BNP and NT-proBNP: Clinical Applications in (Suspicion of) Heart Failure

Joost H. RUTTEN*, Frans BOOMSMA*, Anton H. van den MEIRACKER*

**Joost Rutten** studied medicine at Maastricht University. After obtaining his MD degree, he began his specialization in Internal Medicine at Erasmus MC in Rotterdam, with special focus on Vascular Medicine. He is also currently preparing a PhD thesis on the clinical use of natriuretic peptides.

**Frans Boomsma** studied chemistry at Leiden University. After obtaining a PhD at the same university in 1975, he joined the staff of the Department of Internal Medicine I at Erasmus University in Rotterdam. Since 1987 he has served as associate professor and head of the Cardiovascular Research Laboratory of what is now named the Erasmus MC, in the Department of Internal Medicine, Section of Vascular Pharmacology and Metabolism. He has a special interest in neurohormonal regulation of the vascular system.

**Anton H. van den Meiracker** obtained a degree in medicine at Utrecht University. After specializing in Internal Medicine, he became in 1983 a staff member of the Department of Internal Medicine I of the University Hospital Dijkzigt in Rotterdam, where he also obtained a PhD. At present, he is associate professor in the Department of Internal Medicine of Erasmus MC, where he heads the Section of Vascular Pharmacology and the training program for Vascular Medicine. His main interest is the regulation of blood pressure.

**BNP and NT-proBNP: Clinical Applications in (Suspicion of) Heart Failure**

**Summary**

The biologically active B-type natriuretic peptide (BNP) and the biologically inactive amino-terminal proBNP (NT-proBNP) are compounds produced by the heart that are released into the circulation and give information on the pump function of the heart. Reliable commercial assays are available for both peptides, some of which can be used for rapid point-of-care diagnosis. The accuracy of plasma BNP and NT-proBNP determinations in the diagnosis of heart failure is comparable. Introduction of rapid BNP determination in the Emergency Room for patients with acute dyspnea can lead to more efficient treatment. Sequential BNP or NT-proBNP measurements in patients with heart failure in the (outpatient) clinic can be helpful for optimizing treatment, leading to decreased heart failure-related morbidity and mortality. Measurement of BNP or NT-proBNP in the general population

**BNP ve NT-proBNP: Kalp Yetmezliği Şüphesinde Klinik Uygulamalar**

Biyojlojik olarak aktif olan B-tipi natriüretik peptid (BNP) ve biyojlojik olarak inaktif olan amino-ucu proBNP (NT-proBNP) peptidi, kalp tarafından üretildi ve dolaşımında bulunmuş ve kalbin pompalama işlevi hakkında bilgi veren bileşiklerdir. Piyasa bu peptidlerin tayini için, bazıları hızlı tanı konması amacıyla kullanılmaktadır. Kalp yetmezliğinin tanıında kullanılan plazma BNP ve NT-proBNP tayın yöntemlerinin doğruluğu karşılaştırabilir özellikleri dır. Akut dispne olan ve acil kliniklerine başvuran hastalarda yapılan hızlı BNP tayını, daha etkin tedaviye olanak tanıyabilmektedir. Polikliniklerde, kalp yetmezliği olan hastalarda beli zaman aralıklarında yapılan BNP veya NT-proBNP tayının tedavini optimizasyonunda yardımcı olabileceği ve kalp yetmezliğine bağlı hastalıklar ve olumleri azaltabileceği

* Erasmus Medical Center, Department of Internal Medicine, Section of Vascular Pharmacology, Rotterdam, THE NETHERLANDS
* Corresponding author e-mail: a.vandenmeiracker@erasmusmc.nl
INTRODUCTION

Biomarkers are compounds, usually measured in blood, plasma or serum, which give information about the presence or absence, or the severity, of a pathological condition. A well-known biomarker is T-troponin, used for the determination of decay of heart muscle cells. B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are biomarkers especially for the functioning of the heart as a pump. Since our previous review in 2001, many studies have been published on the prognostic and diagnostic value of measurements of BNP and NT-proBNP, now increasingly being used in clinical practice. In this review, after an introduction about the physiology and assay characteristics of BNP and NT-proBNP, we will focus on the clinical application of these measurements in heart failure or suspicion of heart failure.

Physiology

B-type natriuretic or brain-natriuretic peptide (BNP) was first described in 1988 after isolation from porcine brain. Soon, however, it was found to be mainly derived from cardiac muscles, just like the previously discovered atrial natriuretic peptide (ANP), and thus should similarly be considered a cardiac hormone. BNP is synthesized as a prehormone (proBNP) in cardiomyocytes, especially in the ventricles. During release into the circulation, proBNP is split into equimolar amounts of BNP and NT-proBNP. BNP is a 32-amino acid biologically active peptide, while NT-proBNP is a biologically inactive 76-amino acid peptide. Under physiological conditions, BNP and NT-proBNP are continuously released in small amounts into the circulation. Regulation of the synthesis takes place mainly at the gene expression level, with an increase in ventricular wall tension as the most important stimulus. The synthesis is also increased during cardiac ischemia, and is modulated by various hormones and cytokines.

BNP exerts its effects by binding to the type A natriuretic receptor (NPR-A) in various target organs, leading to the production of cyclic guanosine monophosphate (cGMP) as second messenger. The most important biological effects are natriuresis and diuresis, vasodilatation, and inhibition of renin and aldosterone release. Clearance of BNP occurs through specific clearance receptors (NPR-C), breakdown by neutral endopeptidase, and renal extraction. NT-proBNP is partially cleared by the kidney. The half-life of BNP is 20 min; the longer half-life of 120 min of NT-proBNP explains its higher plasma concentra-

Table 1. Techniques and intra- and inter-assay variabilities of different BNP and NT-proBNP determinations

<table>
<thead>
<tr>
<th>Reference</th>
<th>Parameter</th>
<th>Technique</th>
<th>Company</th>
<th>Suitable for rapid on-site</th>
<th>Intra-assay variability</th>
<th>Inter-assay variability</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 and 11</td>
<td>BNP</td>
<td>Immunochromatographic</td>
<td>Biosite Triage® BNP</td>
<td>yes</td>
<td>10.1-16.2%</td>
<td>9.4-15.2%</td>
</tr>
<tr>
<td>12</td>
<td>BNP</td>
<td>Immunochemiluminescent</td>
<td>Bayer ADVIA centaur</td>
<td>no</td>
<td>1.7-3.1%</td>
<td>2.4-3.4%</td>
</tr>
<tr>
<td>13</td>
<td>BNP</td>
<td>Immuno-enzymatic</td>
<td>Abbot AxSYM BNP</td>
<td>no</td>
<td>4.3-6.0%</td>
<td>7.3-10.0%</td>
</tr>
<tr>
<td>14</td>
<td>NT-proBNP</td>
<td>Sandwich immunosassay</td>
<td>Roche CARDIAC proBNP</td>
<td>yes</td>
<td>7.4-9.6%</td>
<td>&lt;14%</td>
</tr>
<tr>
<td>10 and 11</td>
<td>NT-proBNP</td>
<td>Electrochemiluminescent</td>
<td>Roche NT-proBNP, Elecsys 2010</td>
<td>no</td>
<td>1.3-2.7%</td>
<td>2.3-6.1%</td>
</tr>
</tbody>
</table>
tion compared to BNP. BNP and NT-proBNP plasma concentrations are on average higher in females than in males, and in elderly compared to younger people. The plasma concentrations of both biomarkers are inversely related to creatinine clearance and body mass index.

**Assays**

BNP as well as NT-proBNP concentrations can presently be determined with fully automated commercial methods (Table 1). Rapid tests for “on-site” and “point-of-care” diagnosis are now available for both biomarkers. The available assays have reasonable to high precision. Plasma concentrations are expressed as pmol/L or pg/ml. The conversion factor for BNP is: 1 pg/ml = 0.29 pmol/L, and for NT-proBNP: 1 pg/ml = 0.12 pmol/L. Values for BNP obtained with different assay methods can not always be compared directly. There is no clear-cut conversion factor for comparing BNP with NT-proBNP values. In EDTA-blood at room temperature, BNP is stable for at least 24h and NT-proBNP for at least 72h.

**Prognostic aspects**

BNP and NT-proBNP plasma concentrations correlate reasonably good with the severity of heart failure as based on clinical and/or echocardiographic parameters, and thus, not surprisingly, both biomarkers predict heart failure-related morbidity and mortality. In some studies, the predictive values of BNP and NT-proBNP have been compared. In the largest study (3916 patients with symptomatic heart failure), BNP and NT-proBNP were found to be equally predictive of total mortality and heart failure-related morbidity and mortality. Also, in the general population, BNP and NT-proBNP, after correction for traditional risk factors for heart and vascular diseases, are predictors of mortality and heart failure, as well as of atrial fibrillation, cerebrovascular accidents and ischemic heart diseases. As a consequence, it has been suggested to use these determinations for identification of high-risk patients who should then be checked and treated more intensively.

**Diagnosis of heart failure in the general population**

The prevalence of heart failure, a disease with high morbidity and mortality, is increasing due to the increasing number of elderly people and the much-improved survival after myocardial infarction. Early diagnosis would make it possible to start with drug treatment (such as angiotensin converting enzyme (ACE)-inhibitors and beta-blockers) in an early phase, with proven favorable effect on morbidity and mortality. In the past years, a large number of studies have been published on the test characteristics of BNP and NT-proBNP for diagnosis and exclusion of heart failure in the general population. Golden standard in these studies was echocardiography, with or without clinical characteristics. The conclusion from these studies is that a normal concentration excludes the presence of heart failure with a high degree of certainty. In a recently published nomogram, for instance, the a priori estimated chance of heart failure of 20% decreased a posteriori to 2.9% with a rapid BNP test. The reversal, however, does not hold true, because BNP and NT-proBNP values are influenced by a great number of factors and can also be increased in other diseases such as chronic obstructive pulmonary disease (COPD) and renal insufficiency. The chance of heart failure can therefore be as low 2% with an elevated abnormal test value. Test characteristics can be somewhat improved by correction for age, sex, renal function and body mass index. Because of the low positive-predictive value, screening for heart failure in the general population with BNP or NT-proBNP can not be recommended, as too many people would have to undergo further diagnostic procedures.

**Diagnosis of heart failure in the Emergency Room**

Acute shortness of breath is an important reason for referral to an Emergency Room. For fast and efficacious treatment, it is imperative to know whether the shortness of breath is a result of heart failure or another cause. A number of studies have investigated if this distinction can be made with a rapid “point-of-care” BNP or NT-proBNP test. The ultimate diagnosis of heart failure was made in these studies by a panel of cardiologists on the basis of all patient data,
including anamnesis, imaging techniques, and laboratory data, with the exception of the NP value. The studies show that a rapid “point-of-care” test can more accurately determine heart failure to be the cause of the shortness of breath than clinical judgement18. Cut-off values for BNP and NT-proBNP have been defined in this regard (Table 2).

**Table 2.** Cut-off values, positive predictive (PPV) and negative predictive (NPV) values, and areas under the ROC curve from point-of-care BNP and NT-proBNP determinations for the diagnosis of heart failure in patients reporting to the Emergency Room with acute dyspnea*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Parameter</th>
<th>Cut-off value pg/ml</th>
<th>PPV %</th>
<th>NPV %</th>
<th>Area under the ROC curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>BNP</td>
<td>100</td>
<td>79</td>
<td>89</td>
<td>0.83</td>
</tr>
<tr>
<td>16</td>
<td>NT-proBNP</td>
<td>&lt; 50 yrs</td>
<td>450</td>
<td>76</td>
<td>99</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50-75 yrs</td>
<td>900</td>
<td>83</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt; 75 yrs</td>
<td>1800</td>
<td>82</td>
<td>55</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All ages</td>
<td>300</td>
<td>77</td>
<td>98</td>
</tr>
</tbody>
</table>

* excluding patients with a serum creatinine > 200 µmol/L, dyspnea after thorax trauma and an acute coronary syndrome.

The important question of whether a rapid BNP test in the Emergency Room leads to more efficient treatment for patients referred for shortness of breath has been addressed by Mueller et al.32. In a prospective randomized study, plasma BNP was measured in 225 patients upon presentation to the Emergency Room, and the outcome of the test was communicated to the attending physician. In the other 227 patients, diagnostic work-up was performed as usual. Diagnosis of heart failure was deemed improbable at BNP levels < 100 pg/ml, highly likely at values > 500 pg/ml, and possible at intermediate levels. Knowledge of the BNP concentration decreased the number of hospital admittances (75% of patients in the BNP group vs 85% in the control group) as well as the number of admittances to the Intensive Care (15% vs 24%). The decrease in admittances did not lead to higher mortality in the first 30 days (12% vs 10%). The authors conclude that rapid BNP measurement leads to more efficient diagnosis and treatment and to cost reduction, since unnecessary investigations and admittances to hospital or intensive care are prevented32.

Whether these conclusions hold true for Emergency Rooms at other hospitals needs to be further investigated; such an investigation is currently ongoing at the Erasmus MC, with NT-proBNP as biomarker.

**First-line diagnosis of heart failure**

In case of clinical suspicion of heart failure, a general practitioner can request a plasma BNP or NT-proBNP determination33, and use the outcome to decide on echocardiographic investigation or referral to a cardiologist. The diagnostic value of BNP and NT-proBNP in first-line patients suspected of heart failure has been investigated34-36. These studies all show a high negative-predictive value (88–98%). The positive-predictive value is much lower and highly variable (32–70%). Since a normal ECG also makes the diagnosis of heart failure very improbable, some studies have evaluated the diagnostic accuracy of ECG compared to BNP, and investigated whether ECG plus BNP has greater accuracy than ECG alone37. Not unexpectedly, no significant difference was found between the sensitivity of ECG and BNP determinations, although BNP was more specific (less false-positives) than ECG for the diagnosis of heart failure. Addition of BNP measurement to the ECG does not increase the sensitivity. In conclusion, in case of suspicion of heart failure in first-line patients, either ECG or BNP, but not both, should be performed.

**Diagnosis of diastolic heart failure**

In 40–60% of patients with heart failure, systolic function is not compromised, and the underlying problem is diastolic dysfunction. This implies a problem with the filling of the heart, for instance because of fibrosis or hypertrophy. In diastolic heart failure, plasma BNP and NT-proBNP concentrations are elevated, although less than with systolic heart failure4,38,39. BNP and NT-proBNP tests can thus, in contrast to echocardiography, not distinguish between systolic and diastolic heart failure. At present, that is not clinically important, since medical treatment is
not essentially different between the two syndromes.

Judgement of severity of heart failure and effectiveness of treatment

Patients hospitalized for decompensated heart failure ("wet" heart failure) have high plasma concentrations of BNP and NT-proBNP. Various studies have shown that successful treatment leads to a decrease in the elevated filling pressures of the heart, with concomitant decrease in NP concentrations. It has been suggested, therefore, that repeated measurements of BNP, together with clinical judgement, may be useful for monitoring treatment. Patients should not be discharged until a threshold value of BNP is reached. A few small studies have been published investigating whether changes in NP concentrations during clinical treatment and the value at discharge are predictive of re-admission or mortality. These studies show that the patients with a decrease in BNP or NT-proBNP during clinical treatment are less frequently re-admitted for heart failure, and have less mortality, than the patients with no decrease, or even an increase, in BNP or NT-proBNP. In multivariable Cox-regression analysis, edema and changes in NT-proBNP were the only two independent determinants for heart failure-related re-admission and mortality.

It should be mentioned here that the variation in plasma BNP and NT-proBNP concentrations in patients with stable chronic heart failure can be substantial. One study in 6 patients, followed for 6 weeks with weekly NP determination, showed an average intra-individual variation of 41% (4–232%) for BNP and 35% (8–103%) for NT-proBNP. Another study in 20 patients (2 measurements, 1 week apart) reported an average intra-individual variation of 16% (3–59%) for BNP and 8% (0–47%) for NT-proBNP.

Titration of treatment of heart failure to a specified BNP target value was investigated in a by now classical study by Troughton et al. In this prospective randomized study of 69 patients, the standardized medical treatment was titrated on the basis of a specific NT-proBNP target value or on the clinical Framingham heart failure score (target < 2, the score for compensated heart failure). After a median follow-up period of 9.5 months, the number of patients re-admitted for heart failure as well as the mortality was lower in the NT-proBNP group than in the clinical group. The usefulness of treatment of heart failure based on titration to a specific BNP or NT-proBNP target value is currently being investigated in a number of large-scale studies.

CONCLUSION

Large numbers of studies have now given a reasonably good picture of the place of BNP and NT-proBNP as a diagnostic tool in (suspected) heart failure. Both biomarkers have comparable diagnostic accuracy, with NT-proBNP (probably because of its longer half-life) showing a smaller intra-individual variation than BNP in stable chronic heart failure. In first-line settings, measurement of BNP or NT-proBNP can be useful to exclude the diagnosis of heart failure (as does a normal ECG). Highly elevated BNP or NT-proBNP concentrations are strongly suggestive of heart failure, both in first-line patients as in patients presenting to the Emergency Room with acute shortness of breath. There are indications that a rapid BNP test in the Emergency Room for patients with shortness of breath leads to more efficient treatment and to cost reduction.

Clinical and outpatient clinical treatment of patients with chronic heart failure on the basis of target values for BNP or NT-proBNP is an attractive concept, since judgement of the severity of heart failure by clinical observation is not very reliable. Ongoing studies will ultimately show whether a decrease in heart failure-related hospital admissions and in mortality can be achieved in this way.

REFERENCES


34. Rutten FH, Walma EP, Kruizinga GI, Bakx HCA,


