Original Article

Is Measurement of BNP Worth its Value for the Diagnosis of Congestive Cardiac Failure?

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Objective: To assess the diagnostic role of NT pro BNP assay in patients suffering from heart failure.
Design: Case series study.
Methods: This study was done in the departments of Medicine & Cardiology, Liaquat University of Medical & Health Sciences Hospital Hyderabad, which is a tertiary care center. A total of 104 patients suffering from heart failure, proven via clinical examination, echocardiographic evidence and elevated NT proBNP assay. Receiver operative characteristic curve for NT proBNP was constituted after diagnosing the patients on clinical grounds and then confirmation of CCF via EF of <55% on echocardiography.
Results: A total of 65 males and 39 females were selected. Mean (SD) age was 54.65 (± 12.5). NYHA class II, III and IV had a representation of 21/67/16 (20.2/64.4/15.4%) respectively. NT pro BNP levels were 9045 (±8960). ROC curve had an AUC of 0.88 for NT proBNP assay.
Conclusion: NT proBNP is a useful tool for the diagnosis of heart failure, albeit emphasis should be on full utilization of combination of the ever important clinical examination with elevated levels of NT proBNP, which should be further evaluated via echocardiography.
Key Words: NT proBNP assay, Heart Failure, Diagnosis.

Introduction

Heart failure (HF) is a complex syndrome which is defined by symptoms of HF, typically breathlessness or fatigue either at rest or during exertion or ankle swelling, in combination with objective evidence of cardiac dysfunction at rest. [1] The most common cause of HF is coronary artery disease, but other well known aetiologies are hypertension, valvular disease, cardiomyopathy and myocarditis. [2]Most patients with HF suffer from a variety of signs and symptoms that influence their health status, quality of life and prognosis. For the diagnosis of HF a variety of diagnostic tests is available including assessment of clinical signs and symptoms of HF, laboratory blood tests, radiological examinations, electrocardiography and echocardiography.

The definitive diagnosis of heart failure by clinical means is sometimes questionable, when associated chronic pulmonary and cardiac diseases are present .[3]

In 1988 a new cardiac natriuretic peptide, B-type Natriuretic Peptide (BNP) was discovered. It has shown to have both prognostic as well as diagnostic properties in the emergency department and out-patient settings. [4]

Three types of natriuretic peptides have currently been identified in human serum: atrial type (ANP), brain type (BNP) and C type (CNP).

BNP and ANP are hormones, which are initially synthesized as pro-hormones and later cleaved into their active hormone states, in part due to response to ventricular wall stretch as seen in congestive heart disease. In this process, the active hormone is created (BNP) along with an inactive N-terminal fraction (NT-proBNP) in a 1 to 1 ratio. While both BNP and NT-proBNP are used diagnostically, the serum concentrations of NT-proBNP are considerably higher than BNP due to its longer half-life and greater stability. Consequently NT-proBNP has provided better utilization as a marker for CVD. [5]

Recently, several papers have shown its value in the assessment of individuals with stable coronary heart disease and chronic stable angina. [6]

The diagnosis of congestive heart failure usually rests on symptoms and signs through New York Heart Association (NYHA) functional classification, ECG and chest x-ray. Echocardiography gives specific diagnostic information, but this essential service is not available in many hospitals of our country.

Recent trials provided strong evidence that BNP and NT-proBNP are powerful diagnostic tools in exclusion and diagnosis of HF. The Breathing Not Properly study showed, by means of receiver operating characteristics analyses, that a BNP value of 100 pg/ml was the optimal value to differentiate patients with dyspnoea caused by HF from patients with dyspnoea due to pulmonary pathology at the emergency department. [7]

The rationale of conducting this study was to evaluate the diagnostic potential of NT proBNP assay in our setup and the see whether economic cost of ordering

this assay in every patient who is suffering from congestive cardiac failure is justified or not.

Materials and Methods

Setting: Department of Cardiology (in patients only) of Liaquat University Hospital Hyderabad. Single center tertiary care hospital.
Duration of Study: One year (from January to December 2009)
Sample Size: A total of 104 patients were selected.
Sampling technique: Non probability consecutive sampling.
Sample Selection:
Inclusion Criteria: Confirmed cases of heart failure with a functional class of II, III or IV (New York Heart Association) were selected.
Exclusion Criteria:

- Age <16 years
- AMI at the time of admission
- Pregnancy
- Malignancy
- RHD
- COPD

Study Design: Case series study.
Data Collection:
We recruited 104 consecutive inpatients with the clinical diagnosis of heart failure referred to the Department of Cardiology, Liaquat University of Medical & Health Sciences during January to December 2009.
The local research ethics committee approved the study protocol and all patients gave written informed consent.
Initial reporting criteria were shortness of breath at rest or on mild to moderate exertion. At baseline screening, patients had a full medical history taken, clinical examination performed (via Framingham heart failure criteria) and NYHA class assigned. The patients who were clinically diagnosed as having congestive cardiac failure were further triaged to have a 2-D echocardiogram (with flow Doppler study). If left ventricular dysfunction along with a reduced ejection fraction was reported then the values of proBNP were checked during the first admission. Patients were followed up every month or more frequently as required till six months.
Measurement of NT-proBNP plasma levels
Blood samples were collected in ethylenediamine-tetraacetic acid-containing tubes. The samples were then spun at 3000 rpm for 10 min at 0°C. The plasma was then extracted and frozen in aliquots at −70°C until analysis. NT-proBNP was measured using a chemiluminsecent immunoassay kit (Roche Diagnostics) on an Elecsys 2010 analyser.
Follow-up
The primary end point was all-cause mortality. Secondary end-point was the re-hospitalization rate, and worsening of the cardiac failure. Patients were followed up until the endpoint was reached or December 2009. Median follow up period was 3.4 months.
Data Analysis:
Statistical package for social sciences (SPSSTM) version 16 was used for data processing purpose. Normally distributed, continuous data, unless otherwise stated, are expressed as mean values (±SD).
To compare the predictive value of NT-proBNP, receiver operating characteristic (ROC) analysis was performed and the area under the curve calculated.

Results

The baseline clinical characteristics are presented in Table 1. A total of 104 patients were selected, who were predominantly male (62.5%) whereas only 37.5% female were selected. Overall majority of patients (84.6%) were in NYHA functional class II or III, so it is clear that patients suffering from end-stage cardiac failure were in a minority.

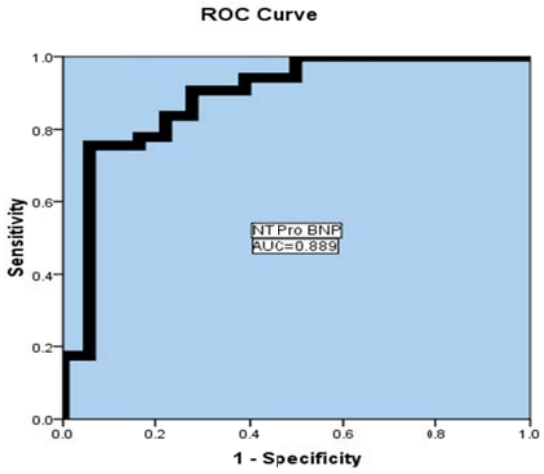
Table I: General patient characteristics in 104 patients with Heart Failure

Demographic	Patient Values (Means ± SD or %age)
Age	54.65 ± 12.5
Male / Female	65/39 (62.5/37.5%)
Weight (kg)	79 ±19
Height (cm)	162 ±8.9
BMI	30.1 ±6.3
NYHA Class (II/III/IV)	21/67/16 (20.2/64.4/15.4%)
NT Pro BNP	9045.93 ±8960.18

NOTE: SD = Standard Deviation, BMI= Body Mass Index, NYHA = New York Heart Association
Rest of the result is presented in Tables and Graphs.
Figure 1 shows the receiver operative characteristic (ROC) curve for the diagnosis of heart failure via only NT proBNP. The area under the curve (AUC) for NT proBNP is 0.889, which translates into approximately 90% of the patients which can be easily diagnosed by utilizing the value of NT proBNP. This shows that NT proBNP is 88.9% sensitive and 100% specific for the diagnosis of heart failure.
Figure No. 1. Receiver Operative Characteristic Curve showing the diagnostic potential of NT Pro BNP in the diagnosis of Heart Failure (N = 104)

Discussion

Natriuretic peptides are peptide hormones released into the circulation in response to increased myocardial stretch and wall tension, producing vasodilatation, natriuresis, and inhibition of the rennin–angiotensin and sympathetic nervous systems. BNP is co-released with



NT pro BNP predominantly from the left ventricle in response to such stimuli.

Indeed NT-pro BNP has come a long way since its importance was witnessed in early nineties. The earliest studies demonstrated that NT pro BNP concentrations were elevated among patients with heart failure, [8] and since then many studies showed similar spectrum of results which ultimately allowed a much deeper understanding of important role of this marker in the evaluation of patients with suspected or proven acute destabilized HF.

The earliest comprehensive studies on NT pro BNP were done in Spain and New Zealand [9, 10]. The New Zealand study was done by Lainchbury et al in Christchurch. This study showed that the concentrations of NT pro BNP were considerably higher among patients with acute HF compared with patients who had dyspnea due to causes other than HF. In that study, Lainchbury et al, compared the diagnostic potentials of the level of NT proBNP using two assays; Roche diagnostic assayTM and Biosite BNP assay™. Both assays showed receiver operating characteristic curve (ROC) value of 0.89 (as an average of both assays). A similar profile with both assays meant that both were very compatible with each other. This finding is exactly same in our study which shows ROC area under the curve value of 0.88 (with Roche diagnostic assay™).

The Spanish study done by Bayes-Genis et al [11] showed an even higher value of area under curve (AUC) of 0.96, which meant that NT proBNP assay was even more sensitive and specific than thought previously. Moreover this study once again highlighted the fact that NT proBNP was accurately diagnosing the true positives and it was also important in discernment of previously unsuspected HF among those with pulmonary disease: a concept known as HF "hidden" by pulmonary disease. The investigators also proposed a novel dual cut point strategy using an NT proBNP value of 253 ng/L as a cut-off point to rule out acute HF (a value below this and the possibility of acute HF was very remote) and a value of 973 ng/L to get true positive cases of HF.

In our study we picked symptomatic HF cases (regardless of cause involved) and proposed a cut off value of 200 pg/ml for the diagnosis of HF.

Mueller et al [12] did a similar study and selected acutely symptomatic individuals with presumed diagnosis of heart failure in the emergency department. They did a head to head comparison of Roche proBNP assay with automated assay of Abbott. This study had a similar ROC result compared to our study and this once again reinforced the idea that all assays had similar potential to diagnose or rule out HF accurately.

The most authentic and up to date study after which proBNP assay became a norm in all healthcare centers was the landmark PRIDE (ProBNP Investigation of Dyspnea in the Emergency department) study. [13] In this study Januzzi et al selected 599 patients presenting with acute dyspnea to the emergency department setting. In PRIDE study a total of 209 patients with acute decompensated HF had significantly higher NT proBNP values than those without acute HF as the cause of their dyspnea. Moreover, the increasing values of NT proBNP paralleled the severity of NYHA functional class of HF. PRIDE study proved that NT proBNP was the "Gold Standard laboratory test" for the diagnosis of HF.

The PRIDE study not only established irrefutable evidence of value of NT proBNP as the diagnostic test of choice for HF, but it also found that NT proBNP screening was also useful in the diagnostic evaluation of several important patient subgroups, including patients with renal impairment, prior COPD and patients with diabetes mellitus.

In contrast to PRIDE study our study only aimed for the diagnosis of HF in symptomatic patients. Our study also showed that a correlation exists between the functional class of NYHA and the levels of NT proBNP, although our study lacked a uniformity of NYHA class as only a minority of patients belonged to class IV NYHA, therefore generalization cannot be made on our study and this issue needs to be explored further.

PRIDE study also analyzed the value of NT proBNP assay with the clinical judgment of the physician. After examining the patients, the physicians were asked to provide an estimate of likelihood for the presence of acute HF, and subsequently this estimate was compared with the value of NT proBNP testing. The ROC curve of NT proBNP was superior to that of clinical estimate of the examining physician.

In our study we compared the Framingham Heart Failure diagnostic criteria with NT proBNP testing and the result was very similar to PRIDE study in that the ROC curve of NT proBNP value was significantly larger than Framingham Heart Failure diagnostic criteria.

The PRIDE study also demonstrated the fact that greatest ROC curve was obtained when clinical

estimation was combined with the testing of NT proBNP. This reinforced the value of clinical judgment in the diagnosis of HF. Similar values were shown to be present in our study.

Similar results were obtained in Improved Management of Patients with Congestive Heart Failure (IMPROVE-CHF) study. [14] The main crux of IMPROVE-CHF study was to compare (via a randomized trial) unblended versus blinded NT proBNP testing for the evaluation of patients with dyspnea in the emergency department. This study optimally proved that unblended NT proBNP testing was associated with shorter stays in the emergency department, and a significant reduction of 35% in rehospitalization during two months of follow up and no adverse outcomes associated with these improvements in utilization.

In our study the cut point for the diagnosis of chronic HF was taken as 200 ng/L. As mean age of study subjects was 54 years the cut-off point was quite appropriate. Usually the diagnostic cut-off point taken for the diagnosis of chronic HF in studies done earlier was 100 ng/L, but soon it came to pass that this cut-off point was riddled with uncertainties. For example PRIDE study showed that only if patients <50 years were considered for data analysis then a level of 450 ng/L would be more appropriate. On the other hand Breathing Not Properly Multinational Study [6] which proved that increasing age causes rise in pro BNP and so can produce a false positive alarm for the presence of normal patient. Another study was designed to explore this issue further. The analysis was performed via ICON-International Collaborative of NT proBNP Study trial. [15] The aim of this trial was to design appropriate cut points for NT proBNP. It ultimately suggested that the cut-off point is related with appropriate age group and so values of 450 ng/L, 900 ng/L and 1800 ng/L were suggested for increasing age groups. When age brackets were ignored then this study proposed a unified cut-off value of 300 ng/L for all ages. We took a value near that mark in our study.

It was noted that on its own the evaluation of NT pro BNP levels had a high sensitivity and specificity. It picked up majority of patients with cardiac failure and its normalcy effectively ruled out the diagnosis of cardiac failure.

Conclusion

The authors felt that measuring levels of NT pro BNP was definitely worth its cost when evaluating a suspected case of cardiac failure. This relatively new and innovative laboratory measurement would definitely provide much help and support in hospitals where dedicated echocardiographic services are not available.

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