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NATRIURETIC PEPTIDES: PATHOPHYSIOLOGY IN HEART FAILURE AND CLINICAL IMPORTANCE: REVIEW

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Abstract

Cardiac biomarkers play an important role for diagnosis and provide better pathophysiological understanding of chronic heart failure. Natriuretic peptides, especially B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), were found to be useful in the diagnostic assessment and prognostic stratification of patients with chronic heart failure.

Natriuretic peptides concentrations are prognostic factors for mortality in patients with chronic heart failure, irrespective of diastolic functional classification. Admission values of all natriuretic peptides can be used to predict cardiac death and all-cause mortality. For clinical application it is suggested that careful interpretation of evaluated natriuretic peptides concentrations is needed in patients with both symptomatic and asymptomatic heart disease. BNP and NT-proBNP levels show change in response to therapies to manage stable chronic heart failure patients.

In acute heart failure, natriuretic peptides correlate with ventricular pressure and volume overload, as well as with New York Heart Association (NYHA) functional class. In patients presenting with acute and chronic dyspnea, other clinical signs of heart failure, early diastolic dysfunction pattern BNP and NT-proBNP concentrations correlate with left ventricular dimensions, echocardiographic indices of systolic and diastolic function.

According to ESC "Guidelines for the diagnosis and treatment of acute and chronic heart failure" (2008) B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) measurements were introduced as tools for diagnosis and management of heart failure.

Keywords: *natriuretic peptides, chronic heart failure, dyspnea, systolic and diastolic dysfunction, mortality.*

At present one of the basic pathophysiologic mechanisms contributing to the progression of chronic heart failure (CHF) is the neurohumoral overactivation. Compensatory activation of renin – angiotensin – aldosterone system, sympathoadrenal system and natriuretic peptides are directed to the decrease of pathologic changes in CHF.

Cardiac biomarkers play an important role for the diagnosis and provide better pathophysiological understanding of CHF. Natriuretic peptides, particularly B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP), were found to be useful in the diagnostic assessment and prognostic stratification of patients with CHF [*Lainscak M. et al., 2007*].

There is an increasing interest in the development of new biomarkers, and a great number of laboratory tests have recently been proposed [*Emdin M. et al., 2007; 2009*]

BNP is a member of a family of 4 human natriuretic peptides. The first was identified in 1981 and named atrial natriuretic peptide (ANP) [*Tsutamoto T., Horie M., 2004*]. ANP is a 28-amino acid polypeptide resulting from the N-terminal end of the prohormone pro-ANP. The source is largely in the cardiac atria, and ANP is quickly secreted in response to atrial stretching. Normal heart secret extremely small amounts of ANP, but elevated levels are found in patients with left ventricle (LV) hypertrophy and mitral valve disease.

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A closely related molecule was first identified in pig brains in 1988 and therefore named BNP [*Sudoh T. et al., 1990*]. However, BNP was subsequently discovered to be present in high concentrations in cardiac tissues, particularly the ventricles. Two additional natriuretic peptides, designated C-type natriuretic peptide (CNP) and dendroaspis natriuretic peptide (DNP), have also been described and are thought to act in the peripheral vasculature and the atria, respectively. High ventricular filling pressures stimulate the release of both ANP and BNP. Both peptides have diuretic, natriuretic, and antihypertensive effects by inhibiting the renin – angiotensin – aldosterone system. They also have systemic and renal sympathetic activity. Although ANP was identified first, concentrations of BNP in the myocardial tissue were higher than those of ANP. Therefore, BNP has been studied more intensely than ANP as a clinically useful marker of increased ventricular filling pressure.

Before its activation, BNP is stored as proBNP, in secretory granules in both ventricles and, to a lesser extent, in the atria. After proBNP is secreted in response to volume overload and resulting myocardial stretch, it is cleaved to a biologically inert N-terminal fragment NT-proBNP and the biologically active hormone BNP. Both fragments are secreted into the plasma in equimolar amounts. Both fragments, NT-proBNP and BNP, have been clinically evaluated for use in the management of CHF. As a laboratory specimen, NT-proBNP is more stable during storage than BNP. NT-proBNP samples are stable at room temperature for 72 hours *versus* less than 4 hours for BNP samples.

Similar to BNP, NT-proBNP is a promising marker in identifying LV systolic dysfunction. Although both assays are reliable and have good analytical performance, their diagnostic cut-off value is dynamic and population-dependent. The slightly wider detection range and the more stable structure of NT-proBNP compared to the BNP assay suggest that NT-proBNP could play an additional role in evaluation of patients with LV systolic dysfunction [*Vanderheyden M. et al., 2006*].

The increase of BNP in plasma may be observed at stages of development of several cardiovascular risk factors such as arterial hypertension, obesity, but the mechanism of this process remains unclear [*Dzau V. et al., 1991*].

German doctors C. Angermann and G. Ertl in their review drew the following conclusions:

In acute heart failure (HF), natriuretic peptides correlate with ventricular pressure and volume overload, as well as with NYHA functional class. They can, however, not reliably discriminate between heart failure due to reduced ejection fraction and heart failure with preserved systolic function.

A variety of noncardiac causes may also lead to moderate elevations of the markers (BNP plasma concentrations of 100-400 *pg/mL*).

In addition, normal marker levels may be observed in >20% of patients with long-term stable heart failure. Diuretics, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor antagonists, and spironolactone have been shown to decrease BNP and NT-proBNP in parallel with clinical and hemodynamic improvement. In patients hospitalized for decompensated heart failure, predischarge plasma BNP levels reflect the risk of future death and rehospitalization [*Angermann C., Ertl G., 2004*].

P. Faggiano and co-workers assessed BNP levels and echocardiography in patients admitted for severe HF: NYHA class III-IV [*Faggiano P. et al., 2009*]. BNP measurements were obtained: at admission, at discharge and at first ambulatory control, after optimization of medical therapy in those with discharge BNP level >250 *pg/mL*. End-points were death and hospital readmission during 6-month follow-up.

According to BNP levels 3 groups of patients were identified:

Group 1, in whom discharge BNP was high and persisted elevated despite aggressive medical therapy; at 6-month follow-up 72% died or were hospitalized for HF.

Group 2, in whom discharge BNP was high but decreased after medical therapy; death and HF-readmission were observed in 26% of the patients.

Group 3, in whom discharge BNP levels were <250 *pg/mL* and persisted below this value at first ambulatory control; death and HF-hospital readmission were observed only in 12% of patients.

These data suggest that 3 BNP measurements, at admission, at discharge and few weeks later can allow to identify HF patients who, despite a further potentiation of medical therapy, will present a worsening or even will die during the short-term follow-up.

The NT-proBNP plasma values may be modified in hepatic or renal failure, which can cause false high levels of hormone. Due to it only the determination of NT-pro BNP level is not enough for a correct diagnosis of CHF. Clinical symptoms and echocardiography are also necessary [*Sagnella G.,2000*]

M. Puschita and associates examined the patients admitted in the hospital during a two-year period [*Puschita M. et al., 2005*]. Every patient had a clinical examination (all of them had dyspnea), an echocardiography (the LV ejection fraction was measured) and the determination of NT-proBNP levels. The NT-proBNP levels were correlated with the diagnosis of the CHF. The minimum level of NT-proBNP at which CHF was diagnosed made 89.9 *pg/mL*. At levels above 125 *pg/mL* the probability of CHF diagnosis and severity of the NYHA class of CHF was six times higher than at lower levels of NT-proBNP. So, there is a link between the NT-proBNP plasma levels and the NYHA class of the CHF.

The purpose of systematic review [*Balion C. et al., 2006*] was to evaluate BNP and NT-proBNP to identify determinants, establish their diagnostic performance in HF patients, determine their predictive ability with respect to mortality and other cardiac endpoints, their value in monitoring HF treatment. Outcomes for prognosis were limited to mortality and specific cardiac events. There were 103 identified determinants, including age, gender, disease, treatment, as well as biochemical and physiological measures. Few studies reported independent associations, among which age, female gender, and creatinine levels, which were positively associated with BNP and NT-proBNP. B-type natriuretic peptides also added independent diagnostic information above traditional measures for HF. Both BNP and NT-proBNP were found to be independent predictors of mortality and other cardiac composite endpoints in patients with risk of coronary artery disease (CAD), diagnosed CAD, and diagnosed HF patients. Studies showed treatment reduced BNP and NT-proBNP, however, relationship to outcome was limited and not consistent. In all settings both BNP and NT-proBNP showed good diagnostic properties as a rule out test for HF. There was insufficient evidence to demonstrate that BNP and NT-proBNP levels show change in response to therapies to manage stable chronic HF patients.

Italian authors [*Masson S. et al., 2006*] used Cox multivariable regression models to evaluate the independent prognostic value for all-cause mortality, mortality and morbidity, and hospitalization for HF. NT-proBNP and BNP had similar relationships with age, left ventricular ejection fraction, and internal diameter and creatinine clearance. The natriuretic peptides BNP and NT-proBNP showed subtle differences in their relation to clinical characteristics and prognostic performance in a large population of patients with chronic and stable HF. They were the most powerful independent markers of outcome in HF.

C. Fonseca and co-workers [*Fonseca C. et al., 2004*] compared the ability of BNP and NT-proBNP to distinguish subjects with HF from healthy volunteers, as well as to differentiate between HF with left ventricular systolic dysfunction and HF with preserved systolic function. Both peptides had an excellent ability to distinguish HF from non-HF subjects. NT-proBNP was more sensitive and specific. NT-proBNP is a simple, highly effective diagnostic test for HF.

American doctor R. Christenson in his review used information on application of BNP and NT-proBNP in critically ill patients being treated in intensive care [*Christenson R., 2008*]. The biomarkers were of sensitivity and modest use for diagnosis of acute lung injury in unselected intensive care patients and for diagnosis of HF in trauma patients. BNP and NT-proBNP were found to have a significant ability to prognosticate adverse outcomes in critically ill patients. A single paper examined the use of BNP as a non-invasive replacement for pulmonary capillary wedge pressure, found mild value. The impact of renal insufficiency on the markers was noted as a confounder in most studies. In the secondary searches, some preliminary data suggested a pos-

sible role for the natriuretic peptides in exclusion of a cardiac cause for certain conditions among intensive care unit (ICU) patients. However, the general findings were that the performance of BNP and NT-proBNP is unimpressive among ICU patients. Thus, utilization of BNP and NT-proBNP does not appear to provide much useful information or have a substantial role in care of critically ill patients in intensive care.

Similar conclusion was drawn by B. Meyer and co-authors [*Meyer B. et al., 2007*].

C. Kragelund and co-workers assessed the relationship between N-terminal pro-BNP (NT-pro-BNP) levels and long-term mortality from all causes in a large cohort of patients with stable coronary heart disease [*Kragelund C. et al., 2005*]. NT-pro-BNP was measured in baseline serum samples from patients referred for angiography because of symptoms or signs of coronary heart disease. The rate of death from all causes was determined after a median follow-up of nine years. At follow-up, approximately 20% of patients died. The median NT-pro-BNP level was significantly lower among patients who survived than among those who died. Thus, NT-pro-BNP is a marker of long-term mortality in patients with stable coronary disease and provides prognostic information above and beyond that provided by conventional cardiovascular risk factors and the degree of left ventricular systolic dysfunction.

American authors in their review presented data about the usage of NT-proBNP and BNP in a variety of clinical scenarios [*McCullough P. et al., 2003*]. In general, a BNP level less than 100 *pg/mL* has strong negative predictive value for CHF. BNP levels can be used to assess the effect of short-term treatment in acutely decompensated CHF. BNP has been shown to be a reliable and independent predictor of sudden cardiac death. In the absence of renal dysfunction, NT-proBNP has also been shown to be of diagnostic value in CHF, related to CHF severity, predictive of sudden death, and prognostic for death in acute coronary syndrome.

G. Moe analyzed BNP role in HF [*Moe G., 2006*]. When used in the appropriate clinical settings, BNP or NT-proBNP testing is extremely useful in establishing diagnosis and predicting prognosis in HF. Nesiritide (recombinant human BNP) holds promise in the management of patients with acute decompensated HF. Large-scale randomized controlled trials to evaluate BNP/NT-proBNP-guided therapy are currently in progress and studies of the impact of exogenous BNP on clinical outcomes in HF are likely to be forthcoming.

W. Miller and associates studied 172 NYHA class III-IV outpatients [*Miller W. et al., 2009*]. Primary endpoints were death/heart transplantation or HF hospitalization. Risk reduction for HF hospitalization was demonstrated only for BNP decreases of >80% from the initial level. BNP level increase more than the cutpoint of 500 *ng/L* was associated with increased risk of events, whereas further increase did not add to risk. In contrast, only substantial natriuretic peptide decreases (>80%) reduced the risk. These data suggest that only robust decreases in natriuretic peptide concentrations should be targeted to reduce mortality and heart failure-related hospitalizations.

J. Doust performed the systematic review of studies assessing BNP for prognosis in patients with HF or asymptomatic patients [*Doust J. et al., 2005*]. In HF patients, each 100 *pg/mL* increase was associated with a 35% increase in the relative risk of death. BNP level in plasma was used in 35 multivariable models of prognosis. In nine of the models, it was the only variable to reach significance, other variables contained no prognostic information beyond that of BNP. The results of the studies in this review show that BNP is a strong prognostic indicator for both asymptomatic patients and for patients with HF at all stages of disease.

Monitoring BNP or NT-proBNP enabled identification of asymptomatic patients at risk for the development of HF. But NT-proBNP showed better accuracy than BNP for identifying mild HF [*Al-Meslmani B. et al., 2007; Emdin M. et al., 2007*].

The aim of another study was to assess the predictive value of the cardiac hormone BNP for long-term outcome in a large cohort of stable angina patients [*Schnabel R. et al., 2006*]. Data

of this large group of CAD patients provide independent evidence that BNP is a strong predictor of cardiovascular risk in patients with stable angina independent of left ventricular systolic performance and known risk factors.

At present, the measurement of natriuretic peptides is largely an addition in the diagnosis of acute HF, as long as possible errors in interpretation are taken into account [*Rottlaender D. et. al., 2009*]. Admission values of all natriuretic peptides can be used to predict cardiac death and all-cause mortality. A preliminary comparison suggests that discharge values of NT-proBNP have the greatest diagnostic yield for predicting these end points [*Waldo S. et al., 2008*].

U. Alehagen and U. Dahlström in their study assessed the follow-up of patients with symptoms of HF during 10 years [*Alehagen U., Dahlström U., 2009*]. High plasma concentration of NT-proBNP predicted almost four times increased risk of cardiovascular mortality up to 10 years. Impaired cardiac function according to echocardiography, and reduced functional capacity as well as diabetes all had influence on risk of cardiovascular mortality up to 10 years. Plasma concentrations of BNP and N-terminal proBNP give important prognostic information concerning the risk of cardiovascular mortality among elderly patients. BNP and N-terminal proBNP were essentially equally useful as prognostic markers in this group of HF patients [*Alehagen U. et al., 2005*].

The combined analysis of cystatin C and NT-proBNP could provide important prognostic information also among elderly patients with symptoms of HF [*Alehagen U. et al., 2009*] aimed to evaluate, whether a combination of two biomarkers might give better prognostic information about the risk of cardiovascular (CV) mortality in patients with symptoms associated with HF compared with only one biomarker. All patients were evaluated using Doppler echocardiography and blood samples, including measurement of cystatin C and NT-proBNP. The patients were followed over a 10-year period. Patients with highest serum cystatin C levels had almost three times more the risk of CV mortality compared with those patients who had low levels. At the same time, if the patient had a highest plasma concentration of NT-proBNP, the risk increased to >13 times during the 10-year follow-up or >17 times after 5 years of follow-up.

The opposite opinion about the value of BNP or NT-proBNP for CHF diagnosis and especially for follow-up and treatment optimization of individuals was also stated [*Bruins S. et al., 2004; O'Hanlon R. et al., 2007*; *Balion C. et al., 2008*].

Short-term therapeutic studies of inpatients have largely resulted in a statistically significant decline in BNP and NT-proBNP with clinical evidence of patient improvements. In contrast, many therapeutic studies involving long-term outpatient monitoring have produced changes in BNP/NT-proBNP that do not exceed the biologic variances [*Wu A., 2006*].

Turkish authors in their study assessed the association of NT-proBNP levels with functional capacity and stage of HF failure in patients with CHF [*Karabulut A. et al., 2005*]. Also, they particularly focused on the presence and significance of neurohormonal activation in the group of patients classified as stage-A according to ACC/AHA guidelines. The New York Heart Association (NYHA) classification system (I, II, III, IV) was used to define the functional capacity; and the stage of the HF was based on the ACC/AHA guidelines (A, B, C, D). Healthy female participants had higher NT-proBNP levels compared to their male counterparts. The severity of CHF can be objectively assessed by measuring the circulating levels of NT-proBNP. Results of their study were the following: even in NYHA I and stage A disease, NT-proBNP levels are higher compared to controls. NT-proBNP can provide objective information regarding the severity of the disease and also aid in treatment decisions in patients with CHF.

B. Al-Meslmani and co-authors compared plasma N-terminal-probrain natriuretic peptide (NT-proBNP) levels with echocardiographic data in patients with systolic HF [*Al-Meslmani B et al., 2005*]. The results were: the left ventricle releases B-type natriuretic peptide in response to volume or pressure overload, its high level reflects the poor cardiac systolic function, which corresponds the echocardiographic data.

The purpose of a study performed by C. Sirithunyanont and co-authors was to determine the

sensitivity and specificity of N-terminal part of brain natriuretic peptide plasma level in the diagnosis of HF in patients who presented with dyspnea [*Sirithunyanont C. et al., 2003*]. The cardiovascular cause of dyspnea such as pulmonary emboli and poor left ventricular ejection fraction (LVEF) were excluded. Plasma level of NT-proBNP increased significantly with increasing NYHA functional class. There was no significant difference of plasma NT-proBNP levels in patients with ischemic and those with non-ischemic cardiomyopathy. Plasma NT-proBNP was associated with neck vein distension, paroxysmal nocturnal dyspnea, rales, cardiomegaly, acute pulmonary edema, serum sodium, ejection fraction and subsequent hospital death. So measurement of plasma NT-proBNP proved to be a useful diagnostic test in differentiating HF from other causes in patients who presented with dyspnea.

Initial natriuretic peptides levels in emergency department may identify the risk of death or readmission within 30 days [*Maisel A. et al., 2008*]. Patients with a BNP at presentation >1730 *pg/mL* had an in-hospital mortality rate that was more than three-times that of patients with BNP levels <430 *pg/mL* NT-proBNP levels in the emergency department >1000 *pg/mL* are assosiated with severe HF and an adverse diagnosis. The "grey zone" (BNP values between 100 and 400 *pg/mL*) needs extra physician attention and ancillary testing. While the final diagnosis is often mild to moderate HF, other causes of high natriuretic peptides levels should be considered. This includes non-cardiac pathology that causes myocardial stress, pulmonary hypertension and RV dysfunction secondary to pulmonary embolism, acute coronary syndrome, atrial fibrillation or chronic obstructive pulmonary disease with *cor pulmonale*. Patients with pneumonia and renal failure also have increases in natriuretic peptides levels. Natriuretic peptides levels are commonly reduced by treatment with diuretics, ACE inhibitors, angiotensin receptor blockers, aldosterone antagonists, and cardiac resynchronization therapy. Beta-blockers may increase natriuretic peptides levels in the first week or month after administration but after 6-12 months may cause natriuretic peptides levels to fall. BNP and NT-proBNP levels are lower in obese persons. Natriuretic peptides testing might be appropriate for screening large asymptomatic populations for left ventricular systolic dysfunction either at low or high risk (post myocardial infarction patients, diabetic patients, poorly controlled hypertension, people aged above 70 years) with echocardiographic assessment of patients with high levels. The results of studies presented at the European Congress of Cardiology (2007) led to the consensus of following diagnostic points regarding BNP role in diastolic dysfunction of the left ventricle:

1. In patients with decompensated CHF and preserved LV ejection fraction BNP level may be high, but not exceeding the levels typical for systolic dysfunction (400-800 *pg/mL*);
2. BNP level cannot be applied as a differential diagnostic marker between systolic and diastolic dysfunction;
3. In cases of outpatient monitoring of patients, levels of BNP below 20-40 *pg/mL* may rule out diastolic HF;
4. Caution should be provided in CHF with preserved ejection fraction and BNP below 40 *pg/mL* [*Maisel A., Kamjada M., 2007*].

According to ESC "Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008" B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) measurements were introduced as tools for diagnosis and management of HF. At BNP level less than 100 *pg/mL* or NT- pro BNP less than 400 *pg/mL* the diagnosis of HF is unlikely, with BNP 100-400 *pg/mL* or NT- pro BNP 400-2000 *pg/mL* the diagnosis of HF is uncertain. Upon BNP above 400 *pg/mL* or NT- pro BNP more than 2000 *pg/mL* CHF is likely.

The review of literature shows that in patients presenting with acute or chronic dyspnea, other clinical signs of HF, early diastolic dysfunction pattern BNP and NT-proBNP concentrations correlate with left ventricular dimensions, echocardiographic indices of systolic and diastolic function.

It may be concluded that natriuretic peptides concentrations represent a continuum of severity of structural and functional HD. Natriuretic

peptides concentrations are strong prognostic factors for mortality in patients with CHF, irrespective of diastolic functional classification. For clinical application it is suggested that careful interpretation of evaluated natriuretic peptides concentrations is needed in patients with both symptomatic and asymptomatic heart disease.

It is very encouraging to see that only a few years after introduction into clinical practice, all major cardiovascular guidelines recommend the use of natriuretic peptides levels for the diagnosis, prognosis and monitoring of treatment in patients with HF.

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