ABSTRACT:

Objective: To evaluate the utility of BNP (B-type natriuretic peptide) in discrimination of cardiac and non-cardiac (Pulmonary) dyspnea.

Background: Traditionally the diagnosis of heart failure has been made on the basis of presence of certain signs and symptoms. In case of chronic outpatients, where the physical signs are usually prominent, the diagnosis is easy, whereas in elderly who present to the emergency department with acute dyspnea it is sometimes challenging and often difficult particularly when associated chronic pulmonary diseases are also present. Elevated plasma B-type natriuretic peptide (BNP) has been demonstrated to be a powerful marker for diagnosis and discrimination of dyspnea in the setting of heart failure from a non-cardiac dyspnea.

Methods: We studied 105 subjects (mean age 51.57±5.11 yr), 35 presenting to the emergency department with dyspnea due to HF [New York Heart Association (NYHA) class III], 35 presenting to the emergency department with dyspnea due to pulmonary causes and 35 normal controls, in Dr. HMI Institute of Pharmacology & Herbal Sciences in collaboration with Arif Medical complex Karachi From June 2004 to Dec 2004.

Results: Baseline characteristics of the two groups were similar. Their serum levels of BNP were estimated and compared. Levels of serum BNP in patients with HF were found to be significantly high as compared to the non-cardiac dyspneic patients and control subjects [680±45.20, 375.21±25.63 and 78.45±16.44 respectively]

Conclusion: BNP level can be a useful tool in differentiation of a heart failure patient from a non-cardiac patient presenting to the emergency department with dyspnea.

INTRODUCTION

Acute Dyspnea is one of the main reasons for admission to emergency department. Rapid diagnosis of congestive left heart failure (CHF) decompensation is important for prompt and appropriate treatment but is often difficult, especially in elderly or obese subjects, and when associated chronic pulmonary and other cardiac diseases are present (Damien et al., 2002). For individuals older than 40 years, the lifetime risk of developing HF has been estimated at 20% for both men and women whereas the incidence of heart failure is highest in people older than 65 years (Brain, 2003 and Davies, 2000).

Brain or B- Type Natriuretic Peptide, which was first originated from the brain of monkeys, is a neurohormone secreted mainly from the ventricles of heart in response to volume and pressure overload. BNP promotes diuresis and vasodilatation and has been found to be elevated in patients with heart failure and correlate well with New York Heart Association (NYHA) classification. (Humberto, 2002). Elevated plasma B-type natriuretic peptide (BNP) has been demonstrated to be a powerful diagnostic marker in the setting of heart failure (Mair et al 2001). It helps in the discrimination of dyspnea from cardiac and non-cardiac (pulmonary) origin in emergency department.
Patients with elevated BNP levels have been shown to be at significantly higher risk of development of heart failure (Coodley E 1999).

**SUBJECT AND METHOD**

The proposed study was carried out at Dr. HMI Institute of Pharmacology & Herbal Sciences in collaboration with National Institute of Cardiovascular Diseases (NICVD) Karachi and Arif Medical Complex Karachi from June 2004 to Dec 2004. The local ethics committee approved the study protocol. Subjects were divided into three groups, group A, group B, and group C.

**Group A:** Thirty-five subjects served as control with no overt cardiovascular or pulmonary disease and no history of hypertension or diabetes. They were age and sex matched with subjects in-group B.

**Group B:** Thirty-five subjects presented to the emergency room of NICVD with acute severe dyspnea due to the known cause of congestive heart failure [New York Heart Association (NYHA) class III] secondary to Coronary artery disease. Hypertension, Valvular heart disease and Dilated Cardio-myopathies.

**Group C:** Thirty-five subjects presented to the emergency room of Arif Medical Complex with acute severe dyspnea due to the known cause of primary lung disorders (Chronic obstructive pulmonary disease, severe Emphysemia, Pneumonia or severe Asthma).

The data collection for various groups was standardized through the use of similar methodology, protocol and procedure using a standard questionnaire.

The questionnaire provided information about type of work, smoking habit, medical history of cardiovascular disease, hypertension and family history of coronary heart disease. Smoking habit of subjects were grouped into current smokers and non smokers, weight was measured on a balance scale while participants were without shoes and heavy outer garments, height was measured in the standing position following weight measurement. Blood pressure of the subjects was measured twice in the right arm after 5 minute of rest, using a standard mercury sphygmomanometer. Values from the second measurement were used in this study. Diagnosed HF patients were selected from National Institute of cardiovascular disease Karachi. Controls, were the attendants of the patients. Diagnosed

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### Table-1
Comparison of Age, Weight, Height and BMI of Group A, Group B and group C Subjects

<table>
<thead>
<tr>
<th>Groups</th>
<th>Age (Years)</th>
<th>Weight (Kg)</th>
<th>Height (m)</th>
<th>BMI (Kg/m²)</th>
<th>Smoker (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-A (Control) (35)</td>
<td>50.34 ± 5.03</td>
<td>64.88 ± 8.29</td>
<td>1.73 ± 0.41</td>
<td>21.59 ± 2084</td>
<td>00</td>
</tr>
<tr>
<td>Group-B (Patients with failure) (35)</td>
<td>51.86 ± 4.10</td>
<td>62.13 ± 7.20</td>
<td>1.69 ± 0.29</td>
<td>21.75 ± 2.45</td>
<td>20* (57.14%)</td>
</tr>
<tr>
<td>Group-C (Patients with PLD) (35)</td>
<td>52.53 ± 6.20</td>
<td>61.69 ± 9.40</td>
<td>1.70 ± 0.40</td>
<td>21.34 ± 3.1</td>
<td>22* (62.85%)</td>
</tr>
</tbody>
</table>

The values are expressed as mean ± SD. The number of observation and units are given in parentheses.

*P< 0.01, significant as compared to control

BMI: Body mass index

PLD: Primary Lungs Disease
primary lung disorder patients were selected from Arif Medical Complex, Karachi. The subjects were asked to fast for 10 – 12 hours, 6 ml of blood was collected from the antecubital vein, (after all aseptic measures) while the subjects were sitting up right. Sampling was done between 0700 and 0900 hours.

Specimen Handling and Storage

Strictly predefined protocol was used for specimen preparation. Blood was collected in a gel Barrier silicone coated neotube from Nipro Japan. Two different samples were made one was additive free, and the other was containing EDTA; blood-tubes were put on ice in the icebox immediately after collection. Whole blood tubes were kept at room temperature until clotting was complete. Samples that showed sign of haemolysis were discarded. Remaining samples were centrifuged at 1000 rpm for 10 minutes within one hour after collection; serum was separated and stored in aliquots in deep freezer at minus 20°C until assayed (with in one month). Samples were analyzed in one run at the end of the study, to omit between run analytical variations, except serum glucose that was analyzed within four hours of the sample collection. Serum total cholesterol, HDL-C, triglycerides and glucose were analyzed enzymatically, using the kits supplied by SPINREACT, Spain. LDL-C was calculated by the Friedwald formula. Plasma BNP was analyzed by MEIA (Microparticle Enzyme Immunoassay) using the AxSYM system of Abbot Laboratories Pakistan for which we are extremely thankful to their diagnostic division.

STATISTICAL ANALYSIS

Comparison of difference of means between Control and Subject groups was made by using Student’s t-test for two samples with n1 + n2 -2 degree of freedom. Using Chi-square test of proportions, where it was valid, we compared the difference in percentages. A p value less than 0.05 was considered significant.
RESULTS

A total of One Hundred and Five subjects were studied. Table 1 shows the mean values and comparison of age, weight, height, body mass index and smoker status, of control (group A), cases group B and group C subjects. Thirty-five healthy normal volunteers, twenty five males (71.42%) and ten females (28.57%) were placed in group A while Thirty-five patients, twenty five males (71.42%) and ten females (28.57%) having Heart failure were placed in group B and Thirty-five patients, twenty five males (71.42%) and ten females (28.57%) having primary pulmonary lungs disease placed in group C. When age, weight, height and BMI of control subjects were compared with group B and group C patients, a nonsignificant difference was seen. In relation to smoking habit, none of the subjects was smoker in control group. In-group B 57.14%, (20) patients were smokers, which is significantly high (P<0.001) as compared to control group while in group C 62.85% (22) patients are smokers which is also significantly high as compared to control, and the percentage has also high when it was compared to group B. Table-2 shows mean values of hypertension, systolic blood pressure diastolic blood pressure, heart rate and family history of ischemic heart disease of control group A, patients group B and C. When history of hypertension was compared between control, group B and group C, control subjects were non hypertensive, In-group B 71.42% (25) patients were hypertensive, the difference being significantly high (p < 0.001) when compared to control while in group C 48.57%(17) patients were hypertensive which is also significantly high as compared to control but percentage of this group was lower when it was compared to group B [71.42%, 48.57% respectively]. When systolic blood pressure (SBP), diastolic blood pressure (DBP), and family history of ischemic heart disease (F/H of IHD) were compared among control, group B and C, non-significant changes were observed in SBP and DBP, while family history of ischemic heart disease was significantly high in group B 62.85%(22) as compared to control while in group C it was 14.28%(5) that is also significantly high as compared to control but lower in percentage as compared to group B.

### Table-3
Comparison of Fasting Serum Glucose, Triacylglycerol, Total Cholesterol among Group-A Group B and Group-C Subjects

<table>
<thead>
<tr>
<th>Groups</th>
<th>Serum glucose (mg/dl)</th>
<th>Triacylglycerol (mg/dl)</th>
<th>Total Cholesterol (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-A (Control)</td>
<td>95.85 ± 10.47</td>
<td>151.6 ± 10.64</td>
<td>179.11 ± 13.49</td>
</tr>
<tr>
<td>(35)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group-B (Patients with failure)</td>
<td>92.35 ± 11.51</td>
<td>155.43 ±13.50</td>
<td>185.0 ± 25.20</td>
</tr>
<tr>
<td>(35)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Group-C (Patients with PLD)</td>
<td>93.72 ± 12.31</td>
<td>153.71 ± 20.50</td>
<td>183.06 ± 14.20</td>
</tr>
<tr>
<td>(35)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The values are expressed as mean ± SD. The number of observation and units are given in parentheses. PLD: Primary Lungs Disease
Table-3 shows the mean values of serum glucose, triacylglycerol and total cholesterol of control, patients group B and C. The value of serum glucose, triacylglycerol and Total cholesterol of group B and C were showing non-significant changes when they were compared to control.


<table>
<thead>
<tr>
<th>Groups</th>
<th>HDL-C (mg/dl)</th>
<th>LDL-C (mg/dl)</th>
<th>BNP (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group-A (Control) (35)</td>
<td>45.11 ± 10.17</td>
<td>103.68 ± 6.19</td>
<td>78.45 ± 16.44</td>
</tr>
<tr>
<td>Group-B (Patients with failure) (35)</td>
<td>** 32.8 ± 7.62</td>
<td>** 124.91 ± 17.25</td>
<td>** 680.00 ± 45.20</td>
</tr>
<tr>
<td>Group-C (Patients with PLD) (35)</td>
<td>38.30* ±10.20</td>
<td>116.01** ±5.31</td>
<td>375.21** ± 25.63</td>
</tr>
</tbody>
</table>

The values are expressed as mean ± SD. The number of observation and units are given in parentheses.

*P< 0.01 Significant as compared to control
**P< 0.001 Significant as compared to control group
HDL-C High density lipoprotein cholesterol
LDL-C Low-density lipoprotein cholesterol
BNP Brain Natriuretic Peptide
PLD Primary Lungs Disease

Table-3 shows the mean values of serum glucose, triacylglycerol and total cholesterol of control, patients group B and C. The value of serum glucose, triacylglycerol and Total cholesterol of group B and C were showing non-significant changes when they were compared to control.

Table-4 shows comparison of Fasting High Density Lipoprotein Cholesterol, Low Density Lipoprotein Cholesterol, and Plasma BNP among Group-A Group-B and Group-C Subjects. A mean value of high-density lipoprotein cholesterol (HDL-C) of group B and C was significantly low (P< 0.001 and P< 0.01) as compared to control subjects [32.8± 7.62, 38.30±10.20 and 45.11±10.17 respectively]. The values of low-density lipoprotein cholesterol (LDL-C) of group B and C, was significantly high (P < 0.001) as compared to control subjects [124.91 ± 17.25, 116.01 ± 5.31 and 103.68 ± 6.19 respectively] while a mean value of plasma BNP of group B and C was also significantly high (P<0.001) as compared to control subjects [680 ± 45.20, 375.21 ± 25.63 and 78.45 ± 16.44 respectively].

Table-5 shows comparison of Fasting High Density Lipoprotein Cholesterol, Low Density Lipoprotein Cholesterol, and Plasma BNP among group B patients with group C patients. A significant difference was found among the mean values, of high-density lipoprotein cholesterol (HDL-C), of group B and C [32.8 ± 7.62 and 38.30 ± 10.20 respectively], and values of low-density lipoprotein cholesterol (LDL-C) of group B (P< 0.02) and group C [124.91 ± 17.25, 116.01 ± 5.31 respectively] while a mean value of plasma BNP of group B was also significantly high (P<0.001) as compared to group C patients [680 ± 45.20, 375.21 ± 25.63 respectively].

**DISCUSSION**

Heart Failure (HF) is one of the main causes of hospitalization in industrialized as well as developing countries. Its most common...
causes are coronary artery disease (CAD), hypertension, valvular heart disease and cardiomyopathies (Mair et al., 2001). The prevalence of HF is higher in men than in women. Heart failure prevalence in people older than 70 years is approximately 10-15%, and in these individuals up to 70% of hospital admission is directly or indirectly related to HF. The five-year mortality in patients with HF is approximately 50%; the annual mortality depends on disease severity and ranges from less than 5% in symptomatic patients to 30-80% in end stage disease (NYHA class IV), with 10% in mild HF (NYHA II) and 20-30% in moderate heart failure (NYHA class III) (Mair et al. 2001). The natriuretic peptide system comprises of 3 peptides, the A – type peptide (ANP, released from the atria), the B-type peptide (BNP, released from ventricles) and the C-type (CNP, released from endothelium cells). Because BNP is released directly from the ventricles, it has been suggested that it is more accurate than the other natriuretic peptides for the diagnosis of CHF. Gensini et al. (1998), reported that smoking is responsible for 29% of the total death from coronary heart disease. In our study also the percentage of smokers is significantly high (P<0.001) in patients with heart failure and patients with primary lung disorders as compared to control subjects.

Elevated blood pressure (Hypertension) is another very significant strong and independent risk factor for coronary artery disease, both in men and women (Brochier et al., 1998). We have found a significantly high (P<0.001) percentage of hypertension in patients with HF and in patients with primary lung disease as compared to control subjects. The study of Hamsten and Fair (1987) shows the presence of familial predisposition to coronary artery disease (CAD) in a substantial number of men with myocardial infarction occurring at a younger age. In our study we have found a significant difference of family history of IHD between controls, patients with HF and patients with primary lung disease. The dyslipidemia, most clearly associated with increased risk for CAD, particularly elevated plasma levels of cholesterol carried in LDL. The association between elevated blood cholesterol and CAD has been established in observational and interventional epidemiological studies.

Table-5
Comparison of Fasting High Density Lipoprotein Cholesterol, Low Density Lipoprotein Cholesterol, and Plasma BNP among Patients Group-B and Group-C Subjects

<table>
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<tr>
<th>Groups</th>
<th>HDL-C (mg/dl)</th>
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<td>375.21 ± 25.63</td>
</tr>
</tbody>
</table>

The values are expressed as mean ± SD. The number of observation and units are given in parentheses.

*P< 0.01, **P< 0.02, ***P< 0.001 Significant as compared to group C

HDL-C High density lipoprotein cholesterol
LDL-C Low-density lipoprotein cholesterol
BNP Brain Natriuretic Peptide
PLD Primary Lungs Disease
In our study we report no significant difference between the total cholesterol and triglyceride levels of case (patients with HF and patients with primary lung disease) and control subjects. Although the mean level was slightly higher in the cases, but statistically it was non-significant. Similarly we report lower mean levels of HDL-C, with a significant difference \((P<0.001)\) in group B and group C subjects as compared to control. We have also observed that, the patients with heart failure and patients with primary lung disease have significantly \((P<0.01)\) high levels of LDL-C and very significant \((P<0.001)\) high values of BNP as compared to control. We have also compared the levels of HDL-C, LDL-C and BNP in between the groups of patients B and C and found a significant difference in the levels of HDL-C and BNP. The BNP levels of group C were low as compared to group B but as these levels are very high from the control and as group C patients were suffering from lungs disorder with no sign of hart failure, the high values are of great concern. Dao et al. (2001) evaluated 250 patients with acute dyspnea and they found significantly high levels of BNP in patients with diagnosis of heart failure as compared to he patients with non heart failure group. Davis M et al 1994 studied BNP and ANP in 52 patients with dyspnea and observed that BNP was more accurate than ejection fraction or ANP for predicting the diagnosis of CHF. Cowie MR et al 1999 and Koom L et al 2000 have assessed the BNP in the primary care setting. Davis M et al 1994 and Cheung BM 1998 also concluded in their study that natriuretic peptides are the powerful biochemical markers of heart failure and they correlate well with inversely measured LV filling pressure Cohn JN 1996. Comparison with other studies, we demonstrated that BNP measurements can be useful in the diagnosis of CHF in patients presenting to the ED with dyspnea and is a very important aid in the differentiation of dyspneic patient of cardiac and non-cardiac origin. To the best of our information this is first comparative study on this field in our country.

Study Limitation: This study included patients with acute severe dyspnea; whether or not our result can be extrapolated to patients with milder dyspnea remains to be shown.

The relatively high values of BNP in non-CHF patients with pulmonary disorders might be because of right ventricular involvement, which has to be resolved.

We conclude that BNP measurement is a sensible and specific strategy for the diagnosis of CHF patients as well as it helps in differentiation of cardiac from non-cardiac patients who present to the emergency department with acute severe dyspnea and may add additional benefit to the management of patients with heart failure and pulmonary disease in this setting.

**ACKNOWLEDGMENT**

The Authors are grateful to the Hamdard University for Research Grant to this project. The assistance of Abbott Laboratories, Pakistan is also acknowledged with gratitude and our sincere thanks to Prof. Dr.Muhammad Irfanullah siddiqui, Chairman Community Health Sciences, Hamdard University, for his help in the statistical analysis.

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