B-type natriuretic peptide in the management of older persons with heart failure

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B-type natriuretic peptide (BNP) and the inactive N-terminal fragment of the precursor (NT-proBNP) are hormones predominantly produced by the cardiac myocyte. It has been shown that very high levels of circulating natriuretic peptides correlate with a diagnosis of heart failure. In view of this, the current NICE, SIGN and European Society of Cardiology guidelines on heart failure recommend the measurement of natriuretic peptides as part of the diagnostic pathway for patients with suspected heart failure in primary care. Patients should be stratified according to results with high risk patients referred and reviewed by specialist services within 2 weeks. There has also been interest regarding the potential use of natriuretic peptides in disease surveillance, therapeutic monitoring and inpatient discharge planning. Consequently, it is a test that we will encounter with increasing frequency in clinical practice.

Heart failure is common in older persons, hence geriatricians need to have an understanding of the implications of natriuretic peptide levels. The test can be affected by both physiological and pharmacological factors and this should be taken into consideration when interpreting results.

Introduction
Heart failure is a prevalent disease with significant associated morbidity and mortality. It affects at least 1 percent of the population with a steep increase to 13.7 percent of men and 12.5 percent of women over 75 years of age. The National Heart Failure Audit of 2010 suggested that 33 percent of heart failure patients will die within a year of hospital admission for decompensated disease. Early diagnosis and initiation of appropriate treatment in these patients is key to improving outcomes. In the past, the diagnosis of heart failure, and identification of those patients at risk of adverse outcomes has been a challenge based upon clinical assessment and echocardiographic evidence of ventricular dysfunction. B-type natriuretic peptide (BNP) and the inactive N-terminal fragment of the precursor (NT-proBNP) have been identified as useful biochemical markers in the diagnosis of heart failure and as a potential adjunct in disease surveillance. The aim of this paper is to give a synopsis of the use of natriuretic peptides in the diagnosis of heart failure and their potential in therapeutic monitoring. We will look specifically at some of the issues surrounding the measurement of BNP and NT-proBNP in the older patient along with interpretation of results.

What are natriuretic peptides?
Secretory granules within the heart were first identified in 1956 by Kisch et al during the study of guinea pig myocardium. This research was furthered by de Bold in 1981 who recognised a rapid and potent natriuretic response when injecting extract of atrial myocardium into rats. In 1988 Sudoh et al identified an amino acid structure within the porcine brain now recognised as BNP. We now know that BNP is in fact predominantly released from the ventricles in response to increased end diastolic pressure and volume. Conditions resulting in ventricular hypertrophy, volume overload or raised haemodynamic pressures such as heart failure lead to an increase in circulating BNP levels. The prohormone proBNP is cleaved inside of the cardiac myocyte to produce BNP and the inactive NT-proBNP. BNP has multiple neuroendocrine effects on the body.
including natriuresis, diuresis, vasodilation and smooth muscle relaxation.\textsuperscript{6,9} Immunoassays available to measure levels of BNP and NT-proBNP are either laboratory-based or rapid point of care testing. Results from different commercial assays are not interchangeable. This must be taken into consideration when interpreting results.\textsuperscript{10} BNP has a half life of 22 minutes,\textsuperscript{11} whereas NT-pro BNP has a half life of 1-2 hours.\textsuperscript{12} It has been hypothesised that given the shorter half life of BNP, it could potentially give a more accurate depiction of current cardiac state.\textsuperscript{13} Conversely NT-proBNP is deemed more stable with less biological variation.\textsuperscript{14} The Scottish Intercollegiate Guidelines Network (SIGN) looked at 19 observational studies on the use of BNP in the diagnosis of heart failure. It pooled the results and found the overall sensitivity of BNP in the diagnosis of heart failure to be 0.91 (95% confidence interval 0.90 to 0.93), and its specificity to be 0.73 (95% confidence interval 0.71 to 0.75). Similar results were found when reviewing NT-proBNP which demonstrated a sensitivity of 0.91 (95% confidence interval 0.88 to 0.93) and specificity of 0.76 (95% confidence interval 0.75 to 0.77).\textsuperscript{8} Clerico et al performed a systematic review of data published comparing the diagnostic accuracy of BNP and NT-proBNP in both acute and chronic heart failure using the online National Library of Medicine to identify studies. Overall, it concluded that both BNP and NT-proBNP had a high level of diagnostic accuracy in heart failure without significant difference between the two markers.\textsuperscript{15}

Factors affecting natriuretic peptide levels – potential pitfalls

Certain physiological factors may affect circulating BNP and NT-proBNP levels and should be taken into account when interpreting results. This is particularly pertinent in the elderly population where there is a higher proportion of patients with multiple comorbidities and polypharmacy. There is an association between increasing age and raised natriuretic peptide levels.\textsuperscript{14} Aside from heart failure, other cardiac abnormalities may be associated with increased levels of natriuretic peptide including atrial fibrillation, valvular disease and ischaemic heart disease.\textsuperscript{14} Additionally, non-cardiac conditions leading to myocardial stress have been shown to raise natriuretic peptide levels. This includes right heart strain secondary to pulmonary embolism, pulmonary hypertension and cor-pulmonale.\textsuperscript{15} Observational studies have shown a link between elevated BNP levels and impaired glomerular filtration rate. Natriuretic peptides are partially excreted by the kidneys, and therefore there is an inversely proportional relationship between eGFR and BNP.\textsuperscript{16} This was supported by Kimmenade et al who found this to be the case in patients with an eGFR of below 30ml/min/1.73 m\textsuperscript{2}. It has also been hypothesised that given the strong association between cardiac disease and chronic kidney disease, the high levels of BNP and NT-proBNP may be partly due to increased production from the stressed myocyte. Consequently, raised natriuretic peptide levels in patients with chronic kidney disease should not be entirely discounted and may signify underlying cardiac disease.\textsuperscript{17} Patients with a high BMI have been shown to have lower levels of natriuretic peptides in both acute and chronic heart failure.\textsuperscript{18} This should be taken into consideration when using natriuretic peptides in the diagnosis of heart failure in obese individuals, as their sensitivity may be reduced in this scenario.\textsuperscript{19} The gold standard pharmacological management of heart failure consists of an ACE- inhibitor, β-blocker, aldosterone antagonist plus a diuretic. It has been shown that treatment with an ACE-inhibitor reduces natriuretic peptide levels\textsuperscript{19}; therefore, a normal natriuretic peptide level from a treated patient does not exclude heart failure and further investigation may be warranted. Surprisingly, treatment with a β-blocker may cause a short term increase in natriuretic peptide levels.\textsuperscript{20} In summary, in isolation a moderately raised natriuretic peptide level does not diagnose heart failure. The aforementioned factors should be taken into consideration, and the results interpreted along with clinical assessment and cardiac imaging, most commonly by transthoracic echocardiography.

**Table 1: Causes of a raised BNP and NT-proBNP.**

<table>
<thead>
<tr>
<th>Causes</th>
<th>Heart failure</th>
<th>Left Ventricular Hypertrophy</th>
<th>Ischaemic Heart Disease</th>
<th>Atrial Fibrillation</th>
<th>Valvular Heart Disease</th>
<th>Hypertension</th>
<th>Chronic Kidney Disease</th>
<th>Pulmonary Embolism</th>
<th>Advanced Age</th>
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<tbody>
<tr>
<td>Drugs that antagonise the rennin angiotensin system</td>
<td>will lower serum levels of BNP and NT-proBNP.</td>
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Indications for BNP assay and current guidelines.

The National Institute of Clinical Excellence (NICE) guidelines on Chronic Heart Failure published in August 2010 recommend that, in patients presenting in primary care, serum natriuretic peptides are measured in patients with suspected heart failure, without a history of previous myocardial infarction. Additionally
it states that any patient with a BNP level of above 400 pg/ml or an NT-proBNP level of above 2000 pg/ml should be referred urgently for transthoracic echocardiogram and specialist review within a 2 week time period. This reflects the poor prognosis that correlates with high levels of BNP. Patients with BNP levels of between 100-400 pg/ml or NT-proBNP levels of 400-2000 pg/ml should have transthoracic echocardiogram and specialist review within 6 weeks. Patients with a known history of myocardial infarction and suspected heart failure should be referred directly for echocardiogram and clinical assessment within two weeks, obviating the need for BNP measurement.

The current SIGN guidelines concur with NICE that low BNP levels make heart failure an unlikely cause of symptoms. High levels in the absence of another cause make heart failure the probable diagnosis; whereas intermediate assays require further investigation. These guidelines do not specify numerical cut-offs for interpretation of BNP results and suggest that this should be decided locally. The 2008 European Society of Cardiology (ESC) guidelines for heart failure again recommend the use of BNP and NT-proBNP in the diagnosis of heart failure.

More recently NICE recommended that in patients presenting with suspected acute heart failure, a single measurement of serum natriuretic peptide should be taken. A BNP level less than 100 ng/litre, or a NT-ProBNP of less than 300ng/litre are the recommended thresholds for ruling out heart failure as a cause of the presentation.

The role of natriuretic peptides in disease surveillance and in guiding therapy

Natriuretic peptides may have a use in disease surveillance and treatment monitoring. Two large trials have explored the hypothesis that patients are more likely to receive aggressive pharmacological management of their heart failure using a natriuretic peptide guided model. The Trial of Intensified vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure (TIME-CHF) Randomized Trial looked at 18-month outcomes for NT-proBNP guided vs symptom guided heart failure treatment. Patients were stratified into either a 60 – 74 or over 75 years age range. It concluded that whilst there was an improvement in overall mortality and heart failure events in the 60 – 74 age range, this was not the case in the over 75s. Infact there was no overall improvement in mortality, and a greater rate of adverse effects. The BATTLESCARRED trial used a randomised control model to compare intensive standardised clinical management, and NT-proBNP guided therapy for heart failure. The results were similar, suggesting that natriuretic peptide guided treatment may well be beneficial in the younger patient, but not in the over 75s, who were less likely to tolerate maximum doses of drugs, and had reduced renal function.

In summary, current evidence suggests that BNP targeted therapy is not a useful strategy in the over 75 age group and could actually lead to an increased risk of an adverse outcomes for the patient. Consequently the titration of drugs is a balancing act between achieving recommended target doses and avoiding side effects, such as bradycardia, hypotension and deteriorating renal function.

What are the potential future uses?
The ESC heart failure guidelines have suggested the potential use of BNP as an aid to hospital discharge decisions and identifying those at high risk of adverse events. One single centre study looked at all admissions with decompensated heart failure to their emergency department over a 5-month period. NT-proBNP was checked within 24 hours of admission and discharge. The patients were then followed up at 6 months. This study concluded that increasing NT-proBNP levels during admission were a strong predictor of hospital admission, or death within 6 months of discharge. Patients with a ≥30% increase proved to have the poorest prognosis. Similar results were found in a study by Logeartetal with a high level of BNP being a strong predictor of either death or readmission at 6 months.

Conclusion
Current evidence suggests that there is a clear role for the measurement of BNP or NT-proBNP in the diagnosis of heart failure in primary care. There is no significant difference between the two tests and either may be used depending on what is available locally. Furthermore, NICE guidelines provide a clear pathway for high risk patients to be stratified and referred for urgent echocardiogram and specialist assessment. Rapid identification of these patients should allow early initiation of heart failure treatment and access to appropriate services. It is hoped that this will lead to an improved quality of life for the patient with a reduction in heart failure related morbidity and mortality.

Natriuretic peptide levels can be affected by various factors and this should be taken into consideration when interpreting results. They should be used in conjunction with clinical assessment. This is clearly relevant when using the test in elderly patients as on the whole they have a higher level of co-morbidity and
polypharmacy. The use of natriuretic peptides in therapeutic monitoring is not currently recommended in the older patient. They are less likely to tolerate maximum drug doses due to a higher rate of impaired renal function, drug interactions and adverse drug reactions.\textsuperscript{23,24} The use of natriuretic peptides as an adjunct when making discharge decisions shows promise, however more research is required in this area before it is utilised in clinical practice.\textsuperscript{25,26}

I have no conflicts of interest to declare.

**Learning points:**
- The test is easy to do and readily available
- It is useful for excluding heart failure in a primary care setting
- It can be used to identify high risk patients and ensure early echocardiogram and specialist review
- Some caution must be used when interpreting results given variability with age, sex, BMI, renal function and medication
- Potential for use in disease surveillance, but monitoring heart failure therapy is not recommended in the over 75s

**References**

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