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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. *J Clin Basic Cardiol 2003; 6: 15–8.*

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

"Is the heart a gland?" wondered Eugene Braunwald in 1960 while he quantified the norepinephrine content of the ventricles [1]. "The heart is a gland!" was the echo two decades later when DeBold [2] saw that intravenous injection of atrial myocardial extracts elicited a rapid and potent natriuretic response in rat experiments. Soon a family of "natriuretic factors" was identified with structurally similar but genetically distinct peptides that have vital actions in cardiovascular, renal, and endocrine homeostasis [3]. Natriuretic peptides derived from the heart have specific effects on renal haemodynamic and tubular function and on vasoactive hormones [4] including natriuresis, vasodilation, renin inhibition, and antimitogenesis. The genetic disruption of ANP production or knockout of the guanylyl-cyclase A receptor results in hypertension and ventricular hypertrophy suggesting a prominent role of ANP and BNP in normal circulatory function and structure [3].

Physiology

Atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP) are of myocardial cell origin and C-type natriuretic peptide (CNP) is of endothelial origin. BNP was originally named brain natriuretic peptide, because it was first detected in porcine brain [5]. The highest concentration of this peptide is found in the myocardium, however [6]. Common to ANP, BNP and CNP is a 17-amino acid ring structure with a disulfide bond between two cysteine residues which is essential for receptor binding. ANP and BNP bind to the natriuretic peptide A receptor, which, via 3',5'-cyclic guanosine monophosphate, mediates natriuresis, vasodilation, renin inhibition, antimitogenesis, and lusotropic properties [3]. CNP lacks natriuretic actions but possesses vasodilating and growth-inhibiting actions via the guanylyl cyclase-linked natriuretic peptide B-receptor [7]. All three peptides are cleared by the natriuretic peptide C-receptor and are degraded by the enzyme neutral endopeptidase, both of which are widely expressed in the kidneys, lungs, and the vascular wall. ANP has higher affinity to this enzyme than BNP and has a shorter half-life (3 minutes vs 20 minutes) ANP (28 aa) and BNP (32 aa) are derived from larger prohormones from which the C-terminals, representing the mature hormones, are cleaved. The precursor prohormone of each is encoded by a separate gene [3]. While the prohormone of ANP is stored in intracellular granules, 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/m^2) 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.

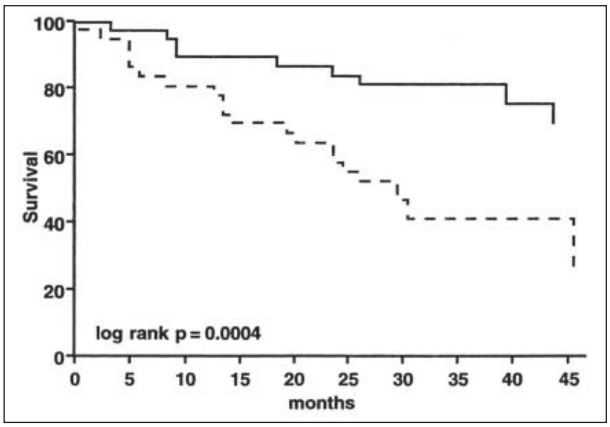

Figure 1. Kaplan-Meier analysis showing survival in 91 heart failure patients stratified into two groups according to ≥ 50 fmol/ml (n = 30, dashed line) and < 50 fmol/ml (n = 61, solid line) plasma B-type natriuretic peptide (BNP) levels at baseline. Mortality was significantly higher (log rank p < 0.0004) in patients with baseline BNP levels ≥ 50 fmol/ml (17 deaths) than in patients with BNP levels below this cut-off point (14 deaths). Reprinted from Stanek et al. [31] with kind permission from American College of Cardiology Foundation

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 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, ischaemia, 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 of 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-

ing for BNP and N-BNP as they may closely reflect any drug-induced change in cardiac filling pressures. Treatments that unload the ventricle and reduce both myocardial wall strain and oxygen requirements are expected to reduce the secretion of these cardiac hormones. Thus, BNP testing can be used to monitor the effect or failure of heart failure treatment. Indeed, several studies have documented that elevated circulating BNP concentrations can be substantially and chronically lowered by intensification of heart failure therapy.

In a randomized single-blind trial of 20 patients with mild to moderate heart failure [33] the clinical group received optimal empirical therapy with either captopril, enalapril, lisinopril, trandolapril, perindopril or quinapril. In the BNP group the dose of these ACE inhibitors was stepwise increased until plasma BNP fell below 50 pg/ml or maximum doses (captopril 300 mg/d, enalapril 40 mg/d, lisinopril 40 mg/d, trandolapril 4 mg/d, perindopril 8 mg/d, quinapril 80 mg/d) were reached. Average plasma BNP levels at baseline were 112 pg/ml in the BNP group and 139 pg/ml in the clinical group (n.s.). After 4 weeks of treatment, a greater fall in plasma BNP levels was noted in the BNP group than in the clinical group (–42 % vs. –12 %, $p < 0.05$). The study suggests that if ACE inhibitors are titrated high enough plasma BNP levels can be reduced toward a normal range (below 50 pg/ml). Titration of ACE inhibitors according to plasma BNP also resulted in a more favourable angiotensin-aldosterone profile than standard therapy.

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, $p < 0.005$). 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 decompensated 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 decompensated heart failure [40].

Summary

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 administered 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.

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