The use of natriuretic peptides in contemporary management of heart failure

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Introduction

Heart failure (HF) is a clinical syndrome with a constellation of symptoms related to pulmonary and hepatic congestion, decreased cardiac output with compromised tissue oxygenation and, in many cases, secondary fluid retention. The prevalence of HF has been steadily increasing, mainly as a result of the ageing population and improved survival of patients with acute coronary syndromes. Indeed ischemic heart disease contributes to around half of presenting cases of HF (ischemic cardiomyopathy). It has been estimated that 1–2% of the adult population has HF, but this proportion increases markedly with increasing age, such that around one in 10 patients over the age of 80 years will suffer from the condition. Accurate diagnosis of the clinical syndrome of HF is important given that it is so common. However, diagnosis of HF remains in many cases challenging. Symptoms, including dyspnoea and fatigue, are not specific and are common in patients with non cardiac diseases (respiratory disease, anemia etc.). Clinical findings in some patients may be subtle and, if available, investigations such as ECG and chest x-ray could be similarly nonspecific. The introduction of brain natriuretic peptide (BNP) assays represents an important advance in the early diagnosis of HF among patients presenting with symptoms of dyspnoea and oedema.

Brain natriuretic peptides – basic facts

The Natriuretic Peptides are a family of three cardiovascular hormones: Atrial (ANP), Brain (BNP) and C-type Natriuretic Peptides (CNP). All are low molecular weight proteins with ANP and BNP being released from the heart (atria and ventricles respectively) and CNP mainly being a vascular endothelium.

BNP-32 (32 amino acids protein) is secreted in response to increased ventricular wall stress after cleavage from its respective prohormone (proBNP).

The residual amino terminal portion (NT-proBNP) is released into the blood in equimolar quantities but remains functionally inactive. The biological actions of BNP-32 include vasodilatation, natriuresis, decrease in central sympathetic outflow and inhibition of renin, aldosteron and endothelin.[1] The plasma half life of NT-proBNP is longer than that of BNP (two hours vs 20 minutes respectively) making it potentially more suitable for diagnostic evaluation in the case of chronic HF.

Several factors influence the levels of BNP independently of cardiac disease, including age, female gender and renal impairment. Paradoxically, treatment with beta blockers may transiently raise BNP levels while obesity, treatment with loop diuretics and, to a smaller degree, with spironolactone and ACE inhibitors may decrease BNP levels.

Use of BNP in HF diagnosis and management

BNP and NT-proBNP levels have been found to be closely correlated with symptomatic status, left ventricular (LV) systolic and diastolic functions in patients with HF.

As a result their use in diagnosis of HF, prognostication, screening and treatment monitoring has been extensively studied. The ex-

isting literature on BNP use is summarised below.

BNP in the diagnosis of heart failure

The clinical utility for BNP to assist in clinical decision-making for the diagnosis of HF has been studied in several settings in both primary and secondary care. Several trials have assessed the diagnostic value of BNP estimation during initial patient assessment by the general practitioner, all of which established superiority over and above other conventional tests (including chest x-ray). [2,3] In a randomised, controlled trial in primary care, the addition of the NT-proBNP to traditional clinical evaluation of patients with suspected HF improved diagnostic accuracy by 21% (compared with only 8% in the control group with clinical review alone). In particular the high negative predictive value of normal BNP (levels below 50pmol/l) helped GPs to rule out heart failure in symptomatic patients.

In a secondary care setting 'The Breathing Not Properly' (BNP) trial enrolled a large cohort of 1586 patients presenting with dyspnoea to emergency departments in the US. BNP-32 was the most accurate predictor (when compared with history, symptoms, clinical signs and baseline investigations) of the presence or absence of HF.[4] Levels of 100pg/ml (220pmol/l for NT-proBNP) and above were highly discriminatory and were associated with 30-fold increased risk of HF.

Further study confirmed that BNP testing in patients with dyspnoea reduced time to correct diagnosis, the need for hospitalisation and intensive care, median hospital stay and overall mean treatment cost.

In summary, the combined data from the existing trials supports the value of BNP testing in the diagnostic work-up of patients with suspected heart failure in both primary and secondary care settings. In general, NT-proBNP levels below 50pmol/l exclude heart failure as a cause of dyspnoea. With results in the indeterminate range however (NT-proBNP levels between 50 and 220 pmol/l) heart failure is possible but other factors (e.g. atrial fibrillation, thyroid disease, LV hypertrophy) may be the underlying reason for the elevated levels. Levels above 220pmol/l in symptomatic patients strongly suggest heart failure.

Obviously availability of BNP assay does not remove the need for appropriate clinical assessment (including ECG and chest x-ray) and treatment of patients with suspected heart failure.

BNP as a prognostic marker

The presence of HF is associated with high morbidity and mortality, poor quality of life and frequent hospitalisations...BNP closely reflects the impaired systolic LV function and correlates with changes in LV ejection fraction and maximal oxygen uptake.

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High pre-discharge BNP levels (350ng/l for BNP-32, 500pmol/l for NT-proBNP) are powerful predictors of death and hospitalisations at six months.[5]

In the setting of acute coronary syndromes BNP adds further prognostic information over and above Troponin levels and LVEF and may even correlate with the degree of epicardial coronary disease and therefore ischemia in non acute settings. Elevated BNP levels have also been found to indicate worse prognosis in patients with pulmonary embolism. In asymptomatic patients with severe aortic valve disease (stenosis and regurgitation) significantly raised BNP may help in guiding the optimal timing of surgery.

BNP in screening for LV dysfunction

Use of BNP as a screening tool for asymptomatic LV dysfunction in unselected population has been generally disappointing. However the test performs well in high risk populations (e.g. patients with known coronary artery disease or referred for echocardiogram from primary care setting) and therefore may be utilised

Key Points

- BNP is secreted in response to increased ventricular wall stress.
- BNP testing in patients with dyspnoea reduces time to correct diagnosis, the need for hospitalisation and intensive care, median hospital stay and overall mean treatment cost.
- NT-proBNP levels below 50pmol/l help to exclude heart failure in symptomatic patients. With results in the indeterminate range however (NT-proBNP levels between 50–220 pmol/l) heart failure is possible but other factors (e.g. atrial fibrillation, thyroid disease, LV hypertrophy) may be the underlying reason for the elevated levels.
- BNP levels above 220pmol/l strongly suggest heart failure.
- BNP and NT-proBNP levels have been found to be closely correlated with symptomatic status, left ventricular (LV) systolic and diastolic functions in patients with HF.
- BNP testing does not remove the need for appropriate clinical assessment and treatment of patients with suspected heart failure.

as an initial test in those identified to be at high risk.[6,7] The potential role in other risk patient groups (such as patients with diabetes) and as screening tool for LVH and diastolic dysfunction is uncertain and further clinical studies are underway.

BNP to guide titration of HF therapy

The serum BNP level correlates closely with pulmonary wedge pressure and treatment outcomes in HF during hospitalisations. Troughton et al. studied 69 patients in whom the HF treatment was either clinically guided or titrated to reduce NT-proBNP levels to below 200pmol/l. The BNP guided treatment appeared superior with significant reduction of combined cardiovascular death, hospital admission and outpatient HF at 12 months.[8] However the use of beta blockers in this study was infrequent, thus no firm guidelines can be drawn at this stage. While the early studies are encouraging, at present the use of BNP to guide titration of therapy for patients with heart failure remains predominantly experimental with at least three large scale randomised trials underway to provide definitive data on the use of BNP for this indication.

BNP in treatment of HF

Native BNP has unique properties as its actions include vasodilatation, natriuresis, decrease in central sympathetic outflow and inhibition of renin, aldosterone and endothelin. The role of recombinant BNP (Neseritide) could therefore be ideal in the setting of decompensated HF. Intravenous Neseritide has been compared with other vasodilators and inotropes with favorable results and is currently indicated for use in acute decompensated HF in the US.[9] Higher costs of Neseritide are offset by lower costs of in-hospital care, lower readmission rates and lower mortality at six months.

Summary

In summary, BNP has multiple potential uses in the management of patients with cardiovascular disease, in particular heart failure. Currently, the clearest indication for BNP is to assist in the initial diagnosis of HF in symptomatic patients, particularly patients presenting in primary care with symptoms of dyspnoea or oedema.

BNP may assist with risk stratification in patients with established HF and potentially in other clinical setting (valvular disease). The role of BNP in screening selected (at risk) populations and guiding HF therapy remain currently the area of intense research.

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