REVIEW ARTICLE

B-type natriuretic peptide in the management of heart failure

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Objective To review the current literature on the use of B-type natriuretic peptide in the diagnosis and management of heart failure.

Data sources Literature search of PubMed was performed up to September 2007.

Study selection Key words for the literature search were 'heart failure' and 'B-type natriuretic peptide'.

Data extraction Original papers and review articles related to the use of B-type natriuretic peptide in the diagnosis and management of heart failure.

Data synthesis Heart failure is common in Hong Kong, and is associated with significant morbidity and mortality. Heart failure is often misdiagnosed. B-type natriuretic peptide may be regarded as a quantitative marker of heart failure; its levels have good diagnostic accuracy and can be measured with a rapid and simple bed-side assay and are useful in the assessment of patients with acute dyspnoea. Factors, such as obesity and renal impairment, alter B-type natriuretic peptide levels. Measurement of B-type natriuretic peptide facilitates improved medical outcomes, is cost-effective, and constitutes a good prognostic indicator for death and cardiac events.

Conclusions Determination of B-type natriuretic peptide levels is useful in the assessment of patients with acute dyspnoea, to exclude or diagnose heart failure, to facilitate improved medical outcomes, and is cost-effective. In addition, it is a good long-term prognostic indicator and can be used to guide heart failure treatment.

Introduction

Heart failure is associated with significant morbidity and mortality; the 5-year mortality rate is approximately 50%.[1] Heart failure is common in Hong Kong, with over 4500 new cases in 1997. In hospitals of the Hospital Authority, it is the 12th commonest reason for hospitalisation.[2] Among those who are over 45 years of age, the annual estimated incidence is 3/1000 in men, and 3.8/1000 in women.[3] In keeping with findings from the Framingham study, the main causes in Hong Kong are hypertension and ischaemic heart disease.[3] Other important risk factors are valvular disease, cor pulmonale, and idiopathic dilated cardiomyopathy.

Heart failure is difficult to assess clinically. Symptoms are not specific, and classically associated signs (including crepitations, peripheral oedema, a third heart sound, and a raised jugular venous pressure) are often absent. Consequently, overdiagnosis and underdiagnosis are common in patients presenting with acute dyspnoea.[1,4-6]

Echocardiography is the gold standard for establishing the presence of left ventricular dysfunction. However, it is not always available in the acute settings, such as accident and emergency departments. In addition, it may be difficult to undertake in a dyspnoeic patient who cannot lie still, and in those with obesity or co-existing pulmonary conditions. Furthermore, the findings may not represent an acute condition.[5]

B-type natriuretic peptide (BNP) is a marker of heart failure; its levels can be measured with a rapid, commercially available bed-side assay.[1,5]

Physiology of B-type natriuretic peptide

A basic understanding of the biochemistry and physiology of BNP can help clinicians

Key words
Diagnosis; Heart failure; Natriuretic peptide, brain

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in using it to assist management. B-type natriuretic peptide is a cardiac hormone produced in the ventricles in response to pressure or volume overload.[5] In the myocardium, the earliest precursor of BNP is pre-proBNP, which contains a signal peptide that is removed to produce pro-BNP. The latter pro-hormone is then cleaved into the inactive N-terminal proBNP (NT-proBNP) and BNP (that has the C-terminal fragment, which is biologically active). Both polypeptides enter the circulation.[7]

B-type natriuretic peptide exerts many physiological effects, which are principally mediated through the natriuretic peptide receptor-A. B-type natriuretic peptide acts by raising intracellular levels of cyclic guanosine monophosphate. The cardiac hormone relaxes vascular smooth muscle and increases capillary permeability. In the kidney, it increases the glomerular filtration, inhibits the release of renin, and reduces sodium re-absorption in the collecting ducts. It also inhibits the release of aldosterone and anti-diuretic hormone, whilst also reducing sympathetic nervous activity. By promoting vasodilatation, natriuresis, and diuresis, BNP reduces preload and afterload.[6,8]

B型鈉尿肽在治療心臟衰竭中的角色

目的 檢閱有關B型鈉尿肽在心臟衰竭的診斷和治療中的角色。

資料來源 利用PubMed搜尋至2007年9月為止的相關文獻。

研究選取 用關鍵詞'heart failure'「心臟衰竭」和'B-type natriuretic peptide'「B型鈉尿肽」搜尋有關文章。

資料選取 所有以B型鈉尿肽來診斷治療心臟衰竭有關的論著和綜述。

資料綜合 心臟衰竭在香港很常見，並造成顯著的致病率和死亡率，但一般難以輕易從臨床上簡單診斷。B型鈉尿肽是心臟衰竭的標記，它的量值臨床上具有準確預測性，而且能夠在病床邊簡單快速地量度，另外對於急性呼吸困難的病人也是個很有用的評估標記。一些因素如肥胖或是腎功能不全也會改變B型鈉尿肽的量值。利用B型鈉尿肽的值來指引治療心臟衰竭能夠提升治療成效，它也是個針對死亡或是心臟疾病預後的良好標記。

結論 B型鈉尿肽對於急性呼吸困難的病人是個有用的評估標記，可用來排除或診斷心臟衰竭。B型鈉尿肽促進了醫學的進步，兼具備高成本效益。此外，它也是個長期預後的良好標記，利用B型鈉尿肽的量值來指引心臟衰竭的治療常會提升治療成效。

Using B-type natriuretic peptide as a diagnostic tool

Thus, BNP appears to be a quantitative marker of heart failure. Rising levels correlate with the degree of left ventricular dysfunction and severity of symptoms.[1,5,9] N-terminal proBNP, which is co-secreted with BNP, has also been shown to be a useful diagnostic tool, with an accuracy comparable to that of BNP. However, cut-off values for NT-proBNP differ from those of BNP.[1,6]

In the acute setting, measurement of BNP levels can help differentiate between cardiac and non-cardiac causes of acute dyspnoea; the higher the level, the more likely that the cause is heart failure. In a study of 250 patients presenting with dyspnoea, the mean BNP value was 1076±138 pg/mL in those with acute heart failure, and 38±4 pg/mL in those without.[10]

A BNP level of lower than 100 pg/mL in the presence of acute dyspnoea virtually rules out heart failure with a negative predictive value of 89%.[5] This cut-off level has a 90% sensitivity, a 76% specificity, and a positive predictive value of 79% for the diagnosis of heart failure. A BNP level of higher than 400 pg/mL confirms a diagnosis of heart failure with a likelihood ratio of 95%.[11] While different cut-off values have been proposed, a systematic review of 10 studies involving over 3300 patients confirmed that the values of 100 and 400 pg/mL respectively, can be reliably used to exclude or diagnose heart failure.[12]

Although heart failure is unlikely with BNP levels below 100 pg/mL, and very likely with values exceeding 400 pg/mL, approximately 25% of patients with acute dyspnoea present with levels between 100 and 400 pg/mL, which is a diagnostic grey zone.[1] In such patients, acute dyspnoea may be cardiac or non-cardiac. Patients with stable left ventricular dysfunction typically have a baseline BNP level of above 100 pg/mL. However, in the absence of an acute exacerbation, their BNP levels tend to be less than 400 pg/mL.[11]

B-type natriuretic peptide values between 100 and 400 pg/mL may also be caused by conditions associated with right-sided strain, such as pulmonary embolism, cor pulmonale, or pulmonary hypertension.[1,11] In patients with pulmonary fibrosis, BNP levels may be raised in those whose degree of pulmonary hypertension is more severe.[13] With BNP values in the range of 100 to 400 pg/mL, and if these pulmonary conditions can be excluded, heart failure is the likely diagnosis.[11] Thus, clinical judgement is very important, and further tests (such as computed tomographic [CT] angiography or high-resolution CT scans) should be considered if there is suspicion of a pulmonary embolism or pulmonary fibrosis.

In the assessment of acute dyspnoea, the use of BNP is associated with better medical and economical outcomes.[14] It reduces the time to appropriate treatment, the need for admission or intensive care, and length of stay in hospital. However, these results

(from the BASEL study conducted in Switzerland[14]) do not necessarily mean that using BNP would also be cost-effective in the Hong Kong health care setting.

The US Food and Drug Administration has approved the use of the BNP assay for the diagnosis of heart failure, using a cut-off value of 100 pg/mL.[11]

The European Society of Cardiology guidelines[15] for the management of chronic heart failure recommend using BNP. If heart failure is suspected clinically, it is suggested that a BNP level be determined, together with an electrocardiogram (ECG) and a chest radiograph, to rule out other conditions. The guidelines state that a normal BNP test result "should obviate the need for further cardiological tests such as in the first instance echocardiography, as well as more expensive investigations", such as nuclear angiography or magnetic resonance imaging.[15]

Similarly the National Institute for Clinical Excellence guidelines[16] on chronic heart failure published in 2003 also recommend using BNP to rule out chronic heart failure: "Exclude a diagnosis through…ECG and/or natriuretic peptides (BNP or NT-proBNP) levels—where available". These guidelines advise that echocardiography should be performed in those with an abnormal BNP or ECG.[16]

Nevertheless, to establish the presence of cardiac dysfunction (a key requirement for the diagnosis of heart failure), echocardiography remains the method of choice.[15] This is in addition, of course, to its role in determining the aetiology (eg valvular disease, ischaemia, or cardiomyopathy).

B-type natriuretic peptide as a prognostic tool

A number of factors have been associated with increased mortality in patients with heart failure, including diabetes mellitus, a high New York Heart Association class, raised serum creatinine level, low left ventricular ejection fraction, oedema, and low blood pressure. However, these indicators are not strong predictors of mortality. In contrast, BNP is a better prognostic indicator—raised levels are associated with a high risk of death or cardiac events. For each 100 pg/mL increase, the relative risk of death increases by 35%.[4]

B-type natriuretic peptide–guided treatment

B-type natriuretic peptide–guided treatment of chronic heart failure is associated with better outcomes.[17] The STARS-BNP trial[17] randomised 220 patients into two groups. In the control group, patients were managed traditionally by clinical assessment and basic investigations such as ECG, complete blood picture, and renal function tests. In the second group, BNP levels were also monitored. Drug dosages of angiotensin-converting enzyme inhibitors, β-blockers, or diuretics, were adjusted to maintain BNP levels to below 100 pg/mL. During follow-up (mean, 15 months), BNP-guided treatment significantly lowered heart failure–related death or hospitalisation (24% vs 52% in the control group). In the BNP-guided group, medications were adjusted more frequently, and dosages of angiotensin-converting enzyme inhibitors and β-blockers were higher.

Similarly, NT-proBNP–based management is associated with better outcomes.[18] However, current guidelines do not recommend using NT-proBNP to monitor treatment of patients with heart failure, so further evaluation is required.[15,16]

Factors affecting B-type natriuretic peptide levels

Age and gender influence BNP levels; they are higher in females and increase with age. However, the standard cut-off values apply at any age and to either gender.[1,6] Renal disease increases BNP levels, and in those who have a glomerular filtration rate of below 60 mL/min, a cut-off value of 200 to 225 pg/mL should be used to exclude heart failure.[1,6] Obesity is associated with lower BNP levels. In patients with a body mass index of higher than 35 kg/m^2, a BNP level of lower than 60 pg/mL rules out heart failure, while levels of higher than 200 pg/mL are diagnostic.[1,6]

Chronic obstructive pulmonary disease is an important differential diagnosis of acute dyspnoea. In this condition, BNP levels are elevated, but not as much as in heart failure.[6] In patients with chronic obstructive pulmonary disease or asthma, a level of lower than 100 pg/mL has a negative predictive value of 97.7%, which makes BNP useful to exclude heart failure.[19]

B-type natriuretic peptide is elevated in atrial fibrillation, even though it is not clear whether this is related to the arrhythmia itself, or to associated factors such as left ventricular hypertrophy or hypertension. For this reason, BNP testing is less useful in the presence of atrial fibrillation. However, using a cut-off value of 200 pg/mL improves diagnostic accuracy. Finally, BNP levels are also raised in acute coronary syndromes and in valvular heart disease. In these conditions, BNP also has a prognostic role.[6]

Conclusions

Heart failure, which is associated with significant morbidity and mortality, is common in Hong Kong. B-type natriuretic peptide is a quantitative marker of

heart failure—rising levels correlate with the degree of left ventricular dysfunction and clinical status. B-type natriuretic peptide is especially helpful for ruling out heart failure when evaluating patients with acute dyspnoea, and when it is used as an adjunct to clinical evaluation, ECGs, and chest radiography. A BNP level of less than 100 pg/mL rules out heart failure with a negative predictive value of 89%. Heart failure is very likely in patients with levels exceeding 400 pg/mL. Intermediate values require further evaluation, and conditions such as pulmonary embolism, pneumonia, or cor pulmonale should be excluded. The use of BNP levels in the evaluation of patients with acute dyspnoea has been proven cost-effective and is associated with improved medical outcomes. However, levels must be interpreted according to the clinical picture. Obesity and renal impairment are associated with lower and higher BNP levels respectively, for which different cut-off values should be used. B-type natriuretic peptide is a strong prognostic indicator in heart failure, and possibly superior to traditional prognostic factors. Raised levels are associated with a greater risk of death or cardiac events. Finally, BNP-guided treatment of chronic heart failure appears superior to standard management.

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