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# The Utility of Brain Natriuretic Peptide in Patients Undergoing an Initial Evaluation for Pulmonary Hypertension

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## Abstract

**Introduction:** Brain natriuretic peptide (BNP) is a polypeptide released from the cardiac ventricles and has been used as a diagnostic marker in cardiovascular diseases. Some patients with pulmonary hypertension have significant increases in BNP levels. This study wanted to determine whether the BNP levels in patients referred for evaluation of possible pulmonary hypertension were associated with a particular functional class or diagnostic group.

**Methods:** Data were collected on patients from the Pulmonary Vascular Disease clinic undergoing right heart catheterization between 1/1/2019 and 5/20/2020. Clinical information, laboratory results including BNP, and hemodynamic parameters were recorded.

**Results:** This study included 117 patients referred for evaluation for PH with measured BNP levels. The mean age was 63; the female to male ratio was 2:1, 25.4% of the patients were Hispanic. The average BNP level for the entire cohort was  $4127.1 \pm 11761.98$  pg/ml. Patients in higher WHO functional classes tended to have higher levels of BNP, but statistical analysis BNP showed no differences between the functional classes. Patients in WHO Group 4 had significantly higher BNP levels than other WHO groups. Hemodynamic group classification demonstrated significant differences in BNP values between the low, intermediate, and high composite score patients.

**Conclusions:** Patients undergoing evaluation for pulmonary hypertension had a wide range of BNP values. Patients with more abnormal composite hemodynamic scores higher BNP levels. Measurement of BNP provides an independent test to help interpret patients' descriptions of their functional limitations and to identify patients with more abnormal hemodynamic parameters.

**Keywords:** Brain natriuretic peptide, Pulmonary hypertension, WHO functional class, WHO group category

## 1. Introduction

Brain natriuretic peptide (BNP) is a 32 amino acid polypeptide released primarily from the cardiac ventricles.<sup>1,2</sup> The 134 amino acid preproBNP and 108 amino acid proBNP are cleaved in succession to produce a 32 amino acid, functionally active, mature BNP peptide and a 76 amino acid NT-proBNP.<sup>3</sup> Brain natriuretic peptide levels are normally low (4–35 pg/ml); however, an increase in production and activity occurs with volume overload, such as during cardiovascular stress.<sup>1,4</sup> Due to its increased production in certain disorders, measurement of BNP levels can provide a diagnostic marker helpful

for establishing a diagnosis and possibly estimating the severity of a cardiac disorder in some patients.

This peptide has several physiological effects in the body. The main stimulus for BNP production and release is ventricular stress or tension on the cardiac walls that causes increased stretch.<sup>5</sup> The increased stretch and overload lead to BNP's effects, which include decreased systemic vascular resistance, blood pressure, and pulmonary capillary wedge pressure.<sup>5,6</sup> Brain natriuretic peptide also increases diuresis and causes vasodilation; these effects may be due to the subsequent stimulation of cGMP.<sup>6</sup> These physiological effects have also been demonstrated experimentally through BNP infusion

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studies, leading to the physiological effects mentioned above.

Patients with pulmonary hypertension (PH) have increased precapillary or postcapillary pressures resulting in elevation of mean pulmonary artery pressures. This syndrome can develop in multiple clinical conditions and likely involves vascular remodeling when longstanding.<sup>7</sup> Patients with PH often present with nonspecific symptoms, such as fatigue, dizziness, chest pain, dyspnea, and edema. An elevated BNP level would suggest a cardiac disorder in these patients, and a very high BNP level might suggest significant hemodynamic stress on cardiac ventricles. This study aims to determine the correlations between BNP levels in patients undergoing an initial evaluation for PH and various classifications involving functional status, disease group, and hemodynamic parameters.

## 2. Methods

Information was collected from the electronic medical record on patients referred to the Pulmonary Vascular Disease Clinic in the Department of Internal Medicine at Texas Tech University Health Sciences Center in Lubbock, Texas, for evaluation who had right heart catheterization at University Medical Center in Lubbock between 1/1/2019 and 5/20/2020. Demographics, clinical information, laboratory results including BNP levels, and right heart catheterization hemodynamic parameters were recorded. Patients were classified using the World Health Organization (WHO) Functional Classification (FC), WHO Group Classification, and a hemodynamic composite score based on right heart catheterization values (Table 1).<sup>8</sup>

Statistical analysis was performed using IBM SPSS Statistics. Results were summarized using

means, standard deviations, and numbers with percentages. Brain natriuretic peptide levels had a minimum value of 1.8 pg/ml, a maximum value of 70,000 pg/ml, and a standard deviation of 11,762 pg/ml; results were converted to log BNP to normalize the data set. The Shapiro–Wilk test for normality demonstrated that log BNP had a p-value of 0.105, indicating log BNP was not statistically different from a normal distribution, and subsequent data analysis was conducted using log BNP values. However, results reported as actual BNP levels in the text since most clinicians work with these levels. Differences in BNP between multiple groups was analyzed using ANOVA with Tukey analysis. T-tests were used to compare means of various groups. Statistical significance was set at  $p < 0.05$ .

This study was approved by the Institutional Review Board at Texas Tech University Health Sciences Center in Lubbock, Texas (L20-174).

## 3. Results

This study included 117 patients presenting for evaluation for PH with measured BNP levels. The mean age was  $62.8 \pm 14.5$  years, 67.8% of patients were female, and 25.4% were Hispanic. These patients presented with multiple pre-existing conditions; the most frequent co-morbidities were hypertension (96 patients, 82.1%), diabetes (52, 44.4%), obstructive sleep apnea (47, 40.2%), coronary artery disease (27, 23.1%), and atrial fibrillation (25, 21.4%). Most patients (112, 95.7%) presented with shortness of breath, and 59 (50.4%) presented with edema. Patients were classified using the WHO FC and the WHO Group classification after evaluation.

The mean BNP for the entire cohort was  $4127.1 \pm 11761.98$  pg/ml with normal value of BNP less than 124 pg/ml in our laboratory. Patients in higher WHO functional classes tended to have higher levels of BNP (Table 2), but statistical analysis showed no differences between functional groups. Patients in WHO Group 4 had significantly higher BNP levels ( $p$  value  $< 0.05$ ) than other WHO Groups (Table 2).

There was a significant correlation between the BNP and the mean pulmonary artery pressure, the right atrial pressure, the pulmonary capillary wedge pressure, and the pulmonary vascular resistance (Table 3). These relationships indicate that a BNP of 276.7 pg/ml predicts a mean pulmonary artery pressure greater  $\geq 25$  mmHg, BNP of 571.5 pg/ml predicts a right atrial pressure  $\geq 10$  mmHg, a BNP of 691.8 pg/ml predicts pulmonary capillary wedge pressure  $\geq 18$  mmHg, and a BNP of 606.7 pg/ml predicts pulmonary vascular resistance  $\geq 3$  Wood

Table 1. Hemodynamic summary score classification.

Hemodynamic Parameter	Value Range	Assigned Score (1–3)
Right Atrial Pressure (mm Hg)	<8	1
	8–14	2
	>14	3
Cardiac Index (L/min/m <sup>2</sup> )	$\geq 2.5$	1
	2.0–2.4	2
	<2.0	3
Mixed Venous Oxygen Saturation (%)	>65	1
	60–65	2
	<60	3
<b>Composite scores</b>		
Low score group	3,4,5	
Mid score group	6,7	
High score group	8,9	

Modified from reference 8.

Table 2. WHO functional class and group category BNP levels.

	BNP <124 pg/ml	BNP >124 pg/ml	BNP mean ± SD
<b>WHO Functional Class</b>			
FC* I, n = 2	1	1	37; 3030**
FC II, n = 5	1	4	1800 ± 1649
FC III, n = 69	20	49	4809 ± 14701
FC IV, n = 29	3	26	3497 ± 4360
<b>WHO Group Category</b>			
Group 1, n = 50	15	35	2139 ± 3643
Group 2, n = 30	5	25	3947 ± 12695
Group 3, n = 7	3	4	470 ± 664
Group 4, n = 4	0	4	42683 ± 33814
Group 2 + 3***, n = 22	0	22	3609 ± 7273

\* FC- functional class; \*\* Individual values; \*\*\*Group 2 + 3 patients had clinically important cardiac disease and respiratory disease and the best explanation for their PH was uncertain.

units. These calculations were made assuming a linear relationship between BNP and each variable, respectively. Patients were then classified into groups based on the hemodynamics score developed after cardiac catheterization (Table 1).<sup>8</sup> BNP levels in both the intermediate and high composite score groups were significantly higher than the BNP levels in the low composite score group (Table 3).

Patients in WHO Group 1 (n = 55) had a mean pulmonary artery pressure of 40.4 ± 16.3 mmHg; patients in WHO Group 2 (n = 56) had a mean pulmonary artery pressure of 35.7 ± 10.1 mmHg (P = 0.036). Patients in WHO Group 1 had a mean pulmonary artery wedge pressure of 11.8 ± 5.3 mmHg; patients in WHO Group 2 had a mean pulmonary artery wedge pressure of 21.6 ± 15.1 mmHg (p < 0.001). Patients in WHO Group 1 had positive correlations between BNP levels and right atrial pressures (r = 0.398, p = 0.004), pulmonary artery systolic pressures (r = 0.309, p = 0.026), pulmonary artery diastolic pressures (r = 0.362, p = 0.008), mean pulmonary artery pressures (r = 0.353, p = 0.01), and right atrial

indices (r = 0.621, p = 0.006). Patients in WHO Group 2 had positive positive correlations between BNP levels and right ventricular systolic pressures (r = 0.333, p = 0.018) and pulmonary artery systolic pressures (r = 0.342, p = 0.015).

#### 4. Discussion

Our results demonstrate that BNP levels have some important associations in a heterogeneous group of patients referred for the evaluation of possible PH. BNP levels had significant positive correlations with multiple hemodynamic parameters, including mean pulmonary artery pressures and right atrial pressures. In addition, BNP levels were higher in patients with more abnormal composite hemodynamic scores. Finally, although the group size was small, patients in WHO Group 4 had significantly higher BNP levels. Therefore, BNP levels can help predict hemodynamic parameters in patients referred for pulmonary hypertension evaluation, and patients with very high BNP levels should be evaluated carefully for the possibility of chronic thromboembolic disease.

Several parameters have been used to measure the severity of PH in patients; these include the WHO FC, the 6-min walk test (6MWT), and formal exercise testing. Safdar et al. reviewed the correlation between BNP and the 6MWT in 38 patients with pulmonary arterial hypertension and found that patients with baseline BNP levels greater than 100 pg/ml had a decreased 6MWT (349 ± 64 m) in comparison to patients with BNP levels less than 100 pg/ml who had a 6MWT of 428 ± 80 m.<sup>9</sup> The 6MWT was decreased in patients in higher WHO FC, and patients with higher BNP levels had a shorter time to clinical deterioration and had increased mortality. In this study, there were no definite associations between BNP levels and hemodynamic variables measured at baseline and at a

Table 3. Correlation between BNP levels and hemodynamic parameters.

Correlation between log BNP and hemodynamic parameters		
Hemodynamic Parameter	R Value	P Value
Mean Pulmonary Artery Pressure (mm Hg)	0.475	0.0000000543
Right Atrial Pressure (mm Hg)	0.427	0.000002
Pulmonary Capillary Wedge Pressure (mm Hg)	0.206	0.027
Pulmonary Vascular Resistance (Wood Units)	0.186	0.044
Hemodynamic composite score group and BNP values		
Hemodynamic Group Score#	BNP pg/ml Mean ± SD	
Low (Group 3,4,5), n = 68	3060.67 ± 9978.24	
Intermediate (Group 6,7), n = 39	624.44 ± 15529.74*	
High (Group 8,9), n = 10	3525.00 ± 2957.65**	

#- see Table 1 for hemodynamic score classification; \*p = 0.002; \*\*p = 0.006 in comparison to the group.

1-year follow-up.<sup>9</sup> Helgeson retrospectively reviewed information on 138 patients with pulmonary arterial hypertension.<sup>10</sup> Patients with BNP levels >240 pg/ml were in higher FC and had more abnormal hemodynamic parameters, larger right atria and right ventricles on echocardiograms, shorter 6MWT distances, and increased mortality.

Leuchte et al. measured BNP levels in patients with 28 patients with pulmonary arterial hypertension and found strong correlations between BNP levels and WHO FC, particularly Groups II and III, and an inverse relationship with the 6MWT.<sup>11</sup> There was a positive direct correlation with pulmonary artery pressures, right atrial pressures, and pulmonary vascular resistance. These authors suggested that the BNP level parallels the degree of the hemodynamic abnormality in these patients, and serial measurements might help improve the management of these patients. Nagaya et al. demonstrated that prostacyclin therapy decreased BNP levels, providing an indicator for responses to changes in drug management.<sup>12</sup>

Leuchte et al. reviewed risk stratification and assessment of prognosis in patients with pulmonary arterial hypertension.<sup>13</sup> Their analysis indicated that patients with a mortality risk of greater than 10% at 1 year had a higher WHO FC (IV), a reduced 6-min walk distance (<165 m), and an elevated BNP (>300 pg/ml). They noted these parameters provide noninvasive methods for risk classification and are particularly useful for follow-up evaluations. Lewis and co-authors have reviewed the use of point-of-care testing for either BNP or NT-proBNP for the management of patients with pulmonary arterial hypertension.<sup>14</sup> The methods used for this testing typically can provide results in 10–20 min, and currently available point-of-care test devices have excellent correlations with clinical laboratory results.

The WHO classification includes patients with cardiac disease and increased post capillary pressures (Group 2), patients with parenchymal lung disease and/or obstructive sleep apnea (Group 3), and patients with chronic thromboembolic vascular disease (Group 4). These patients usually present with significant dyspnea and exercise limitation and frequently have additional comorbidity, especially if older.<sup>15</sup> Determining the predominant disease process and the pathophysiologic mechanism for pulmonary hypertension, if present, can be difficult. Patients with chronic interstitial lung disease usually have significant dyspnea which could reflect their lung disease or could also reflect a contribution from pulmonary vascular disease. Leuchte et al. analyzed the clinical significance of BNP levels in

patients with PH associated with pulmonary fibrosis and found that elevated BNP levels with a strong correlation between BNP and pulmonary vascular resistance. There were no significant correlations between lung function parameters and BNP levels.<sup>16</sup> This study supports the use of BNP as a potential diagnostic marker for moderate to severe PH in patients with interstitial lung disease. Ruocco et al. reported the use of BNP levels with diffusion capacity of the lung for carbon monoxide and echocardiography to identify pulmonary hypertension in patients with interstitial lung disease.<sup>17</sup> Reesink et al. studied BNP levels in patients with chronic thromboembolic pulmonary hypertension and found that these levels were increased in patients with right ventricular dysfunction, especially with an ejection fraction of less than 0.30.<sup>18</sup> Iwanaga et al. studied patients with chronic systolic and diastolic heart failure who were clinically stable at the time of catheterization.<sup>19</sup> These patients had a wide range of BNP levels which were significantly higher in patients with systolic heart failure. Patients with systolic heart failure and diastolic heart failure had similar left ventricular end-diastolic pressures, but patients with systolic heart failure had significantly higher left ventricular end-diastolic wall stress. That parameter correlated best with elevated BNP levels. Consequently, in this study BNP levels helped identify the underlying pathophysiology in patients with chronic heart failure.

Our study involves a retrospective review of clinical information developed on patients referred to pulmonary vascular disease clinic for evaluation of possible pulmonary hypertension. This was a heterogeneous group of patients and not limited to patients with pulmonary arterial hypertension. This study has several limitations. First, there were very few patients in WHO FC I and II; this is not necessarily unexpected since patients with limited symptoms may not undergo right heart catheterization, an inclusion criterion for this study. However, FC III and IV had a significant number of patients and had higher BNP levels than patients in FC I and II. Second, the information in this study is based on evaluations done at one clinical center and may not be generalizable. Third, in general, BNP levels were measured at the time of initial evaluation which included right heart catheterization. However, longer time intervals between the laboratory test and a right heart catheterization could reduce correlations. Fourth, although there were significant correlations between BNP measurements and right heart hemodynamic measurements, the *r* values for these correlations were relatively low.

## 5. Conclusions

Patients with PH can have very high BNP levels in comparison to normal individuals. In our cohort of patients with pulmonary hypertension, BNP tended to be higher in patients with more functional limitation. In addition, BNP levels in patient groups based on hemodynamic classification were increased in the groups with more abnormal hemodynamic parameters, demonstrating the utility of BNP measurements as a clinical marker for PH severity. Therefore, the initial BNP level can help clinicians make decisions regarding the next steps in the evaluations of patients who are often have complex clinical presentations and should encourage more assessment of their hemodynamic status. Finally, BNP levels provide a simple method to follow responses to change in treatment and to follow the progression in these patients.

## Conflict of interest

This study had no financial support. The authors have no conflict of interest related to this project. Specifically, Sanjana Rao has no conflict of interest related to this project. Benjamin Daines has no conflict of interest related to this project. Omid Hosseini has no conflict of interest related to this project. Victor Test has no conflict of interest related to this project. Kenneth Nugent has no conflict of interest related to this project.

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