Original Article

Diagnostic Accuracy of BNP Levels in Detection of Heart Failure

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Objective: Evaluation of serum Brain Natriuretic Peptide levels as screening test in the diagnosis of left ventricular failure or congestive heart failure

Material and methods: This cross-sectional survey was conducted at the Department of Medicine, Nishtar Hospital and Ch Parvez Ellahi Institute of Cardiology Multan from Feb 2006 to August 2006. A total of 50 patients were studied. Sampling was performed by non probability convenient type sampling technique.

Results: Out of the 50 patients, 47(94%) patients had ejection fraction of less than 45% and were diagnosed as cardiac failure, as confirmed by echocardiography. Among these cases BNP levels were found to be elevated in 36(72%) patients, whereas in 11 (22%) cases, BNP levels were falsely negative. Only 3 patients (6%) in whom initial clinical diagnosis was heart failure, were later found to have negative echocardiography (EF > 45%). Two patients (4%) with negative echocardiography (EF > 45%), had the BNP levels also negative i.e. below the cut-off point, whereas BNP was falsely positive in 1 patient Sensitivity and specificity of BNP (by ELISA) was found to be 80% and 66% respectively and accuracy was 80%.

Conclusion: BNP measurements in the blood, is a new technique to diagnose heart failure. The clinical sensitivity and specificity of BNP (by ELISA) was although lower than echocardiography but it can be a good alternative for echocardiography.

Key words: Heart failure, B-type natriuretic peptide, Left ventricular failure, Echocardiography.

Introduction

Brain natriuretic peptide is a cardiac neurohormone specifically secreted from the ventricles in response to volume expansion and pressure overload.[1] Levels of Brain natriuretic peptide have been shown to be elevated in patients with left ventricular dysfunction and correlate with the New York Heart Association class, as well as with prognosis[2,3] A plasma Brain natriuretic peptide > 100pg/ml diagnosed congestive heart failure with a sensitivity, specificity, and predictive accuracy of 90,76 and 83 percent respectively.[8] Lower values were associated with more accurate negative predictive values (for a value of 50 pg per milliliter, the negative predictive value was 96 percent).Choosing values > 125 or > 150 pg/ml decreased sensitivity, increased specificity, and did not change overall predictive accuracy[4]. Plasma concentration of Brain natriuretic peptide levels falls after effective pharmacological therapy of congestive cardiac failure. Drugs like Angiotensin converting enzyme inhibitors, ß-Blockers & Digoxin can alter the level if taken for more than three months[5]. Brain natriuretic peptide may be useful in distinguishing between cardiac and non cardiac causes of acute dyspnea. Heart failure is sometime difficult to diagnose particularly in urgent care setting. Although echocardiography is considered the gold standard for the detection of left ventricular dysfunction[6,10] it is expensive, is not always easily accessible. This study was designed to evaluate serum Brain Natriuretic Peptide levels as screening test in the diagnosis of left ventricular failure or congestive heart failure.

Material and Methods

This cross-sectional survey was conducted at the Department of Medicine, Nishtar Hospital and Ch Parvez Ellahi Institute of Cardiology Multan from Feb 2006 to August 2006. 50 patients with clinical evidence of heart failure were admitted during the study period. Sampling was performed by non probability convenient type sampling technique. All the patients with clinical evidence of heart failure such as: Raised Jugular venous pulse, S3 gallop, Pulmonary congestion, basal crackles, narrow pulse pressure, irrespective of age, sex, etiology like Ischemic Heart Disease, Hypertension, valvular heart diseases and concomitant illnesses like Diabetes Mellitus & Ischemic dilated cardiomyopathy were included in the study for echocardiographic assessment of severity of heart failure & measurement of Brain Natriuretic peptide levels.

Patients on pharmacological therapy of congestive heart failure like Angiotensin converting enzyme inhibitors, ß-Blockers and Digoxin for more than 3 months were excluded. Unstable angina unless their predominant symptoms at presentation was dyspnea. Patients whose dyspnea was clearly not secondary to, like congestive heart failure Chest trauma or cardiac tamponade. Renal Failure, Chronic Obstructive Pulmonary diseases (COPD) who didn't have baseline ventricular dysfunction were also excluded.

After admission of the patient in ward, Patients with acute shortness of breath were assessed clinically for evidence of congestive heart failure and designed proforma was filled up to rule out exclusion criteria.

Patients with heart failure were classified on the basis of functional class defined by New York Heart association to asses the clinical severity.[7]

A single blood sample was taken from each patient in a tube and allowed to coagulate. Serum was separated for analysis to find Brain Natriuretic peptide levels in serum. Enzyme Immunoassay (ELISA) technique was applied to measure Brain Natriuretic peptide levels.

Echocardiography was performed on every subject to find ejection fraction.

To make an effective diagnosis of congestive heart failure 45% cut off value of ejection fraction was applied as provided in literature i.e, patients with ejection fractions less than 45% were labeled as heart failure[9].

The normal limit for serum brain natriuretic peptide levels, provided by the manufacturer of the kit was applied to diagnose the patients of heart failure [8].

Later serum Brain Natriuretic Peptide levels were compared and correlated with the ejection fractions to find out the efficacy of this in vitro technique relative to echocardiography.

Data analysis

Data was analyzed on computer program SPSS v 10.0. Relevant descriptive statistics frequency and percentage were computed for qualitative variables like Gender, Ejection fraction and Brain Natriuretic Peptide. Mean and standard deviation for quantitative variable like Age was calculated.

Clinical sensitivity and specificity of the Enzyme Immunoassay (ELISA) relative to echocardiography was calculated taking the number of positive cases observed in echocardiography as true positive. Finally correlation was computed for Brain Natriuretic Peptide and Ejection fraction.

Results

BNP level were found to be elevated in 36 (72%) patients, whereas in 11 (22%) cases, BNP levels were found to be negative i.e. below the cut-off point. However clinical heart failure with negative echocardiography (EF > 45%) and positive BNP value was found in one patient. Two patients (4%) had clinical heart failure with negative echo result (EF > 45%) and BNP levels were also negative i.e. below the cut-off point. Sensitivity, specificity and accuracy of BNP relative to echocardiography was found to be 81%, 75% and 80% respectively.

Validity of BNP test was evaluated by measuring its sensitivity, specificity and accuracy. The following two-by-two table is a tool, used, for the evaluation of BNP test in this study.

Discussion

In this study we evaluated the importance of the BNP as a new diagnostic tool to diagnose heart failure in addition to echocardiography which is a gold standard.[16,18]

Table 1: *Modes of presentations of heart failure patients in the study (n = 50).*

Presenting Manifestation	No of cases	Percentage
History IHD	42	89%
Idiopathic	7	14%
VHD	1	2%
Symptoms & Signs Orthopnea	32	64%
PND	28	28%
Nocturnal Cough	24	48%
Elevated JVP	28	56%
Basal Crackles	46	96%
Wheezing	16	32%
Pedal Edema	24	48%

VHD=Valvular Heart Disease; IHD=Ischemic Heart Disease; PND=Paroxysmal Nocturnal Dyspnea; JVP=Jugular Venous Pulse

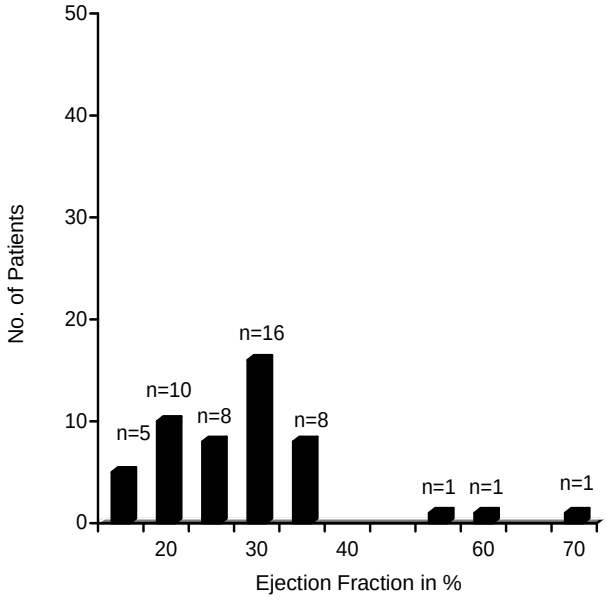

Figure 1: *Ejection Fractions of Various Patients.*

To date several studies have been done on BNP for its role in HF of any etiology. In one study it was observed that best clinical predictor of CCF was increase in heart size[4]. Diagnostic accuracy of CCF by history was 95%, by PND was 65% and by basal crepts 69%.[4] But in cases where the

diagnosis of heart failure is not clear, especially in the presence of lung diseases, which may have similar clinical presentation. In these situations clinician usually takes help from other modalities.

Among non invasive techniques to diagnose heart failure echocardiography, radionuclide ejection fraction and chest radiograph are preferred tools. Sensitivity and specificity of echocardiography was more than 95%.[17]

Heart failure can be due to impairment in the contractility of myocardium or diastolic dysfunction. BNP is an independent predictor of high LV end-diastolic pressure and elevated BNP levels can accurately depict diastolic abnormalities seen on echocardiography, regardless of whether the patient had symptoms of heart failure. Evaluation of patients with diastolic dysfunction was observed by Doppler echocardiography at Mayo Hospital Lahore in 1998 by Liaqat Ali and colleagues.

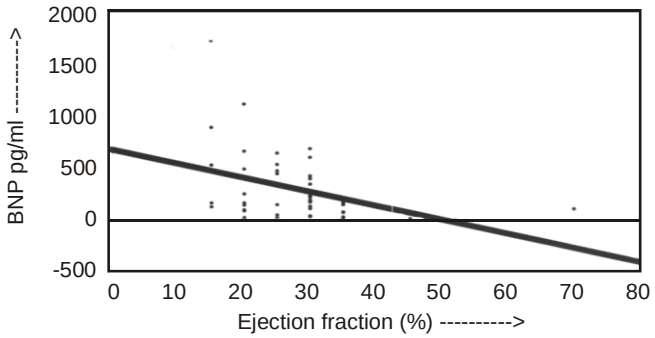

Figure 2: *BNP Levels versus ejection fractions.*

The most authentic study until now on BNP was by seven centered multinational study "(Breathing Not Properly -BNP)"by Maisel et al in 2002 on rapid measurement of BNP levels in emergency diagnosis of heart failure They did a prospective study on 1586 patients, who presented to emergency with complaints of dyspnea and confirmed HF in 744 patients on basis of chest radiograph, echocardiography etc. However they did not find any clue of HF in 770 patients. They finally got BNP levels of all the 1586 cases of dyspnea, they used 100 pg/ml as a cut off value and found BNP level were markedly elevated in CHF group They calculated the sensitivity and specificity of BNP to be 90% and 76% respectively.

In our study the sensitivity and specificity we calculated was 81% and 75% respectively. Their results underscore our observations. Probable difference in the results was due to number of reasons. Firstly, the difference between the sample sizes in two studies was quite significant. Secondly, time factor was important as they analyzed BNP as bed side assay (rapid point of care test). There is a median time delay of 30 hrs in present study, from withdrawal of sample to its analysis by ELISA technique. This was due to non availability of the test in Multan; samples had to be sent to other city at a distance place. This unavoidable delay in analysis might have changed the results.[19] Thirdly stability and recovery of different natriuretic peptide at different settings of frozen storage could be different, this can also effect the interpretation of results with other researchers. BNP values which has been indicated by Valli N in 2000 that time delay in analysis may result in underestimation of BNP. We would have gone for bedside analysis of BNP which could have reflected the sensitivity and specificity values approachable to international studies but non availability of bed side kits limits such approach.

Our findings correlated to some extent with the study performed by Bettencourt and colleagues. They selected 100 cases who were suspected to have HF. They confirmed 85 cases to have the cardiac dysfunction. Their statistical data revealed that BNP levels showed an excellent accuracy for diagnosis of heart failure. The accuracy of BNP we calculated was 80%

The present study also demonstrates the relation of BNP levels with severity of HF. In our study the patients with class IV have high levels of BNP as compared to those who presented in NYHA F-c III which is relatively less severe stage of heart failure as compared to class IV (Figure 3). This thing was also observed by Maisel A in 2001. He correlated the levels of BNP with LV pressure and amount of dyspnea and concluded that BNP increase with severity just as "white count" do in infection.

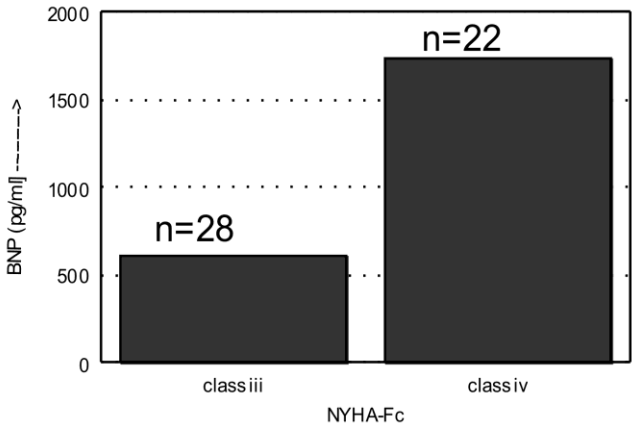

Figure 3. *Relation of bnp levels with the severity of heart failure*

BNP in an urgent care setting is a useful tool in diagnosis as well as deciding the appropriate treatment. He measured BNP and reliably predicts the presence or absence of LV dysfunction. In addition to its importance in emergency settings, rapid BNP testing is likely to be of particular

value for diagnosis in primary care, where it may find a role in rationalizing demand for echocardiograohy.[3,12]

BNP is a sensitive test to rule out HF. It has several potential diagnostic uses: screening populations to identify asymptomatic ventricular dysfunction, assisting in the diagnosis of patients with nonspecific symptoms (e.g., dyspnea), monitoring the effectiveness of heart failure therapy and estimating prognosis.[13,15] Studies have also confirmed that BNP is a novel marker of increased risk of death and CHF in patients presenting with UA and NSTEMI (with or without CHF) and elevated levels of BNP are also associated with higher mortality risk among patients with non–ST-elevation ACS.[11] BNP exhibiting a stronger relationship with death and CHF, and cardiac troponin[14] being predictive of death and recurrent ischemic events.

Diastolic dysfunction is difficult to diagnose especially when systolic function of heart is normal.[20,21,23] As we have discussed that BNP as also an effective tool to detect diastolic dysfunction. Rapid measurement of BNP in the settings of normal systolic function correlates with the presence or absence of diastolic abnormalities on echocardiography.[22,23] Thus, future studies will determine whether BNP levels can be a part of a gold standard for diagnosis of heart failure especially diastolic dysfunction.

Conclusion

Based on this discussion, it is clear that BNP is a reliable tool for the rapid bedside diagnosis of heart failure.

The use of this should be encouraged among emergency department physicians. BNP also provide a very sensitive tool for detecting early CHF and may serve to identify patients with unsuspected hemodynamic consequences of coronary ischemia. Furthermore elevated plasma concentration of BNP at presentation in patients with UA and NSTEMI predicts higher short-and long-term mortality as well as new onset CHF. Another potential use of BNP is management of heart failure.

References

1. Maeda K, Tsutamota T, Wada A, Hisanaga T, Kinoshita M. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. Am Heart J 1998; 135: 825-32.
2. Krishnaswamy P, Lubien E, Clopton P, et al. Utility of B-natriuretic peptide levels in identifying patients with left ventricular systolic or diastolic dysfunction. Am J Med. 2001; 111: 274-9.
3. Maisel AS, Koon J, Krishnaswamy P. Utility of B-natriuretic peptide as a rapid, point-of-care test for screening patients undergoing echocardiography to determine left ventricular dysfunction. Am Heart J 2001; 141: 367-74.
4. Maisel AS, Krishnaswamy P, Nowak RM, McCord J, Hollander JE, Duc P, et al. Rapid measurement of B-type natriuretic peptide in the emergency diagnosis of heart failure. N Engl J Med 2002; 347: 161-7
5. Stanek B, Frey B, Hulsmann M, Berger R, Sturm B, Strametz-Juranek J, et al. Prognostic evaluation of neurohumoral plasma levels before and during beta-blocker therapy in advanced left ventricular dysfunction . J Am Coll Cardiol 2001; 38: 436-42.
6. Khawar S, Qureshi HJ. Normal value of Echocardiographic measurements in healthy individuals of Pakistan. Biomedica.sec. 1996; 12: 64-7
7. Massie B M, Amidon T M. Functional classification of heart disease. In: Lawrence M, McPhee S J, Papadakis M A, editors. Current medical diagnosis and treatment. 43rd ed. New York: McGraw-Hill, 2004: 307.
8. Mair J, Hammerer-Lercher A, Puschendorf B. The impact of cardiac natriuretic peptide determination on the diagnosis and management of heart failure. Clin Chem Lab Med 2001; 39: 571-88.
9. Caroll J D, Hess Otto M. Assessment of cardiac function. In :Zipes D P, Libby P, Braunwald E, editors. Braunwald Heart Disease. 7th ed. New York: McGraw–Hill, 2005: 495.
10. Haneef N, Shah S A, Khan R A, Khan A H. Left Ventricular Ejection Fraction determination in post Myocardial Infarction patients.A comparison of Gated blood pool (GBP) ventriculography and contrast ventriculography. Pak J Cardiol 2003; 14: 84-90.
11. Bonow RO. New Insights Into the Cardiac Natriuretic Peptides. Circulation 1996; 93: 1946-50.
12. Dao Q, Krishnaswamy P, Kazanegra R, et al. Utility of B-type natriuretic peptide in the diagnosis of congestive heart failure in an urgent-care setting. J Am Coll Cardiol 2001; 37: 379-85.
13. Morrison LK, Harrison A, Krishnaswamy P, Kazanegra R, Clopton P, Maisel AS. Utility of a rapid B-natriuretic peptide assay in differentiating congestive heart failure from lung disease in patients presenting with dyspnea. J Am Coll Cardiol 2002; 39: 202-9.
14. Suzuki S, Yoshimura M, Nakayama M, Mizuno Y,et al. Plasma Level of B-Type Natriuretic Peptide as a Prognostic Marker After Acute Myocardial Infarction. Circulation 2004; 110: 1387-91.
15. Colucci WS, Elkayam U, Horton DP, Abraham WT, Bourge RC, Johnson AD, et al. Intravenous nesritide, a natriuretic peptide, in the treatment of decompensated congestive heart failure. Nesritide Study Group. N Engl J Med 2000; 343: 246-53.
16. Rutten FH, Moons KGM,Grobbee DE et al. Recognising heart failure in elderly patients with stable chronic obstructive pulmonary disease in primary care: cross sectional diagnostic study. BMJ 2005; 331: 1379.
17. Rumberger JA, Behrenbeck T, Bell MR et al. Determination of ventricular ejection fraction : a comparison of available imaging methods. The cardiovascular Imaging Working Group. Mayo Clin Proc 1997; 72: 860-70.

18. Guidelines for the evaluation and management of heart failure. Report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines (Committee on Evaluation and Management of Heart Failure). J Am Coll Cardiol 1995; 26: 1376-98.
19. Valli N, Georges A Corcuff JB et al. Stability of brain natriuretic peptide (BNP) in human whole blood and plasma. Clin Chem. 2003; 9: 1560-62.
20. Caruana L, Petrie MC, Davie AP, McMurray JJ. Do patients with suspected heart failure and preserved systolic function suffer from "diastolic heart failure" or from misdiagnosis? A prospective descriptive study. BMJ 2000; 321: 215-8.
21. Banerjee P, Banerjee T, Khand A, Clark AL, Cleland JG. Diastolic heart failure: neglected or misdiagnosed? J Am Coll Cardiol 2002; 39: 138-41.
22. Mills RM, LeJemtel TH, Horton DP et al. Sustained hemodynamic effects of an infusion of nesritide (human b-tybe natriuretic peptide) in heart failure : a randomized, double –blind, placebo-controlled clinical trial. Natrecor Study Group. J AM Cardiol 1999; 34: 155-62.
23. Ali L, Abid AR, Mohyuddin MT, Azhar M. Echocardiographic evaluation of patients with diastolic dysfunction Pak J Cardiol 2005; 16: 143-8.