Role of NT-Pro BNP Estimation in Patients with Acute Dyspnoea presenting to Emergency Department

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Abstract :

Dyspnoea can be defined as an unpleasant or uncomfortable sensation of difficult breathing experienced by an individual. The differential diagnosis includes acute heart failure (AHF), acute coronary syndrome (ACS) and pulmonary embolism (PE) as the main diseases to be excluded for their potential acute severity and mortality. NT-pro BNP is a sensitive and specific marker of ventricular dysfunction. **Materials & Methods :** Observational cross sectional study was done from October 2016 to October 2017 with 70 patients of acute dyspnoea presenting to emergency department. An automated immuno-analytical test for NT-pro BNP was carried out. Data was analyzed using appropriate statistical tests. **Observation :** Out of 70 cases of breathlessness, 48 patients were diagnosed with cardiovascular disease, 17 had Respiratory disease and 5 were of other causes (non respiratory, non cardiac). In Cardiovascular causes of breathlessness (n=48) the mean NT-pro BNP level was 2234 pg/ml, and in Non cardiovascular causes of breathlessness (n=22) the mean NT-pro BNP level was 677 pg/ml. Thus, there was a significant difference in the levels of mean NT-pro BNP. **Conclusion :** The statistically significant difference was observed when plasma NT-pro BNP levels of cardiovascular disease were compared to non cardiovascular disease (in respiratory causes levels were significantly lower) .Thus it supports the ability of NT pro BNP to provide specific information about the cardiac involvement in acute dyspnoea.

Key Words : Dyspnoea, Emergency Department, NT-pro BNP

Introduction :

Dyspnoea or breathlessness can be defined as an unpleasant or uncomfortable sensation of difficult breathing experienced by an individual due to pathophysiological, social, psychological and environmental factors. The differential diagnosis of dyspnoea is very broad but AHF, ACS and PE are the main diseases to be excluded for their potential acute severity and mortality. [1]

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The differential diagnosis of dyspnoea in patients presenting in the emergency department is challenging, mainly when congestive heart failure or other cardiovascular disease is the underlying cause responsible for the symptoms. The signs and symptoms may or may not be specific or sensitive enough to distinguish between different causes of dyspnoea.[2] In fact, systematic tests like blood analysis, Echocardiogram (ECG) and chest X-ray lack sensitivity and specificity.[3,4] And investigations like echocardiography, bronchoscopy and angiography, though effective but are not always available and sometimes do not reveal an acute condition.[5] In recent decades, new molecules such as cardiovascular natriuretic hormones (ANP, BNP, NT-pro BNP etc) have

emerged as interesting biochemical tools. NT-pro BNP is a sensitive and specific marker of ventricular dysfunction. [6]

The aim of this work is to assess the usefulness of NT-pro BNP in differentiating between cardiovascular and non cardiovascular causes of breathlessness and also to observe NT-pro BNP values in various diseases of dyspnoeic etiology, presenting in Emergency department (ED) of Civil Hospital Ahmedabad.

Materials & Methods :

This observational cross sectional study was done from October 2016 to October 2017 with 70 patients of acute dyspnoea presenting to emergency department included in the study, after applying inclusion and exclusion criteria. Data was collected using a pretested proforma meeting the objectives of the study. The purpose of the study was explained to each patient and written consent was obtained. Each patient characteristics were recorded including demographics, symptoms, signs, medication use, and diagnostic studies in the emergency department. Electrocardiography, chest X-ray, routine blood tests, echocardiography and separate blood sample for NT-pro BNP measurement were done. An automated immuno-analytical test for NT-pro BNP that takes less than 20 minutes to complete, was determined in patients with acute dyspnoea in the emergency room setting. The results of any laboratory testing, outcome of diagnostic tests and patient discharge information were recorded. The definition of the cut-off levels based on previous studies, each patient's ER diagnosis was compared with NT-pro BNP concentration in order to verify if these two classifications were in agreement in identifying the origin of the dyspnoea (cardiovascular or non-cardiovascular) and if NT-pro BNP determinations could improve the accuracy of ER diagnosis. The discharge diagnosis was adopted as "gold standard" when the information provided (ER diagnosis vs. NT-pro BNP concentration) was contradictory.

Data was analyzed using appropriate statistical tests like mean, standard deviation and p value. Sensitivity, specificity, positive predictive value, negative predictive value was also computed.

Inclusion criteria were, (i)Age > 18 years, (ii)Patients presenting with acute dyspnoea, & (iii)Patients willing to participate in the study and gave the consent. Exclusion criteria were, (i) Patients with age>80 years, renal failure, cirrhosis of liver with ascites, obvious traumatic cause of dyspnoea & obese patients (BMI more than 30).

Observations and Results :

In the present study, 70 patients who presented with chief complaint of breathlessness to the Emergency Department of Civil Hospital, Ahmedabad were included. The youngest patient was of 21 years and the oldest patient was of 79 years. The majority of patients were in the age group of 41-60 years (47.1%) followed by 61-80 years (34.33%) and 21-40 years of age (18.57%). It was observed that of the 70 patients, 41 patients were Male and 29 were Female. Male to Female ratio was 1.41.

Out of 70 cases of breathlessness, 48 patients were diagnosed with cardiovascular disease, 17 patients had Respiratory disease and 5 patients were of other causes (non respiratory non cardiac).

Of those 48 patients, 17 patients had Congestive Heart Failure(CHF), 15 patients had MI, 6 patients had Cor-Pulmonale, 7 patients had hypertension associated heart failure, 2 patients had valvular abnormality and 1 patient had Pulmonary embolism.

Of those 17 patients with respiratory diseases, 8 patients had COPD, 7 had Pneumonia and 2 had Pleural effusion. Other causes of breathlessness

which were found in our population group were hyperthyroidism in 2 patients, anemia in 2 patients and diabetic ketoacidosis in 1 patient.

In the present study population, breathlessness (100%) was most commonly associated with chest pain (68.57%) followed by Cough (65.71%), pedal oedema (37.14%), paroxysmal nocturnal dyspnoea (28.57%), and orthopnoea (18.57%) and fever (5.71%). In our study, 36 patients had associated hypertension, 28 patients had diabetes mellitus and 15 had personal history of smoking and 9 patients had history of alcoholism. The mean levels of NT-pro BNP in present study in males and females were found to be comparable (1753;1732 pg/ml), thus indicating that gender might not play a significant role in affecting NT-pro BNP levels.

Mean NT-pro BNP levels in cardiovascular causes was 2234 pg/ml as compared to non cardiovascular causes at 677 pg/ml.

In cardiovascular causes of breathlessness, in the age group of <50 years which included 17 patients, the mean of NT-pro BNP levels was 1098 pg/ml. In the age group of 50-75 years which included 25 patients, the mean of NT-pro BNP levels was 2535 pg/ml. In the age group of >75 years which included 6 patients, mean of NT-pro BNP levels was 4200 pg/ml.

In Non Cardiovascular causes of breathlessness, in the age group of <50 years which included 7 patients, the mean of NT-pro BNP levels was 377.7 pg/ml. In the age group of 50-75 years which included 12 patients, the mean of NT-pro BNP levels was 979.16 pg/ml. In the age group of >75 years which included 3 patients, the mean of NT-pro BNP levels was 173.33 pg/ml.

In Heart Failure patients and MI, the mean NT-pro BNP levels increased consistently as the age group moved in ascending order. Also the minimum and maximum NT-pro BNP levels increased consistently as the age group moved in ascending order. In Myocardial Infarction patients also, the mean NT-pro BNP levels increased consistently as the age group moved in ascending order. Also the minimum and maximum NT-pro BNP levels increased consistently as the age group moved in ascending order. The mean NT-pro BNP levels of MI patients was higher than that of Left Ventricular Failure patients.

The same increasing pattern of mean levels of NT-pro BNP was found as we moved up higher in age group in patients of Cor Pulmonale.

NT-pro BNP in respiratory breathlessness group was below the "Rule In" reference levels of NT-pro BNP.

Discussion :

There have been many studies in recent years to investigate and support the role of NT-pro BNP in identifying causes of breathlessness, primarily differentiating between cardiovascular and non cardiovascular causes of dyspnoea in Emergency.

In our study, 60% patients had X-ray abnormality. Shaikh K et al[8], in their study had 61.8% patients with X-ray abnormality. Barcelona et al[11], in their study had 60.5% patients with X-ray abnormalities.

Gender might not play a significant factor in affecting NT-pro BNP in our study.

In the present study it was found that as mean EF (Ejection Fraction) decreases, mean NT-pro BNP levels increase non linearly.

NT-pro BNP level in cardiovascular cause of breathlessness was above the age related "Rule IN" reference level of NT-pro BNP.

In our present study when rule out criteria for heart failure diseases of optimal NT pro BNP levels was applied as <300 pg/ml (cut off point accepted

Table 1 : Correlation between Mean NT-PRO BNP and Specific disease related Etiology (CARDIOVASCULAR)

Disease(n)	Mean NT -pro BNP(pg/ml)	Age of patients	No. of Patients (n=48)	Mean NT-pro BNP (pg/ml)	Min NT -pro BNP (pg/ml)	Max NT-pro BNP (pg/ml)
HF (17)	2054	<50	8	780 ± 380	460	1600
		50-75	6	2213 ± 876	1010	3370
		>75	3	5133 ± 416	4800	5600
Myocardial Infarction (15)	2344	<50	6	1665 ± 1307	600	4050
		50-75	9	2797 ± 2356	610	8300
Cor Pulmonale (6)	2050	<50	1	1200	-	-
		50-75	3	1667 ± 569	1200	2300
		>75	2	3050 ± 1202	2200	3900
Valvular Abnormality (2)	675	<50	1	650	-	-
		50-75	1	700	-	-
Hypertension associated heart failure (7)	3342	<50	1	600	-	-
		50-75	5	3820 ± 837	3000	4800
		>75	1	3700	-	-
Pulmonary Embolism (1)	120	50-75	1	120	-	-

Table 2 : Correlation between Mean NT-pro BNP and Specific disease related Etiology (RESPIRATORY)

Disease	No. of Patients (n=17)	Mean NT-pro BNP(pg/ml)
COPD	8	145.5
Pneumonia	7	308
Pleural Effusion	2	280

Table 3 : Causes of Breathlessness

Causes	Our study n=70	Antoni BG[7] n =89	Chen AA[9] n =599	Shaikh k[8] n =100	Martina Z[10] n = 105
Cardiovascular	48	74	205	79	75
Non cardiovascular	22 (17+5)	15	394	21	30

Table 4 : Symptomatic Distribution

Symptoms	Patients	Shaikh K[8]	Barcelona[11]	Christ church[12]	Chen AA[9]
Breathlessness	(n=70) 100%	100%	100%	100%	100%
Chest Pain	(n=48) 68.57%	-	29.5%	51.3%	42.7%
Cough	(n=46) 65.71%	70%	55.8%	46.7%	36.9%
Pedal oedema	(n=26) 37.14%	61%	54.7%	32.8%	17.2%
PND	(n=20) 28.57%	57.6%	61.1%	13.8%	12.4%
Orthopnoea	(n=13) 18.57%	85%	81.1%	39.5%	17.4%
Fever	(n=4) 5.71%	-	6.3%	7.2%	9.3%

Table 5 : ECHO findings in various causes of Breathlessness

Study	Mean EF % of all patients
Present study	45.13%
Shaikh K[8]	41.8%
Chen AA[7]	49%

Table 6 : Correlation between Mean NT-pro BNP and causes of Breathlessness

Causes	Our Study Mean NT-pro BNP(pg/ml),(n)	Shaikh K[8] Mean NT-pro BNP(pg/ml),(n)	Antoni BG [7] Mean NT-pro BNP(pg/ml),(n)	Januzzi J [13] Mean NT-pro BNP(pg/ml),(n)
Cardiovascular	2234, (48)	9690, (79)	1060, (74)	4639, (720)
Non Cardiovascular	677, (22)	461,(21)	65,(15)	108, (536)

Table 7: Co-relation between Sex Distribution and Mean NT-pro BNP

Gender	Our Study Mean NT-pro BNP (pg/ml)	Shaikh K [8] Mean NT-pro BNP (pg/ml)	Januzzi J [13] Mean NT-pro BNP (pg/ml)
Male	1753	7125	2597.76
Female	1732	4472	2472.44

Table 8: Correlation between LV dysfunction and NT-pro BNP

Parameter	Our Study Mean EF (%)	Our Study Mean NT-pro BNP (pg/ml)	Antoni BG[7] Mean EF (%)	Antoni BG[7] Mean NT-pro BNP (pg/ml)	Januzzi J[13] Mean EF (%)	Januzzi J[13] Mean NT-pro BNP (pg/ml)
LV dysfunction	46.56	2150	< 50	1318	< 50	6536

Table 9: Statistical analysis in our study compared to other studies.

Age (years)	Sensitivity (%)			Specificity (%)			Positive predictive value (%)			Negative predictive value (%)		
	Our study	Shaikh et al[8]	Januzzi J et al[13]	Our study	Shaikh et al[8]	Januzzi J et al[13]	Our study	Shaikh et al[8]	Januzzi J et al[13]	Our study	Shaikh et al[8]	Januzzi J et al[13]
<50	100	100	**97**	57.14	**33.33**	**93**	85	**80**	**76**	57.14	**100**	**99**
50-75	88.46	96.82	**90**	81.81	**86.66**	**82**	92	**96.82**	**83**	75	**86.66**	**88**
>75	100		**90**	100		**84**	100		**88**	100		**66**
<Mean	96.15		**92.33**	79.65		**86.33**	92.33		**82.33**	77.38		**84.33**

widely by consensus); 14 patients out of 70 had NT-pro BNP level less than 300pg/ml ; of these none had the final diagnosis as heart failure. Thus it can be deduced that this optimal cut off point of <300pg/ml of NT pro BNP to "RULE OUT" heart failure showed comparable results in our study also.

Limitations:

1) The limitation of our study is a small number of patients included non-consecutively.
2) In our study, each patient's actual mortality risk may be influenced by many factors not measured or considered in this analysis. Hence NT-pro BNP levels are intended to supplement and not replace physician assessment of individual patients.
3) In our study, echocardiography and NT-pro BNP assays were performed at only a single time point. The relationship of NT-pro BNP levels to echocardiographic indices at serial time points following changes in therapy (e.g. thrombolysis in MI) cannot be deduced from our study.

Conclusion:

The patients presenting with acute dyspnoea to emergency department are managed on the basis of their history and physical examination findings; aided by basic laboratory tests and investigations like chest x ray , electrocardiogram, troponins and echocardiography. But at times it becomes difficult to differentiate between cardiac cause of breathlessness and non cardiac cause of breathlessness; especially in emergency care settings. The limited accuracy and availability of current laboratory and clinical criteria particularly in acute care settings, demands for a sensitive and specific biomarker reflecting the haemodynamic changes due to cardiac conditions of dyspnoea. The plasma concentrations of NT-pro BNP should be interpreted within the clinical context of the patient as a function of age and the renal function and BMI of the patient taken into consideration.

In the present study, in patients of acute dyspnoea the statistically significant difference was observed when plasma NT-pro BNP levels of cardiovascular disease were compared to non cardiovascular disease(in respiratory causes levels were significantly lower) .Thus it supports the ability of NT pro BNP to provide specific information about the cardiac involvement in acute dyspnoea and so it is of value to clinicians in making differential diagnosis between the above said two clinical conditions. In acute Myocardial infarction, the levels of peptide were higher than in most other conditions supporting the role of natriuretic peptides, which can be synthesized locally in the ventricles, in response to different stimuli such as ischaemia, necrosis and enhanced parietal wall stress. It is also observed that elevated NT-pro BNP levels correlated with several important echocardiography indices of cardiac structure and function being abnormal.

Even if progress has been made in the understanding of the pathophysiological mechanisms underlying acute dyspnoea and its causes, the differential diagnosis is still a major problem. NT-pro BNP is a useful biomarker for both the exclusion and diagnosis of various cardiac conditions of acute dyspnoeic patients in the emergency department. The rapid information provided by this biomarker may allow an accurate and rapid evaluation of patients; especially when the clinical scenario is not straightforward.

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