

**THE ROLE OF B-TYPE NATRIURETIC PEPTIDE IN HEART FAILURE
MANAGEMENT**

Abstract

Heart failure is a complex clinical syndrome that manifests itself with signs and symptoms which are neither sensitive nor specific for the diagnosis of heart failure. Natriuretic peptides and in particular b-type natriuretic peptide (and nt-proBNP) are widely used in clinical practice around the world as a marker of heart failure. BNP is primarily released from the left ventricle in response to pressure and volume overload. The strongest evidence for the use of BNP is to rule in or rule out heart failure as cause of breathlessness in people who present to the emergency room. There is enthusiasm for use of BNP as a marker of heart failure severity as well as a predictor of outcomes in people with heart failure and trials are ongoing. Nesiritide, a recombinant form of BNP is currently being tested as a possible treatment in people with acutely decompensated heart failure.

Introduction

Heart failure (HF) is an important cause of morbidity and mortality internationally, particularly among people aged 65 years and older.¹ Whilst there is no definitive data on the incidence and prevalence of heart failure in Australia, using data from clinical trials and international data, it is estimated that there is at least 325,000 Australians (2.8% population) who have symptomatic heart failure, with 30,000 new cases reported each year.² Recent advances in pharmacological and device therapy for HF in recent years have resulted in increased survival, leading to more people living longer with HF and its progressive symptoms.³

Difficulty with diagnosing heart failure

The common signs and symptoms typically associated with heart failure such as oedema, shortness of breath and fatigue are non-specific for heart failure. Whilst they may provide a provisional diagnosis, further investigation is needed to confirm the presence of heart failure.³ Further making the diagnosis of heart failure difficult is that signs and symptoms may not appear until late in the course of the disease for people with left ventricular dysfunction.

This difficulty associated with diagnosis can be seen in two studies which attempted to estimate the prevalence of heart failure in Australia. Both of these studies reported levels of previously undiagnosed HF.^{2,4} In the Canberra Heart Study for example, 44 (59%) of the subjects diagnosed with HF were in the preclinical stage of the illness.⁴ This has led to calls for a national health survey to explore the epidemiology and burden of HF in Australia.⁵ An

echocardiogram is the single most useful investigation for determining the presence of heart failure and the current Australian heart failure guidelines⁶ recommend that all patients with suspected heart failure should have an echocardiogram to investigate underlying structural abnormalities and systolic and diastolic function. However, there is currently limited access to echocardiographic services due to a lack of trained technicians, lack of services in rural and remote communities and increasing demand of services.⁷ In light of this, there is a need for other investigations with high sensitivity (proportion positive cases correctly identified as having the condition) and specificity (proportion of negative cases that are correctly identified as not having the condition) that determine the presence or absence of heart failure.

Physiology of BNP

Belonging to the family of natriuretic peptides that includes atrial natriuretic peptide (ANP) and c-type natriuretic peptide (CNP), BNP (b-type natriuretic peptide) has been proposed as a biomarker of cardiovascular disease and in particular a marker of heart failure.^{8,9} BNP was originally found in porcine brains and called brain natriuretic peptide.¹⁰ However subsequent investigation determined that ProBNP (the precursor of BNP) is a 108 amino acid prohormone released primarily from the ventricles into the bloodstream in response to cardiac wall stress caused by volume expansion or pressure overload.^{11,12} Whilst cardiac wall stress related to volume expansion and increased filling pressures are the primary causes of proBNP release, other conditions can also produce cardiac wall stress such as pulmonary embolism,¹³ pulmonary hypertension,¹⁴ and atrial fibrillation.¹⁵ Other factors that influence BNP levels will be discussed later.

ProBNP is cleaved into two parts, the biologically active 32 amino acid chain BNP and the inactive 76 amino acid neurohormone NT (n-terminal) proBNP.¹¹ New molecular forms of BNP are being found and work is being undertaken to discover their biological effects.¹¹ The role of BNP like other natriuretic peptides is to counteract the effects of the renin-angiotensin-aldosterone system. When released, BNP opposes the effect of the renin-angiotensin-aldosterone system through counter-acting vasoconstriction and producing natriuresis and diuresis.^{9,11} The clearance mechanism of BNP is through natriuretic peptide receptors and whilst it was initially thought that nt-proBNP was cleared solely by the kidneys, data is emerging to suggest that other mechanisms are involved.^{16,17}

Role of BNP in the emergency room

As discussed above, shortness of breath is a common symptom across many conditions and determining the underlying cause in some with an acute presentation is difficult. The Breathing Not Properly Study,¹⁸ was a multinational study which assessed the usefulness of BNP for 'ruling in' or 'ruling out' heart failure as the likely cause of breathlessness. The emergency room treating physicians were blinded to the BNP levels, and heart failure was determined by two independent cardiologists who were also blinded to the BNP level and the emergency room physician's diagnosis. This study showed that if the BNP level was less than 100pg/ml, heart failure was unlikely, and a BNP level above 500 pg/ml was likely to indicate heart failure as the cause of breathlessness. The utility and cost effectiveness of BNP testing in the emergency room was confirmed in the BASEL (B-Type Natriuretic Peptide for Acute Shortness of Breath Evaluation) study.¹⁹ The PRIDE (ProBNP Investigation of Dyspnoea in the Emergency Department) study showed that nt-pro BNP

could also be used to detect HF as the likely cause in people who present to the emergency department with dyspnoea.²⁰ In this study, a level below 300 pg/ml was proposed to “rule-out” HF. Different levels were proposed to “rule-in” HF depending on age and this will be discussed later.

Role of BNP in the Community

As the evidence for the use of BNP as a test to ‘rule in’ or ‘rule out’ heart failure increases, there is growing interest for its use as a screening tool for heart failure in the community. Currently, the gold standard for heart failure diagnosis includes a comprehensive physical examination and history and an echocardiogram.⁶ Unfortunately, due to current resources, a comprehensive screening program with echocardiography is not feasible, particularly the case in rural and regional Australia.⁵ It has been proposed that BNP testing could be used to screen whole populations with those with abnormal BNP results evaluated further.²¹ There are several issues with using BNP for population screening for the detection of subclinical HF. Firstly, the high specificity of (nt-pro) BNP is good to ‘rule out’ heart failure, however data from the Framingham Heart Study showed a low positive predictive value suggesting that mass screening with (nt-pro) BNP as suboptimal in low risk people.²² With a low prevalence of heart failure in many sectors of the community, using BNP a population screening tool is not feasible.²³ Furthermore, recent evidence suggests that elevated pre discharge levels of BNP are superior predictors of adverse cardiac events in patients with heart failure, rather than BNP levels on admission or during hospital stay.²⁴

Predictive value of BNP

Data from several large clinical trials have shown the usefulness of nt-proBNP to predict outcomes. The Copenhagen Hospital Heart Failure Study (CHHF), identified patients with preserved and reduced systolic function who had elevated nt-proBNP levels were at greater risk of adverse cardiac events.²⁵ Analysis of the Valsartan Heart Failure (Val-Heft) trial, a large multinational trial of valsartan in people with a reduced left ventricular ejection fraction (<40%) showed that BNP and nt-proBNP were the first independent predictors of outcome (all cause mortality, mortality or morbidity and HF hospitalisation) after adjustments had been made for clinical characteristics.²⁶ In the head-head comparison, nt-proBNP was a stronger predictor of mortality and morbidity and HF hospitalisation than BNP. The most powerful predictors of BNP and nt-proBNP levels in this analysis were age, LVEF and renal function. The predictive outcomes of nt-proBNP has also been seen in the COPERNICUS (Carvedilol prospective randomized cumulative survival) trial²⁷ and data from the Australia-New Zealand Heart Failure Group.²⁸

Association between BNP and disease severity

Investigators have demonstrated that the BNP level is associated with symptom burden and disease severity by correlating the level of BNP with the New York Heart Association functional class. However, some Investigators hypothesis that BNP levels in advanced heart failure may be elevated as a result of chronic wall stress and therefore may be less useful in evaluating treatment in this group of heart failure patients. Furthermore, incongruity exists between physician's perception of patients severity of heart failure and comparative biomarker results for BNP.²⁹

Biological caveats

- **Age**

Age has been shown to independently increase the level of circulating BNP and nt-pro BNP.^{30,31} This is thought to be due to age-related myocardial fibrosis and subtle diastolic dysfunction that current techniques may not be able to detect and reduced renal clearance.³² Data from the Breathing Not Properly trial showed that BNP levels independently increased with age.³³ Whilst some of this increase may be explained by the increased likelihood of diastolic dysfunction in this population, a study by Redfield and colleagues in a normal subset (in sinus rhythm without cardiovascular, renal, pulmonary disease or diabetes; on no cardiovascular medications; and with normal systolic, diastolic, and valvular function on Doppler echocardiogram) showed that a relationship still existed between age and BNP level.³⁰ This has led to calls for age specific values to be used in determining the levels to classify heart failure.

- **Gender**

The role of gender in contributing to BNP levels has been the subject of much debate in the literature.^{30,31,34} The study by Redfield above showed that in the normal subset ($n=767$) BNP levels were significantly higher in women (32% [CI 15% to 51%] Shionogi assay and 80% [CI 50%-116%] higher with the Biosite assay).³⁰ Several studies have shown females to have a higher BNP level than males.^{30,31,34} However, data from the Breathing Not Properly trial found that there were no differences in the BNP levels between males and females.¹⁸

- **Renal function**

The effect of renal function on the level of circulating levels of BNP is multifaceted. Whilst it would seem logical that impaired renal function would cause higher circulating nt-proBNP levels because nt-proBNP is primarily excreted from the kidneys, recent work has indicated that higher BNP and nt-proBNP in the setting of renal dysfunction is not solely related to reduced renal clearance.^{16,17} It may be that the higher natriuretic peptide levels may reflect a true level of disease rather than simple reduced clearance. In people with renal dysfunction, it is not uncommon to find higher atrial pressure, systemic pressure and ventricular mass, all factors that contribute physiologically to natriuretic peptide release.⁹ The commonality of renal dysfunction in people with HF may also blur the results of interpreting higher BNP levels in people with HF and renal dysfunction.

Three large trials of BNP^{18,19} and nt-proBNP²⁰ have shown the versatility of these natriuretic peptides to detect acute HF in people presenting to the emergency room irrespective of their eGFR. Whilst there was some decrease in the accuracy of the peptide to detect HF in people with reduced eGFR (<60 ml/min/1.73m²), if the age adjusted levels from the ICON trial³⁵ are used, there is no further need to change the cut points.³⁶

- **Obesity**

Obesity plays several key roles in the level of circulating natriuretic peptide. Obesity is a key risk factor for cardiovascular disease, a major precursor of HF. It has been shown that in obese people there will be a lower than expected natriuretic peptide level.^{37,38} The reason for this is yet to be elucidated although it is more likely to be reduced secretion than increased

secretion.³⁹ Because of this relationship, cut points should be used (<50 pg/ml to rule out HF if BMI >35 kg/m²).⁸ It has also been suggested that the BNP level should be doubled in obese people to correct for the effect of obesity.⁸

Interestingly, nt-proBNP appears to be less effected by obesity then BNP. An analysis of the data form the ICON study showed that when participants were categorised according to their BMI (lean <25.0, overweight 25.0-29.9, obese >30), nt-proBNP levels were relatively low, however nt-proBNP retained its diagnostic and prognostic capability.³⁵ A recent consensus panel determined that no adjustment of cut points for nt-proBNP was needed in obese people.³⁹

Issues with cut-points

The debate surrounding the usefulness of BNP in HF largely centres on what values should be used to 'rule in' or to 'rule out' HF. The general consensus based on data from the clinical trials is that that a BNP level below 100 pg/ml would 'rule out' HF as the cause of dyspnoea where levels above 400 pg/ml would 'rule in' heart failure (Nt-pro BNP <300pg/ml and for those under 50 years>450 pg/ml; 50-75 years 900 pg/ml and greater then 75 years 1800 pg/ml).⁸ These levels of course leave the so call 'grey zone' where HF can not be excluded, nor can be confirmed. Furthermore, adding to the ambiguity of grey zones and HF severity, in the REDHOT study (Rapid Emergency Department Heart Failure Outpatient Trial), researchers identified patients with HF whose BNP levels where within the 'grey zone' yet, had a NYHA class of III or IV.⁴⁰ But the issue is more complicated then this. As discussed above BNP levels can be influenced by various factors including

renal function, age, gender and BMI. BNP can also be elevated in other conditions including pulmonary hypertension, myocardial infarction/acute coronary syndromes, cirrhosis and septic shock.^{8,9} The BNP level like all pathology or physical findings can not be taken in isolation but must be considered as part of the whole clinical picture.

As the discussion above highlights, the utility of BNP is not as a stand alone test for the diagnosis of HF but should be used to compliment a comprehensive physical examination and history taking. The controversy surrounding the use of BNP by some clinicians and commentators is the desire for a test to replace the role of the clinician and eliminate the uncertainty that can come with a complex clinical syndrome such as heart failure.⁴¹

Acute vs chronic HF

Whilst much work has been done in people presenting to the Emergency Department with an acute onset of symptoms, the utility of BNP as a diagnostic tool in people with a more chronic onset of symptoms is less well known.³² It is yet to be determined how useful serial measurements are in people with HF. Whilst BNP increases in BNP levels have been shown to be predictive of outcomes, due to large intraindividual variability in levels,⁴² determining the extent to which an increase in BNP level is an indication of decompensation is yet to be determined.

Therapeutic role of BNP

Serial measurement of BNP as a way of monitoring disease progression is another way proposed that BNP can be used in heart failure. Whilst limited data is currently available,

data from trials such as STARS-BNP (Systolic heart failure treatment supported by BNP)⁴³ and STARBRITE (Strategies for tailoring advanced heart failure regimens in the outpatient setting: brain natriuretic peptide versus the clinical congestion score) have indicated that treatment guided by BNP levels may provide improved outcomes. In STARS-BNP, 220 subjects who were optimally treated with ACE Inhibitors, beta blockers, and diuretics by their treating HF specialists, were randomised to usual care or a goal of decreasing plasma BNP levels below 100 pg/ml. This study showed that the BNP guided strategy reduced the risk of CHF-related death or hospital stay. Whilst the smaller STARBRITE trial ($n = 130$) failed to reach its primary outcome of non-hospital days alive, like STARS-BNP, subjects who were randomised to BNP guided treatment had higher levels of ACE Inhibitors and beta blockers prescribed. Several other BNP guided trials are underway and their results are eagerly awaited. The largest trial completed to date, the TIME-CHF (Trial of Intensified vs Standard Medical Therapy in Elderly Patients With Congestive Heart Failure) study enrolled 499 people with systolic HF and a nt-proBNP level greater than 400 pg/ml (60-75 years) or greater than 800 pg/ml (75 years or older) and randomised them to either symptom guided therapy or symptom guided.⁴⁴ At the completion of 18 months follow up, no significant differences were seen in all cause hospitalisation or quality of life. There was a significantly higher survival free of HF hospitalisation in the nt-proBNP guided group. Interestingly, significant differences were observed between the two groups in the younger patients (60-74 years) but not in the older patients.

A recombinant form of BNP (nesiritide) has been approved by the Federal Drug

Administration in the United States for use in acute HF patients. Analyses of the early nesiritide trials raised concerns of possible adverse events including worsening renal failure and increased mortality.⁴⁵ In the FUSION II (The second follow-up serial infusions of nesiritide) study,⁴⁶ patients with two recent heart failure hospitalizations, ejection fraction < 40%, and New York Heart Association class IV symptoms, or New York Heart Association class III symptoms with creatinine clearance < 60 mL/min, were randomized to nesiritide (2- μ g/kg bolus plus 0.01- μ g/kg-per minute infusion for 4 to 6 hours) or matching placebo, once or twice weekly for 12 weeks. This study failed to show any clinical benefit over intensive outpatient management in these people with advanced HF. Whilst there was a higher incidence of hypotension in the nesiritide group, there was less predefined worsening renal function in the FUSION II trial. The safety and efficacy of nesiritide is continuing to be evaluated in the ASCEND-HF (Acute study of clinical effectiveness of nesiritide in subjects with decompensated heart failure) trial.

Conclusion

The role of natriuretic peptides, and in particular BNP, in the diagnosis and management of HF continues to be debated around the world. Whilst there is strong evidence for BNP testing in people presenting to the emergency department with shortness of breath where there is uncertainty about the diagnosis, the role of BNP in other areas of HF diagnosis and management including population screening, BNP guided treatment and prognostication with BNP requires further research. Opponents to the use of BNP argue that BNP or nt-proBNP provides no more information than what a comprehensive physical exam provides. Those in favour of its use argue that the research supports its use through improving

clinical certainty about the diagnosis, reduces time to initiation of the appropriate treatment, reduces length of stay and overall costs.

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