ORIGINAL ARTICLE

Pro-Brain Natriuretic Peptide Plasma Levels, Left Ventricular Dimensions and Ejection Fraction in Acute Dyspnoea

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ABSTRACT

Objective: To determine the association of the pro-brain natriuretic peptide (NT-proBNP) plasma levels with two-dimensional echocardiographic determination of left ventricular dimensions and ejection fraction (EF) in acute dyspneic patients.

Study Design: An observational cross-sectional study.

Place and Duration of Study: Tabba Heart Institute, Karachi, from January to June 2010.

Methodology: One hundred patients were selected by consecutive purposive non-probability sampling who had presented with acute dyspnoea. NT-proBNP levels were assessed by commercial tests (Roche Diagnostics). The clinical diagnosis of congestive heart failure (CHF), echocardiographic assessment of left ventricular dimensions and function were compared with NT-proBNP levels. Receiver operating characteristic (ROC) curve was estimated for NT-proBNP and compared. The chi-square test was applied for categorical and student's t-test for numerical data at 0.05 levels of significance were used to compare patients with and without heart failure. Further comparative analysis between groups on the basis of ejection fraction was done by one way ANOVA test.

Results: Seventy-nine patients (79%) had CHF as a cause of their dyspnoea. Patients with CHF were older (61.9 ± 14 years vs. 58.6 ± 14 years, p=0.368), had a lower EF (36.9% vs. 61%, p < 0.0001), had a higher LV dimensions, left ventricular end diastolic dimension - LVEDD (49.94 ± 5.6 vs. 42 ± 7.9 mm, p < 0.0001), left ventricular end systolic dimension - LVESD (37.31 ± 6 vs. 29.21 ± 10.9 mm, p < 0.0001) and a higher NT-proBNP (10918 ± 1228 vs. 461 ± 100 pg/mL, p < 0.0001) than patients without CHF. NT-proBNP values increased with the severity of ventricular impairment. Significant differences were found between patients with LVEF < 25 % and patients with moderate ventricular impairment (LVEF = 26 – 40%) and mild ventricular impairment (LVEF = 41-60%, p < 0.001). The group of patients with LV dilation, had significantly higher BNP levels than those with normal LVEDD (12416 ± 1060 pg/ml vs. 6113 ± 960, p = 0.009) and LVESD (10416 ± 1160 vs. 4513 ± 960 pg/ml, p = 0.008). Area under ROC curve for the diagnosis of CHF was significantly higher for NT-proBNP (AUC 0.99, p < 0.003). The sensitivity of NT-proBNP value of > 300 pg/mL for the diagnosis of CHF was 100% and specificity was 42%. A cut-point of 300 pg/mL NT-proBNP had 100% negative predictive value to exclude acute CHF.

Conclusion: NT-proBNP is strongly associated with two-dimensional echocardiographic determination of left ventricular dimensions and EF in identifying CHF in patients with acute dyspnoea.

Key words: *NT-proBNP. Dyspnoea - echocardiography. Congestive heart failure. Left ventricular dimension. Ejection fraction.*

INTRODUCTION

Heart failure is a progressive disease affecting 1 – 2% of the general population.[1] Congestive heart failure (CHF) patients usually present with breathlessness but low specificity of dyspnoea often leads to misdiagnoses, even with recent advances in therapeutics, the mortality and morbidity rates remain high. Moreover, this disease is becoming the most costly cardiovascular illness,[2] thus an early and reliable diagnosis of left ventricular dysfunction is important for these patients. Because of their costs and limited availability, echocardiography and radio-nucleotide ventriculography are not suitable as primary diagnostic screening tools, and new cost-effective diagnostic tools are needed. In this respect, neurohormonal markers could be useful in the diagnosis of left ventricular dysfunction.[3]

In 1981, de Bold and his colleagues observed that infusion of extracts of atrial tissue into rats caused a copious natriuresis. This then led to the isolation and cloning of atrial natriuretic peptide, the first member of a family of peptides with potent natriuretic, diuretic, and vasorelaxant activity. The brain natriuretic peptide (BNP) is a recently discovered natriuretic hormone of cardiac origin.[4] BNP is secreted from the cardiac ventricular myocytes in response to an increase in ventricular wall tension and is related to left ventricular (LV) filling pressures.[5] Previous human studies have suggested correlations between BNP levels and cardiac functional or dimensional indexes such as end-diastolic pressure

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(EDP), ejection fraction (EF), pulmonary capillary wedge pressure, and LV volume.[6] Human pro-BNP consists of 108 amino acids; processing releases the biologically active 32-amino acid peptide and an amino-terminal fragment (NT-proBNP). NT-proBNP are cleaved in equimolar amounts from proBNP; thus, NP levels correlate with each other.[7]

B-type natriuretic peptide (BNP) and N-terminal pro B-type natriuretic peptide (NT-proBNP) are quantitative markers of cardiac wall stress.[8] In patients with CHF, serial evaluations of BNP and NT-proBNP levels may be useful for guiding therapy decisions by indicating the need for treatment intensification.[9-11] It was shown that NT-proBNP is a sensitive and specific marker of ventricular dysfunction.[12] In addition, NT-proBNP is stable in whole blood for > 24 hours at 20°C and is not significantly influenced by exercise and position of the patient.[13] This makes it a potential additional tool in the assessment of ventricular systolic dysfunction. Therefore, the purpose of this study was to determine the association of pro-brain natriuretic peptide plasma levels with two-dimensional echocardiographic determination of left ventricular dimensions and ejection fraction in acute dyspneic patients.

METHODOLOGY

The study protocol was approved by the ethical and research committee of the institute. This observational cross-sectional study was done from January to June 2010, with purposive non-probability sampling technique.

Inclusion criteria were consecutive patients who presented to the Emergency Department of Tabba Heart Institute, Karachi with primary complaint of dyspnoea. Patients with severe renal insufficiency (serum creatinine level > 2.5 mg/dl), dyspnoea after chest trauma, dyspnoea secondary to severe coronary ischaemia that was identified as > 0.1 mV ST-segment elevation or ST-segment depression on a 12-lead electrocardiogram were excluded.

Estimation of NT-proBNP was performed with a commercially available immunoassay (Elecsys proBNP, Roche Diagnostics, Indianapolis, Indiana) on an Elecsys 1010 Analyzer according to established methods, the assay range being 5 – 35,000 pg/ml. Echocardiographic-Doppler study was performed with 2.5-MHz transducers. The echocardiographic measurements were taken according to American Society of Echocardiography guidelines.

After enrollment, clinical characteristics of each patient were recorded, including demographics, symptoms, signs, medical history, medication use, and diagnostic studies in the emergency department, such as electrocardiography, chest X-ray, and standard blood tests were categorized in a structured checklist. An additional blood sample was collected for NT-proBNP measurement, which was performed after patient enrollment had been completed. On disposition from the Emergency Department (ED), patients were followed by research personnel through the hospital course, the results of any laboratory testing, outcomes of diagnostic tests, and pertinent discharge information (including discharge diagnoses made by in-hospital physicians and discharge medications) were recorded. All information was used to calculate the Framingham scores (requiring 2 major or 1 major and 2 minor criteria for CHF). Major criteria included paroxysmal nocturnal dyspnoea, neck vein distention, *rales*, radiographic cardiomegaly (increasing heart size on chest radiography), acute pulmonary oedema, S3 gallop, increased central venous pressure (> 16 cm H_2O at right atrium), hepatojugular reflux and weight loss > 4.5 kg in 5 days in response to treatment. Minor criteria included bilateral ankle oedema, nocturnal cough, dyspnoea on ordinary exertion, hepatomegaly, pleural effusion, decrease in vital capacity by one-third from maximum recorded and tachycardia (heart rate >120 beats/minute).

Patients were stratified by diagnosis at discharge into either of the two categories: CHF or no CHF. Patients were further stratified according to ejection fraction (EF) into four groups; EF < 25%, 26 – 40%, 41 – 59% and > 60%. Baseline characteristics were reported in counts and proportions or mean, median and standard deviation values as appropriate. Comparisons of clinical characteristics between patients who had CHF and those who did not were performed with chi-square tests for categorical data and student's t-test for numerical data with p-value of 0.05 level of significance after checking the data for normality with Kolmogorov-Smirnov. Receiver operating characteristic (ROC) curve was estimated for NT-proBNP, the area under the ROC curve for NT-proBNP was compared by a non-parametric test. Sensitivity, specificity, positive predictive value and negative predictive value was computed using echocardiography as the gold standard and likelihood ratios, defined as the sum of the concordant cells divided by the sum of all cells in the two-by-two table. Positive likelihood ratios were defined as the probability of true-positive/the probability of false-positive results. Negative likelihood ratios werse defined as the probability of false-negatives/the probability of true-negative results. All analyses were performed with statistical software (SPSS 16).

RESULTS

One hundred eligible patients were enrolled over 6 months. Baseline characteristics were presented in Table I. The study population comprised relatively elderly patients (mean age = 61 ± 14 years; ranging from 25 to 90 years). Gender analysis showed a slight female predominance (52%). Final cardiology assess-

Table I: Baseline characteristics of patients with dyspnoea.

Age in years (mean ± SD)	61.92 (14)
Men	48%
Hypertension	83%
Diabetes mellitus	50%
Stable angina	69%
Chronic obstructive pulmonary disease or asthma	21%
Fatigue	78%
Paroxysmal nocturnal dyspnoea	59%
Heart rate/minutes (mean ± SD)	99.56 ± 59
Systolic blood pressure, mmHg (mean ± SD)	136.34 ± 32
Elevated jugular venous pressure	44%
Orthopnoea	86%
Third heart sound	65%
Oedema	61%
Enlarged cardiac Silhouette	81%
Cephalization of pulmonary vessels	71%
Ejection fraction (mean ± SD)%	43.92% ± 19.680
End-diastolic dimension (mm ± SD) mm	43.92 ± 19.680
End-systolic dimension (mm ± SD) mm	36.18 ± 10.7
NT-proBNP (mean ± SD) pg/ml	6834.80 ± 1078

Table II: Baseline characteristics of patients who had dyspnoea with or without acute congestive heart failure.

Characteristic	CHF	no CHF	p-value
Age (mean ± SD) (years)	61.92 (14)	58.71 (14)	0.368
Men	49%	43%	0.117
Hypertension	86%	71%	0.634
Diabetes mellitus	57%	29%	0.021
Chronic obstructive pulmonary disease or asthma	19%	29%	0.030
Paroxysmal nocturnal dyspnoea	59%	52%	0.623
Systolic blood pressure, mmHg	136.34 ± 32	142.05 ± 25	0.477
Elevated jugular venous pressure	44%	4.7%	0.001
Third heart sound	65%	19%	< 0.001
Enlarged cardiac Silhouette	81%	29%	< 0.001
Cephalization of pulmonary vessels	71%	14%	< 0.001
Ejection fraction	36.9% ± 4.6	61% ± 19.2	< 0.001
End-diastolic dimension (mm)	49.94 ± 5.6	42 ± 7.9	< 0.001
End-systolic dimension (mm)	37.31 ± 6	29.21 ± 10.9	< 0.001
NT-proBNP (mean ± SD) pg/ml	10918 (1228)	461 (100)	0.001

ment revealed that 79 patients (79%) had CHF as a cause of their dyspnoea, while 21 patients (21%) had some other cause. Comparisons of clinical characteristics at presentation between those patients who had acute CHF and those who did not are presented in Table II. The mean NT-proBNP levels were 10918 ± 1228 pg/ml compared with 461 ± 100 pg/ml (p = 0.001). NT-proBNP values increased with the severity of ventricular impairment (Figure 1). Significant differences were found between patients with LVEF < 25% and patients with moderate ventricular impairment (LVEF = 26 – 40%) and mild ventricular impairment (LVEF = 41 – 60%, p < 0.001). Patients with LV dilation had significantly higher BNP levels than those with normal left ventricular end diastolic volume (LVEDD) 12416 ± 1060 pg/ml vs. 6113 ± 960, p = 0.009 and left ventricular end systolic dimension (LVESD) 10416 ± 1160 pg/ml vs. 4513 ± 960 pg/ml, p = 0.008). NTproBNP concentrations were higher in males (8267 ± 1141 pg/ml) compared to 5313 ± 885 pg/ml in females. NTproBNP concentrations were higher for patients with higher creatinine (11704 ± 971 vs. 9717 ± 1170 pg/ml). ROC analysis showed diagnostic performance for NT-proBNP (AUC = 0.990, respectively, Figure 2) The cut off values of NT-proBNP for the diagnosis of left ventricular systolic dysfunction were 300 pg/ml and accuracy appeared to be optimal at this concentration, NT-proBNP showed very high sensitivity and negative predictive value thus emphasizing the value of these cut point for ruling out the diagnosis of CHF and extending their value to the emergency department setting. A summary of the analytical parameters and predictive values of different variables were listed in Table III.

DISCUSSION

In this study, NT-proBNP measurements and its accuracy to correlate with two-dimensional echocardiographic determination of left ventricular dimensions and ejection fraction was determined. Measurement of NT-proBNP and BNP levels is increasingly utilized in the evaluation of dyspneic patients with suspected CHF.[14]

Table III: Univariate Analysis of Variables of patients with acute dyspnoea.

Variables	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Positive likelihood ratio (%)	Negative likelihood ratio (%)
Hypertension	86.07 (76 – 92)	28.57 (11 – 52)	81.92 (71 – 89)	35.29 (14 – 61)	1.2 (0.9 – 1.6)	0.487 (0.204 – 1.16)
COPD	18.98 (11 – 29)	71.42 (47 – 88)	71.42 (47 – 88)	18.98 (11 – 29)	0.66 (0.29 – 1.5)	1.134 (0.847 – 1.56)
PND	59.49 (47 – 70)	47.61 (25 – 70)	81.03 (68 – 90)	23.8 (12 – 39)	1.13 (0.72 – 1.77)	0.85 (0.504 – 1.43)
Orthopnoea	87.34 (77 – 93)	19.04 (5 – 41)	80.23 (70 – 88)	28.57 (8 – 58)	1.07 (0.86 – 1.34)	0.664 (0.231 – 1.9)
Oedema	67.08 (55 – 77)	61.9 (38 – 81)	86.88 (75 – 94)	33.33 (19 – 50)	1.76 (0.99 – 3.1)	0.531 (0.335 – 0.84)
Elevated JVP	44.3 (33 – 55)	95.23 (76 – 99)	97.22 (85 – 99)	31.25 (20 – 44)	9.3 (1.35 – 64.01)	0.584 (0.469 – 0.72)
Crepts	92.4 (84 – 97)	23.8 (8 – 47)	82.02 (72 – 89)	45.45 (16 – 76)	1.21 (0.94 – 1.55)	0.318 (0.107 – 0.94)
Third heart sound	64.55 (52 – 75)	80.95 (58 – 94)	92.72 (82 – 97)	37.77 (23 – 53)	3.38 (1.38 – 8.3)	0.437 (0.304 – 0.62)
Cephalization of pulmonary vessels	70.88 (59 – 80)	85.71 (63 – 96)	94.91 (85 – 98)	43.9 (28 – 60)	4.96 (1.72 – 14.28)	0.339 (0.23 – 0.49)
Enlarged cardiac Silhouette	81.01 (70 – 88)	71.42 (47 – 88)	91.42 (82 – 96)	50 (31 – 68)	2.83 (1.42 – 5.62)	2.83 (1.42 – 5.62)
Interstitial oedema	58.22 (46 – 69)	85.71 (63 – 96)	93.87 (83 – 98)	35.29 (22 – 49)	4.07 (1.4 – 11.81)	0.487 (0.356 – 0.66)
NT-proBNP	100 (95 –100)	42.85 (21 –65)	86.81 (78 – 93)	100 (66 – 100)	1.75 (1.2 – 2.53)	0 (0 – no any number)

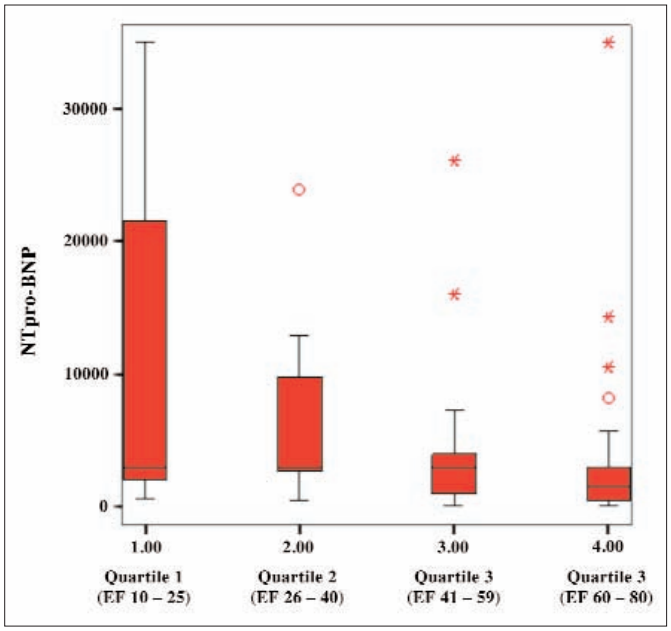

Figure 1: Quantitative relationships between left ventricular ejection fraction and plasma NT-proBNP values.

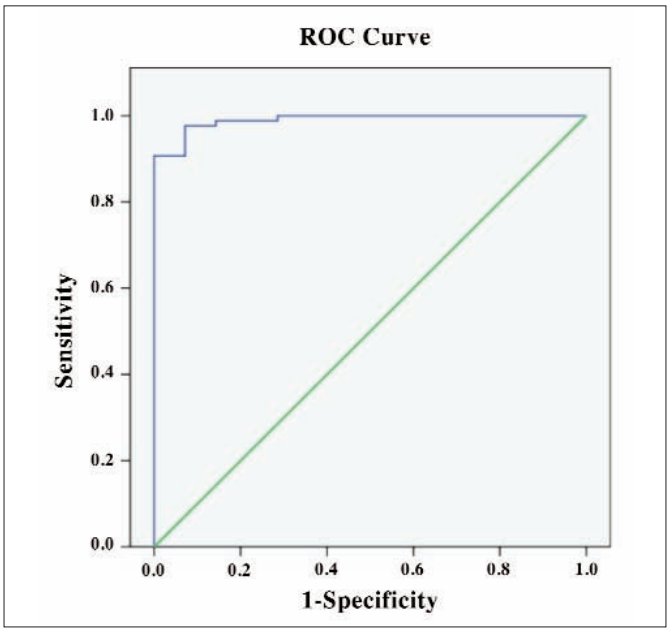

Figure 2: ROC curve for the ability of NT-proBNP to detect heart failure in patients with dyspnoea. Area under curve = 0.99 ($p < 0.001$).

Natriuretic peptide levels can reflect LV systolic and diastolic function, RV function and valvular heart disease.[15-18] Understanding these complex relationships may elucidate the physiology of natriuretic peptide release and guide the management of dyspneic patients.

Logeart *et al*. used two-dimensional and Doppler echocardiography in their study of emergency patients with dyspnoea; they found that both the bedside BNP assay and echocardiography added important diagnostic information to the clinical findings.[19] The analysis of the area under the ROC curve of the current data suggests that NT-proBNP shows greater ability to discriminate patients with dyspnoea of cardiac and non-cardiac origin. Obviously, the usefulness of a screening test relies on a high predictive value of a negative test (PVneg). Nevertheless, NT-proBNP gave higher sensitivity, lower specificity and higher negative predictive value so that advantage of using natriuretic peptides is to screen a large number of patients at risk of LVSD (left ventricular systolic dysfunction). This would allow patients with LVSD who have less classical symptoms as well as asymptomatic high-risk patients to be identified and in turn referred for echocardiographic evaluation and treatment. Both BNP and NTproBNP have similar negative predictive values with a difference of almost 1% only, although there is an age and gender specific cut off values of the NTproBNP and BNP. In one study, it was pointed out that the negative predictive value of both of them does not change with the use of generic cut off value or age and gender based values.[20] The specificity of NT-proBNP in our study was in part influenced by the presence of several disease processes that increase NT-proBNP levels. Among these were acute coronary syndromes and pulmonary thromboembolism. Although not specifically related to acute CHF, detection of high NT-proBNP levels in patients who have acute coronary syndromes or pulmonary thromboembolism adds powerful prognostic information.

Predominantly, in-hospital patients referred for echocardiography, Talwar *et al*. found a close correlation between NT-proBNP and left ventricular systolic dysfunction in 243 patients; reduced left ventricular systolic function was predicted with a sensitivity of 94% and a specificity of 55%.[21] The assessed cut-off values for NT-proBNP do not differ significantly from the cut-off values presented in other studies presenting the cut-off values at the levels of 125 – 895 pg/ml for NT-proBNP. In the present study, a diagnosis of moderate to severe LVSD was made in 50 patients (50%); thus, in the present study population, approximately 2 echocardiograms were required to detect one patient with LVSD. These results differ from previously reported results showing 5, 6, or 10 echocardiograms per LVSD diagnosis.[22] As a result, routine NT-proBNP testing may be valuable not only to diagnose or exclude HF but also to discriminate between patients in whom a more timely echocardiographic evaluation would be indicated and those in whom echocardiography might be deferred or avoided altogether. NT-proBNP assays cannot replace cardiac imaging, but both provide independent and complementary information for the evaluation of cardiac function and clinical patient status. In particular, increased NT-proBNP concentrations in patients with suspicion of HF are highly suggestive of a correct diagnosis. On the other hand, in patients with low NT-proBNP concentrations, diagnosis of CHF is unlikely.

This study was limited by its being a single-centre from a large urban teaching hospital and being a cardiac

centre was a selection bias with low number of patients, another limitation was that NT-proBNP measurement and echocardiography were not performed simultaneously as well as echocardiographic study were not performed by a single person. The delay until echocardiography was expected to influence the identification of correlations between NT-proBNP levels and echocardiographic parameters, and our observations may not apply to all situations. In summary, these results with LV areas and function are at least the same as those previously calculated with LV volumes. On the other hand, LV areas determination, measured from two-dimensional echocardiography directly from planimetered ventricular images, improves accuracy and reproducibility with respect to LV volumes as the need for standardized imaging planes or geometric assumptions is not necessary.[23] Therefore, correlation with peptide levels are more reproducible.

CONCLUSION

NT-proBNP was strongly associated with two-dimensional echocardiographic determination of left ventricular dimensions and EF in identifying CHF in patients with acute dyspnoea.

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