Original Article

Evaluation of "Point of Care" Brain Natriuretic Peptide Level in Differentiating between Cardiogenic and Noncardiogenic Acute Dyspnea (A Hospital-Based Study)

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Abstract

Introduction: Acute dyspnea is one of the most common reasons for admission to emergency rooms. It could be due to potentially life-threatening cardiac or respiratory conditions. Differentiation among these three disorders is frequently needed. In the condition of heart failure, where there is clinical need for early and appropriate treatment but no objective method for rapid diagnosis, the potential benefits are enormous for any biomarker that can reliably rule in or rule out this syndrome. **Objectives:** The objectives of this study are as follows: (i) To evaluate the role of point of care of brain natriuretic peptide (BNP) in acute dyspnea and (ii) To determine the cutoff level of BNP to differentiate between cardiogenic and noncardiogenic causes of dyspnea. **Materials and Methods:** This was an in-hospital cross-sectional study conducted at a tertiary care center. Patients were evaluated using predetermined performa. All these patients were subjected to routine blood investigations, digital chest X-ray, and 12-lead electrocardiography. At the same time point of care, BNP was done in each patient after obtaining informed written consent. All patients with BNP >100 or clinical suspicion for heart failure underwent two-dimensional echocardiography (ECHO) with color Doppler. **Results:** A cross-sectional study was conducted on 238 patients presenting with acute dyspnea. Almost all patients with BNP level >415 pg/ml had <45% ejection fraction, but patients with BNP level <415 pg/ml had echocardiographic findings not suggestive of heart failure. **Conclusion:** This study gives us a reliable cutoff level of 415 pg/ml of BNP which clearly distinguishes between cardiogenic versus noncardiogenic dyspnea.

Keywords: Brain natriuretic peptide, cardiogenic dyspnea, heart failure

Introduction

Acute dyspnea is one of the most common reasons for admission to emergency rooms. It could be due to potentially life-threatening cardiac or respiratory conditions. Because of the prevalence of Congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), and asthma in the general population (2%, 5%–10%, and 5%, respectively), differentiation among these three disorders is frequently needed.[1,2] Moreover, these conditions could coexist such that differentiation of heart failure from other causes of shortness of breath is often difficult. In the condition of heart failure, where there is clinical need for early and appropriate treatment but no objective method for rapid diagnosis, the potential benefits are enormous for any biomarker that can reliably rule in or rule out this syndrome. Brain natriuretic peptide (BNP) qualifies all criteria for ideal biomarker, as it is well characterized, completely cardiac specific, easy to measure accurately, and precise with defined clinical role.[3] Unlike other natriuretic peptides, it is not stored in the granular form within the myocytes, but it is produced *de novo* in response to cardiac strain, thus making it more specific.[4,5] Moreover, BNP is mainly cleared by proteolysis by peptidases, so unlike other natriuretic peptides its value is not significantly affected by renal function status.[6-9] Although the gold standard for diagnosing congestive heart failure is two-dimensional-echocardiography (2D-ECHO) with color

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Doppler, there is limited accessibility to 2D ECHO in acute care settings such as emergency departments (EDs) and urgent care centers, especially in our resource-poor country. Due to its cost-effectiveness and easy availability, it is suitable alternative in acute care settings. Morrison *et al*., in 2002, concluded that BNP differentiated dyspnea due to congestive heart failure from pulmonary and other clinical presentations with remarkable specificity, sensitivity, and accuracy.[10]

Despite all these landmark studies, there is a lack of any universal cutoff value of BNP at which cardiogenic cause of dyspnea can be precisely ruled in or out. Moreover, no such studies had been done in our setting till date.

Objectives

The objectives of this study are as follows:

i. To evaluate the role of point of care of BNP in acute dyspnea
ii. To determine the cutoff level of BNP to differentiate between cardiogenic and noncardiogenic causes of dyspnea.

Materials and Methods

This was an in-hospital cross-sectional study conducted on adult patients presenting with acute dyspnea to the Department of General Medicine at a tertiary care center. The study was approved by the Institutional Ethical Committee.

Inclusion criteria

Males and females >18 years of age presenting with acute dyspnea were included in the study.

Exclusion criteria

Age <18 years, cases clearly not likely to be cardiogenic as traumatic pneumothorax/patient with acute ST-elevation myocardial infarction/end-stage renal disease were excluded from the study.

Patients were evaluated using predetermined performa. A brief history with special emphasis on duration of dyspnea, the presence or absence of orthopnea and paroxysmal nocturnal dyspnea, palpitation, chest pain, pedal edema was taken. Past history of congestive heart failure, hypertension, coronary artery disease (CAD), coronary artery bypass graft was taken. A history suggestive of risk factors for COPD such as smoking, cooking on smoky chulha, and any occupational exposure was taken along with drug history. History taking was followed by thorough general and systemic examination with special emphasis on the examination of the chest and cardiovascular system. Based on the history and clinical findings, patients were divided among two groups as follows:

1. Patients with clear-cut clinical diagnosis of noncardiogenic dyspnea such as acute respiratory distress syndrome (ARDS), acute exacerbation of bronchial asthma, and massive pleural effusion were clubbed in one group. They served as controls
2. Others were clubbed in the second group.

All these patients were subjected to routine blood investigations, digital chest X-ray, and 12-lead electrocardiography. At the same time, point of care BNP was done in each patient after obtaining informed written consent. All patients with BNP >100 or clinical suspicion for heart failure underwent 2D ECHO with color Doppler. The cardiologist doing ECHO was blinded of the BNP result but had access to the chest X-ray along with other investigations. ECHO was considered as the gold standard in differentiating between cardiogenic versus noncardiogenic dyspnea. Ejection fraction of <45% was considered as the left ventricular dysfunction. Measurement of BNP-2 ml ethylenediaminetetraacetic acid anticoagulated venous blood was collected from patients to measure BNP on Alera Triage-Cardio product insert by kit provided by Alera. It measures BNP in pg/ml through the 3rd-generation immunoassay method.

Statistical analysis

Statistical analysis was performed using SPSS software version 16.0 (SPSS Inc., Chicago, IL, USA). Evaluation of causes of acute dyspnea among patients in ED was done. Role of point of care of BNP in acute dyspnea was evaluated. Noncardiac causes of elevation in serum level of BNP were discussed. Receiver-operator curve (ROC) was generated to determine cutoff level of BNP, its sensitivity, specificity in diagnosing or excluding cardiogenic dyspnea [Figure 1].

Results

This was a cross-sectional study conducted on 238 patients presenting with acute dyspnea. The median age of patients was 47.8 (20–76) years. There was almost equal distribution among different age groups. Most of the patients were male ($n = 133$) 55.9%. A total of 158 patients had serum level of BNP >415 pg/ml. One-hundred and fifty-eight patients had ejection fraction <45% [Table 1]. Data from Table 1 suggest that there was a clear-cut significant negative correlation between the level of BNP and ejection fraction. Thus, patients with serum level of BNP >415 pg/ml had <45% ejection fraction. Most of them (35.3%) had multivalvular disease with CHF

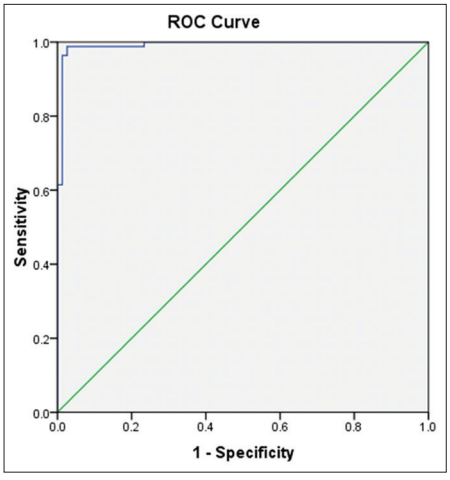

Figure 1: Receiver-operator curve (ROC) to determine cutoff level of BNP

followed by CAD with CHF (20.6%), ARDS (19.3%), dilated cardiomyopathy (DCMP) with hypothyroidism (7.1%), acute exacerbation of COPD (5.3%), chronic kidney disease (CKD) with DCMP, right-sided heart failure (RSHF), interstitial lung disease, massive pleural effusion, acute exacerbation of bronchial asthma, COPD with anemia, pericardial effusion with CHF, bilateral pneumonitis with CHF, pulmonary embolism, and atrial fibrillation with severe anemia [Table 2]. Most patients with BNP level <415 pg/ml had echocardiographic findings not suggestive of CHF. Only one case with a diagnosis of ARDS was discordant in this respect. Patients with BNP level either <100 or >415 had clinical diagnosis. However, those with BNP level between 101 and 415 were difficult to diagnose clinically. Many of them had discordance between clinical and echocardiographic diagnosis. However, in almost all patients, BNP level >415 pg/ml was concordant with 2D ECHO [Tables 3 and 4]. Median value of BNP in patients with cardiogenic dyspnea was 885 pg/ml and among those with noncardiogenic dyspnea was 106 pg/ml. The median value of serum creatinine was 1.5 mg/ml and 1.2 mg/ml in patients with noncardiogenic and cardiogenic cases, respectively. ROC at BNP level was 415 pg/ml. At confidence interval of 95% and *P* value of 0.001, the area under the curve was 0.995. Optimum cutoff point for the detection of cardiogenic dyspnea was 415 pg/ml. The sensitivity and specificity were 98.7% and 95%, respectively [Figure 1].

Table 1: Baseline characteristics of patients

	Frequency (%)
Age (years)	
20-30	30 (12.6)
31-40	55 (23.1)
41-50	48 (20.2)
50-60	55 (23.1)
>60	50 (21.0)
Sex	
Male	133 (55.9)
Female	105 (44.1)
Creatinine (mg/ml)	
<1.5	140 (58.8)
>1.5	98 (41.2)

BNP (pg/ml)	Frequency (%)	ECHO (ejection fraction) (%)
<415	80 (33.6)	>45
>415	158 (66.4)	<45

BNP: Brain natriuretic peptide, ECHO: Echocardiography

Table 2: Etiological analysis of acute dyspnea

Diagnosis	Frequency (%)
Acute exacerbation of COPD	14 (5.9)
Acute exacerbation of bronchial asthma	2 (0.8)
ARDS	46 (19.3)
Multiple valvular disease with CHF	84 (35.3)
Atrial fibrillation with severe anemia	2 (0.8)
Pulmonary embolism	2 (0.8)
CAD with CHF	49 (20.6)
Hypothyroidism with DCMP with CHF	17 (7.1)
CKD with DCMP	4 (1.7)
Bilateral pneumonitis with CHF	2 (0.8)
RSHF	4 (1.7)
Interstitial lung disease	4 (1.7)
COPD with severe anemia	2 (0.8)
Massive pleural effusion	3 (1.3)
Pericardial effusion with CHF	2 (0.8)
Severe anemia	1 (0.4)
Total	238 (100)

COPD: Chronic obstructive pulmonary disease, CHF: Chronic heart failure, DCMP: Dilated cardiomyopathy, ARDS: Acute respiratory distress syndrome, CAD: Coronary artery disease, CKD: Chronic kidney disease, RSHF: Right-sided heart failure

Discussion

One of the most common reasons for in-hospital admissions, especially to ED and acute care units is acute dyspnea. This study gives us useful insight in the importance of BNP in acute care settings in diagnosing etiology and accordingly, management of acute dyspnea. According to previous studies, the prevalence of common diseases which cause dyspnea in general population is 2%, 5–10%, and 5% for congestive heart failure, COPD, and asthma, respectively.[1,2] Depending on the hospital setting, acute heart failure syndromes (AHFS) accounts for 30%–70% of acute dyspnea in the ED.[11] Similar to previous studies, this study also had 56% of patients with AHFS. This was followed by other etiologies such as ARDS (19.3%), DCMP with hypothyroidism (7.1%), acute exacerbation of COPD (5.3%), CKD with DCMP, RSHF, interstitial lung disease, massive pleural effusion, acute exacerbation of bronchial asthma, COPD with anemia, pericardial effusion with congestive heart failure (CHF), bilateral pneumonitis with CHF, pulmonary embolism, and atrial fibrillation with severe anemia and severe anemia. The high prevalence of AHFS is account of the high prevalence of rheumatic heart disease (RHD) in our population. In our setting, RHD is the most common cause of AHFS. Biomarkers, measurable biological markers of a pathological process, have established a growing role in modern medical practice over the past 50 years. Biomarkers are of great utility when they can provide information required for making clinical and therapeutic decisions. In case of cardiogenic dyspnea, where there is need for early and appropriate treatment but there is no objective method for a rapid diagnosis, the potential benefits are enormous for any biomarker that can reliably rule in or rule out this condition. Moreover, cardiogenic dyspnea requires prompt diagnosis and urgent management. There must be a bedside screening test with high sensitivity to distinguish between cardiogenic and noncardiogenic causes of dyspnea. Although BNP is a very sensitive marker for cardiogenic dyspnea, application of this analysis in clinical setting is often limited by the absence of universally accepted cutoff level. Very few studies has been done to determine the cutoff level of BNP to distinguish between cardiogenic and noncardiogenic dyspnea, and none of them had sensitivity of >80%. Cutoff

Table 3: Clinical diagnosis versus brain natriuretic peptide and echocardiography correlate

Final diagnosis	BNP (pg/ml)			Clinical diagnosis		2D ECHO CHF (yes/no)
	<100	101-415	>415	Cardiogenic	Noncardiogenic	
Acute exacerbation of COPD	4 (11.1)	10 (22.7)	0 (0.0)	4	10	No
Acute exacerbation of bronchial asthma	2 (5.6)	0 (23)	0 (0.0)	0	25	No
ARDS	22 (61.1)	23 (52.3)	1 (0.6)	0	46	No
Multiple valvular disease with CHF	0	0 (0.0)	84 (53.2)	84	0	Yes
Atrial fibrillation with severe anemia	0 (0.0)	0 (0.0)	2 (1.3)	2	0	Yes
Pulmonary embolism	0 (0.0)	2 (4.5)	0 (0.0)	2	0	No
CAD with CHF	0 (0.0)	0 (0.0)	49 (31)	49	0	Yes
Hypothyroidism with DCMP with CHF	0 (0.0)	0 (0.0)	17 (10.8)	15	2	Yes
CKD with DCMP	4 (11.1)	0 (0.0)	0 (0.0)	0	4	No
Bilateral pneumonitis with CHF	0 (0.0)	0 (0.0)	2 (1.3)	0	2	Yes
RSHF	0 (0.0)	4 (9.1)	0 (0.0)	4	0	No
Interstitial lung disease	0 (0.0)	4 (9.1)	0 (0.0)	0	4	No
COPD with severe anemia	2 (5.6)	0 (0.0)	0 (0.0)	2	0	No
Massive pleural effusion	2 (5.6)	1 (2.3)	0 (0.0)	0	2	No
Pericardial effusion with CHF	0 (0.0)	0 (0.0)	2 (1.3)	2	0	Yes
Severe anemia	0 (0.0)	0 (0.0)	1 (0.6)	1	0	No
Total	36 (100)	44 (100)	158 (100)			

BNP: Brain natriuretic peptide, ECHO: Echocardiography, CHF: Chronic heart failure, COPD: Chronic obstructive pulmonary disease, ARDS: Acute respiratory distress syndrome, CAD: Coronary artery disease, DCMP: Dilated cardiomyopathy, CKD: Chronic kidney disease, RSHF: Right-sided heart failure

Table 4: Diagnosis versus brain natriuretic peptide (at 415 pg/ml)

Diagnosis	Group 1 (BNP <415 pg/ml)	Group 2 (BNP >415 pg/ml)	2D ECHO CHF (yes/no)
Acute exacerbation of COPD	14 (17.5)	0 (0.0)	No
Acute exacerbation of bronchial asthma	2 (2.5)	0 (0.0)	No
ARDS	45 (56.2)	1 (0.6)	No
Multiple valvular disease with CHF	0 (0.0)	84 (53.2)	Yes
Atrial fibrillation with severe anemia	0 (0.0)	2 (1.3)	Yes
Pulmonary embolism	2 (2.5)	0 (0.0)	No
CAD with CHF	0 (0.0)	49 (31.0)	Yes
Hypothyroidism with DCMP with CHF	0 (0.0)	17 (10.8)	Yes
CKD with DCMP	4 (5.0)	0 (0.0)	No
Bilateral pneumonitis with CHF	0 (0.0)	2 (1.3)	Yes
RSHF	4 (5.0)	0 (0.0)	No
Interstitial lung disease	4 (5.0)	0 (0.0)	No
COPD with severe anemia	2 (2.5)	0 (0.0)	No
Massive pleural effusion	3 (3.8)	0 (0.0)	No
Severe anemia	0 (0.0)	2 (1.3)	Yes
Total	80 (100)	158 (100)	

χ^2=23.36; *P*=0.000. BNP: Brain natriuretic peptide, ECHO: Echocardiography, CHF: Chronic heart failure, COPD: Chronic obstructive pulmonary disease, ARDS: Acute respiratory distress syndrome, CAD: Coronary artery disease, DCMP: Dilated cardiomyopathy, CKD: Chronic kidney disease, RSHF: Right-sided heart failure

values that provided a reasonably high sensitivity had a very low specificity and *vice versa*. The screening test must be simple and quick and based on the routine procedure. In contrast to previous studies on BNP, this study was successful in deciding exact cutoff level of BNP in differencing between cardiogenic versus noncardiogenic dyspnea. This study gives an optimum cutoff point for the detection of cardiogenic dyspnea at 415 pg/ml with sensitivity and specificity of 98.7% and 95%, respectively. This study had large cohort of 238 patients presenting with acute dyspnea. Point of care BNP level was estimated in all these patients, and all these patients were subjected to 2D ECHO as the gold standard and the most important part was that the cardiologist doing ECHO was blinded of BNP result. The study also focused on clinical diagnosis versus BNP and ECHO correlation. Serum BNP level of >415 pg/ml had cent percent ECHO correlation with cardiogenic causes. Four patients with noncardiogenic clinical diagnosis had ejection fraction of <45% on 2D ECHO, i.e.,

were actually cardiogenic. Of these four, two had a final diagnosis of pneumonitis with CHF and another two had hypothyroidism with DCMP with CHF. However, all four of them had BNP >415 pg/ml. Similarly, 13 patients with cardiogenic clinical diagnosis had no CHF in 2D ECHO. Six of them had an acute exacerbation of COPD, four had RSHF, two had pulmonary embolism, and one was severely anemic. Serum level of BNP in all of them was <415 pg/ml. Thus, bedside measurement of serum BNP had diagnostic sensitivity and specificity almost equivalent to that of 2D ECHO which is itself the gold standard. Median age of patients was 47.8 (20–76) years. Most of the patients were >30 years of age in both groups (cardiogenic vs. noncardiogenic). This is similar to previous studies which showed that serum BNP is not affected by age of the patient. There was male predominance among patients (133 males and 105 females). In our setting, male: female disparity is commonly seen for most disease conditions suggesting a gender bias in healthcare-seeking behavior of population. When compared to previous studies which showed that BNP level is higher in females, this study concluded that there is no effect of sex on BNP level. Vasan *et al*. looked at the value of BNP as a screening tool in the Framingham Offspring cohort study.[12] They evaluated 3177 adult patients with no history of heart failure and measured BNP levels and performed ECHO in each of the included patients. Patients with renal impairment (creatinine ≥2.0 mg/dl) or who had inadequate views on echocardiogram were excluded. The authors found that although there was a correlation between BNP and left ventricular systolic dysfunction and left ventricular mass, there was little value demonstrated as a screening test. In contrast to it this, we found strong-positive correlation between high levels of BNP at precise cutoff and cardiogenic dyspnea. Moreover, this study did not excluded patients with high serum creatinine level and concluded that even at high serum creatinine levels, patients with noncardiogenic dyspnea did not have BNP level above cutoff value of 415 pg/ml. In this study, of total 238 cases, BNP level of <415 pg/ml was estimated among 80 cases. Among these 80 cases, 15 patients had serum creatinine of ≥1.5 mg/dl. In contrast to previous studies which concluded that although BNP is mainly cleared by proteolysis by peptidases levels do correlate with glomerular filtration rates (GFRs), this study showed that even at high-serum creatinine levels, BNP is often able to distinguish between cardiogenic and noncardiogenic dyspnea.[6-9,13] This study had median value of serum creatinine of 1.5 mg/ml and 1.2 mg/ml in cases with noncardiogenic and cardiogenic cases, respectively, thus value of BNP was not confounded by high levels of serum creatinine. The "Breathing Not Properly" study was a multi-national, international study recruited 1586 patients. BNP had a diagnostic accuracy of 83.4% at a cutoff value of 100 pg/ml and a cutoff value of 50 pg/ml had a negative predictive value of 96%. In contrast to it, current study concluded with high-cutoff level of BNP, but at the same time, diagnostic accuracy was also higher. This study also showed that even in patients with acute exacerbation of COPD, rise in BNP is significant among only those with cor pulmonale that too not in cardiogenic range. There were 14 cases of acute exacerbation of COPD, among them only those with cor pulmonale had BNP level of ≥250 pg/ml. However, none of them had BNP >415 pg/ml. None of the cases with RSHF and normal left ventricular function had a significant rise in BNP. With cutoff value of 415 pg/ml, we can easily differentiate patients with left-sided heart failure from those with acute exacerbation of COPD, the two most common and confusing diagnosis among patients presenting with acute dyspnea. In contrast to other studies which have shown that while evaluating acutely dyspneic patients, it is important to keep in mind other noncardiogenic etiologies of acute dyspnea when an elevated BNP level is noted, especially when BNP levels fall in the "gray" zone (100–500 pg/ml for BNP), this study clearly determines that chances of cardiogenic dyspnea is <5% at BNP level of <415 pg/ml. Strength of the study lies in its large cohort (238 patients, and the fact that serum BNP was measured in all of them, and every patient underwent 2D ECHO as the gold standard. Limitations of the study – Only 15 patients in the noncardiogenic group had low GFR. Hence, in order to validate this cutoff in patients with low GFR, study could be extended to patients with poor renal function. Results of this study could be extrapolated in patients with normal to mildly deranged renal function. Although 2D ECHO is the gold standard to rule out cardiogenic dyspnea, it requires cardiologist for interpretation. Thus, this study is especially important for common hospital setting in our country where cardiologist is not available for 24 × 7 h. Measurement of BNP is an easy and quick bedside method which does not require any specialized skill.

Conclusion

Thus, this study gives us a reliable cutoff level of 415 pg/ml of BNP, which clearly distinguishes between cardiogenic versus noncardiogenic dyspnea. This differentiation is very crucial because it decides management in these patients.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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