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The Role of N Terminal Pro-BNP in Assessing Severity of Coronary Artery Disease: A Prospective Study

Siddharth Raut¹, Chandan Saurav Mohapatra², Abdul Wasay³, Nooruddin Owaisi⁴, Aleem Ahmed Khan^{*5}

¹Department of Cardiology, Owaisi Hospital and research centre, Hyderabad, Telangana, India

²Department of Cardiology, Fortis Hospital, Karnataka, Bangalore, India

³Department of Pathology, Owaisi Hospital and research centre, Hyderabad, Telangana, India

⁴Deccan College of Medical Sciences, Hyderabad, Telangana, India

⁵Centre laboratory for Stem cell research and translational Medicine, DCMS, Hyderabad, India

Corresponding Author: Aleem Ahmed Khan, Centre Laboratory for Stem Cell Research and Translational Medicine, Deccan College of Medical Sciences, Hyderabad, Telangana, India. **Email:** aleem_a_khan@rediffmail.com

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Abstract:

BNP is a peptide consisting of 2 aminoacids produced by the myocytes as a prohormone. It is released as a response to ventricular dilatation and pressure overload in its active form after peptidases degradation, into the cardiovascular system.

BNP levels are increased after myocardial infarction and high levels are related to increased risk of adverse events. Acute coronary syndromes without ST elevation encompass a wide range of events and have different prognostic values in relation to the type of plaque lesions and diffusion of coronary atherosclerosis. The risk assessment, based on clinical history and examination, ECG changes and markers of myocardial damage, still remains relatively inaccurate.

So this study was planned to better assess the role of NT pro BNP in assessing severity of CAD in real world practice in a prospective manner with well defined patient inclusion and exclusion among a spectrum of NSTEMI/ACS

Keywords: CAD, BNP, ST Elevation, NT Pro BNP and Angiographic Lesions

Introduction

Atherosclerosis has venerable history having left traces in arteries of human mummies. It displays heterogeneity in time, being a disease with both chronic and acute manifestations. Despite its indolent time course and prolonged period of clinical inactivity, the dreaded complication of atheroma such as myocardial infarction, unstable angina or stroke typically occurs suddenly.

CAD is assuming serious dimension in developing countries. It is expected to be the single most important cause of death in India by the year 2015. There is a considerable increase in prevalence of CHD in urban areas in India during the last decade. Although there is increase in prevalence of CHD in rural areas also, but it is not that steep because life style changes have affected people in urban areas more than in rural areas (1).

The pooled estimates from studies carried out in 1990s upto 2002 shows the prevalent rate of CHD in urban area as 6.4 percent and 2.5 percent in rural areas. In urban areas the pooled estimate was 6.1 percent for males and 6.7 percent for females, in rural areas the estimate was 2.1 percent for males and 2.7 percent for females (2). According to medical certification of cause of death data, 25.1

percent of total deaths in urban areas are attributable to diseases of the circulatory system (1).

BNP is a peptide consisting of 2 aminoacids produced by the myocytes as a prohormone. It is released as a response to ventricular dilatation and pressure overload in its active form after peptidases degradation, into the cardiovascular system (3). BNP levels are increased after myocardial infarction and high levels are related to increased risk of adverse events. Recently it has been demonstrated that BNP and N terminal pro-BNP (NT pro-BNP) also provide predictive information on acute coronary syndrome and they appear related to the severity of CAD in patients affected with ACS (4,5).

Acute coronary syndromes without ST elevation encompass a wide range of events and have different prognostic values in relation to the type of plaque lesions and diffusion of coronary atherosclerosis. The risk assessment, based on clinical history and examination, ECG changes and markers of myocardial damage, still remains relatively inaccurate (6).

Elevated BNP and NTproBNP concentrations at admission in the

setting of acute coronary syndrome (ACS) are associated with poor prognosis, including increased mortality, development of congestive heart failure (CHF), and recurrent ischemic events (3,7,8). Several studies in ACS patients demonstrated a strong association between increased NT PRO BNP and poor clinical outcome however the underlying mechanism responsible for this association is unclear: BNP and NTPROBNP could be indicators for multivessel disease, poor TIMI flow as well as markers of coronary disease extension (5,7).

The present study was planned to better assess the role of NT pro-BNP in assessing severity of CAD in real world practice in a prospective manner with well defined patient inclusion and exclusion among a spectrum of NSTEMI. There are very few reports from India on these studies.

Aims & objectives

1. To estimate the serum level of NT-pro-BNP and Troponin at the time of admission within 24 hours in patients with symptoms suggestive of an acute coronary syndrome and ECG showing no ST-segment elevation.
2. To perform coronary angiography and assess Gensini score.
3. To correlate the NT pro BNP levels with angiographic lesions and extent and severity of coronary artery disease.

Material and Methods

The present study "N -terminal pro- b-natureitic peptide levels predict extent and severity of coronary artery disease in unstable angina and non ST elevation acute coronary syndrome and normal left ventricular function" was undertaken in the Dept. Of Cardiology of S.C.B. Medical College and Hospital, Cuttack during the period of September 2013 to September 2014.

Selection of Cases

In the present study 72 patients with history of chest pain and other symptoms suggestive of an acute coronary syndrome admitted to the Department Cardiology, S.C.B. Medical College, Cuttack were taken as subjects.

The diagnosis of NSTEMI was made when a patient with the clinical features of UA develops evidence of myocardial necrosis, as reflected by Troponin I >0.06 ng/ml and Troponin T > 14 pg/ml. ECG findings suggestive of UA / NSTEMI (i.e. ECG was considered abnormal) when with the above clinical findings ECG shows ST depression > 0.05 mV, T wave inversion > 0.3mV,

Exclusion Criteria

Patients with past H/o Myocardial infarction, ST elevation on admission, evolution of ECG showing new LBBB or pathological Q WAVES, UA/NSTEMI with LV dysfunction, age more than 80 years, acute or chronic heart failure, Cardiomyopathy, Systolic dysfunction with EF <50%. Patients with Renal, Liver, neoplastic and inflammatory and infectious disease were excluded.

Examination during admission included medical history, clinical examination, routine blood chemistry, Chest X-Ray, ECG, Echocardiography, coronary angiography, Troponin-I/T and NT-proBNP.

NT-pro BNP Analysis

NT-proBNP concentration was measured by Enzyme-linked fluorescent Assay (VIDAS Automated quantitative test).

Troponin – I

Troponin-I concentration was measured by Enzyme-linked fluorescent Assay (VIDAS Automated Quantitative Test). The analyte range was 0.01 to 30 g/L.

Echocardiography

In our study all patients were subjected to M-mode as well as Colour Doppler echocardiography. It was performed with the use of a wide angle rotatory mechanical sector scanner with 3.5 mHz transducer tall tracing for LV dimensions recorded at the level of tips of mitral valve.

The wall motion for each segment was assessed visually in each view and was recorded as – Normal, Akinetic, Hypokinetic, dyskinetic.

Coronary Angiography

Coronary angiography was performed using Judkins catheter following a standard technique. The Gensini scoring system (9) was utilized in the evaluation of CAD severity.

Statistical Analysis

All results for continuous variables were expressed as means $\pm$ SD (standard deviation). However, since the distribution of NT-proBNP was skewed, therefore median values were also considered. Difference between mean values was evaluated with unpaired T-test. To compare the patient characteristics defined by the groups with low and high levels of NT-proBNP, we used the Fishers exact test. Correlation coefficients reported between continuous variables were based on Pearson correlation coefficient. A p value <0.05 was considered statistically significant. The data analyses were performed using the SPSS system 16.0 (Statistical Package for the Social Sciences, Chicago) and GraphPad Instat 3.

Results

In the present study, out of 72 cases of UA / NSTEMI, 43 (59.7 %) were males and 29 (40.3%) were females. Majority of male cases was in the age group of 50–69 yrs and majority of females were also seen in the same group (Table 1). Among the two groups of ACS patients selected from the study, largest group was NSTEMI consisting of 56 (77.7%) cases. In the UA group there were 16 (22.3%) cases. Mean NT – proBNP values were higher in cases of NSTEMI compared to cases of UA. The mean NT-proBNP level in NSTEMI was 633 pg/ml and in UA was 381.4 pg/ml (Table 2). There was a significant difference in patients with abnormal ECG (n=52) having higher NT-proBNP levels (832.24 pg/ml) as compared to that of normal ECG (n=16) and levels of 111.67 pg/ml.

Mean NT pro BNP levels were higher in NSTEMI group than in UA Patients and the association was statistically significant (p=0.03) (Table 3). Among the various risk factors present in the cases, it was observed that <2 risk factors were seen in majority (41 cases, 56.9%) and > 2 risk factors were seen in 42.1% of cases. The NT-proBNP levels in patients (n=31) having more than 2 risk factors was higher (931 pg/ml) as compared to the patients (n=41) having less than 2 risk factors (NT-proBNP levels 301.4 pg/ml) which was statistically significant (P=0.12). The patients who had NT-proBNP level more than 258 pg/ml were older, of female gender, had hypertension, smoking history, positive Trop-T/I level. But the difference was not statistically significant (Table 4). Out of

72 cases that underwent Angiography, majority (38 cases, 52.7%) had SVD and 18 cases (25%) had DVD followed by TVD in 16 cases (22.22%) (Table 5). The LAD was the most common artery to be involved in 50 cases (69.4%). The LCX was the next most common artery to be involved in 37 (51.3%) cases. It was followed by RCA artery which was involved in 35 (48.64%) cases (Table 6). Both NT proBNP and Gensini score were higher in TVD group as compared to DVD and SVD group and the association was statistically significant with p value of 0.022 and 0.014 respectively (Table 7). Patients having NT-proBNP level > 258 pg/ml had more incidences of TVD and also higher Gensini score. This observed difference was statistically significant (Table 8).

Discussion

In the present study, 72 cases of Unstable Angina (UA)/Non ST Elevation Myocardial Infarction (NSTEMI) were taken. The cases were divided into 3 age groups: <50 yrs, 50 – 69 yrs and 70 – 79 yrs (Table -1). Maximum number of cases 48 (65.2%) were in the 50-69 year age group. 14 cases (19.44%) were in the age group <50 yrs while 10 cases (13.8%) were in the age group of 70-79 years. The youngest case recorded was a male aged 34 yrs. The median age of cases in the group where NT-proBNP ≤ 258 pg/ml was 54 yrs, while in the group where NT-proBNP > 258 pg/ml the median age of cases was 68 yrs. Thus, higher baseline levels of NT proBNP was directly associated with age i.e. patients with NTproBNP > 258pg/ml were older (median age 68 yrs). These findings were consistent with earlier studies by Sadanandan S. et al, Morrow DA et al and Bassan R et al, who also reported that higher level of BNP was seen in older patients (10,11,12). Out of 72 cases NSTEMI was seen in 56 (77.7%) of cases and UA was seen in 16 (22.3%) of cases. Both UA/NSTEMI were seen predominantly in males. The mean value of NT-proBNP in males was 547.96 pg/ml whereas in females it was 433.3 pg/ml. The overall mean serum NT-proBNP level was significantly higher in NSTEMI patients compared to UA (Table 2). This again was consistent with studies by Palazzuoli et al (13).

Patients having abnormal ECG had a significant higher NT-proBNP levels compared to those having normal ECG. This finding was consistent with earlier studies by Bassan R et al, Lindahl et al and Heesch. (12, 14-15).

Diabetes, hypertension, smoking and dyslipidemia were seen more in NSTEMI group than in UA patients but difference was not statistically significant (Table-3). It is consistent with studies by Palazzuoli et al (13). It was observed that <2 risk factors were seen in majority (41 cases, 56.9%) and > 2 risk factors were seen in 42.1% of cases. The NT-proBNP levels in patients having more than 2 risk factors was higher than the patients having less than 2 risk factors which was statistically significant (P=0.12). It was consistent with earlier studies by Goyal et al (16).

The median value of NT-proBNP in the case group was 258.0 pg/ml (Table 4). The median value obtained in our study (258.0 pg/ml) was consistent with study by Heesch. C. et al (where the median was 250pg/ml) (15). The median NT-proBNP level in the Galvani M. et al & Estrada JLN et al studies were 354 pg/ml and 278.7 pg/ml respectively (17,18). The 25th, 50th, 75th percentile values of NT-proBNP were 105.0, 258.0 and 1149.5 pg/ml respec-

tively in our study. This was similar to findings of Jernberg et al where it was 112.0, 400.0 and 1654.0 pg/ml (19) and Estrada et al (18) where it was 109.8, 278.7 & 758.5 pg/ml respectively.

Out of a total number of 29 female patients, 17 (58.67%) had NT-proBNP levels > 258.0 pg/ml, while only on 20 males (46.11%) out of a total 43 males had supramedian NT-proBNP levels. Thus, higher NT-proBNP levels were seen in the female gender. Similar observation was seen by James SK et al in the GUSTO-IV sub-study (21).

It was clear that though NT-proBNP level was higher among hypertensives, diabetics and smokers, still, the association was not significant. Similar observations were noted by Sadanandan et al (10).

The patients who had NT-proBNP level more than 258 pg/ml were older, of female gender, had hypertension, had smoking history, positive Trop-T/I level. But the difference was not statistically significant, similar observation was seen in the study by Goyal et al.

Of the 72 cases, undergone angiography (Table 5). 38 (52.7%), 18 (25%) and 16 (22.22%) cases had single, double and triple vessel disease respectively. This was consistent with study by Estrada JLN et al (18) who also reported SVD was more common (in 32% cases) than DVD (in 26% cases) and TVD (in 25% cases).

It was seen that predominant artery involved was LAD (69%) cases followed by LCX (51%) cases, followed by RCA in 48% cases (Table 6). This is consistent with earlier studies by Estrada JLN et al and Hong SN et al (18,22).

From Table 7, it was observed that patients with double / triple vessel disease had higher NT-proBNP levels while patients with single vessel disease had significantly lower NT-proBNP levels. Similar observations were made by Sadanandan S. et al, Estrada JLN et al, and Hong SN et al in their studies (10,18,22).

The mean NT pro BNP levels and Gensini scores were higher in TVD cases as compared to DVD and SVD cases. This marked difference was statistically significant. This observation was also seen by studies by Palazzuoli et al and Goyal et al (13,16).

It was observed that patients having higher median NT-proBNP level (> 258 pg/ml) had more incidence of TVD and also higher Gensini score as compared to lower median BNP levels (Table 8). This observed difference was statistically significant which was similar to the observations in a study by Goyal et al (16).

Elevated NT-proBNP levels had a close relation with the number of vessels involved (23). Even in patients with normal LV function, the level of NT-proBNP maintains the same relation with the extension of CAD (24). Thus a mechanism other than LV dysfunction might be responsible for the adverse outcome in patients with NSTEMI and high levels of NT-proBNP. Toth et al (25) have found evidence that tissue hypoxia alone triggers release of BNP in absence of LV dysfunction. These results were confirmed by a recent physiological study showing that ventricular BNP gene expression is up-regulated by myocardial hypoxia resulting in augmented plasma concentrations of BNP and NT-proBNP (26). The association of elevations of BNP with a greater severity and extent of ischemia may explain, at least in part, the adverse clinical outcomes of such elevation.

Many studies have shown that the elevation of BNP levels, as well as NT-proBNP levels, obtained after the acute phase in patients with a broad range of ACS independently predicts mortality. However, in most of the reports, authors did not distinguish between subjects with low ejection fraction and LV enlargement (27). Because of its release in response to increased ventricular chamber pressure or wall tension, in ACS patients with decreased LV ejection fraction, elevated BNP levels reflect a high degree of myocardial dysfunction, with a higher risk of death and congestive heart failure

The main finding of this study is that BNP levels are related to the severity of coronary atherosclerosis. Patients with multi-vessel disease showed higher BNP levels than subjects with only one or two vessel involvement. This trend was confirmed independently of the diagnosis of UA or NSTEMI groups. Elevation of BNP levels appears strictly related to coronary artery disease. Our results are in accordance with those of Sadanandan et al showing a correlation between TIMI flow, thigh of culprit stenosis and BNP levels (10).

However, with respect to the cited study, our sample was characterized by the absence of left ventricular dysfunction and enlargement which are the main factors responsible for BNP increase.

Again, we demonstrated that NT PRO BNP threshold of 258 pg/ml appears able to predict the extension of coronary disease independently from LV systolic dysfunction and enlargement. The same value has been previously recognized as cutoff for mortality and risk for adverse events in patients with ACS. This study result is also in accordance with study by Goyal et al (16)

Importantly our study showed that high NT PRO BNP (>258 pg/ml) is a strong predictor of Triple vessel disease irrespective diagnosis of UA/NSTEMI.

The exact mechanisms of natriuretic peptides rise in coronary disease are not completely understood. Ischemia may constitute an independent stimulus for BNP release towards a transient decrease of systolic function and compliance, reflecting not only the impairment in left ventricular function, but also the severity of the ischemic insult (28).

Alternatively, BNP secretion may be due to the augmented regional wall stretch which occurs during ischemic attacks even in the absence of pump dysfunction inducing the neurohormonal activation.

The detection of BNP gene expression in ischemic and infarcted regions together with BNP receptor recruitment in coronary plaques could explain a novel mechanism of BNP induction (29,30).

The strong correlation between the Gensini Score and BNP levels extend previous findings demonstrating that a further stimulus for BNP increase could be the severity and diffusion of coronary plaques that, consistent with this observation, lead to a worsening of the ischemic myocardial area (29). All together these data could explain the mechanisms linking BNP to an adverse outcome in CAD: it represents a marker of coronary disease severity and is related to the presence of plaques diffusion and narrowing. For the above mentioned reasons NT pro BNP may considered as an indicator of regional ischemia and as a predictor for adverse events in patients UA/NSTEMI.

The present study suffers from several limitations, the major one is the small sample size. However our sample was carefully defined and selected on the basis of echocardiographic and clinical criteria. Age and sex could have influenced the findings even if the population studied had similar demographic characteristics in all groups. Our study did not compare BNP levels to other biomarkers of myocardial injury such as Troponin, high sensitive CRP or cytokine levels. Conclusion

BNP represents a biomarker for left ventricular dysfunction and enlargement as well as for myocardial ischemia. It appears able to gives additional prognostic information to existing traditional biomarkers (i.e. troponin and C-reactive protein).

BNP is a candidate for entry into the setting of principal risk scores. Our findings indicate that the level of BNP may reflect the extent or severity of ischemic insult even when irreversible injury and systolic dysfunction have not occurred.

High NT pro BNP levels significantly associated not only with multivessel coronary artery disease but also adverse cardiovascular risk and outcomes.

Future trials should be designed to evaluate targeted therapies based on elevations in the levels of one or more markers occurring in conjunction with the pathophysiologic mechanisms of necrosis, inflammation, or ischemia causing myocardial stretch. Such trials will provide further insights into the interaction between troponins, inflammatory markers, and natriuretic peptides in the pathogenesis and dynamic risk assessment of NSTEMI/UA patients.

Table 1: Age & Sex Distribution in Cases

Age Groups (in yrs)	Case (n=72)	
	Male (n = 43)	Female (n =29)
<50	9	6
50-69	26	21
70 – 79	8	2

Table 2: Incidence of Non-ST Elevation Myocardial Infarction (NSTEMI)/Unstable Angina (UA) cases and their Mean NT-ProBNP levels

Types	Males		Females		Mean NT-proBNP level (pg/ml)
	Number	NT-proBNP level (pg/ml)	Number	NT-proBNP level (pg/ml)	
NSTEMI	34 (79%)	687.6	22 (75%)	579.4	633
UA	9 (21%)	408.4	7 (25%)	287.7	381.4

Table 3: Clinical characteristics and risk factors

Risk factors	UA (n=16)	NSTEACS (n=56)	p value
Male	9	34	0.9
Diabetes	4	16	0.44
Hypertension	6	24	0.29
Smoking	4	22	0.07
Dyslipidemia	6	16	0.22
NT-ProBNP (mean $\pm$ SD)	277 $\pm$ 191	669 $\pm$ 540	0.03

Table 4: Baseline Characteristics (Taking median into account)

Serum NT proBNP Level (pg/ml)			p value
Baseline Character	$\leq$ 258	> 258	
Age, median (yrs)	54	68	0.332
Males (n = 43)	23 (53.16)	20 (46.84)	0.156
Females (n = 29)	12 (43.33)	17 (56.67)	0.075
Diabetes Mellitus (n = 24)	14 (62.50)	10 (37.50)	0.342
Hypertension (n = 37)	15 (42.86)	22 (57.14)	0.45
Smoking (n = 24)	10 (40)	14 (60)	0.14
Dyslipidemia (n=25)	13 (52%)	12 (48%)	0.32
Trop-I (n = 43) (>0.11 pg/L) /Trop-T (>14 pg/ml)	14 (32.86)	29 (67.14)	0.0065

The 25th, 50th, 75th percentile values of NT-proBNP were 105.0, 258.0 and 1149.5 pg/ml respectively. Taking the median value (258 pg/ml) the baseline characteristics were compared.

Table 5: Coronary angiography profile- incidence of single vessel disease / Double vessel disease / Triple vessel disease in coronary angiography in case group

Coronary artery involved	Cases (n= 72)	Percentage
SVD (Single Vessel Disease)	38	52.7%
LAD	20	
LCX	8	
RCA	10	
DVD (Double Vessel Disease)	18	25%
LAD + LCX	9	
LAD + RCA	5	
LCX + RCA	2	
TVD (Triple Vessel Disease)	16	22.2%

Table 6: Prevalence of vessel involvement seen in angiography

Vessel involved	No. of cases Percentage (n = 72)
LAD	50 (69.4%)
LCX	37(51.3%)
RCA	35 (48.6%)

Table 7: NT ProBNP and extent of CAD

No. of cases	SVD	DVD	TVD	p value
	38	16	18	
NT ProBNP (pg/ml)	331.2±270.8	775.2±439.3	1164.4±596.1	0.022
Gensini score	16.8±7.8	38.6±9.4	62.2±20.6	0.014

Table 8: NT-ProBNP (median) and association with severity of CAD

Baseline Character	Serum NT proBNP level (pg/ml)		p value
	≤ 258	> 258	
TVD (n=16)	3(18.75%)	13(81.25%)	0.003
G. Score	12.4±15.8	42.6±27.9	0.012

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