BNP Testing in Heart Failure - One Fits All?

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In patients with cardiac dysfunction natriuretic hormones originating from the ventricles (B-type natriuretic peptide and N-terminal BNP) are abnormally elevated in the peripheral circulation reflecting the degree of ventricular jeopardy and foretelling adverse outcomes including sudden death. The potential to monitor the progression of left ventricular dysfunction non-invasively has led to the development of hormone assays for BNP and N-BNP which are now available for clinical use as screening tests in the outpatient center as well as in the invasive care setting at the bedside. These tests have opened exciting new avenues to improve the diagnostic progress, to select patients for further cardiac investigations and to identify the optimum time for surgical intervention. In addition, they have proved useful in guiding intensified medical treatment.

Key words: heart failure, BNP, N-BNP, prognosis, therapeutic implications

BNP secretion is directly regulated at the level of gene expression [8, 9]. The respective N-terminal portions, namely N-ANP (98 aminoacids in length) and N-BNP (76 aminoacids in length) are the residuums of the prohormone. These N-terminal hormone fragments are also degraded by NEP. Their half-lifes are about 1 hour and 1 to 2 hours, respectively [10]. Mechanical stretch of the atrial and ventricular myocytes due to volume overload and other factors is sensed by the heart and results in increased production of ANP and BNP [6, 11–14]. This process involves interaction of myocytes and non-myocytes [15]. Experimental data hint towards a predominant role of endothelin to mediate BNP expression [16].

Pathophysiology

Elevation of the circulating levels of the natriuretic peptides or the N-terminal portion of their prohormones occurs early in the course of ventricular dysfunction prior to the onset of symptoms [17–24]. This could be expected for hormones released in response to increasing transmural atrial and ventricular pressure [25]. They show a modest inverse correlation with LV ejection fraction on one side, but are also importantly influenced by the diastolic properties of the heart on the other [26]. Numerous studies have investigated the potential clinical use of natriuretic peptides for the diagnosis of ventricular dysfunction and it has been hypothesized that in the detection of heart disease, plasma BNP levels perform better than N-ANP levels, which perform better than ANP levels [17, 19, 20–22, 27]. In about 100 patients referred for cardiac catheterization measuring plasma BNP was the best test to detect systolic ventricular dysfunction defined as LVEF < 45 % or LV hypertrophy (> 120 g/m2) and also to identify impaired diastolic function either defined as impaired relaxation in echocardiography or an elevated LV enddiastolic pressure [20]. Due to this property BNP seemed to be an optimal candidate for diagnostic biochemical screening in individual patients. In an unselected population of more than 1000 outpatients BNP was superior to N-ANP in the diagnosis of LV systolic dysfunction (LVEF < 30 %) defined by echocardiography [28]. Also, plasma N-BNP level is a sensitive marker of cardiac impairment [9]. Findings of elevated N-BNP levels in patients with clinical heart failure and ejection fractions greater than 45 % indicated that N-BNP levels may be particularly sensitive to cardiac dysfunction associated with normal systolic properties [24].

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Influence of Renal Function

As natriuretic peptides and their N-terminal portions are cleared in part by the kidneys, plasma N-BNP levels are markedly increased in patients with renal failure [9]. Campbell has reported plasma levels of N-BNP in renal failure, after myocardial infarction and in patients with cardiorespiratory symptoms [24]. As expected, the highest N-BNP levels occurred in patients with combined renal and heart failure in the presence of a reduced ejection fraction followed by renal failure with preserved systolic function. Accordingly, natriuretic peptide levels should always be interpreted in conjunction with serum creatinine. An elevated plasma level associated with appropriate symptoms, and in the absence of renal failure, strongly suggests the presence of heart failure.

Prognostic Value of BNP and N-BNP Plasma Levels

Congestive heart failure represents a pathological state in which the activation of the natriuretic peptides exceeds those of all other states. Tsutamoto was the first to show that measuring circulating BNP concentrations in patients with chronic heart failure based on systolic dysfunction can be used to foretell prognosis [29]. He studied 85 patients, all with documented left ventricular systolic dysfunction and tracked their outcomes for more than one year, when 25 patients had died from cardiac causes. Use of ACE inhibitors and β-blockers was similar in all patients. As expected, patients in the negative outcome group had more symptoms at rest, lower ejection fraction, and higher heart rate and filling pressures at index evaluation. Norepinephrine, ANP and BNP plasma levels differed also significantly between outcome groups. In univariate analysis, BNP, NYHA-class, ANP, NE, PCWP, PAP, LVEF, RAP, age, and cGMP were all significantly related to mortality, whereas gender, heart rate, cardiac index, and blood pressure were not. Only BNP plasma levels and PCWP provided independent prognostic information, however. This study was a great progress in regard to the new option to use BNP measurements as prognostic markers in the clinical setting. The role of repetitive BNP levels, in particular as influenced by adjustments in therapy, remained unknown, however.

This issue was addressed in a substudy of a recently published clinical trial from our group [30, 31]. During this double-blind placebo-controlled trial of atenolol repetitive measurements of BNP, N-BNP and N-ANP plasma levels (and other neurohumoral factors) were performed to establish their relative prognostic significance. The original study was designed to evaluate treatment effects (with worsening heart failure or death as combined endpoint) after 2 years but stopped early because of a significant treatment benefit of atenolol at interim analysis. At entry the degree of left ventricular systolic dysfunction correlated significantly with the plasma levels of BNP, N-BNP and N-ANP (in descending order) confirming previous studies. After 4 years 31 patients (34%) had died, 21 patients randomised to placebo and 10 patients randomised to atenolol in the original study. Each plasma hormone level was substantially increased in non-survivors over survivors throughout (Fig. 1).

In survivors, LVEF increased after atenolol (from 18% to 30%) as well as after placebo (from 20% to 25%) accompanied by a decrease in N-BNP levels. In contrast, in non-survivors of the placebo group there was a striking 4-fold increase in plasma BNP levels. In multivariate analysis incorporating only variables obtained at entry (“one point analysis”) BNP predicted prognosis independently from LVEF and, importantly, independently from allocation to atenolol or placebo. With BNP in the model, N-BNP and N-ANP were not significantly related to mortality. Using a cutoff value of 50 fmol/ml BNP, mortality was significantly higher in 30 patients with higher BNP plasma levels than in 61 patients with lower N-BNP plasma levels (Fig. 1). However, the main aim of this study was to find out which marker could identify patients at highest risk during intensified treatment. Again, BNP (the last available level before death or up to 2 years) was the strongest predictive marker, but now also N-BNP was significantly related to mortality thus providing prognostic information independent from BNP. For use in clinical practice, a cutoff value of 300 fmol/ml N-BNP was chosen. 50 patients had lower N-BNP plasma levels, and of these 44 patients were still alive at closing. Among the remaining 41 patients with higher N-BNP levels 25 patients had died (Fig. 1).

A large body of evidence suggests that besides mechanical stimuli under physiologic conditions, ischemia, cell damage and necrosis of adjacent tissue may be involved to induce BNP gene expression in the myocardial texture. Electrophysiological instability is a key feature of such vulnerable cells and is postulated to favour the development of malignant arrhythmias in patients with heart failure. Therefore, it was hypothesized that BNP, produced in excess by the most affected regions, would reflect the hidden and insidious danger of sudden death. Indeed, in a data base study of 451 patients with heart failure with a wide range of left ventricular systolic dysfunction, the potency of plasma BNP levels to predict sudden death was confirmed [32].

Therapeutic Implications

The fact that the degree of BNP elevation in the peripheral circulation not only mirrors the degree of myocardial jeopardy and injury, but also foretells survival has important therapeutic implications. It is commonly understood that reduction of negative neurohumoral factors, such as angiotensin, norepinephrine and endothelin, plays a key role to mediate the survival benefits and ACE-inhibitors and β-blockers in the treatment of heart failure. However, BNP and N-BNP originating from the myocardium can mark the decline of ventricular function more directly than the previously used “extracardiac” vasoconstrictive factors. A new role is emerg-
The measurement of cardiac peptides in blood has shown promise over the last decade in clinical diagnosis and prognosis. Because heart failure is a major health problem worldwide, BNP is proposed as a biochemical marker that might provide a useful screening test to select patients for further cardiac investigations and to tailor therapy. Such a hormone assay is inexpensive and available. With further study, however, BNP-N-BNP and N-ANP may each open avenues for risk stratification in patients with ventricular disorders [41]. Yet, there is another side to the coin, too. The effects of BNP administration to humans would likely include vasodilation, renin aldosterone antagonism, effective diuresis, and natriuresis, all of which are potentially beneficial for patients with heart failure and acute decompensation. A recently completed study evaluated the clinical effect of BNP (nesiritide) in patients admitted with overt heart failure [42]. The results showed that most patients had significant improvement in their overall symptoms from the time of hospitalization. Whether these effects are durable and whether this type of therapy changes the natural history of decompensated heart failure are not known. Clearly, as a vasodilator this agent may point the way to new therapeutic strategies.

Summary

The measurement of cardiac peptides in blood has shown promise over the last decade in clinical diagnosis and prophylaxis. In the past decade in clinical diagnosis and prophylaxis, the measurement of cardiac peptides in blood has shown promise over the last decade in clinical diagnosis and prophylaxis. The measurement of cardiac peptides in blood has shown promise over the last decade in clinical diagnosis and prophylaxis. Therefore, plasma BNP or N-BNP concentrations provide a new approach to guide drug treatment in the clinical setting. In another dose ranging study [34] the change in BNP plasma levels during increasing doses of ACE inhibitors reflected benefit in functional capacity. At time of referral, patients with stable heart failure were receiving either 10 mg enalapril/d (16 patients), 20 mg enalapril/d (18 patients) or 40 mg enalapril/d (11 patients). This dosage was changed 3 times to treat all patients with lower, higher, and the initial dosages for 4 weeks each. After augmentation of enalapril to 40 mg/d, BNP decreased by average 62 pg/ml to average 18 pg/ml (p < 0.05) in the low dose group. The opposite changes were observed after reduction of enalapril to 10 mg/d in the normal dose group and in the high dose group. Within-patient comparison showed that BNP levels were higher (average 193 pg/ml) while patients were receiving 10 mg enalapril/d than when they were receiving 40 mg enalapril/d (average 152 pg/ml, p < 0.0005). It is tempting to speculate that the reduced BNP levels under the high dose of enalapril (and high enalaprilat trough levels ) in that study might indicate a better outcome during long-term therapy.

Also the haemodynamic effects of endothelin antagonists are accompanied by a decrease in BNP plasma levels [35]. Thus, plasma BNP or N-BNP concentrations provide a new approach to guide drug treatment in the clinical setting. In particular in cardiac patients the conventional tests for cardiac function take time and often do not correlate with symptomatic changes in the patient's conditions. In one study, significantly fewer cardiovascular events were recorded after N-BNP tailored heart failure therapy compared with conventional (clinically guided) treatment [36]. BNP has also drawn interest to its ability as an emergency hormone that responds immediately to ventricular overload matching the decompenated state of circulatory congestion [14, 37–39]. Therefore, bedside BNP testing is also currently used throughout hospitalization in assessing therapeutic responses and outcome of patients admitted with decompenated heart failure [40].

References:

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