Review Article — Special issue: Heart Failure

Natriuretic peptides in heart failure

Jan Krupicka*, Tomas Janota, Jaromir Hradec

Third Department of Internal Medicine, First School of Medicine and General University Hospital, Charles University in Prague, 128 08 Prague 2, Czech Republic

Abstract

The worldwide incidence of heart failure is steadily increasing over the past several decades, partly due to population aging and improved survival of patients with cardiovascular diseases. Therefore the importance of biochemical substances raises which would uncover ongoing cardiac overload, enable the treatment monitoring and make care of the patients with heart failure more effective. According to the results of many clinical trials, this task is fulfilled at most by natriuretic peptides which become gradually a part of standard clinical practice. Both, brain natriuretic peptide and its N-terminal propeptide help to detect heart failure in patients presenting with acute dyspnoea. Moreover, the natriuretic peptide levels reflect the severity of the disease and can predict future clinical outcomes in the heart failure patients. The role of natriuretic peptides as an objective target for heart failure therapy in the outpatient care was not so well established.

The human recombinant brain natriuretic peptide nesiritide was approved in the United States as a new therapeutic agent for acute heart failure. Although the first results were promising, questions regarding nephrotoxicity and possible higher mortality connected with this substance avoided its broader therapeutic use to date.

© 2013 The Czech Society of Cardiology. Published by Elsevier Urban & Partner Sp.z.o.o. All rights reserved.

Contents

1. Introduction ................................................................. 371
2. Essential characteristics ................................................. 371
3. Role in heart failure diagnostics ...................................... 371
4. Prediction of prognosis .................................................. 372
5. Management of heart failure therapy ................................. 373
6. Therapeutic use .......................................................... 373
7. Conclusion ................................................................. 374
Acknowledgments .......................................................... 374
References .................................................................. 374

*Corresponding author. Tel.: +420 224962363.
E-mail address: j.krupicka@centrum.cz (J. Krupicka).

0010-8650/$ - see front matter © 2013 The Czech Society of Cardiology. Published by Elsevier Urban & Partner Sp.z.o.o. All rights reserved.
http://dx.doi.org/10.1016/j.crvasa.2013.03.010
1. Introduction

Prevalence of chronic heart failure (HF) in general population is about 1.3%. However, it substantially rises above the age of 75 where it reaches at least 8% and is one of the most frequent causes of morbidity and mortality in this population [1]. Every year, approximately 40,000 new cases of HF are diagnosed in the Czech Republic. Over 40% of them die in the following 4yr [2]. This represents significant problem for the healthcare system and the economy. One of the most important goals in the management of HF is to make the correct diagnosis early and to start the appropriate treatment as soon as possible. Nevertheless, symptoms of HF are unspecific and the typical clinical picture can be found in less than 50% of the patients. The utilization of other diagnostic methods, such as echocardiography, is often limited. Consequently there is an increasing interest in new biochemical markers that could be used for early and reliable HF diagnostics, prediction of the clinical outcomes in HF patients, as well as an objective measure of treatment effect. The biomarkers also should be accessible at reasonable cost. At present, such conditions are fulfilled at most by B-type natriuretic peptide (BNP) and its N-terminal propeptide (NT-proBNP), which became a substantial part of algorithms for HF diagnosis [3]. Over the last years other biochemical substances bring some novel information on HF patients. Among the most promising belong mid-regional propeptides, ST2-receptor for interleukin-33 and chromogranins which are discussed elsewhere in this issue. The aim of this article is to review information concerning the basic characteristics of natriuretic peptides (NP) and their clinical use in HF.

2. Essential characteristics

B-type natriuretic peptide (BNP) was discovered in 1988. It was originally isolated from porcine brain—that is the explanation for generally used term “brain natriuretic peptide.” Afterwards, it was found that the main source of BNP are cardiac myocytes, the ventricular in larger quantity than the atrial [4]. The release of BNP is triggered by increased myocardial wall stress due to volume and/or pressure overload [5]. Natriuretic peptides realize their effects through receptors connected with cyclic guanosine monophosphate–depending signaling cascade in renal, suprarenal, vascular, cerebral and other tissues, which leads to diuresis, natriuresis, inhibition of renin-angiotensin-aldosterone system and vasodilatation. Ultimately, all these effects contribute to blood pressure lowering. The antiproliferative effect of NP on cardiac and vascular myocytes is also known well [6]. Recently, Polak et al. reported increased lipolysis in abdominal adipose tissue after the microdialysis perfusion with BNP in both, HF patients and healthy subjects [7].

Natriuretic peptides are believed to have an important protective role in pathophysiology of HF. In the case of body volume overload the NP increase diuresis, keep the balance of body salt and act as a counterweight of the renin-angiotensin-aldosterone axis and the sympathetic nervous system effects. Due to these abilities they can contribute to a longer asymptomatic stage of the systolic left ventricular dysfunction. On the other hand, the lack of an active form of BNP as well as BNP resistance because of down-regulation and inactivation of receptors were described in patients with advanced HF [8]. Brain natriuretic peptide is synthesized in cardiac myocytes as a precursor which is called proBNP. After a cell stimulation by increased myocardial wall stress proBNP is cleaved to the biologically active hormone (BNP) and to the inactive N-terminal part of the molecule (NT-proBNP). Both peptides are released to circulation. Brain natriuretic peptide is eliminated from the body by clearance receptors, neutral endopeptidase and renal filtration. On the contrary, NT-proBNP is cleared from circulation mainly by renal excretion. Halftime of BNP is approximately 20 min; NT-proBNP has the halftime of 60–120 min [9]. Plasma concentrations of both peptides correlate to each other very well and they reach similar levels within physiological conditions. Under the circumstances of left ventricular dysfunction, NT-proBNP plasma concentration rises exponentially and run to values several times higher than BNP. The advantages of NT-proBNP over BNP measurement are a longer biological halftime and a higher stability which result in no need of immediate assessment or deep freezing of the blood sample. On the contrary, the renal insufficiency influences BNP less than its N-terminal propeptide [10].

3. Role in heart failure diagnostics

In spite of a substantial progress made in the treatment of HF, the disease prognosis remains poor [11]. An early and appropriate diagnosis is very important, particularly at an emergency department (ED). The evidence gathered during the past 15 yr clearly demonstrates that both, the BNP and the NT-proBNP plasma concentrations rise significantly in the patients with HF and correlate with their functional status expressed by the New York Heart Association (NYHA) class [10]. Many trials confirmed the contribution of BNP and NT-proBNP to clinical judgment for diagnosing acute HF in dyspnoeic patients. The best known is the Breathing Not Properly (BNP) study which comprised almost 1600 patients presenting with acute breathlessness at the ED. According to the results of this study the BNP plasma concentration below 100 pg/ml itself excludes the HF diagnosis with 90% sensitivity and together with clinical examination makes the estimation of a cause of acute dyspnoea more accurate [12]. The results of similar multinational trial with NT-proBNP were also published [13]. Based on their findings the authors established the NT-proBNP plasma level below 300 pg/ml to rule out HF in breathlessness patients [13]. The cut off values to confirm the diagnosis of acute HF were not set uniformly. According to the majority of studies BNP plasma concentrations > 400 pg/ml and NT-proBNP > 2000 pg/ml have high positive predictive value for HF. This is why the past recommendations enabled to set the diagnosis on the basis of high NP levels [3]. Recently, the new ESC Guidelines for HF were published [14]. In comparison with the previous one, NP should serve now mainly as a tool for preselection of the patients in whom echocardiography should be performed. Echocardiography is supposed to be the final confirming method in the HF diagnostic algorithm [14] (Fig. 1). Moreover, the authors of the newer ESC Guidelines for HF recommended...
lower NP cut off values (35 pg/ml for BNP, 125 pg/ml for NT-proBNP respectively) to rule out HF in patients with slow onset of HF signs and symptoms which reflects lower NP values among the patients presenting with the HF symptoms in the primary care setting in comparison with the emergency department [14].

There are several factors conducing to higher NP levels besides failing heart ventricles. Age, renal insufficiency and atrial fibrillation belong to the most important ones [15–18]. The feasible mechanisms leading to elevation of NP concentrations are their lower clearance due to either a decreased glomerular filtration rate or a loss of clearance receptors with aging, higher left atrial filling pressure and atrial dilatation [5,19]. On the other hand, an inverse relationship between BNP and body mass index was described [20]. Abundant clearance receptors expressed in adipose tissue increase the removal of NP from circulation and could thus contribute to salt and water retention and consequently lead to early HF manifestation in obese patients [20]. Therefore, some authors recommended special BNP cut-offs in these situations to secure its sensitivity and specificity [21] (Table 1). Similarly to BNP, NT-proBNP plasma levels are influenced by age [15]. This resulted in the manufacturers recommendation of age-adjusted cut offs for the exclusion of acute HF (125 pg/ml for the patients <75yr of age and 450 pg/ml for those ≥75yr of age). However, the statistical analysis of the multicentre study made by Januzzi et al. [13] showed that the single age independent cut-off value of 300 pg/ml is superior to the age dependant cut-off strategy.

4. Prediction of prognosis

Natriuretic peptides could serve not only to assess the HF diagnosis, but also for determination of the patient’s prognosis. The retrospective analysis of the data from theValsartan in Heart Failure Trial (Val-HeFT), which included patients with moderate to severe HF, showed a significant rise in the relative risk of mortality and morbidity through out each quartile (<41 pg/ml, 41–97 pg/ml, 97–238 pg/ml, >238 pg/ml) of BNP levels. Moreover, patients with the greatest percent decrease of BNP values during the study had the lowest mortality while the patients with the greatest percent increase of BNP had the highest mortality [22]. In the COPERNICUS NT-proBNP substudy the patients with severe heart failure due to ischemic or non-ischemic cardiomyopathy and NT-proBNP concentrations below 199 pg/ml had substantially lower one-year mortality rate than those with NT-proBNP above 504 pg/ml (3.9% vs. 27.9%) [23].

After hospitalization of a patient with acutely decompensated HF the initial NP level can predict the patient’s future clinical outcome. Fonarow et al. reported that patients in the highest quartile of BNP values on admission had the highest in-hospital mortality, the highest probability of mechanical ventilation, the longest time spent at intensive care unit as well as in hospital at all [24]. In another study published by Bettencourt et al., the prognosis of HF patients with
5. Management of heart failure therapy

As the incidence of HF and the number of HF hospitalizations rises [1], the clinicians search for some objective target which would help them to tailor the therapy of HF for each patient’s individual needs. Natriuretic peptides appear to be the most suitable tool for this task. They correlate strongly with the hemodynamic parameters such as pulmonary capillary wedge pressure [28] and left ventricular end-diastolic pressure [29] and therefore, reflect the actual hemodynamic status of the patients. Moreover, the results of several studies proved the ability of HF pharmacotherapy to lower NP plasma concentrations. Such an effect was observed with angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor antagonists, spironolacton, diuretics and also with vasodilating betablockers during long-term therapy [22,30–33]. The relationship between the decrease of the BNP level and the improvement of patient’s symptoms during hospitalization suggests that intensifying HF therapy guided by serial measurements of NP may bring better outcomes [10]. The neurohumoral background for this theory was set by Murdoch et al. [30] They observed more profound inhibition of the RAAS and a significant fall in heart rate in the group of HF patients whose vasodilator therapy was titrated according to plasma BNP compared to the patients with empiric therapy. After the successful pilot clinical study published by Troughton et al., where the goal of reaching NT-proBNP values below 200 pg/ml in symptomatic HF patients had positive impact on number of cardiovascular events [31], several larger trials with BNP and NT-proBNP guided therapy were initiated. However, the results of these trials are ambiguous [27] (Table 2). The STARS-BNP (Systolic Heart Failure Treatment Supported by BNP) multicenter study comprised of 220 chronic HF patients, who were randomized either to medical treatment according to current guidelines or to therapy with the target of decreasing BNP plasma concentrations below 100 pg/ml. After 15 months of treatment significantly fewer patients met the combined clinical end point (hospitalization for HF or death related to HF) in the BNP guided group [34]. On the contrary, in The Trial of Intensified vs. Standard Medical Therapy in Elderly Patients With Congestive Heart Failure (TIME-CHF) there was no difference in clinical outcomes between the group of patients treated according to the NT-proBNP levels and the control group with symptom guided therapy [35]. The BATTLESCARRED trial using also NT-proBNP as a biomarker brought similar results [36]. Nevertheless, both studies showed that the therapy of chronic HF according to plasma NP have positive impact on morbidity and mortality in younger patients (<75 yr). The investigators try to explain the effect difference depending on patient’s age by worse tolerability of intensified HF medication as well as higher incidence of renal insufficiency in the elderly patients [36]. Recently, Felker et al. published a meta-analysis of six available randomised controlled studies, including altogether 1627 patients, which tested the strategy of tailoring HF therapy according to NP values. They clearly demonstrated that incorporation of this strategy into the clinical approach was connected with significant reduction of all-cause mortality [37]. In the majority of published studies the NP guided therapy led to more frequent adjustments of HF medication as compared to symptoms guided therapy [37].
in patients receiving the nesiritide infusions compared to non-inotrop based controls [39,40]. Recently, the large multicentre acute study of clinical effectiveness of nesiritide and decompensated heart failure (ASCEND-HF) was presented comprising 7141 acute HF patients receiving either nesiritide or placebo. No significant difference was found either in 30-day mortality from any cause or in the rates of worsening renal functions between the two groups. Moreover, nesiritide had only a small, statistically non-significant influence on dyspnea improvement [41]. The investigators concluded that nesiritide cannot be recommended for routine use in wide population of patients with acute HF [41].

Ularitide is a recombinant form of urodilatin, the natriuretic peptide synthesized by the kidney which is involved in body salt and water regulation. The SIRIUS II study regarding the clinical effect of ularitide infusions in patients with acute decompensated heart failure proved the reduction of PCWP as well as the improvement of dyspnoea 6 h after the completion of the 24 h infusion. In higher doses, ularitide also decreased systemic vascular resistance and increased cardiac output in these patients [42]. Nevertheless, further clinical trials are necessary to confirm the clinical significance of ularitide in comparison with standard therapy of acute heart failure.

7. Conclusion

In conclusion, natriuretic peptides proved their added value to clinical judgement and echocardiography for diagnosing HF in the patients with acute breathlessness. Once the appropriate diagnosis is established, the NP plasma concentrations of the individual patient reflect his/her current hemodynamic status and can predict future clinical outcomes. The role of NP in tailoring HF therapy was yet not proved unambiguously and still needs further clinical investigation. Similarly, the therapeutic use of human recombinant BNP nesiritide remains controversial.

Acknowledgments

The authors have no conflict of interests with respect to the topic of this article. This paper was supported by the investigational grant of the Charles University in Prague PRVOUK-P55/1F/5.

References


