N-proBNP undergo a greater proportional rise in disease states (ie, higher “signal-to-noise” ratio), and thus have emerged as the preferred biomarkers for clinical development. With commercially available assays now available, measurement of BNP or N-proBNP can be integrated readily into the care of patients with suspected heart failure. Although data are limited, BNP and N-proBNP seem to provide qualitatively similar information, and for purposes of this editorial, will be referred to interchangeably.

Incorporation of BNP measurement into the clinical evaluation facilitates the diagnosis of heart failure due to either left ventricular (LV) systolic or diastolic dysfunction; a normal BNP level virtually rules out the diagnosis of decompensated heart failure, whereas a markedly elevated BNP has a high positive predictive value for heart failure. Although BNP levels are correlated with age, sex, intracardiac filling pressures, LV mass and ejection fraction (LVEF), renal function, and symptoms, BNP provides prognostic information in patients with heart failure that is independent of these variables. Recently, it has been appreciated that BNP levels may be useful as a target for specific heart failure therapies and as a convenient and safe alternative to invasive monitoring, although much work remains to be done in these important areas.

BNP in Acute Coronary Syndromes

After the description of BNP elevation in patients with chronic heart failure, several investigations focused on the clinical implications of neurohormonal activation after acute myocardial infarction (MI). BNP concentration rises rapidly over the first 24 hours after MI and then tends to stabilize; patients with a large infarct may have a second peak approximately 5 days later, perhaps reflecting the remodeling process. When measured 1 to 7 days after MI, BNP elevation identifies patients at risk for LV dysfunction, heart failure, and death. Here, as in chronic heart failure, the prognostic value of BNP seems to be greater than (but complimentary to) that of LVEF.

These initial studies of BNP in acute coronary syndromes (ACS) were small case-control studies, limited mostly to patients with ST-elevation MI, who are likely to have at least minor LV dysfunction. More recently, the prognostic application of BNP has been extended to include patients with unstable angina and non–ST-elevation MI (non–ST-elevation ACS). In a small case-control study of patients with non–ST-elevation ACS, Omland et al found that N-proBNP levels were higher among patients who died than those who survived. This pilot study was followed by a 2525 patient substudy of the Orbofibin in Patients with Unstable coronary Syndromes (OPUS)-TIMI 16 trial in which BNP was measured approximately 40 hours after symptom onset. Rates of death and heart failure through 10 months increased with higher baseline levels of BNP. This association was observed across the spectrum of ACS, including patients with ST-elevation MI, non–ST-elevation MI, and unstable angina, those with and without elevated troponin I, and those with and without clinical evidence of heart failure. In multivariate analyses, the association between BNP and mortality was independent of age, renal function, evidence of heart failure, ST deviation, troponin I, and C-reactive protein (CRP). More recently, in a consecutive series of patients with chest pain...
and no ST elevation on the presenting ECG, Jernberg et al.\textsuperscript{10} found that N-proBNP levels measured at admission were strongly associated with long-term mortality, again independent of ECG changes, troponin levels, and the index diagnosis (MI versus unstable angina).

In this issue of \textit{Circulation}, Omland et al.\textsuperscript{11} report findings from a cohort study in which N-proBNP levels were measured approximately 3 days after ACS and correlated with outcomes over an average follow-up period of more than 4 years. This study is important for several reasons. First, most previous studies demonstrating the prognostic value of BNP (or N-proBNP) in patients with non–ST-elevation ACS were substudies within randomized controlled trials and thus may have enrolled highly selected patients. More importantly, prior studies of BNP in non–ST-elevation ACS did not include routine measurement of LVEF, and concern has been raised that the association between BNP and mortality was confounded by LV dysfunction. In the present study, Omland et al.\textsuperscript{11} enrolled a heterogeneous, unselected patient population and performed routine echocardiography, thus directly addressing the primary limitations of prior analyses. After adjusting for potential confounders, including age, Killip Class, and LVEF, an N-proBNP level above the median remained associated with long-term mortality. These findings were essentially unchanged after further adjustment for troponin T. Furthermore, the results appeared similar in patients with ST-elevation MI, non–ST-elevation MI, and unstable angina, although the small sample size limits demonstration of statistical significance in each subgroup.\textsuperscript{11}

One variable not reported in the study by Omland et al.\textsuperscript{11} was LV mass. Because BNP levels are positively associated with LV mass, and LV hypertrophy (LVH) is associated with cardiovascular mortality, it is possible that unmeasured confounding from LVH may influence the present observations. The magnitude of risk associated with elevated BNP in this and other studies, however, is greater than would be expected if the effect were merely due to LVH.

**What Is the Source of BNP Elevation in ACS?**

BNP differs from other biomarkers used for risk-stratification in ACS, such as troponins and creatine kinase-MB, in that it is a counter-regulatory hormone that may play an active role in the response to ischemic injury. The level of BNP may reflect the size or severity of the ischemic insult, even when myocardial necrosis has not occurred. Several observations support this hypothesis. First, in experimental acute MI, BNP synthesis is augmented not only in infarcted tissue, but also in non-infarcted tissue.\textsuperscript{12} Second, BNP levels have been shown to increase transiently after uncomplicated percutaneous transluminal coronary angioplasty (PTCA), even when intracardiac filling pressures remain unchanged.\textsuperscript{13} Finally, BNP rises rapidly and transiently after exercise in patients with coronary disease, and the magnitude of BNP increase is proportional to the size of the ischemic territory.\textsuperscript{14} In aggregate, these findings suggest that transient ischemia increases wall stress and induces BNP synthesis and release in proportion to the degree of ischemic insult. Moreover, the rapid early rise in BNP levels after PTCA and exercise-induced ischemia suggests that release of stored BNP, as opposed to de novo synthesis, may be more important in the response to hemodynamic stress and ischemia than previously appreciated.

**Should We Measure BNP Routinely in Our Patients With Suspected ACS?**

The results of the important study from Omland et al.\textsuperscript{11} in this issue of \textit{Circulation} add to a rapidly growing body of literature demonstrating that BNP elevation is associated with an adverse prognosis, regardless of the cause of hemodynamic perturbation. For example, BNP elevation has been associated with adverse prognosis in cardiovascular conditions ranging from unstable angina to heart failure (due to either systolic or diastolic dysfunction); processes involving the right ventricle as diverse as primary pulmonary hypertension, cor pulmonale, arrhythmogenic RV dysplasia, and congenital heart disease; and even the general population.\textsuperscript{15}

Before a biomarker is measured routinely in clinical practice, several criteria should be met. First, rapid high-quality assays should be available at a reasonable cost. Second, the test should augment the diagnostic or prognostic value of currently available tools; and finally, the results should help to guide specific patient management decisions. Cardiac troponins T and I are examples of biomarkers that fulfill these criteria in patients with suspected ACS; they can be measured rapidly and accurately, can facilitate the diagnosis of acute MI, and can help to guide decisions with respect to the choice and intensity of antiplatelet, antithrombotic, and interventional strategies. Similarly, the 12-lead ECG helps to make the diagnosis of ischemia, provides important prognostic information, and directly guides therapeutic decisions. In patients with suspected heart failure, BNP (and N-proBNP) seem to fulfill most of these criteria, although more work remains to determine the optimal decision-limits for clinical interpretation, as well as the specific therapeutic implications of persistent BNP elevation.

In patients with suspected ACS, BNP and N-proBNP clearly add important and unique prognostic information, but to date we do not know how this information should be used to inform clinical decision-making. Because BNP levels are associated with LV dysfunction as well as the extent of coronary disease, one might presume that patients presenting with non–ST-elevation ACS and an elevated BNP level may derive incremental benefit from an early invasive management strategy, as has been demonstrated for troponin T and I. A preliminary report from the Treat angina with Aggrastat and determine Costs of Therapy with Invasive or Conservative Strategies (TACTICS)-TIMI 18 study, however, does not support this hypothesis. There was no difference in the benefit of the early invasive strategy between patients with and without BNP elevation.\textsuperscript{16}

Clinical investigation of BNP in general, and in particular its application in ACS, is still in its infancy. Whereas the prognostic association between BNP and subsequent heart failure and death is now clear, directed efforts are needed to address the therapeutic implications of BNP elevation. In addition, many other specific issues need to be resolved. For example, the optimal timing of measurement is not yet clear, although in studies performed to date the association between
BNP and mortality seems to be relatively independent of the timing of measurement. In addition, for clinical use, it will be helpful to define specific threshold value(s), but this may be complicated by the effects of age, sex, and assay characteristics on neurohormone levels. Finally, direct comparisons of BNP and N-proBNP are needed.

Conclusions
The report by Omland et al\textsuperscript{11} answers several critical questions and contributes to a consistent emerging message: in patients with ACS, BNP adds important prognostic information to clinical and laboratory variables, including ECG and echo findings, as well as levels of troponins and CRP. The magnitude of the risk relationship associated with BNP seems to be greater than that associated with most currently available markers. Clearly, BNP is telling us something that we did not previously know about factors associated with risk in patients with ACS. The consistent findings from Omland and others support the emerging concept that, along with a careful history and physical examination, the evaluation of a panel of several pathobiologically distinct biomarkers will provide an optimal assessment of risk in ACS.\textsuperscript{17}

References

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