Correlation of Spirometric Parameters with N-Terminal Pro B-Type Natriuretic Peptide Levels in Chronic Obstructive Pulmonary Disease Patients

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Abstract

Introduction: Brain natriuretic peptide (BNP) is widely used as diagnostic test for the management of left ventricular dysfunction. Brain Natriuretic Peptide (BNP) and N-terminal-pro-BNP (NT-pro-BNP) are derived from pro-BNP that is synthesized in response to stretching by ventricular myocytes. BNP is helpful for diagnosing patients suspected of having heart failure. BNP assays are more easily available for diagnosing heart failure as compared to other tests like echocardiography. However, studies designed for assessing the diagnostic credibility of BNP for detecting or ruling out heart failure in COPD patients are less.

Method: This cross-sectional research was done from January 2020 to June 2021 on 100 randomly selected COPD patients>18 years of either gender. N terminal-proBNP test-NT-proBNP levels were done and was compared with spirometry findings of patients.

Results: The mean age was 63.26 years, the mean duration of illness was 8.98 years and the mean pack years were 44.89. The mean BMI was 22.54 in the current study. 88% patients were smokers in the current study. According to spirometry findings, 50 patients belonged to stage 2, 42 patients belonged to stage 3 and 8 patients belonged to stage 4. There was significant difference in FEV_1, $FEV_1(\%)$, FVC, $FEV_1/FVC(\%)$ between maximum and minimum values at stage 2. The mean NT-PRO BNP values were 109.40 ± 22.60, 198.57 ± 50.71 and 330 ± 32.95pg/ml for GOLD stage II, III and IV respectively. The mean NT-PRO BNP increased from stage 2 to stage 4. It was maximum at stage 4. Multiple linear regression analysis shows fairly strong negative relationship among $FEV_1(\%)$ and $FEV_1/FVC(\%)$ with NT-PRO BNP. While no corelation was seen with FVC.

Conclusion: Results from this study demonstrate statistically significant negative correlation between NT-pro BNP and FEV_1. Also, NT-pro BNP level increases with the increase in severity of airway obstruction based on the GOLD criteria hence NT-pro BNP level can be used for the

staging of COPD patients in whom spirometry is either contraindicated or cannot be done. NT-pro BNP level can also be used as a prognostic marker for predicting the clinical outcome.

Keywords: COPD, ProBNP, Heart Failure, Spirometry

Introduction

Chronic obstructive pulmonary disease (COPD) is a common preventable disease having great implications on global health. It is the third leading cause of death worldwide, exceeded by cardiovascular diseases and stroke [1].

Spirometry is economical, repeatable, feasible, safe and practical test that is used as an objective measure of lung function. Spirometry is a useful screening tool to detect the airflow restrictions in the very early course of COPD [2]. FEV1 and FVC are the most commonly used spirometric parameters and their ratio is important for COPD diagnosis and staging.

Disease burden and health care utilization in COPD is mainly associated with the management of its exacerbations and associated comorbidities.

Multiple cardiovascular complications of COPD have been recognized for decades [3] which include right ventricular (RV) dysfunction, pulmonary artery hypertension (PAH), coronary artery disease (CAD) and arrythmias [4]. Pulmonary vascular disease secondary to COPD increases morbidity and decreases survival [5] COPD patients having cardiovascular complications have increased risk of mortality due to multiple factors like myocardial infarction, arrhythmia, or CHF as compared to those who do not have [6].

The Lung Health Study revealed that cardiovascular complications may cause significant death toll in patients with mild COPD and particularly in younger patients with age less than 45 years with COPD [7,8].

Brain natriuretic peptide (BNP) is widely used as diagnostic test for the management of left ventricular dysfunction. Brain Natriuretic Peptide (BNP) and N-terminal-pro-BNP (NT-pro-BNP) are derived from pro-BNP that is synthesized in response to stretching by ventricular myocytes [9].

COPD is associated with structural and mechanical changes in the pulmonary vascular bed that increase RV afterload. Pulmonary vascular remodeling occurs not only in patients with advanced COPD but also in patients with mild disease and even in smokers with normal lung function [10].

BNP is also helpful for diagnosing patients suspected of having heart failure. BNP assays are more easily available for diagnosing heart failure as compared to other tests like echocardiography. However, studies designed for assessing the diagnostic credibility of BNP for detecting or ruling out heart failure in COPD patients are less [11].

So, the present study is conducted to correlate the spirometric parameters with N-Terminal Pro B –Type Natriuretic peptide levels in various stages of chronic obstructive pulmonary disease patients.

Methods

This cross-sectional research was done in the Department of Medicine at J.L.N. Medical College & Hospitals from January 2020 to June 2021 on 100 randomly selected COPD patients>18 years of either gender. Data was collected through a preformed and pre- tested proforma from each patient with written consent. Study participants underwent detailed history, clinical examination, biochemical investigations, chest X-ray, Echocardiography and pulmonary function test (Forced Expiratory Volume in first

second (FEV1), Forced Vital Capacity (FVC), FEV1/FVC, Hb, TLC, DLC, ESR, Blood urea, Serum creatinine, LFT, Urine routine and microscopy, ECG were done in all patients.

N terminal-proBNP test-NT-proBNP Fast Test Kit (Immunofluorescence Assay)is intended for use together with Getein1100 Immunofluorescence Quantitative Analyzer (Getein1100) to quantitatively determine the concentrations of NT-proBNP level. The cut off values of NT-pro BNP and BNP for patients with chronic heart failure are 125 pg/ml and 35 pg/ml respectively.

Cut off levels of NT-pro B-type natriuretic peptide levels in acute heart failure are:

<300pg/ml- Heart failure unlikely

Age <50 years, >450pg/ml- Heart failure likely

Age 50-75 years, >900pg /ml- Heart failure likely

Age >75 years, >1800 pg/ml-Heart failure likely.

The computerized spirometry gives age, sex, race, weight and height matched predicted and test values. The best of the three attempts was selected. forced expiratory volume in first second and FEV_1/FVC ratio were analysed and categorized as per GOLD staging [12].

Appropriate statistical tests was applied where required using IBM SPSS version 20. All statistical tests were done at 95% confidence interval with P value less than 0.05.

Results

Table 1: Demography and spirometric characteristics

Parameter		Minimum	Maximum	Mean	Std. Deviation
Age (in years)		36	85	63.26	10.531
Duration of illness (in years)		3	20	8.98	4.266
Pack yrs.		20	60	44.89	9.498
BMI		15.00	31.25	22.5486	4.17833
SPIROMETRIC PARAMETERS	FEV_1 Lit.	0.53	1.84	1.12	.34
	FEV_1(%)	25.70	77.00	49.76	14.18
	FVC Lit.	1.03	3.21	2.246	.49
	FEV_1/FVC(%)	21.5	70.00	52.57	13.53
Blood Investigations	Hb(gm%)	10	16	13.10	1.352
	TLC	3200	14000	7303.16	2670.292
	ESR	3	25	12.58	5.574
NT- pro BNP (pg/ml)		80	370	164.50	75.057

The mean age was 63.26 years, the mean duration of illness was 8.98 years and the mean pack years were 44.89. The mean BMI was 22.54 in the current study. 88% patients were smokers in the current study.

Table 2: Spirometric parameters and severity by gold staging

Spirometric Parameters	Gold-Stage	N	Mean	Std. Deviation	Minimum	Maximum	P value
FEV$_1$ Lit.	II	50	1.3456	0.31304	0.53	1.84	0.001 (S)
	III	42	0.9457	0.20896	0.56	1.25	
	IV	8	0.7125	0.03495	0.66	0.74	
FEV$_1$(%)	II	50	62.0800	6.57844	51.00	77.00	0.001 (S)
	III	42	39.1714	6.65961	25.70	49.50	
	IV	8	28.3750	1.71776	25.90	29.80	
FVC Lit.	II	50	2.2676	0.40357	1.50	3.21	0.68
	III	42	2.1957	0.53039	1.10	3.15	
	IV	8	2.3325	0.82657	1.03	3.06	
FEV$_1$/FVC (%)	II	50	60.5452	6.77587	45.70	70.00	0.001 (S)
	III	42	46.1095	12.02586	31.40	69.10	
	IV	8	19.2000	12.15542	0.00	28.10	

50 patients belonged to stage 2, 42 patients belonged to stage 3 and 8 patients belonged to stage 4. There was significant difference in FEV$_1$, FEV$_1$(%), FVC, FEV$_1$/FVC(%) between maximum and minimum values at stage 2 in the current study.

Table 3: NT-Pro BNP levels and severity by GOLD staging

Gold Stage	Number	Mean NT-PRO BNP (pg/ml)	Std. Deviation	Minimum NT-PRO BNP	Maximum NT-PRO BNP	P value
2	50	109.40	22.60	80	150	0.001 (S)
3	42	198.57	50.71	110	300	
4	8	330.00	32.95	300	370	

The mean NT-PRO BNP values were 109.40±22.60, 198.57±50.71 and 330±32.95pg/ml for GOLD stage II, III and IV respectively. The mean NT-PRO BNP increased from stage 2 to stage 4. It was maximum at stage 4.

Table 4: Correlations between spirometric parameters and NT- PRO BNP levels

Spirometric Parameters	NT- PRO BNP LEVELS	
	Pearson Correlation	Sig. (2-tailed)
FEV$_1$ Lit.	-.593**	.001(S)
FEV$_1$(%)	-.769**	.001 (S)
FVC Lit.	0.01	0.894
FEV$_1$/FVC(%)	-.737**	.001 (S)

Multiple linear regression analysis shows fairly strong negative relationship among FEV$_1$(%) and FEV$_1$/FVC (%) with NT-PRO BNP. While no corelation was seen with FVC.

Discussion

In the present study 100 patients with various stages of COPD were selected by simple random sampling method from the Medical Wards, emergency and outdoor. The study analysed relation between spirometric parameters and N-terminal pro B-type

natriuretic peptide levels in various stages of COPD.

Most of the patients belonged to 60-70 years, followed by 50-60 years; out of them 90% were males in the current study.

NT-pro BNP in COPD patients

There are three types of Natriuretic peptide-A, B and C. These are responsible for regulation of intravascular volume homeostasis and released in response to hemodynamic stress. Nartriuretic peptide A and B type are mainly elevated in corpulmonale even in absence of left ventricular dysfunction [13].

In current study the NT pro BNP values ranged from 80 to 370 pg/ml. The mean NT Pro BNP was 164.50 ± 75.05 pg/ml which was higher than normal. The mean NT-PRO BNP increased from stage 2 to stage 4.

Bodrug Nicolae et al [14] showed similar results that Plasma levels of BNP/NT-proBNP were significantly higher in men with stable COPD in stages II, III, and IV compared to control group subjects (healthy smoking men) [15], in patients with COPD in stage III and IV, had higher levels of BNP/NT-proBNP compared to patients with COPD in stage II [16].

Chi S Y et al [16] demonstrate in their study that levels of plasma NT-proBNP significantly increased in patients with stage IV and stage III COPD compared to individuals with stage II COPD.

The finding that the plasma concentration of pro-BNP with severity could probably be due to the presence of hypoxia in patients with severe COPD that leads to an increased secretion of BNP. hypoxia-mediated contraction of small pulmonary arterioles may be the possible mechanism of the increased BNP level during exacerbation of COPD. The arteriole contraction could lead to an increase in pulmonary arterial pressure

and the subsequent cardiac stress could cause secretion of BNP [17-18].

Correlations between COPD and NT-PRO BNP levels

In Ghobadi, Hassan et al [18] in their study found that plasma pro-BNP levels were significantly associated with pulmonary function parameters such as %FEV1 (r = -0.238, p = 0.031), %FVC (r = -0.291, p = 0.008), and GOLD stages (r = 0.230, p = 0.038). Pro BNP levels were higher with increasing disease severity based on the GOLD classification, similar to the current study findings.

Chi S Y et al [16] in their study reported that plasma NT-proBNP levels significantly correlated with %FEV1 (P < 0.001), arterial blood gas parameters such as $PaCO_2$ (P < 0.001) and PaO_2 (P = 0.031), and systolic pulmonary artery pressure (P = 0.001).

In current study the plasma pro-BNP levels were significantly negative correlated with pulmonary function parameters such as %FEV1 (r = -0.769, p = 0.001) and FEV1/%FVC (r = -0.737, p = 0.001).

Thus, it is concluded that an increase in plasma levels of BNP/NT-proBNP along with the severity of the disease, progression of chronic respiratory failure and development of secondary PAH and cor pulmonale in patients with previous stable COPD suggests that plasma BNP/NT-proBNP may be a useful prognostic marker to monitor COPD progress and identify cases of secondary PH in patients with stable COPD.

Limitations

In this study, the sample size is 100, indicating that the study sample is small, and the primary limitation is the interpretation of results.

Results for small studies are less reliable compared to larger studies. Larger studies with more subjects produce narrow confidence intervals (95% to 99%) and more accurate results

Conclusion

Results from this study demonstrate statistically significant negative correlation between NT-pro BNP and FEV_1. Also, NT-pro BNP level increases with the increase in severity of airway obstruction based on the GOLD criteria hence NT-pro BNP level can be used for the staging of COPD patients in whom spirometry is either contraindicated or cannot be done. NT-pro BNP level can also be used as a prognostic marker for predicting the clinical outcome.

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