Brain natriuretic peptide in heart failure and beyond

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ABSTRACT

Hospital admissions with heart failure (HF) are increasing worldwide. It is the main reason for hospitalization of elderly patients. Heart failure affects nearly 15% of patients aged >75 years. Prognosis after diagnosis of HF is comparable to that of cancers with 50% survival after 4 years of mild HF and 50% after one year in more severe cases. Current data increasingly suggest that measurement of brain natriuretic peptide (BNP) is very useful in diagnosis, treatment, prognosis and risk stratification of patients with HF and beyond. This paper reviews the available literature concerning the BNP and N-terminal pro brain-type natriuretic peptide to assess their role in current medical practice.

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Heart failure (HF) is a serious cardiac condition with high and increasing incidence, especially in the elderly population. It is one of the major causes of hospital admissions in people >75 years of age, and it carries a poor prognosis comparable to cancer. Symptoms of HF can be similar to those of other cardio-pulmonary and systemic diseases, and it is very important to make an early and confident diagnosis of HF in order to be able to provide the proper management as soon as possible. It has always been rather difficult to make a firm diagnosis of HF based on the clinical picture alone. In recent years, brain natriuretic peptide (BNP) and N-terminal pro brain-type natriuretic peptide (NT-proBNP) have emerged as a very helpful tool in making diagnosis and differentiating HF from other causes of dyspnea. Brain natriuretic peptide >500 pg/ml is highly suggestive of HF whereas level <100 pg/ml can be reassuring that we are not dealing with a case of HF. Brain natriuretic peptide and NT-proBNP are also very useful in following the response to treatment, in assessing the prognosis and outcome of patients with HF. However, BNP can be elevated in other cardiac conditions such as valvular heart diseases where it can be used in the future to decide on the timing of the valvular surgery and in certain congenital conditions such as patent ductus arteriosus (PDA). It can also be used as a prognostic marker in patients with acute coronary syndrome (ACS) and chronic stable angina. Yet, one has to be careful that BNP may be elevated in elderly, female, renal impairment, atrial fibrillation, hypertrophic obstructive cardiomyopathy (HOCM). Although at sometime exogenous recombinant human BNP (Nesiritide) has been used in treating patients with acute heart failure, there is less enthusiasm these days to use it in view of its suspected side-effects.

Physiological consideration. Brain natriuretic peptide is a cardiac neurohormone, so named as it was initially identified in the brain but later found to be also released more importantly from the heart, particularly from the ventricles. It is released as pre pro BNP then cleaved enzymatically to the NT-proBNP and BNP on ventricular myocardial stretch.[1] Measurement of BNP or NT-Pro BNP is useful in appropriate clinical setting. In normal subjects, plasma concentration of BNP and

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NT-Pro BNP are similar (approximately 10 pmol/l). However, in patients with left ventricular dysfunction, plasma NT-Pro-BNP rises more than BNP, with NT-Pro-BNP concentration approximately 4-fold higher than BNP concentration.[2] Brain natriuretic peptide and NT-proBNP may be equally useful as an aid in the diagnosis of congestive heart failure (CHF) in patients presenting to the emergency department with dyspnea.[3] But, in one study it was found that BNP assay is a more useful diagnostic indicator for cardiogenic pulmonary edema than proBNP in patients aged ≥65.[4] Furthermore, the Investigation of Dyspnea in the Emergency Department (PRIDE) study concludes that levels of both NT-proBNP and BNP are significantly lower in patients with non-systolic CHF (NS-CHF); however, in contrast to NT-proBNP, BNP may be falsely negative in up to 20% of patients with NS-CHF and does not correlate with symptom severity in NS-CHF. N-terminal pro brain-type natriuretic peptide appears superior to BNP for the evaluation of suspected acute CHF with preserved left ventricular ejection fraction.[5] In general, a BNP level <100 pg/ml excludes acute decompensated HF and levels >500 pg/ml indicates decompensation. Brain natriuretic peptide is elevated in HF. Other causes of elevated BNP includes ACS, pulmonary embolism and sepsis and it implies sub-clinical left ventricular dysfunction. Further, BNP is also elevated in valvular heart diseases such as aortic stenosis, aortic regurgitation, mitral regurgitation and in atrial fibrillation, HOCM, elderly, female patients, and patients with renal impairment. Brain natriuretic peptide has multiple physiological functions. It has natriuretic, diuretic and hypotensive effects. Other effects include inhibition of Renin angiotensin system (RAS), endothelin secretion, and systemic and renal sympathetic activity. These effects of BNP may be beneficial for the heart failure patients. It is also suggested that BNP may protect against collagen accumulation in the heart.

Measurement of BNP and cost effectiveness. Initially BNP concentration used to be assessed by competitive radio immunoassays (RIAs) method, later replaced by noncompetitive immuno radiometric assays (IRMAs) because they are more precise and sensitive and do not require preliminary sample extraction.[6-9] In 2000, a rapid BNP assay became available, which takes only 10-15 minutes in comparison to 12-36 hours of earlier methods. While interpreting the results of BNP measurement, few important factors need to be remembered. Plasma BNP concentration can vary with the method of assay, genetic factors, age, gender, body weight and the renal status of the patient. Normal values tend to be higher with increased age, women, non-obese and in renal insufficiency. But PRIDE Study concludes that the use of NT-proBNP testing is valuable for the evaluation of the dyspneic patients with suspected CHF, irrespective of renal function.[10] Other studies showed that NT-proBNP closely correlates with BNP and rapid measurement of NT-proBNP or BNP useful in establishing or excluding the diagnosis of CHF in patients of acute dyspnea when used in conjunction with other clinical information.[11] Increasing volume of evidence showed that measurement of BNP is cost effective in the diagnostic evaluation of the patients presenting with dyspnea in the emergency department. Measurement of plasma BNP concentration is a very efficient and cost effective mass screening technique for identifying patients with various cardiac abnormalities regardless of aetiology and degree of left ventricular systolic dysfunction that could potentially develop into obvious HF and carry a high risk of cardiovascular events.[12]

Clinical utility of BNP. **To evaluate the suspected HF** in patients presenting with acute dyspnea of uncertain aetiology in the emergency room. Brain natriuretic peptide values > 400 pg/ml is diagnostic of HF and <100 pg/ml have a very negative predictive value for HF whereas values between 100-400 pg/ml are not very helpful in this setting due to lack of adequate sensitivity and specificity. Other causes to be considered in intermediate values includes pulmonary embolism, cor pulmonale, left ventricular dysfunction without current exacerbation. Brain natriuretic peptide increases proportionately to the left ventricular dysfunction and HF severity and it is not a useful tool to distinguish systolic from diastolic HF.[13] N-terminal pro brain-type natriuretic peptide appears to be a sensitive and specific means of distinguishing pulmonary from cardiac causes of dyspnea in elderly patients. An optimal diagnostic strategy requires use of 2 cut-offs and further investigations of the patients with values in the grey area namely values between 100 pg/ml and 400 pg/ml.[14] But, it was found that audiometric parameters (S3-3rd heart sound and electromechanical activation time [EMAT] are the interval from the onset of Q wave of the ECG to the S1) have better overall performance for detecting decompensated HF than does BNP.[15]

To monitor patients with an established diagnosis of HF, especially those with moderate to severe HF. Such measurement can be made as an adjunct to out-patient follow up visits. A rise in plasma BNP above patient's own baseline value should trigger closer assessment for a possible exacerbation of HF.[6]

To assess the efficacy of treatment of HF. Significant reduction of BNP level indicates response to current therapy and may obviate further modification/titration of treatment. All the drugs used to treat HF reduce BNP except digoxin. Heart failure patients with high BNP values after one month of cardiac resynchronization therapy (CRT) have worse prognosis during follow-up. Therefore, in these patients, other therapeutic options should be considered.[16] Brain natriuretic peptide guided therapy is superior to home-based nursing care (HBC) alone in HF patients who were hospitalized due to cardiac decompensation.[17]

Brain natriuretic peptide also used to assess the prognosis of HF. Serial determination of plasma BNP help in the prognostication in patients with chronic HF. Persistent elevation of plasma BNP despite optimal medical therapy implies poor prognosis. Analysis of more than 4000 patients from the Val-HeFT trial showed that a plasma BNP level in the highest quartile (≥238 pg/ml) at baseline had a significantly greater mortality at 2 years than those with a plasma BNP in the lowest quartile (<41 pg/ml) (32.4% versus 9.7%).[18] Plasma BNP level has a linear correlation with the prognosis in HF. Every 100 pg/ml increase in plasma BNP is associated with 35% increase of the relative risk of death. Plasma BNP level also correlates with New York Heart Association (NYHA) functional class, ranging from 244-917 pg/ml for class I to Class IV. Increased BNP also identifies patients with high risks of sudden death, and may be a better predictor than other parameters, such as NYHA class.[19] In addition to assisting in the emergency department diagnosis and triage, NT-proBNP concentrations at presentation are strongly predictive of 1-year mortality in dyspneic patients.[20] A simple multimarker strategy combining the 3 best single biomarkers; BNP, blood urea nitrogen and troponin I (TnI) is not superior to BNP alone in predicting outcomes in HF.[21]

Brain natriuretic peptide as a therapy in HF. Exogenous recombinant human BNP (nesiritide) has an ever increasing role in the treatment of decompensated HF. The US Food and Drug Administration approved it as the first new parenteral agent for the treatment of HF a decade ago. It produces prompt hemodynamic and clinical improvement in patients with decompensated HF by reducing pulmonary capillary wedge pressure (PCWP), pulmonary artery pressure, right atrial (RA) pressure and systemic vascular resistance and thus results an increase in cardiac output (CO). Nesiritide is the best indicated for patients with decompensated HF, NYHA class 1V and has clinical evidence of fluid overload. Patients who are relatively hypotensive, hypovolemic and over-diuresed should not receive Nesiritide treatment. Other patients who should not be treated with Nesiritide are those with aortic stenosis, HOCM, cardiogenic shock. Nesiritide is more effective for rapid hemodynamic and symptomatic improvement, better tolerated and has fewer side effects than other vasodilators in these sets of patients as indicated by the Vasodilation in the Management of Acute Congestive Heart Failure (VMAC) Study Group Trial and the Prospective Randomized Evaluation of Cardiac Ectopy with Dobutamine or Natrecor Therapy (PRECEDENT) Trial. It binds to A-type natriuretic peptide receptor of vascular smooth muscle and endothelial cells and produces vasodilatation via Guanosine monophosphate pathway. Nesiritide is inactivated by a clearance receptor on the cell surface and also by neutral endopeptidase cleavage. Recommended dose of Nesiritide is 2 mic/kg intravenously bolus followed by infusion of 0.01 mic/kg/min. Unfortunately, the safety of nesiritide is now questioned based on 2 meta-analyses suggesting that nesiritide may be responsible for a worsening of renal function and an increased mortality. In the absence of further large scale studies with relevant end points, which are now unlikely to be conducted, nesiritide is rapidly disappearing from the therapeutic armamentarium.[22]

Brain natriuretic peptide in acute coronary syndrome (ACS). Elevated plasma BNP and NT-Pro- BNP found to be associated with an increased mortality in patients with ACS.[6] One of the important study in this area is Global Utilization of Strategies To Open Occluded Arteries (GUSTO IV) ACS trial[23] wherein the analysis of 6809 patients with non-STE ACS were assayed for N-Pro-BNP retrospectively. Patients with lowest decile of NT-Pro-BNP (≤98 ng/L) had a significant lower mortality rate at one year than those in the highest decile (>4634 pg/L), 0.4% versus 27.1%. This prognostic correlation of N-Pro-BNP is stronger than other prognostic markers such as cardiac troponin T and I (cTnT) and C-reactive protein (CRP). In addition to increased mortality, higher BNP is also associated with increased risk of new or recurrent myocardial infarction (MI) and new or worsening HF in this group of patients.

Brain natriuretic peptide in stable angina. Study of the role of NT-Pro-BNP in stable angina showed that those with significantly higher level of NT-Pro-BNP at presentation had a much higher mortality than those with lower level. The clinical correlate of those patients with higher NT-pro-BNP level were old

age, low left ventricular ejection fraction (LVEF), Diabetes, old MI. N-terminal pro brain-type natriuretic peptide provides prognostic information on all-cause mortality independent of conventional cardiovascular risk factors and left ventricular dysfunction.[24]

Brain natriuretic peptide in screening asymptomatic left ventricular dysfunction. Asymptomatic left ventricular dysfunction (ALVD) defined as an left ventricular ejection fraction ≤40-35% in asymptomatic patient, is quite common in the community. Incidence varies between 1-4% depending upon the age in different studies. Therapy in ALVD with EF ≤40% proven beneficial, while the efficacy of treatment in patients with mild ALVD (EF = 41-54%) is not known. Another rationale for screening is that outcome is better if effective Rx initiated earlier as shown in Studies of Left Ventricular Dysfunction (SOLVD) prevention trial and SOLVD treatment trial. Screening for ALVD with plasma BNP is more cost effective than echocardiography. However, plasma BNP is not always dependable. At present, routine screening with plasma BNP or echocardiography for ALVD is not recommended.[25] The more sensible approach is to select patients with multiple risk factors for ALVD and screen them with plasma BNP.

Brain natriuretic peptide in valvular heart disease. There is increasing body of evidence that the level of BNP is also important in valvular heart diseases. Brain natriuretic peptide level increases in aortic stenosis (AS), aortic regurgitation (AR), mitral regurgitation (MR). N-terminal pro-BNP is linked to the severity of AS and NYHA class and is an indicator for AVR. Therefore, it is a useful biomarker to evaluate severity of AS, monitor disease progression at an early stage and decide on optimal time for AVR.[26] In severe AS, natriuretic peptides provide important prognostic information beyond clinical and echocardiographic evaluation. N-terminal-proBNP independently predicts symptom free survival and preoperative NT-proBNP independently predicts postoperative outcome with regard to survival, symptomatic status and left ventricular function. Thus, neurohormones may gain particular importance for timing of surgery in asymptomatic severe AS.[27] Some studies suggested that plasma BNP concentration in left ventricular systolic dysfunction is associated with left ventricular diameter and function, rather than causes of HF.

Brain natriuretic peptide in congenital heart disease. The BNP test showed highly predictive diagnostic values in PDA. Brain natriuretic peptide levels were significantly higher in this group of premature infants with PDA.[28]

Limitations of use of plasma brain natriuretic peptide. In the evaluation of the patients with acute dyspnea, the intermediate rise of BNP (100-400 pg/ml) will not differentiate between different causes of dyspnea (decompensated HF, pneumonia, acute pulmonary embolism). Furthermore, some patients with symptomatic HF may have normal BNP level. While assessing the response to therapy for severe chronic HF, plasma BNP level may not be helpful in guiding therapy because in some patients level may remain high regardless of the treatment. Clinical assessment remains the cornerstone to guide therapy in this group of patients. Only plasma NT-Pro-BNP can be used to guide therapeutic response in patients treated with nesiritide.

In conclusion, BNP is proving to be of growing importance in the diagnosis and management of patients with HF, yet its final role is still to be fully defined, as its role in many other cardiac conditions. In this article, we tried to discuss the evidence supporting the use of BNP or NT-proBNP in HF and other conditions. We hope it will help in wider application of this valuable test in Saudi health system with ultimate goal of improving patient's care , which so far seems not to have adopted it fully.

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