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Correlation between Amino Terminal Pro Brain Natriuretic Peptide (NT-ProBNP) Level and Pulmonary Arterial Systolic Pressure in Patients with Pulmonary Hypertension

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Abstract—
Background: *Right heart catheterization is the gold standard for diagnosing and estimating pulmonary artery pressure in patients with pulmonary hypertension (PH). However, it is invasive, expensive and not amenable to repeated measurements that are necessary to monitor disease progression. Clinicians in Nepal mostly rely on the indirect measurement of pulmonary pressure via trans-thoracic echocardiography. Amino Terminal Pro Brain natriuretic Peptide (NT-proBNP) is found to be increased in proportion to the increased pulmonary artery pressure. Thus, this study aims to see the correlation of pulmonary artery pressure with NT-proBNP level. Since measurement of NT-proBNP is less expensive and easier to perform its repeated measurement can be used for monitoring disease progression and treatment outcome.*
Materials and Methods: *Patients with Pulmonary Hypertension admitted under department of cardiology, Manmohan cardiothoracic vascular and transplant center were enrolled in this study over 6 months period. Cases were further divided into 3 different groups based on etiology of pulmonary hypertension into rheumatic heart disease (RHD), dilated cardiomyopathy (DCM) and COPD with corpulmonale. In all cases systolic and mean pulmonary artery pressure were measured by transthoracic echocardiography. Serum levels of NT-proBNP was measured in all the patients. SPSS ver. 20.0 was used to analyze the data. Spearman, Mann Whitney U and Kruskal Wallis tests were used for statistical analysis and statistical significance was established at 'p' value less than 0.05.*
Result: *A total of 91 PH diagnosed patients were enrolled in the study. The mean age of the total identified patient was 53.76 ± 15.5 yrs. A total of 31(34%) patients had primary diagnosis of corpulmonale, 30 (33%) had primary diagnosis of DCM and 30 (33%) were diagnosed with RHD. Majority of patients (34.1%) belonged to NYHA class III. Mean serum values of NT-proBNP was 175.27 ± 163.38 pmol/L. Co-morbid conditions including, smoking, alcohol intake, advancing age, gender and diabetes mellitus were not found to be associated with NT-proBNP. Whereas hypertension showed significant relation with NT-proBNP. Mean serum values of NT-proBNP was higher in patients with DCM compared to RHD and corpulmonale. Mean serum values of NT-proBNP was significantly higher in patients of class IV NYHA grade. With decrease in LVEF, NT-proBNP was found to increase significantly. Serum NT-proBNP levels were compared with PASP which showed positive correlation (spearman's* $r_s = .409$, $p=0$).
Conclusions: *In this study PASP showed strong correlation with NT-proBNP. In patients with PH, PASP is difficult to estimate without either invasive or non-invasive techniques that require expertise and equipment. Although release of NT-proBNP is not the direct consequence of PH, its release and correlation with PASP can be clinically useful in estimating PASP in resource poor settings. The data in this study suggest that NT-proBNP may have potential as a marker of increased PASP in PH.*

Keywords— *LVEF; NT-proBNP; PASP; Pulmonary hypertension*.

I. INTRODUCTION

Pulmonary hypertension (PH) is characterized by presence of high pulmonary vascular pressure which can be the consequences of different underlying disorders[1]. It is defined as a pulmonary artery systolic pressure (PASP) > 35mmHg or mean pulmonary artery pressure (MPAP)> 25 mm Hg at rest or >30 mmHg with exercise measured during right heart catheterization [2, 3]. After coronary heart disease and systemic hypertension, PH is the third most common cardiovascular condition [4]. For the proper diagnosis of PH, invasive procedure like cardiac catheterization of right heart is considered as gold standard [5]. But there are noninvasive tests like echocardiogram which has shown good correlation with the invasive procedure [6, 7]. This is the only method used routinely for screening of PH in our setup but is not easily available. Apart from these, there are blood parameters like brain natriuretic peptide (BNP) and the N-terminal fragment of BNP (NT-proBNP) which are released from cardiac ventricles and have shown correlation with invasive methods. Among these, NT-proBNP is more advantageous over BNP as it is more stable both *in vivo* and *in vitro* [8]. Based on these facts, this study aimed to investigate the relation between NT-proBNP and pulmonary arterial Systolic Pressure in patients with pulmonary hypertension in our setup.

II. METHODOLOGY

This is a single center, cross sectional, observational study conducted in Department of Biochemistry, Maharajgunj

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Medical Campus (MMC); General ward, Intensive care unit and Critical care unit of Manmohan Cardiothoracic Vascular and Transplant Center (MCVTC) and Institute of Medicine (IOM), Tribhuvan University (TU), Kathmandu, Nepal and its clinical laboratory. All patients admitted to the MCVTC from mid of March till mid of September 2016 with pulmonary hypertension, who provided written consent for the study were included. Patients were excluded if they had evidence of congenital heart disease (CHD), either at echocardiography or as a previous diagnosis; History of other condition that might cause elevation of [NT-proBNP] like ischaemic heart disease (IHD), myocardial infarction (MI), chronic kidney disease (CKD); Patients on specific therapies for PH [prostanoids (epoprostenol), Endothelin receptor antagonist (bosentan)]; Patients with prosthetic heart valve; Patients on hemodialysis. In this study, Non-probability (convenience) sampling was done.

The research protocol was approved by Institutional Review Board (IRB), Institute of Medicine after submission and presentation of research proposal. All the study participants were explained about the research (including an interviewer-administered questionnaire, clinical examination and a blood sample) and were asked if they would like to participate, and when asserted, they were asked to sign a consent form for having their blood sample collected and analyzed in the hospital laboratory. The participants were assured that the information provided by them would be maintained confidential. There was no risk for human participants and no interventions were carried out.

A performa sheet was filled at the bed side with brief history including the chief complaints, past medical, surgical, drug history and body mass index was also measured. Then 5ml of blood was withdrawn from the patients under aseptic condition and analyzed later.

Random blood samples were drawn and collected. The blood was then taken to the laboratory within 2 hours and centrifuged at 4000 rpm for 5 minutes. An aliquot of serum was then separated. Routine investigation including serum glucose (for screening of diabetes), urea and creatinine (to rule out kidney disease), troponin I and CKMB (for recent MI) were done on the same day of sample collection and remaining serum was stored at -20^0 C until analysis of NT-proBNP was done.

The serum concentrations of glucose, urea and creatinine were measured by fully automated analyzer, BT 3000, Italy, in the clinical biochemistry laboratory. The autoanalyzer uses spectrophotometric technique and the reagents and along with the calibrators and controls were supplied by the reagent company.

The serum NT-pro BNP concentration was determined by Enzyme Linked Immunosorbent Assay (ELISA) using DRG ® NT-proBNP direct (EIA-4827) from DRG International Inc., USA.

ECHO report of the patient that was done after/before admission, as a part in his/her management, within one week of blood sample collection was recorded and the values of PASP, MPAP and LVEF were noted. PASP was used to diagnose PH and all the patients were further classified into mild, moderate and sever PH using PASP value [9]. Patients were also classified on the basis of functional severity of PH given by world health organization (WHO) which is modified from New York Heart Association (NYHA) classification[10].

The data was entered and analyzed into SPSS v 20.0. Normality for NT-proBNP was tested using Shapiro-Wilk test which showed positively skewed graph. Thus, the non-parametric tests were used in this study. For the continuous variables, spearman correlation was used. To compare the relation between two categories, Mann Whitney U test was used and for more than two categories, Kruskal Wallis test was used. Statistical significance was established at p value less than 0.05.

III. RESULTS

After applying the inclusion and exclusion criteria, a total of 91 patients of pulmonary hypertension were included in this study. The mean age of the patients was 53.76 ± 15.5 yrs. The range extended from 22 years to 75 years. Of the total patients included in the study, 52 were females and 39 were males. The mean BMI of study population was 21.76 $\pm$ 1.81 kg/m^2. Most of the patients in the study were within normal range of BMI. Echocardiographic parameters were studied in three dimension that included PASP, MPAP and LVEF. Mean PASP was 60.88 $\pm$ 19.26 mm Hg (range 30-115), MPAP was 38.67 $\pm$ 11.76 (range 20-72) mm Hg and LVEF was 50.27 $\pm$ 14.65% (range 20-75). The most common cause of PH was the disease of left heart (66%) and among these 50% were diagnosed with dilated cardiomyopathy (DCM) and 50% were of rheumatic heat disease (RHD). The second common cause was corpulmonale (34%). The distribution of different study parameters and the clinical characteristics on the basis of etiologies of PH are shown in Table 1 and 2.

TABLE 1. Different parameters on the basis of etiology of PH.

Patient's parameters		Diagnosis			
		Cor Pulmonale [N (% within diagnosis)] N = 31	DCM [N (% within diagnosis)] N = 30	RHD [N (% within diagnosis)] N = 30	Total [N (% within diagnosis)] N = 91
Gender	Male	13 (41.9%)	16 (53.3%)	10 (33.3%)	39 (42.9%)
	Female	18 (58.1%)	14 (46.7%)	20 (66.7%)	52 (57.1%)
NYHA CLASS	CLASS II	8 (25.8%)	10 (33.3%)	11 (36.7%)	29 (31.9%)
	CLASS III	13 (41.9%)	11 (36.7%)	11 (36.7%)	35 (38.5%)
	CLASS IV	10 (32.3%)	9 (30.0%)	8 (26.7%)	27 (29.7%)
Smoking Status	Yes	28 (90.3%)	16 (53.3%)	10 (33.3%)	54 (59.3%)
	No	3 (9.7%)	14 (46.7%)	20 (66.7%)	37 (40.7%)
Alcohol status	Yes	17 (54.8%)	11 (36.7%)	6 (20.0%)	34 (37.4%)
	No	14 (45.2%)	19 (63.3%)	24 (80.0%)	57 (62.6%)
Hypertension	Yes	7 (22.6%)	4 (13.3%)	2 (6.7%)	13 (14.3%)
	No	24 (7.4%)	26 (86.7%)	28 (93.3%)	78 (85.7%)
Diabetes Mellitus	Yes	11 (35.5%)	11 (36.7%)	8 (26.7%)	30 (33.0%)
	No	20 (64.5%)	19 (63.3%)	22 (73.3%)	61 (67.0%)

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TABLE 2. Clinical parameters of patients with PH on the basis of etiology of PH.

	Cor-pulmonale (Mean ± SD)	DCM (Mean ± SD)	RHD (Mean ± SD)
BMI kg/m^2	22.00 ± 1.85	20.85 ± 1.63	22.42 ± 1.62
PASP mmHg	68.48 ± 22.37	52.83 ± 13.02	61.06 ± 18.32
MPAP mmHg	43.32 ± 13.72	33.73 ± 7.82	38.8 ± 11.18
LVEF (%)	58.06 ± 9.63	35.83 ± 13.33	56.67 ± 8.34
NT PRO-BNP (pmol/L)	156.97 ± 135.78	256.99 ± 212.01	105.82 ± 79.86

Patients with PH were classified into NYHA classes as Class II, class III, and class IV based on NT-pro BNP value. Study findings revealed that a greater proportion of patients belonged to class III (38.5%), followed by class II (31.9%), and class IV (29.7%). The average NT-pro BNP level of the overall patient was 175.3 pmol/L (SD ± 163.4). Patients with PH were also stratified into disease severity as mild, moderate, and severe, defined based on the PSAP value. The study findings indicated that, majority of the patients had moderate PH (37.4%), followed by mild form of PH (31.9%), and severe PH (30.8%) as shown in Table 4. The average PSAP value of the severe PH patients was 233.1 mm Hg (SD + 172.8).

Findings on the association between baseline demographic and clinical characteristics and NT-pro BNP demonstrated that hypertension was significantly associated with NT-pro BNP (p=0.018), however other parameters of interest such as gender, smoking status, alcohol consumption, and diabetes mellitus had no significant association with NT-pro BNP level (Table 3).

TABLE 3. Association between baseline demographic and clinical parameters and NT-pro BNP Level.

Baseline Demographic and Clinical Parameters	p value
Gender	0.369
Smoking	0.115
Alcohol	0.417
Hypertension	0.018*
Diabetes mellitus	0.543

* Indicate statistical significance at 0.05 level of significance from Mann–Whitney U test.

Study findings on the relationship between NT-pro BNP level and different categories of listed independent factors revealed that categories of NYHA class, severity of PH on the basis of PASP, and etiologies of PH were significantly associated with NT-pro BNP level (Table 4).

TABLE 4. Relation between the NT-pro BNP and between different independent categories.

Independent Factors	p value
NYHA classes	0.000*
Severity of PH on the basis of PASP	0.000*
Etiologies	0.002*

* indicate statistical significance at 0.05 level of significance from Kruskal Wallis test.

Furthermore, association of NT-proBNP levels with PASP, ($\mathbf{r_s}$= 0.409, p=0.000) and LVEF ($\mathbf{r_s}$= -0.311, p=.003) showed positive and negative correlation, respectively and was found to be statistically significant. While association of age, ($\mathbf{r_s}$= -0.072, p=0.495) was not statistically significant at p<0.05 level as illustrated in Table 5.

TABLE 5. Result showing correlation analysis of age, PASP and LVEF with NT-pro BNP.

	Spearman's Rho (r_s)	p value
Age	-0.072	0.495
PASP	0.409	0.000*
LVEF	-0.311	0.003*
MPAP	0.412	0.000*

* indicate significant difference at 0.05level of significance from Spearman's correlation.

IV. Discussion

NT-pro BNP are the peptides which are released from the cardiac ventricles in response to cardiac wall stress and unlike atrial natriuretic peptide (ANP) these are not stored in granules in the ventricles. Instead when there is increased cardiac wall stretch due to volume over load, thereby increases the transcription of BNP. These are the body's defense mechanism which leads to increased glomerular filtration rate, diuresis, loss of sodium in urine, along with various other actions [11, 12]. So any factor that increase the pressure in the ventricles, leads to release of NT-proBNP. Present study was conducted to evaluate the level of NT-proBNP in patients with pulmonary hypertension and examine the association between PASP and NT-proBNP. The study findings revealed statistically significant positive correlation between PASP and NT-proBNP, which was one of the major finding of the study. Similar results were obtained in other prospective and cross sectional studies [13, 14]. Also there was significant relation between the severity of PH and value of NT-proBNP, which is an indicative that the value of NT-proBNP can be used to assess the condition of the patient. However, the study did not use the parametric tests to examine the significant differences within the group, further studies are warranted to validate this information.

Another major finding of this study was the relation between NT-proBNP and patients with HF. In patients with HF, due to over stretch of the cardiac wall, the levels of BNP mRNA are markedly increased [15]. Various studies have shown a highly significant relation between NT-poBNP and NYHA classification and have demonstrated progressive increase in the value of NT-proBNP with the increase in the severity [16, 17]. In the current study, patients of NYHA class II to IV were present because only the hospitalized patients were taken as study subjects. The relation between the different classes of NYHA and NT-proBNP was highly significant. Here we could not compare within the groups as it was not normally distributed. Another important parameter that we look for in patients with HF is LVEF. The study found that NT proBNP levels increased significantly with an increase in the severity of LV systolic dysfunction. Similar findings were obtained in various large studies [18, 19].

Likewise, we found a significant positive correlation between PASP and NT-proBNP. We also classified the patients into mild, moderate and sever categories on the basis of values of PASP and found it to be statistically significant

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which indicated that, with the increase in the severity of the disease, the value of NT-proBNP also rises. Thus we can conclude that higher values of NT-proBNP indicates sever disease state.

Apart from these, we also looked for the relation between NT-proBNP and various demographic and clinical parameters, of which only hypertension was found to have significant association with NT-proBNP. It is known that high blood pressure is the risk factor for congestive heart failure [20], which is associated with raised NT-proBNP. This finding shows that hypertension could be a confounding factor for NT-proBNP and thus caution needs to be taken while assessing heart failure and PH in hypertensive patients on the basis of NT-proBNP.

V. Conclusions

For the diagnosis of PH, invasive methods are considered to be gold standard. But in countries where performing echocardiography is also a problem, simple ways to diagnose PH by blood tests would be a preferred method. The study found significant association between NT-proBNP and parameters of interest (i.e. PASP, severity of PH on the basis of PASP, NYHA grading and LVEF) among patients with PH who were diagnosed via echocardiography. Thus, we can conclude that NT-proBNP can be used to assess the patients with PH and heart failure however, caution needs to be taken when a patient has comorbid condition like hypertension.

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