Natriuretic peptides- physiology, pathophysiology and clinical use in heart failure

Short title: Natriuretic peptides in heart failure

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Summary

The natriuretic peptides– atrial, brain and C-type- were discovered during the last twenty years. Their effects on cardiovascular, renal, cerebral and other tissues through guanylyl cyclase were uncovered. Over the past decade natriuretic peptides (NPs) became a very useful tool in the management of heart failure patients. Results of many clinical trials have shown that BNP and NT-proBNP are helpful for diagnosis of heart failure. They are also independent markers of prognosis, not only in heart failure patients, but also in patients with other cardiovascular diseases. Recently published data document the utility of NPs in guiding of heart failure patients treatment. In this article, we focus on basic biochemical and physiological characteristics of NPs as well as on their significance in heart failure patients management. Some limitations and pitfalls of NPs levels interpretation in diagnosing heart failure are also discussed.

Key words: heart failure diagnosis, heart failure treatment, natriuretic peptides, BNP, NT-proBNP, OPTIMA Study

Introduction

Incidence of heart failure (HF) is steadily increasing over the past several decades, partly due to the population aging and improved survival of patients with cardiovascular diseases (Ho *et al.* 1993). The clinical assessment of HF is notoriously difficult, especially in daily clinical practice of primary physicians (GP's) with an abundance of both, the false positive and false negative diagnosis. The diagnosis of HF has remained fundamentally unchanged over the past several decades and has been based on the clinical history, physical examination, chest x-ray, and the assessment of left ventricular function, most often using echocardiography. Together with other neurohormonal responses in HF, increased synthesis and release of cardiac natriuretic peptides (NPs) depending on severity of cardiac dysfunction was observed (McCullough *et al.* 2002; Januzzi *et al.* 2006). With regard to this evidence, brain natriuretic peptide (BNP) and its aminoterminal propeptide (NT-proBNP) became valuable biomarkers for HF diagnosis in clinical practice. They are sensitive and specific enough for the disease process, and their measurement is rapid and at a reasonable cost (Collinson *et al.* 2004). Abundant observational data confirm the diagnostic and prognostic power of NPs in acute and chronic HF (Maisel *et al.* 2002; McCullough *et al.* 2002; Anand *et al.* 2003; Bettencourt *et al.* 2004; Gustafsson *et al.* 2005; Januzzi *et al.* 2006). However, there is very little information available concerning the utility of NP measurements in therapeutic decision making. Meanwhile, the treatment of heart failure patients is usually guided by their clinical status.

The aim of this article is to review information concerning basic physiological characteristics of NPs and the role of plasma BNP and NT-proBNP concentrations measurement in the management of HF.

Biochemical characteristics and physiological effects of natriuretic peptides

The natriuretic peptides family contains three major polypeptides - atrial (ANP), brain (BNP) and C-type (CNP). They all have a typical 17 amino-acid ring residue structure formed by an intramolecular disulfide bridge and they all also exist as a pro-hormone which is further cleaved into N-terminal peptide and C-terminal active hormone (Nakao *et al.* 1992) (Fig. 1). A separate natriuretic peptide created from ANP pro-hormone and called urodilatin is released from distal tubular cells (Carstens *et*

al. 2007). Three natriuretic peptide receptors have been detected (NPR-A, NPR-B, NPR-C). NPR-A and NPR-B are guanylyl cyclase receptors with cyclic guanosin monophosphate as the second messenger which mediate all known effects of NPs. On the contrary, NPR-C has a clearance function due to the mechanism of receptor-mediated endocytosis and subsequent lysosomal hydrolysis. Together with renal excretion and plasma neutral endopeptidase NPR-C participates in the removal of NPs from circulation (Nakao *et al.* 1992; Kone 2001). All natriuretic peptide receptors are presented in cardiovascular, renal, cerebral, bone and other tissues (Maack 2006).

ANP, the first known NP discovered in 1981 by Adolpho de Bold, consists of 28 amino acids and is produced by cardiac atrial cells (de Bold *et al.* 1981; Levin *et al.* 1998). On the other hand, BNP formed by 32 amino acids, which was firstly purified from brain, is produced predominantly by cardiac ventricular myocardium, much less by atrial myocardium. Synthesis and secretion of both peptides is stimulated by increased cardiac wall stress during volume and/or pressure overload. Their bond to NPR-A results in diuresis, natriuresis, vasodilatation and renin-angiotensin-aldosteron system (RAAS) inhibition. This mechanism consequently leads to blood pressure lowering (Levin *et al.* 1998). The antiproliferative effect of the peptides on cardiac and vascular myocyte growth is also well known. NPR-A knock-out mice exhibit hypertension, cardiac hypertrophy and fibrosis (Vanderheyden *et al.* 2004; Maack 2006).

CNP, consisting of 22 amino acids, is expressed in the central nervous system, vascular tissues and bones (Sudoh *et al.* 1990). It binds preferentially to NPR-B. CNP has an important local paracrine and autocrine role in ossification process, vasoreactivity, vascular smooth muscle proliferation, endotelial cell migration and it possibly acts as a neurotransmitter (Kone 2001; Vanderheyden *et al.* 2004). The clinical utilization of CNP in HF management hasn´t yet been studied.

Diagnostic and prognostic use of natriuretic peptides

Although a huge progress has been made in the treatment of heart failure, the prognosis of the disease remains poor. Early and appropriate diagnosis is very important, particularly at an emergency department (ED). Unfortunately, the signs and symptoms of HF are not specific enough, especially in the elderly, obese patients with respiratory diseases and physical deconditioning. Over the last 10 years, evidence has emerged that the levels of NPs are considerably higher in patients with HF and

correlate closely with the functional status of the patients expressed by the New York Heart Association (NYHA) class (Fig. 2) (Maisel *et al.* 2002).

Multiple studies established the additive value of BNP and NT-proBNP to history, clinical examination and chest X-ray for facilitating the diagnosis of HF in patients presenting with dyspnoea at an ED (Maisel *et al.* 2002; McCullough *et al.* 2002; Januzzi *et al.* 2006). The prospective multinational Breathing Not Properly study, which included 1586 patients who were referred to an ED with acute dyspnoea showed that BNP level <100 pg/ml for itself excluded the diagnosis of HF with a sensitivity of 90% and together with clinical judgement made the evaluation of acute dyspnoea more accurate (McCullough *et al.* 2002). Similar multinational study with NT-proBNP was also performed. The cut-point level of 300 pg/ml for exclusion of acute HF was established (Januzzi *et al.* 2006).

The increased levels of both, BNP and NT-proBNP correlate well with impaired LV ejection fraction (Gustafsson *et al.* 2005) and could be also used for detection of an asymptomatic LV systolic dysfunction. NT-proBNP seems to be more sensitive for this purpose (Costello-Boerrigter *et al.* 2006).

The NPs also reflect the actual haemodynamic status of the patients in agreement with haemodynamic parameters such as pulmonary capillary wedge pressure (Kazanegra *et al.* 2001) and left-ventricular end-diastolic pressure (Richards *et al.* 1993).

Diastolic dysfunction, which is a common cause of HF in the elderly, is also associated with elevated BNP values, although these values are not as high as in patients with systolic dysfunction. Together with diastolic abnormalities on echocardiography, BNP might help to asses the diagnosis of diastolic HF (Lubien *et al.* 2002).

Natriuretic peptides could be used not only to determine the diagnosis of HF, but also for assessing the patient's prognosis. The retrospective analysis of Valsartan in Heart Failure Trial (VaL-HefT) including patients with moderate to severe HF revealed significant increase in the relative risk of mortality and morbidity throughout each quartile (<41 pg/ml, 41-97 pg/ml, 97-238 pg/ml, >238 pg/ml) of BNP levels (Anand *et al.* 2003). The results of the COPERNICUS NT-proBNP substudy evaluated NT-proBNP for prediction of all cause mortality in patients with severe heart failure due to ischemic or non-ischemic cardiomyopathy. Concentrations under 199 pg/ml and over 504 pg/ml were connected with one-year mortality rates 3.9% and 27.9%, respectively (Hartmann *et al.* 2004).

Bettencourt *et al.* 2004 reported that the prognosis of patients with > 30% decrease in NT-proBNP concentrations during the hospitalization for heart failure worsening was significantly better than that of

patients with no significant change or even an increase in NT-proBNP concentrations, suggesting that these patients really improved during hospitalization.

Limitations and pitfalls of natriuretic peptide values interpretation

In addition to cardiac dysfunction, plasma concentrations of BNP and NT-proBNP are affected by many physiological and pathophysiological factors with different impacts on the evaluation of HF.

Age and gender: plasma levels of NPs tend to be higher in women and older patients with or without cardiac dysfunction (Redfield *et al.* 2002; Gustafsson *et al.* 2005; Hogenhuis *et al.* 2005). The increase in elderly could be explained by the loss of clearance receptors with aging (Kawai *et al.* 2004). The fact that hormone replacement therapy was associated with higher BNP levels shows a possible relationship between estrogen status and BNP concentrations (Redfield *et al.* 2002). For this reasons age and gender- modified cut-points were recommended for routine interpretation of NP values in HF diagnosis (Redfield *et al.* 2002).

Obesity: is a well-known risk factor for the coronary artery disease and HF. Wang *et al.* 2004 published an inverse relationship between BNP and body mass index. The feasible mechanism is abundant clearance receptors expressed on adipocytes which participate in the removal of NPs from circulation inducing salt and water retention (Wang *et al.* 2004).

Renal dysfunction: recent studies have shown that BNP and NT-proBNP correlate with renal function. Decreased glomerular filtration rate can markedly influence the cut-points for the HF diagnosis. To help preserve the predictive power of BNP, a cut point of 200 pg/ml for estimated glomerular filtration rate (GFR) <60ml/min was recommended (McCullough *et al.* 2003). As a result of its solely renal excretion, NT-proBNP is probably more sensitive to renal dysfunction than BNP (Anwaruddin *et al.* 2006). Using the cut-point of 1200 pg/ml for those with GFR <60ml/min preserves the diagnostic value of NT-proBNP in patients with suspected HF (Anwaruddin *et al.* 2006).

NP levels are also increased by early myocardial ischemia in **acute coronary syndromes**, especially without ST elevation (Ogawa *et al.* 2006), **hypertension** particularly accompanied by left ventricular hypertrophy (Jakubik *et al.* 2006) and **atrial fibrillation** (Corell *et al.* 2007). However, NP release in such situations is more modest than in HF and there is a considerable overlap between healthy and ill subjects.

Use of BNP assessment for management of heart failure therapy

As was mentioned above, NPs are strong predictors of cardiovascular morbidity and mortality. Several studies documented beneficial effect of heart failure pharmacotherapy on lowering NP plasma concentrations. Such benefit was accomplished with angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor antagonists, spironolacton and diuretics (Murdoch *et al.* 1999; Troughton *et al.* 2000; Tsutamoto *et al.* 2001; Anand *et al.* 2003). The effects of betablockers on BNP concentrations are more complex. When implemented to the therapy, betablockade slightly increases NP levels by the inhibition of adrenergic stimulation (Sanderson *et al.* 1995). Nevertheless, during long-term therapy NP levels are reduced in parallel with the LVEF improvement. This is observed especially with vasodilating betablockers (Sanderson *et al.* 1995; Richards *et al.* 1999).

The correlation between the drop of BNP level and improvement of patient`s symptoms during the hospitalization suggests that adjustment of anti heart failure therapy guided by serial measurements of NP in conjunction with other features of history and physical examination may offer improved outcomes (Silver *et al.* 2004). Murdoch et al. reported that titration of vasodilator therapy in patients with mild to moderate HF according to plasma BNP was associated with a more profound inhibition of the RAAS and a significant fall in heart rate when compared with empiric therapy (Murdoch *et al.* 1999).

Troughton *et al.* 2000 randomized 69 patients with symptomatic HF and LVEF <40% to NT-proBNP guided treatment with the goal of reaching values below 200 pg/ml vs. clinically guided therapy. The patients were treated with diuretics, ACEi with or without digoxin. If the target values of NT-proBNP were not met, then doses of drugs were augmented. After 6 months, patients receiving NT-proBNP guided treatment had lower NT-proBNP levels along with reduced total number of cardiovascular events (death, hospitalization and new episodes of decompensated HF). This trial had potential limitation in the low rate of betablockers, angiotensin-receptor blockers and spironolactone use, but it encouraged other investigators to proceed with further studies with BNP and NT-proBNP guided therapy of HF.

Results of the STARS-BNP multicenter study were reported recently. A total number of 220 patients with chronic HF and functional class NYHA II-III was randomized to medical treatment according to

either current guidelines or with the goal of decreasing BNP plasma levels below 100 pg/ml (BNP group). After 15 months of treatment significantly fewer patients reached the combined clinical end-point (hospitalization for HF or death related to HF) in the BNP guided group (Jourdain *et al.* 2007). To prove this hypothesis we designed the OPTIMA Study (OPTIMAlization of heart failure treatment guided by plasma BNP levels). Our preliminary results show a trend to lower incidence of major cardiovascular events (cardiovascular deaths and HF hospitalizations) in patients whose treatment was guided by BNP plasma concentrations compared to patients treated by clinical status only (fig. 3) (Krupicka *et al.* 2007).

Conclusion

Natriuretic peptides are synthesised and released by myocardium in response to increased cardiac wall stress. Their major physiological effects are natriuresis, diuresis and vasodilation. Plasma levels of NPs increase early in congestive heart failure, to lesser degree also in other clinical situations, e.g. acute coronary syndroms and pulmonary embolism.

According to results of many clinical trials, NPs become valuable tools for diagnosing HF. In patients presenting to an ED with acute dyspnoea high plasma levels of NPs support diagnosis of decompensated HF while normal concentrations almost exclude this diagnosis. Plasma levels of NPs are also independant predictors of prognosis. They are related to both, cardiovascular morbidity and mortality.

Several clinical studies indicate that treatment of HF guided by BNP and NT-proBNP levels could improve clinical outcomes. There are several ongoing trials to prove this hypothesis.

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Table 1. Natriuretic peptides BNP and NT-proBNP in diagnosis of heart failure

	BNP	**NT-proBNP**
Half-life	20 minutes	120 minutes
Major clearance mechanism	Natriuretic peptide receptors	Renal clearance
Cut points for HF diagnosis	100 pg/ml	300 pg/ml
- in patients with GFR <60ml/min./1.73m2	200 pg/ml	1200 pg/ml

HF= heart failure; GMR= glomerular filtration rate.

Figure 1. Chemical structure of natriuretic peptides. Identical aminoacid sequence is marked grey.

ANP= atrial natriuretic peptide; BNP= brain natriuretic peptide.

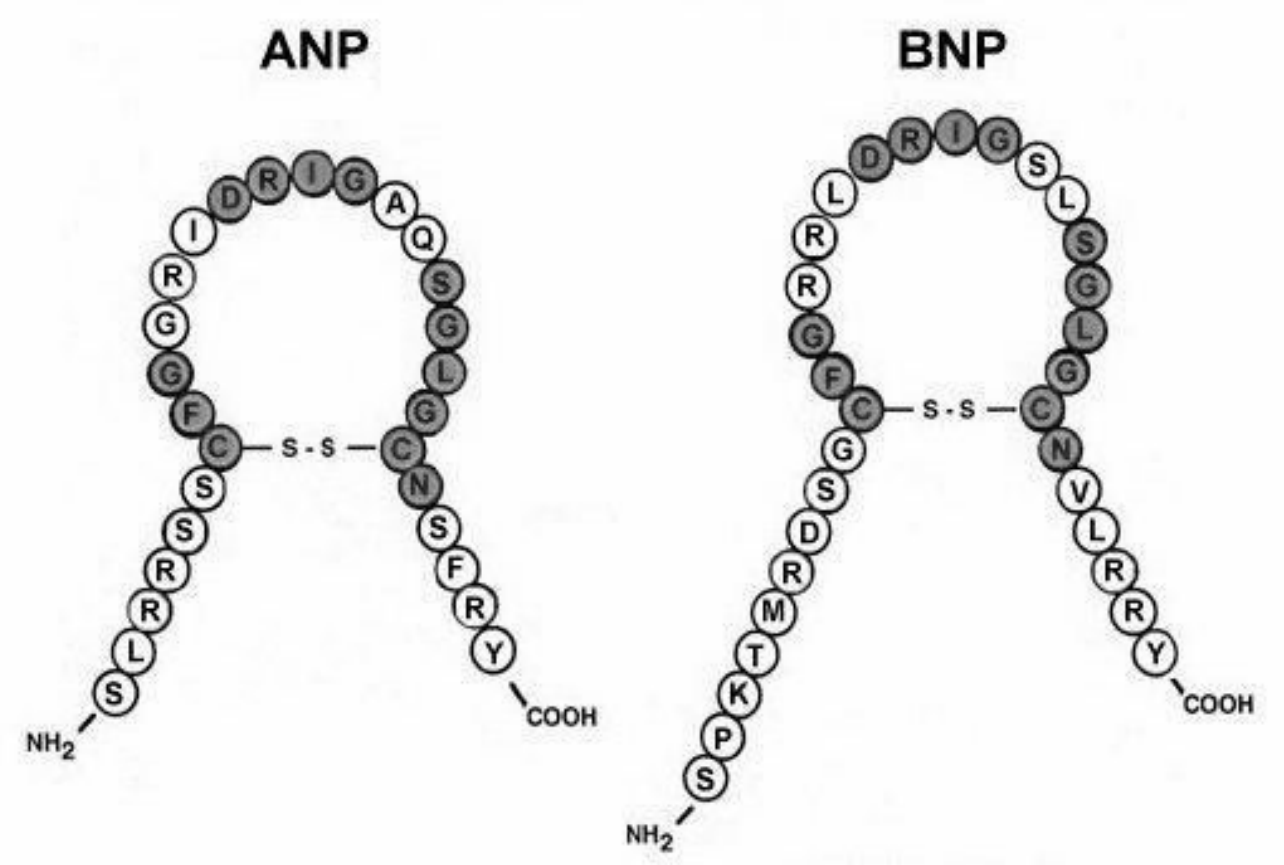

Figure 2. Median plasma levels of brain natriuretic peptide (BNP) in patients with heart failure according to their functional class (P<0,001). Freely adapted from reference 10.

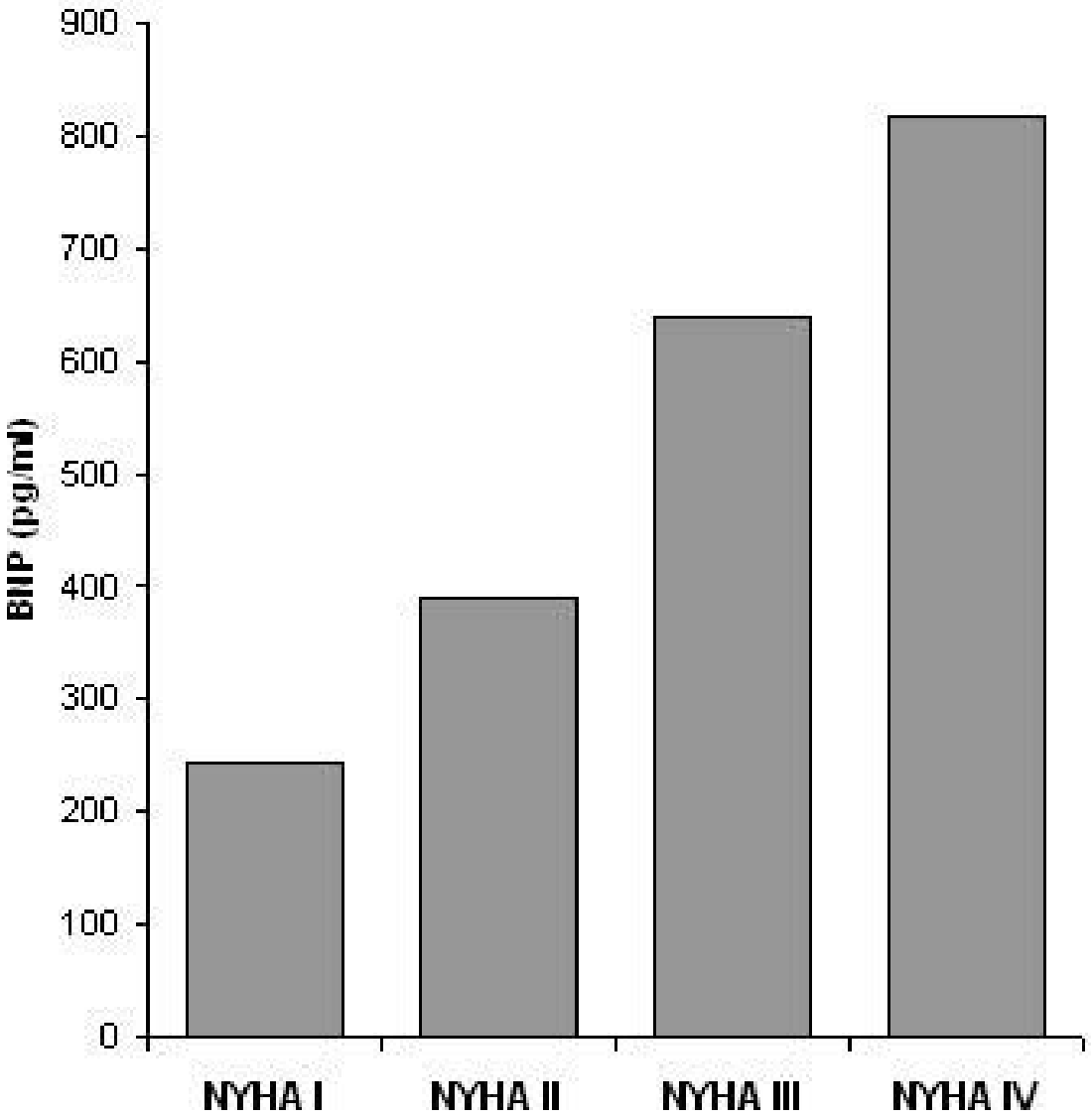

Figure 3. Preliminary results of the OPTIMA Study: Composite primary endpoint - deaths, heart failure hospitalizations, and outpatient episodes of heart failure worsening in both, the BNP group and the Clinical group during one-year follow-up. Because of small number of both, the patients and the events no statistical analysis was performed.