

THE ROLE OF BNP AND NT-PROBNP IN HEART FAILURE

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Abstract: An increasing prevalence of heart failure is seen in the general population and especially the aging population in the last years. Biggest challenge for the future is not only slowing disease progression, but even stopping the evolution of the heart failure, obtaining also an improvement in the patient's quality of life. Given the fact that heart failure is a progressive disease, the earlier the diagnosis is established, the more are reduced the risk of complications and the mortality. For this reason, it was felt the need to detect serum markers that correlate with a proper prognosis, NT-proBNP being one of those

Cuvinte cheie: insuficiența cardiacă, peptide natriuretice, NT-proBNP

Rezumat: În ultimii ani se constată o creștere extraordinară a prevalenței insuficienței cardiace în populația generală și în special la populația vârstnică. Pentru viitor cea mai mare provocare vizează nu numai încetinirea progresiei bolii, ci chiar stoparea evoluției insuficienței cardiace, odată cu aceasta obținându-se și o ameliorare a calității vieții bolnavului. Ținând cont de faptul că insuficiența cardiacă este o boală progresivă, cu cât diagnosticul este stabilit mai precoce, cu atât mai mult se reduce riscul complicațiilor și al mortalității. Din acest motiv, s-a simțit nevoia să se depisteze markeri serici care să se coreleze într-un mod adecvat cu prognosticul bolii, unul dintre aceștia fiind și NT-proBNP-ul.

INTRODUCTION

Heart failure (HF) is a complex syndrome which is defined by symptoms of HF, typically breathlessness or fatigue either at rest or during exertion or ankle swelling, in combination with objective evidence of cardiac dysfunction at rest. The most common cause of HF is coronary artery disease, but other well known aetiologies are hypertension, valvular disease, cardiomyopathy and myocarditis. Most patients with HF suffer from a variety of signs and symptoms that influence their health status, quality of life and prognosis. The syndrome of HF is a large problem in Western societies, especially since its prevalence will probably increase further in the near future due to aging of the population and more successful treatment of acute cardiac disease. Additionally, HF puts a substantial burden on health care facilities and costs. For the diagnosis of HF a variety of diagnostic tests is available including assessment of clinical signs and symptoms of HF, laboratory blood tests, radiological examinations, electrocardiography and echocardiography. In 1988 a new cardiac natriuretic peptide, B-type Natriuretic Peptide (BNP) was discovered, which in the following years was shown to have prognostic properties and later also appeared to have diagnostic properties in the emergency department and out-patient settings. In addition, one study also reported improved prognosis when patients' medication was guided by NT-proBNP compared to 'clinical view' guided treatment. Therefore, primary care physicians, and other clinicians became enthusiastic about the role of natriuretic peptides in diagnosis, prognosis and guidance of medical treatment of HF patients. The use of natriuretic peptides in the diagnosis of HF was included in recent guidelines, including the European Society of Cardiology and Dutch primary care guidelines.⁽³⁾

Before explaining the potential benefits and

limitations of BNP and NT-proBNP in clinical practice, and before outlining the aims of this thesis, an introduction to the mechanism of action of BNP and NT-proBNP will be given.

Differences between BNP and NT-proBNP: BNP is a hormonally active natriuretic peptide that is mainly released from the cardiomyocytes in the left ventricular wall. In reaction to stretch and tension of the myocardial wall the prohormone proBNP splits into BNP and the hormonally inactive remnant N-terminal proBNP (NT-proBNP) by proteolytic cleavage. This process occurs under influence of integrins, structures at the Z-disc of sarcomeres, that measure stretch of these sarcomeres after which both peptides will be secreted in equimolar amounts into the circulation. Circulating BNP acts as an antagonist of the renin angiotensine aldosterone system, and protects the body from plasma overload by inducing diuresis, natriuresis, vascular dilatation and inhibition of the sympathetic nerves system.⁵ The half life of BNP is around 20 minutes and the half life of NT-proBNP is around 120 minutes. BNP is known to be cleared from the blood by natriuretic peptide clearance receptors, by neuro endopeptidases and by the kidneys. Little is known on the exact clearance mechanism of NT-proBNP, although it has been suggested that the kidneys play a major role in this clearance.¹² Absolute values of BNP are significantly lower than values of NT-proBNP, despite equimolar secretion. The reference ranges for BNP and NT-proBNP vary depending on the assay that is used and the nature of the control population. In general, the suggested normal range for circulating BNP is 0.5 – 30 pg/ml and for circulating NT-proBNP the suggested normal range is 68 – 112 pg/ml.¹³ These natriuretic peptides may be beneficial in clinical practice since plasma levels of BNP and NT-proBNP are elevated in patients with HF and are related to the severity of the disease.

BNP and NT-proBNP in clinical practice: promises

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BNP and NT-proBNP plasma levels are promising tools in the daily management of suspected or established HF. Most studies on the use of BNP and NT-proBNP in clinical practice addressed their diagnostic properties. However, an increasingly amount of evidence is available on the prognostic value of BNP and NT-proBNP and a single study provided hopeful results for the benefits of NT-proBNP guided medical treatment.

Diagnosis

Recent trials provided strong evidence that BNP and NT-proBNP are powerful diagnostic tools in exclusion and diagnosis of HF. The Breathing Not Properly study showed, by means of receiver operating characteristics analyses, that a BNP value of 100 pg/ml was the optimal value to differentiate patients with dyspnoea caused by HF from patients with dyspnoea due to pulmonary pathology at the emergency department.

This value of 100 pg/ml also discriminated non-systolic HF (LVEF <45%) from non-HF patients at the emergency department. It has also been suggested that BNP could be used to discriminate systolic from diastolic HF. Although non-systolic HF patients had significantly lower BNP plasma levels than systolic HF patients (LVEF >45%), BNP only had modest added value in differentiating non systolic from systolic HF. In another study, a BNP value of 100 pg/ml added significant value to the diagnosis of HF on top of clinical judgement. An international pooled analysis of 1256 patients provided cut off values for NT-proBNP in an emergency department setting. An age independent cut point of 300 pg/ml had a negative predictive value of 98%. Additionally, an optimal strategy to identify acute HF was to use age stratified cut off points of 450, 900 and 1800 pg/ml for ages <50, 50-75, and >75 respectively which yielded 90% sensitivity and 84% specificity for acute HF. Furthermore, BNP and NT-proBNP seem useful as diagnostic tools in primary care (where most patients with suspected HF are encountered and where only limited diagnostic tools are available) and as such are recommended in recent guidelines. The *added* value of these natriuretic peptides on top of established diagnostic tools, including symptoms and signs, has not been properly studied, in particular in relevant subgroups, and currently large studies are underway addressing this issue.

Discharge diagnosis have been instrumental in providing estimates and time trends in prevalence and incidence of HF. However, previous studies in the Netherlands, Sweden and in the United States showed that respectively 20%, 18% and 33% of the patients that were given the discharge diagnosis 'HF' at close examination did not have HF at all. Evidence is lacking on potential independent predictors of the discharge diagnosis HF, including BNP and/ or NT-proBNP and an easy applicable scoring rule could be helpful in this setting.(1,2,3)

Moreover, it is unknown whether the established BNP cut off value of 100 pg/ml can also be used at discharge after admission for HF.

Prognosis

The prognostic value of BNP and NT-proBNP is well established in several groups of patients.

An early study on 85 patients with chronic HF revealed that BNP is a strong independent predictor of mortality.⁶ Another study confirmed these results in a larger research population of 452 systolic HF patients (LVEF <35%). In this study BNP was found to be a strong independent predictor of sudden death during a follow up period of 3 years. Furthermore, NT-proBNP was a predictor of sudden death in this study population.(4,5,6.) A substudy of the COPERNICUS trial (n=1011) revealed that NT-proBNP was consistently associated with an increased risk for all-cause mortality and

hospitalisation for HF in patients with severe HF (LVEF <25%). Another study by Gardner et al. on 142 patients with advanced HF also reported that NT-proBNP was an independent predictor of all cause mortality.(7)

Guidance of treatment

BNP and NT-proBNP are influenced by drugs that are prescribed to HF patients like diuretics, beta blockers, ACE inhibitors or angiotensine II receptor blockers and therefore these natriuretic peptides could possibly be used to guide medical treatment.(1) A small study by the Australia-New Zealand Heart Failure Group including 69 patients with symptomatic HF provided evidence of the possible benefit of a NT-proBNP guided approach to therapy. Half of the patients received therapy guided by plasma NT-proBNP, therapy in the remaining patients was guided by clinical monitoring at the same frequency, but with the physician blinded to the NT-proBNP result. Clinical monitoring was based on scores assigned to 10 symptoms or signs of HF used in the Framingham criteria for HF. The study found significantly lower mortality, fewer hospitalisations and episodes of decompensated HF in the NT-proBNP-guided therapy group (target 1680 pg/ml).

Larger studies are underway that are about to provide firmer evidence as to whether or not BNP and NT-proBNP can be used as a marker in the monitoring of treatment of HF patients.

Assay considerations

Recently, the US Food and Drug Administration (FDA) approved two rapid and fully automated assays for natriuretic peptide measurement assessing diagnosis and prognosis in cardiac abnormalities. These assays, the Triage BNP meter (Biosite Incorporated, San Diego, CA) and the Elecsys NT-proBNP assay (Roche diagnostics, Mannheim Germany), are used to determine BNP and NT-proBNP levels in this thesis. BNP is stable in EDTA plasma without addition of aprotinin at room temperature for at least 24 hours 30 and NT-proBNP is stable for at least one year when stored at -80°C in several different serum and plasma conditions amongst which EDTA plasma. Both assays have been validated repeatedly, but the Elecsys NT-proBNP assay showed an approximately 2 – 3 fold better precision compared to the Triage BNP assay.

Although there are pre-analytical and analytical differences between the Triage BNP assay and the Elecsys NT-proBNP assay, they do not seem to translate into clinically significant differences in their diagnostic and prognostic application. Before the two assays that are used for most determinations in the present study became available, another commercially available assay, the Shionoria BNP assay and in house developed radioimmunoassay kits for NT-proBNP were used. These systems show good performance.

Altogether, BNP and NT-proBNP are promising tools for the management of suspected and established HF in clinical practice, but it is time for a critical evaluation of their limitations to their usefulness in daily care, especially in the typical older patient with relevant co-morbidity.

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