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B-type natriuretic peptide (BNP): can it improve our management of patients with congestive heart failure?

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Summary

Until recently no simple specific test existed for the differentiation of decompensated heart failure from other causes of acute dyspnoea, or to assess the prognosis of patients with severe heart failure or to optimize heart failure therapy in an individual patient. Measurement of B-type natriuretic peptide has become available as an easy-to-perform bedside test. Several studies have demonstrated it's usefulness in the emergency room to differentiate heart failure from other causes of acute dyspnoea or to guide the complex drug therapy in an individual patient with heart failure. This article gives a short overview on the clinical experience to use BNP-blood levels for the diagnosis and treatment guidance of heart failure.

Key words: BNP; heart failure; diagnosis; treatment

Introduction

The epidemic of heart failure (HF) is characterised by a steadily increasing incidence and prevalence and several studies predict a further increase over the next decades. This is due to demographic changes, ie, a larger proportion of elderly people, the higher prevalence of HF with increasing age, and an improved survival in patients with coronary artery disease [1]. However, the diagnosis of HF remained over all unchanged and is based on clinical history, physical examination, ECG, chest x-ray, and assessment of left ventricular function.

For the first time since the introduction of echocardiography some 20 years ago, a simple blood test appears to offer a significant advance in this area.

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B-type natriuretic peptide (BNP) is a 32-amino acid polypeptide secreted from the cardiac ventricles (figure 1) in response to ventricular volume expansion and pressure overload [2, 3]. BNP levels are elevated in patients with left ventricular dysfunction, and levels correlate with severity of symptoms and with prognosis. Numerous studies [3–38] including the paper by Kuster et al. [38] in this issue indicate that BNP does have the potential to considerably improve our management of patients with HF failure and may become a routinely assessed serum parameter in clinical medicine. In this review we will discuss the utility of BNP in different clinical situations of HF with specific focus on the differential diagnosis of dyspnoea and the optimisation of therapy.

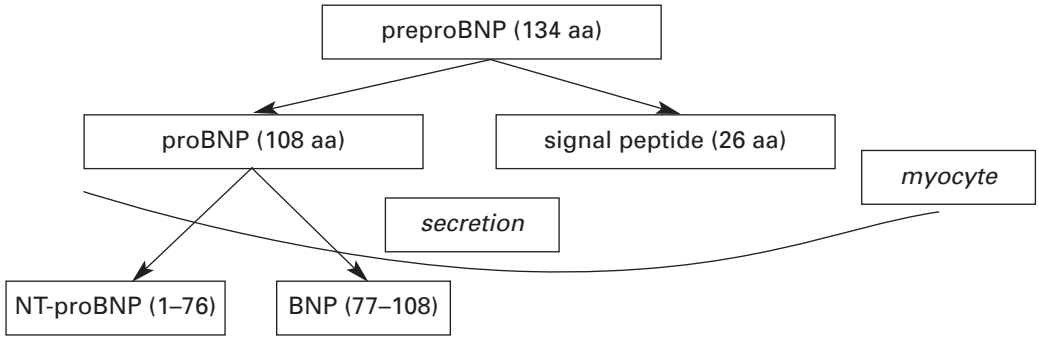

Figure 1

BNP is produced from the cardiac myocytes as a prepro hormone of 134 amino acids, which is clipped into a proBNP hormone. Upon stimulus for secretion, it is released into the blood as the fragment protein N-terminal proBNP and the BNP molecule itself. The N-terminal portion is made of 77 amino acids and is a biologically inactive protein. BNP holds the biological activity.

Diagnosis of dyspnoea

Acute dyspnoea is a common symptom in patients presenting in the emergency department. Heart failure and primary lung disorders account for the majority of cases. In general, a careful history and physical examination, often completed with laboratory tests for inflammation (pneumonia) and chest X-ray, have a good diagnostic yield. However, in some circumstances, particularly in the elderly and/or obese patients, and in the presence of primary lung disorders, early diagnosis of decompensated HF may be difficult yet critical to determine the most effective management [2, 3]. Atypical presentation, language barriers, comorbidity, the busy and often noisy atmosphere in the emergency room, difficulty in evaluating the acute breathless and the low diagnostic yield of chest X-ray in this situation render the correct diagnosis of decompensated HF a real challenge.

Numerous studies have shown that BNP levels are elevated in patients with left ventricular dysfunction [4–12]. In addition, BNP is significantly higher in patients with HF as the cause of acute dyspnoea as compared with patients whose dyspnoea is due to lung disease [13–19, 37]. Dao et al. [16] used the newly available point-of-care rapid assay for BNP (Triage Assay, Biosite Inc) in 250 patients presenting to the San Diego VA Healthcare Urgent Care Center. Patients diagnosed with HF (n = 97) had a significantly higher mean BNP concentration than the non-HF group (n = 139, 1076 ± 138 vs. 38 ± 4 pg/mL, figure 2). BNP at a cut off point of 80 pg/mL was found to be highly sensitive and highly specific for the diagnosis of HF. The negative predictive value of BNP concentrations under 80 pg/mL was 98% for the diagnosis of HF. Multivariate analysis revealed that a BNP added significant diagnostic information after all useful diagnostic tools in the emergency department were taken into account.

These results lead the FDA to approve the routine use of BNP for the differential diagnosis of acute dyspnoea in the emergency room. Moreover, the European Society of Cardiology Task Force for the Diagnosis and Treatment of Chronic heart Failure recently recommended the use of natriuretic peptides in the initial evaluation of patients with suspected HF [20].

The pilot studies mentioned above set the stage for a recently reported multicenter study [19, 37]. The Breathing Not Properly Multinational Study was a prospective diagnostic test evaluation study conducted in 7 centers. Of 1586 participants who presented with acute dyspnoea, 1538 (97%) had clinical certainty of HF determined by the attending physician in the emergency department. Participants underwent routine care and had BNP measured in a blinded fashion. The reference standard for HF was adjudicated by 2 independent cardiologists, also blinded to BNP results. The final diagnosis was HF in 722 participants (47%). At an 80% cut-off level of certainty for HF, clinical judgement had a sensitivity of 49% and specificity of 96%. At 100 pg/mL, BNP had a sensitivity of 90% and specificity of 73%. In determining the correct diagnosis (HF versus no HF), adding BNP to clinical judgement would have enhanced diagnostic accuracy from 74% to 81%. In those participants with an intermediate (21% to 79%) probability of HF, BNP at a cut-off of 100 pg/mL correctly classified 74% of the cases (figure 3). The areas under the receiver operating characteristic curve were 0.86, 0.90, and 0.93 for clinical judgement, for BNP at a cut-off of 100 pg/mL, and for the 2 in combination, respectively ($p < 0.0001$ for all pairwise comparisons). These data led the authors to conclude that evaluation of acute dyspnoea would be improved with the addition of BNP testing to clinical judgement in the emergency department.

However, it is important to note that there is still a lack of prospective data from randomised clinical trials establishing that a team in the emergency performs better with the use of this promising marker. One such trial randomising more than 400 patients has recently been completed at the University hospital of Basel. The final results of this and future trials will help define the role of BNP in this clinical setting.

In our own institution, we have found that the negative predictive value of BNP levels under 100 pg/mL is the strongest feature of this peptide. Although the positive predictive value in a given patient at a cut-off of 100 pg/mL is 80%, most patients with significant HF as a cause of their dyspnoea will have levels of >500 pg/mL, particularly with dyspnoea present at rest at the time of

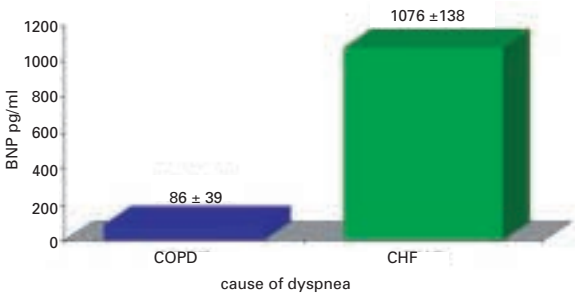

Figure 2

Patients with congestive heart failure (CHF) do have significantly higher BNP levels as compared with patients with dyspnoea due to chronic obstructive lung disease (COPD) [16].

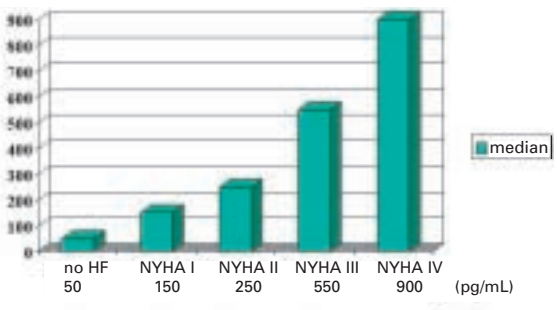

Figure 3

Correlation between the clinical severity of heart failure and BNP levels in the Breathing Not Properly (BNP) Multinational Study [19].

(or the hour preceding) venipuncture. Patients with pulmonary oedema often have a BNP >1000 pg/mL. Thus, in patients presenting with levels between 100 and 500 pg/mL, one may need to exclude baseline LV dysfunction without systolic HF, pulmonary embolism, and cor pulmonale.

Prognosis in HF

The assessment of an individual heart failure patient's prognosis is difficult. In patients with HF, there is a strong correlation between BNP and left ventricular end-diastolic pressure. Therefore, it is not surprising that BNP has been shown to be a powerful marker for prognosis and risk stratification in the setting of heart failure [21–31, 38]. Very high BNP levels, particular if unresponsive to medical therapy, herald a dismal prognosis.

Prognosis in primary pulmonary hypertension

In disorders primarily affecting the right ventricle, such as primary pulmonary hypertension (PPH), a strong correlation between BNP levels, the extent of volume and pressure overload (mean pulmonary artery pressure [32–34]) and prognosis has been reported. PPH patients with a BNP <180 pg/ml had a cumulative survival rate of 90% at 2-years as compared with only 20% in those with BNP >180 pg/ml [33].

Optimisation of therapy in HF

As a low BNP level at discharge is associated with a favourable prognosis, maximal suppression of BNP-levels may be a reasonable goal of medical therapy. This concept has been tested in two randomised trials [35, 36]. Because BNP is a volume-sensitive hormone with a short half-life (18 to 22 minutes), there may be a future for BNP levels in guiding diuretic and vasodilator therapy on presentation with decompensated HF. Most patients with chronic heart failure (HF) receive the same dose of angiotensin-converting enzyme (ACE) inhibitors because there is currently no measure of treatment efficacy. Murdoch et al. [35] sought to determine whether titration of vasodilator therapy according to plasma brain natriuretic peptide (BNP) concentration may be of value in the individual optimisation of vasodilator therapy in HF. Twenty patients with mild to moderate HF receiving stable conventional therapy including an ACE inhibitor were randomly assigned to titration of ACE inhibitor dosage according to serial measurement of plasma BNP concentration (BNP group) or optimal empirical ACE inhibitor therapy (clinical group) for 8 weeks. Only the BNP-driven approach was associated with significant reductions in plasma BNP concentration throughout the duration of the study and a significantly greater suppression when compared with empiric therapy after 4 weeks (–42% vs –12%, p = 0.03). Both treatment strategies were well tolerated and associated with favourable neurohormonal and haemodynamic effects; however, in comparison between groups, mean heart rate fell (p = 0.02) and plasma renin activity rose (p = 0.03) in the BNP group when compared with the clinical group. Whether the concept of pharmacotherapy BNP guided would produce a superior outcome to empirical trial-based therapy dictated by clinical judgement was tested in the second study. Troughton et al. [36] randomised 69 patients with impaired systolic function (left-ventricular ejection fraction <40%) and symptomatic HF (NYHA class II–IV) to receive treatment guided by either plasma NT-proBNP concentration (BNP group) or standardised clinical assessment (clinical group). During follow-up (median 10 months), there were fewer total cardiovascular events (death, hospital admission, or heart failure decompensation) in the BNP group than in the clinical group (19 vs 54, p = 0.02). At 6 months, 27% of patients in the BNP group and 53% in the clinical group had experienced a first cardiovascular event (p = 0.03). Changes in left-ventricular function, quality of life, renal function, and adverse events were similar in both groups. The authors concluded that NT-proBNP-guided treatment of HF reduced total cardiovascular events, and delayed time to first event compared with intensive clinically guided treatment.

Readmission after hospitalisation for heart failure is surprisingly common, estimated at 40–50% at 6 months in Europe and the United States. Considering that hospitalisation is the principal component of the cost for patient care (70% of the total direct costs), a reduction in HF hospitalisations is an appropriate goal, regardless of which treatment modalities are in place.

Limitations and area of uncertainties

In patients with chronic renal insufficiency, the half-life and therefore serum levels of BNP are significantly increased. Therefore, different thresholds need to be defined for this patient population. In our own experience, current cut-off values should only be applied in patients with a serum creatinine below 200 µmol/L.

In addition to the bed-site test measuring BNP, a second assay measuring NT-proBNP (Roche) has recently become widely available. Although both test seem to work comparably well, it is important to note their different cut-off values.

Data from randomised clinical trials are eagerly awaited and absolutely necessary to establish the role of BNP in different clinical settings. Particularly, its value as an adjunct or alternative to echocardiography will have to be defined. As BNP is considerably less costly, cost-effectiveness analyses are highly desirably.

The future for BNP looks promising. Patients with HF despite poly-pharmacotherapy have a tremendous morbidity and mortality exceeding that of most solid organ cancers. Improvement of care and outcome in these patients is definitely needed. BNP testing may be a significant first step.

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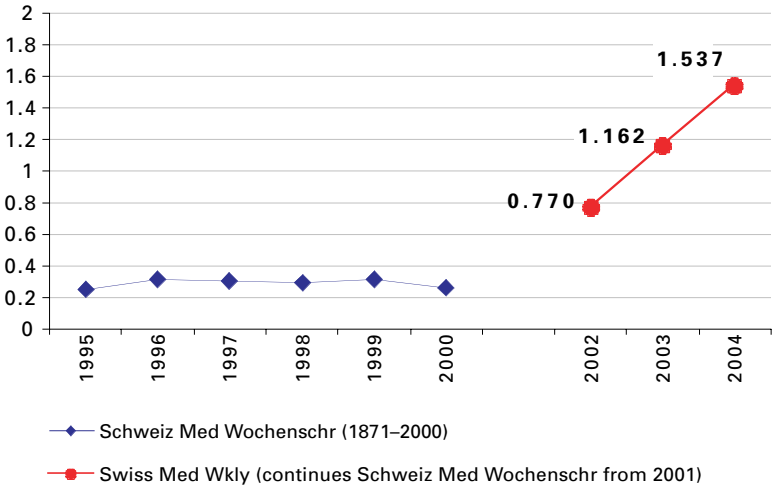

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