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Full Length Research paper

Rapid measurement of B- type natriuretic peptide in the diagnosis of congestive heart failure in patients presenting to the emergency department with acute shortness of breath

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The goal of this study was to evaluate the utility of a rapid measurement of BNP in diagnosing heart failure in patients presenting to the emergency department with dyspnea. B- Type natriuretic peptide (BNP) is a protein secreted from the cardiac ventricles in response to pressure and volume overload. One potential application of measurement of BNP is to distinguish dyspnea of cardiac origin from non cardiac causes. BNP levels were measured in 72 patients presenting with dyspnea to the emergency department of a tertiary care hospital. Results of BNP levels were withheld from emergency physician. Two cardiologists reviewed the clinical data, laboratory parameters which included echocardiography and reached a consensus opinion about the diagnosis while being blinded to BNP results. The diagnostic accuracy of the BNP estimation was tested. The mean BNP concentration in patients with CHF (n= 44) was significantly higher than in patients without CHF (399+289.2 pg/ml versus 84.9±42.4 pg/ml (p<0. 001). Univariate analysis of plasma BNP level at different cut off levels revealed that, a value of 175 pg/ml had a sensitivity of 81.8%, specificity of 96.4% and accuracy of 87.5% for differentiating CHF from lung disease. BNP measurements added significant, independent explanatory power to other clinical variables used in predicting CHF. Rapid measurement of BNP appears to be a sensitive and specific test for differentiating patients with heart failure from those without, in urgent care setting.

Key words: B- type natriuretic peptide, congestive heart failure, Dyspnea.

INTROUCTION

Congestive heart failure (CHF) has assumed epidemic proportions worldwide which can be partly attributed to increasing life expectancy and improved survival in patients having other cardiovascular diseases (Bhatia et al., 2003). The life time risk of developing heart failure is 1 in 5. Although evidence shows that, age adjusted incidence of heart failure has plateaued, however the coexistent morbidity and mortality continues to increase (Bui et al., 2011). The cardinal manifestations of heart failure are dyspnea and fatigue which limit exercise tolerance and also fluid retention which may lead to pulmonary congestion and peripheral edema (Hunt et al., 2001) . Many patients with heart failure having NYHA class I and II are often under diagnosed (McDonagh et al., 1997). However, it has been shown that appropriate treatment, when instituted promptly, delays the progression of disease in these patients (Packer and Cohn, 1999; Niklas et al., 1992). In order to provide cost effective treatment to patients of congestive heart failure, rapid and accurate differentiation from other causes of dyspnea needs to be accomplished, more so in the

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Abbreviations: BNP, B- Type natriuretic peptide; **CHF,** congestive heart failure; **COPD,** chronic obstructive pulmonary disease.

emergency department. The symptoms may be non-specific and physical findings are not sensitive enough to provide an accurate diagnosis (Stevenson and Perloff, 1989; Remes et al., 1991). Although echocardiography is considered the gold standard for the detection of left ventricular dysfunction, it is relatively expensive, is not often readily available and may not always be diagnostic in acute presentation (Devereux et al., 1987).

Misdiagnosis of CHF can be hazardous and at times life threatening, if treatment for heart failure is erroneously initiated in conditions such as exacerbation of chronic obstructive pulmonary disease (COPD) that have symptoms simulating heart failure at presentation (Bales and Sorrentino, 1997; Wurez and Meador, 1992). Thus, it becomes imperative to obtain accurate and rapid bedside diagnosis of heart failure especially in the emergency department. Brain type natriuretic peptide (BNP) is a member of a family structurally related to hormone, the natriuretic peptides. It is secreted from cardiac ventricles in response to volume expansion, pressure overload and increased wall tension. It has emerged as a potential marker of congestive heart failure (Sudoh et al., 1988; Bhatia et al., 2003). Its plasma concentration correlates well with pulmonary capillary wedge pressure, left ventricular end-diastolic pressure and ejection fraction in patients with systolic dysfunction (Nakagawa et al., 1995; Wei et al., 1993). It has been shown that BNP concentration increases with the clinical severity of the disease not only in patients with systolic dysfunction but with diastolic dysfunction as well (Ogawa et al., 1998; Cowie et al., 1997; Ceyhan et al., 2008). Plasma BNP level has been shown to be a strong independent predictor of mortality in patients of acute dyspnea and serial measurement of BNP is useful in risk stratification of acute heart failure (Christ et al., 2007; Faggiano et al., 2010). BNP estimation provides useful insight into various aspects of CHF which include diagnosis, risk stratification, prognosis, response to treatment and even screening for asymptomatic LV dysfunction in high risk patients. It is being incorporated in most national and international cardiovascular guidelines for heart failure (Maisel et al., 2008).

MATERIALS AND METHODS

72 patients, who were presented to the emergency department of our institute with acute onset dyspnea with or without associated orthopnea, edema feet, weight gain, cough or wheeze were studied. Already diagnosed cases of CHF, lung disease (COPD), renal disease and acute coronary syndrome were excluded from the study. COPD encompasses chronic bronchitis and emphysema and is characterized by obstruction of the airways with limitation of air flow in and out of the lungs. It is usually detected on routine lung function tests (spirometry). The diagnosis of COPD in our patients was based on medical follow up records of the concerned pulmonologist.

Upon enrollment, a detailed medical history and clinical examination was undertaken in all the patients. The patients were subjected to laboratory investigations which included complete blood count, arterial blood gas analysis, blood sugar, blood urea, serum creatinine estimation, ECG and X-ray chest. Echocardiography was strongly encouraged at initial contact to assess the left ventricular functions. Emergency physician or first contact cardiologist was asked to make an assessment of the patient on the basis of history, physical examination and baseline investigations and give probable diagnosis while blinded to the results of BNP level. The final diagnosis about the cause of dyspnea was given by two cardiologists, after reviewing all records and any additional information that became available after evaluation in the emergency department including echocardiography and also response to treatment with diuretics or bronchodilators, while being blinded to results of BNP levels.

Measurement of plasma BNP levels

4 ml of blood sample was centrifuged and plasma removed, aliquited and frozen at -70°C before analysis. All samples were analyzed within 4 h by chemiluminescent sandwich immunoassay (Siemens, Germany). The assay completion time was approximately 15 min with a dynamic range 0 to 5000 pg/ml, the cut off level for heart failure diagnosis being 100 pg/ml (Davis et al., 1994).

Statistical analysis

Group comparison of BNP values was made using t-test for independent samples. The diagnostic utility of BNP in separating heart failure from no heart failure group was determined using Receiver operating characteristic (ROC) curves. The results are expressed in terms of area under the curve and the 95% of confidence interval of this area was determined. Sensitivity, specificity and accuracy was computed for BNP using a selection of possible cut off points. To evaluate the utility of BNP in the diagnosis of heart failure, we compared the sensitivity, specificity, and accuracy of BNP measurement to individual findings, to a multivariate model of clinical findings and to clinical judgment. To determine whether BNP measurement added independent diagnostic information to commonly collected clinical variables, we applied multivariate stepwise logistic regression. A predictive model based on history, clinical examination and X-ray findings using a p value of <0.01 for entry into the model was used. After obtaining a stable model, BNP measurement was added to the predictive model and improvement in the degree of fit was assessed.

RESULTS

The base line characteristics of 72 patients are shown in Table 1. All patients had dyspnea as presenting symptom. The first contact diagnosis of heart failure as cause of acute dyspnea was made in 76.4% and non cardiac (pulmonary) in the remaining 23.6% of patients by the emergency department Physician on the basis of clinical assessment and baseline investigations while blinded to the result of BNP (Table 2). The final diagnosis was heart failure in 44 (61.1%) and no heart failure in 28 (38.9%) patients as confirmed by two cardiologists after reviewing the clinical and investigative profile including echocardiography while being blinded to result of BNP assay results. This diagnosis was based on Framingham

Table 1. Baseline characteristics of 72 studied patients.

Characteristic		n	%
Age	Mean ± SD (Range)		58.6 ± 10.2
Gender	Male	47	65.3
	Female	25	34.7
	Hypertension	54	75.0
	Diabetes Mellitus	20	27.8
	Pulse/min		96.8 ± 9.6
	Systolic BP-mm Hg		138.4 ± 30.9
	Diastolic BP-mm Hg		81.6 ± 15.6
	Edema Feet	35	48.6
	Lung Crepitations	68	94.4
	Wheeze	44	61.1
	Third heart sound-LVS3	21	29.1
	Fourth heart sound-S4	8	11.1

Table 2. Diagnosis made by emergency department physician.

Diagnosis	n	%
No heart failure	17	23.6
Heart failure	55	76.4

criteria, supportive corroborative findings and response to treatment with diuretics or bronchodilators (Table 3). Plasma BNP levels of the 72 patients in relation to final diagnosis of heart failure (n = 44) versus no heart failure (n = 28 patients) are shown in (Table 4). Subgroup analysis in the heart failure group comprised of three categories:

1. Systolic heart failure (ejection fraction < 50%) n = 28. Their BNP level was significantly higher than the other groups with range of 196 to 1125 pg/ml (625$\pm$45). The patients in this subgroup who had ejection fraction < 40% had significantly higher plasma BNP than the group having ejection fraction < 50%.
2. Diastolic heart failure. Patients having normal ejection fraction and echo documented diastolic dysfunction between grade I to grade III (n = 14). Their BNP level was 98 to 697 pg/ ml (250$\pm$154).
3. Miscellaneous group (n = 2). It comprised of patients having atrial fibrillation with fast ventricular rate and flash pulmonary edema. Their BNP levels were 187 and 196 pg/ml.

The ability of BNP to differentiate CHF from pulmonary disease was assessed with ROC curve analysis (Figure 1). The area under the curve is 0.92 with a range of 0.860 to 0.992 and confidence interval of 95%. BNP level of 175 pg/ml had a sensitivity of 81.8%, specificity 96.4% and accuracy of 87.5% for differentiating CHF from pulmonary disease. Listed in Table 5 are accuracies of various cutoff points of BNP.

DISCUSSION

An acutely ill patient presented to the emergency department needs to be diagnosed correctly and promptly because misdiagnosis could place such a patient at risk of increased morbidity and mortality (Wurez and Meador, 1992; Bales and Sorrentino, 1997). It is imperative to institute appropriate treatment early in the course of disease to derive maximum survival benefit (Packer and Cohn, 1999). The signs and symptoms of heart failure are often nonspecific (Wei et al., 1993). A helpful history is not readily obtainable in an acutely ill patient. Moreover dyspnea, a key symptom of heart failure may be a nonspecific finding in elderly or obese patients in whom respiratory disease and physical deconditioning are common (Nakagawa et al., 1995). Routine laboratory tests like electrocardiogram and X -ray chest are also not accurate enough to always make the appropriate diagnosis (Hunt et al., 2001; Davie et al., 1996). Thus, it becomes difficult for clinicians to differentiate patients with heart failure from other diseases, such as pulmonary disease, on the basis of routinely available laboratory tests.

Echocardiography, although currently the gold standard for diagnosing left ventricular dysfunction, is relatively costly and has limited availability in urgent care settings. Severely dyspneic patients may be unable to stay still long enough for an echocardiographic study, while in others imaging may be suboptimal due to co- morbid conditions like obesity or lung disease. Therefore, even if emergency echocardiographic assessment is available, a rapid estimation of BNP can prove to be a useful cost effective investigation for the diagnosis of heart failure, saving valuable time. The source of plasma BNP is cardiac ventricles and is indicative of ventricular dys-function. Its release appears to be directly proportional to the ventricular volume and pressure overload (Nakagawa et al., 1995; Dickstein, 1998; Maeda et al., 1998; Luchner et al., 1998).

BNP is an independent predictor of high LV end diastolic pressure and correlates well with grade of NYHA class (Maeda et al., 1998; Clerico et al., 1998; Ceyhan et al., 2008). NT-proBNP, a peptide similar to BNP, is also being used for diagnosing CHF, however it has been shown that its plasma levels are vulnerable in patients with renal insufficiency as compared to BNP. The investigators in the PRIDE study evaluated the relationship between renal function, NT-proBNP and CHF. They found an inverse relationship between renal function and NT-proBNP and also refuted the claim

Table 3. Final diagnosis confirmed by two cardiologists.

Diagnosis		n	%
Heart failure (n = 44)	Heart failure (flash pulmonary odema)	2	2.8
	Heart failure	42	58.3
No heart failure (n = 28)	COPD with acute exacerbation	24	33.3
	COPD with pneumonia	2	2.8
	HRCT proved interstitial lung disease	2	2.8

Table 4. Plasma BNP levels (pg/ml) in the studied patients.

Characteristic	Heart failure (n = 44)	No- heart failure (n = 28)	Result P value
Plasma BNP level (pg/ml)	399.6 ± 289.2 (47-1125)	84.9 ± 42.4 (20-181.5)	<0.001 Sig

Table 5. Accuracies of various cutoff points of BNP.

BNP (pg/ml)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
50	97.7	17.9	65.2	83.3	66.7
80	97.7	42.9	72.9	92.3	76.4
100	93.2	71.4	83.7	87	84.7
125	86.4	85.7	90.5	80	86.1
150	84.1	85.7	90.2	77.4	84.7
175	81.8	96.4	97.3	77.1	87.5

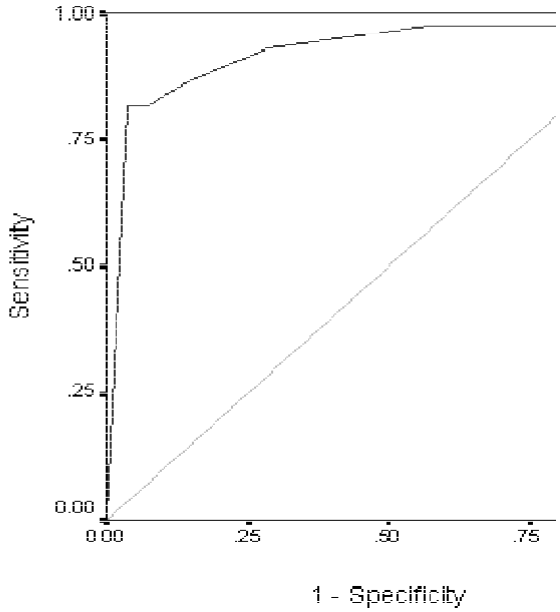

Figure 1. Shows receiver operating characteristic (ROC) curve for various cutoff levels of BNP in differentiating dyspnea due to heart failure vs. no heart failure with area under curve 0.92 (range 0.86 to 0.99). Confidence interval 95%.

that, it loses its specificity for the diagnosis of acute CHF due to impaired renal functions, although patients with serum creatinine of more than 2.5 mg/dl were excluded in their study. They also observed that NT- proBNP was the strongest risk factor of death regardless of renal function (Anwaruddin et al., 2006).

However, in our study we used BNP which has been shown to be more stable and predictable, irrespective of renal functions, in the diagnosis of CHF. In our study BNP assay was able to distinguish heart failure from pulmonary disease with a high degree of sensitivity, specificity, and accuracy. In our study, plasma BNP levels of heart failure patients were significantly higher as compared to those with no heart failure (399.6$\pm$289.2 pg/ml vs. 84.9$\pm$42.2 pg/ml. $p< 0.001$). Heart failure patients were categorized into 3 subgroups. Subgroup analysis revealed that, BNP levels were equally useful in differentiating systolic heart failure, diastolic heart failure, and the miscellaneous category. In patients with predominantly systolic heart failure (n = 28) the BNP level was significantly higher than other groups with range of 196 to 1125, mean 652$\pm$ 345 pg/ml. In patients having diastolic heart failure (n = 14), the BNP levels were high but less than those with systolic heart failure (98 to 697, mean 250$\pm$154 pg/ml). The miscellaneous group (n=2) which included patients with atrial fibrillation and fast ventricular rate presented with flash pulmonary edema. Their BNP levels were 187 and 196 pg/ml. Similar observations in various forms of heart failure have been reported in earlier studies (Yamamoto et al., 1996; Logeart et al., 2002; Hammerer et al., 2004).

In our study, the plasma level of BNP correlated well with the severity of LV dysfunction. Similar results have been reported by other investigators (Ogawa et al., 1998; Cowie et al., 1997) . Univariate analysis of plasma BNP assay showed that, it is the most accurate variable at 175 pg/ml for the diagnosis of heart failure with accuracy of 87.5%, sensitivity 81.8%, specificity 96.4% and positive predictive value of 77.1%. The results of our study are consistent with other reported studies (Maisel et al., 2002; Morrison et al., 2002; Koulori et al., 2004).

Using multiple variable logistic regression analysis of various factors used for differentiating patients with and without heart failure with significant p value, we observed that addition of BNP at cut off level of 175 pg/ml increased the combined explanatory power of the symptoms, signs, radiological study and other laboratory findings. Our data showed that, plasma BNP level of 175 pg/ml was the strongest independent predictor of the heart failure diagnosis with odds ratio of 41.9, followed by history of paroxysmal nocturnal dyspnea (odds ratio of 37.3), decreased ejection fraction (odds ratio 29.0), cardiomegaly on chest x-ray and pulmonary edema (odds ratio of 27.0). These findings of multiple variable analysis are almost consistent with other reported studies with some variations which can be explained on the basis of differences in population studied and sample size (Logeart et al., 2002; Hammerer et al., 2004; Maisel et al., 2002; Morrison et al., 2002).

Conclusion

Rapid measurement of the BNP concentration in blood is a sensitive and specific test for the identification of patients of heart failure presenting with acute dyspnea to the emergency department. It appears to hold promise as a potent and cost-effective test of choice for acutely dyspneic patients which could replace chest x-ray and echocardiography as first investigation in such patients in urgent care settings.

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