

# Utility of Brain Natriuretic Peptide in Diagnosis of Congestive Heart Failure and Comparison with Trans-Thoracic Echocardiography: A Multicenter Analysis in South Asian and Arabian Population

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## ABSTRACT

**Objective:** To evaluate serum Brain Natriuretic Peptide levels (BNP) as a screening test in the diagnosis of congestive heart failure.

**Study Design:** Comparative cross-sectional study.

**Place and Duration of Study:** Prince Salman Heart Center, King Fahad Medical City, Riyadh, Saudi Arabia between December 2010 to January 2012 and Nishtar Hospital, Multan, Pakistan, from February to August 2006.

**Methodology:** A total of 80 patients with clinical diagnosis of Congestive Heart Failure (CHF) underwent measurement of serum BNP and had a trans-thoracic echocardiography to measure Ejection Fraction (EF). The normal limit for serum BNP levels, provided by the manufacturer of the kit was applied as a cut-off value for BNP. EF of > 45% was considered normal.

**Results:** Forty seven patients (94%) had an EF < 45%. BNP levels were elevated in 36 patients (72%). Sensitivity and specificity of BNP was found to be 80% and 66% respectively and accuracy was 80%.

**Conclusion:** BNP measurements as a screening tool for CHF has good sensitivity and accuracy when compared to echocardiography.

**Key Words:** B-type Natriuretic Peptide (BNP). Ejection Fraction (EF). Congestive Heart Failure (CHF). Echocardiography.

## INTRODUCTION

Brain Natriuretic Peptide (BNP) is a cardiac neuro-hormone specifically secreted from the ventricles in response to volume expansion and pressure overload.<sup>1</sup> Levels of BNP 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.<sup>1</sup>

Heart failure is a leading cause of cardiac mortality and prompt early diagnosis and treatment is important. Major heart failure trials show average mortality at one year of 35 - 37%.<sup>3</sup> In 1979, De Bold described how atrial granularity was altered according to systemic water and electrolyte balance.<sup>4</sup> The peptide was named Brain Natriuretic Peptide (BNP). Although this peptide was called brain (B-type) natriuretic peptide (BNP), the primary site of BNP synthesis is ventricular myocardium.

A plasma brain natriuretic peptide level of > 100 pg/ml diagnosed congestive heart failure with a sensitivity, specificity, and predictive accuracy of 90%, 76% and 83% respectively.<sup>6</sup> For practical clinical purposes a 'decision cut point' of 100 pg/ml appears to provide optimum diagnostic accuracy. If the BNP is < 100 pg/ml in untreated patients, then heart failure is highly unlikely.<sup>7</sup>

BNP may be useful in distinguishing between cardiac and non-cardiac causes of acute dyspnea. Various invasive modalities like pulmonary capillary wedge pressure or cardiac catheterization<sup>8</sup> are available to further evaluate heart failure but these techniques are invasive and may not be feasible in urgent settings.

Moreover, BNP levels have also been utilized to diagnose diastolic heart failure,<sup>11,12</sup> and for differentiating the etiology of dyspnea both in an emergency room<sup>13</sup> as well as outpatient setting. In United Kingdom (2003 - 2005) multi-centre study (United Kingdom Natriuretic Peptide study-UKNPS) was conducted to determine the diagnostic accuracy of the measurement of plasma B-type natriuretic peptide (BNP) and N-terminal pro-BNP (NT-proBNP) in patients referred by their General Practitioners (GPs) with symptoms suggestive of heart failure.<sup>14</sup> BNP levels may also have prognostic value after an acute myocardial infarction.<sup>15</sup> BNP exhibit a stronger relationship with death and CHF, and cardiac troponin being predictive of death and recurrent ischemic events.<sup>15</sup>

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Various studies have shown very high overall diagnostic accuracy of BNP for diagnosis of heart failure as well as a rapid point of care test for screening patients with left ventricular dysfunction<sup>1,2,9,10</sup> and is increasingly used in cardiovascular medicine. However, none of these studies have been validated in the population in Pakistan. Therefore, the aim of this study was to determine the utility of BNP as a reliable screening test for CHF when compared with echocardiography especially in settings, where echocardiography is not readily available such as districts hospitals.

### METHODOLOGY

A comparative cross-sectional study was conducted on 80 adult patients with a new clinical diagnosis of heart failure underwent echocardiography and BNP measurement. After informed consent, 50 patients were studied in Department of Medicine and Cardiology at Nishtar Hospital, Multan, from February to August 2006 and additional 30 patients were added from Prince Salman Heart Center, King Fahad Medical City, Riyadh, Saudi Arabia, between December 2010 to January 2012 to complete the sample size of 80 patients. Data was updated to 2012 to validate the results and reassuring role of BNP in the diagnosis of heart failure. Clinical diagnosis of heart failure was based on the presence of dyspnea, elevated JVP, S3 gallop, and pulmonary congestion with basal crackles. Data on basic demography, co-morbid conditions and current medications was collected. Patient with recent acute coronary syndrome, previous diagnosis of CHF, renal failure and severe COPD were excluded. All patients were classified on the basis of New York Heart Association (NYHA) Functional Class (NYHA-FC) to assess the severity and extent of heart failure.<sup>16</sup> Only NYHA-FC III and IV (advanced heart failure) patients were included. Enzyme Immunoassay (ELISA) technique was utilized to measure serum BNP levels. Left ventricular dysfunction was defined as an ejection fraction of < 45% on echocardiography.<sup>17</sup>

Statistical analysis was performed on the Statistical Package for Social Sciences (SPSS) version 22 (SPSS Inc., Chicago, Illinois). Relevant descriptive statistics frequency and percentage were computed for categorical variables like ejection fraction and brain natriuretic peptide. Mean and standard deviation was calculated for age.

Normality of data was statistically checked using Kolmogorov-Smirnov and Shapiro-Wilk test and based on the results; Mann-Whitney U test was conducted to compare BNP levels for heart failure severity in functional class-III and class-IV of heart failure. Significant p-value was considered  $p \leq 0.05$ .

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 in SPSS for brain natriuretic peptide and ejection fraction using Spearman's rank correlation. The correlation was considered significant at  $p \leq 0.05$  level.

### RESULTS

In the present study, a total of eighty (n=80) patients with clinical evidence of heart failure were included. Clinical characteristics of patients with heart failure, etiology and distribution of patients in different functional classes of heart failure is shown in Table I. The mean age was  $56.4 \pm 13.5$  years.

Seventy seven (94%) patients of the total studied population (n=80) had Ejection Fraction (EF) of less than 45% and were diagnosed as CHF as compared by echocardiography. Mean EF was  $26.6 \pm 9.1\%$  ( $p=0.001$ ). Three patients (4%), initially diagnosed to have left

**Table I:** Baseline clinical characteristics of patients .

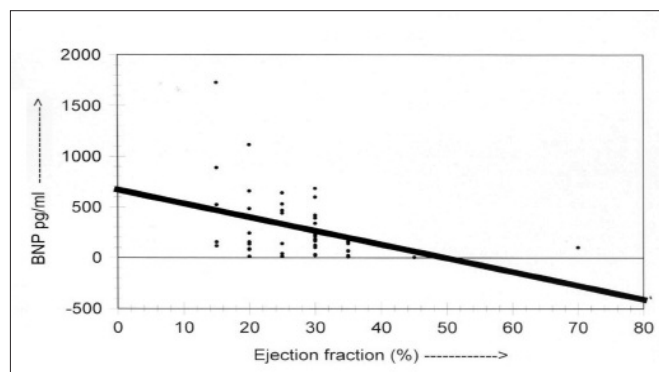
Characteristics	Categories	n (n%)
NYHA-FC	III	45 (56.6%)
	IV	35 (4.8%)
Diagnosis	CHF	35 (45%)
	Post MI failure	14 (17.5%)
	Acute LVF	6 (7.5%)
	DCMP	5 (6.3%)
	IHD	4 (5.0%)
	Others	16 (18.7%)
NYHA-FC III	Yes	45 (56.3%)
	No	35 (43.8%)
NYHA-FC IV	Yes	35 (56.3%)
	No	45 (43.8%)
Age (years)	56.4± 13.5	

NYHA-FC = New York Heart Association (NYHA) Functional Class (NYHA-FC)

**Table II:** Comparative analysis of BNP level for heart failure severity in class-III and IV.

	NYHFC	Minimum	Maximum	Mean rank	Median	p-value
BNP levels	III	5.12	3280	33.19	184.0	0.001 <sup>a</sup>
(pg/ml)	IV	40	40000	49.90	658.4	0.001 <sup>b</sup>

a. Significant at Kolmogorov at  $p < 0.05$ ; b. Shapiro-Wilk at  $p < 0.05$ ; BNP = Brain Natriuretic Peptide.



**Figure 1:** BNP levels versus ejection fraction.

ventricular failure were later found to have ejection fraction above 45%.

In the total cohort, BNP levels were found to be elevated (BNP levels  $1373.3 \pm 4483.5$ ,  $p=0.001$ ) in 65 (81%) patients, whereas in 12 (15%) patients, 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 (1.2%) patient. Two patients (2.5%) had clinical heart failure with negative echocardiographic results (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 84.4%, 66% and 83.75% respectively. A comparative analysis of BNP level for heart failure severity in class III and IV is shown in Table II.

Correlation of BNP with EF was computed by using SPSS software. Spearman correlation coefficient was used to calculate correlation. P-value for this correlation was 0.001. There was a negative correlation between the two variables ( $r = -0.429$ ,  $n = 50$ ,  $p < 0.005$ , Figure 1).

Normality of data was assessed by using Kolmogorov-Smirnov and Shapiro-Wilk test and showed that comparing BNP levels with two classes-III and IV of heart failure revealed median values of 113.60 and 454.70 and interquartile range of 155.0 and 481.62 respectively.

Mann-Whitney U test was conducted to compare BNP levels for heart failure functional class-III and class-IV which showed Z value of -3.833 with significance level of  $p < 0.001$ .

The relationship between ejection fraction and BNP level was investigated using Spearman rank correlation. There was a negative correlation between the two variables ( $r = -0.371$ ,  $n=80$ ,  $p < 0.001$ ).

## DISCUSSION

Heart failure is sometime difficult to diagnose, particularly in emergency setting, especially when patients have concurrent lung diseases. BNP is a biomarker that has been used for the diagnosis of heart failure. In this study, BNP was evaluated as a screening tool for left ventricular dysfunction when compared to echocardiography which is a gold standard.<sup>18</sup> 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 (AC). Three diagnostic accuracy was 84% for BNP in diagnosing left ventricular dysfunction. Bettencourt *et al.* showed a diagnostic accuracy of BNP measurement to be 83.75% in confirming left ventricular dysfunction for BNP levels.<sup>9</sup> Echocardiography has excellent sensitivity and

specificity for diagnosing left ventricular dysfunction, however, this modality is not universally available. Other modalities, such as right heart catheterization with pulmonary artery wedge pressure or left heart catheterization with left ventriculography and measurement of LVEDP are very accurate but invasive techniques. Furthermore, morbidity is far higher in non-invasive tools.

In the Breathing Not Properly (BNP) study, BNP levels were measured in the emergency room on 1586 patients who presented with dyspnea. BNP levels above 100 pg/ml were found to be associated with congestive heart failure with calculated sensitivity and specificity of BNP to be 90% and 76% respectively.<sup>13</sup> In this study, the sensitivity and specificity we calculated was 84% and 66% respectively, which are comparable results of "breathing not properly" study. This mild difference in this study is probably due to difference in population size.

An association of BNP levels was also demonstrated with NYHA functional class for severity of heart failure as well as negative correlation with ejection fraction as measured on echocardiography. These findings are persistent in patients studied in Arabian population in KSA.

Similar observations were documented by Maisel *et al.* in 2001. They correlated the levels of BNP with LV pressure and amount of dyspnea and concluded that BNP levels increase with severity just as the white cell counts do in case of infection.<sup>21</sup> This study validates the use of BNP measurements in the urgent setting to reliably confirm left ventricular dysfunction as well as defining the severity of heart failure.<sup>22</sup> Data on sensitivity, specificity and accuracy for BNP measurements in heart failure population in Pakistan are limited. The use of BNP levels should be encouraged among emergency department physicians as it is a reliable tool for the rapid bedside diagnosis of heart failure.

Limitations include a small sample size. A larger study with more patients will further validate the present findings.

## CONCLUSION

In the present study, BNP levels have shown to have good sensitivity and accuracy as an initial screening test for left ventricular dysfunction when compared to echocardiography in patients with clinical heart failure.

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