



## ROLE OF N TERMINAL PRO BRAIN NATRIURETIC PEPTIDE IN PREDICTING THE SEVERITY OF CORONARY ARTERY DISEASE IN PATIENTS WITH CHRONIC STABLE ANGINA.

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**ABSTRACT** **BACKGROUND** :- N terminal-pro Brain Natriuretic peptide (NT-pro BNP) a biomarker, has been extensively studied as a prognostic marker in acute clinical settings in acute coronary syndrome and heart failure.

**OBJECTIVES**- The aim of the study is to evaluate correlation between a non invasive biomarker N terminal-pro Brain Natriuretic Peptide (NT pro BNP) and severity of coronary atherosclerosis confirmed by coronary angiogram in patients with chronic stable angina with preserved left ventricular systolic function.

**METHODS** :- 61 patients with chronic stable angina having preserved ejection fraction were enrolled. Echocardiographic left ventricular ejection fraction was calculated either by QUINONES method or by SIMPSON'S method. NT Pro-BNP was measured in all recruited patients within 12h of hospitalization using GLORIA method. All patients underwent diagnostic coronary angiography. GENSINI scoring system was used to calculate the coronary artery disease severity. The levels of NT pro-BNP were correlated with angiographic disease severity including GENSINI score.

**RESULTS** :- NT-pro BNP levels were significantly higher in patients with coronary artery disease. Highest levels of NT pro BNP was 420pg/ml noted in patients with triple vessel disease with a mean value of 211.33±89.84. Finally inference was there is statistically significant difference between 0-2, 0-3 and 1-2, 1-3 vessel involvement but no significant difference between 0-1 and 2-3 vessels involvement in view of rise NT pro BNP (0=Minor CAD, 1=SVD, 2=DVD, 3=TVD).

**CONCLUSION** :- Level of NT pro BNP may be useful to predict the presence of angiographically determined significant coronary artery disease in patients with chronic stable angina with preserved left ventricular systolic function. The NT pro BNP levels were positively correlated with number of coronary vessel involved. NT pro BNP has a good correlation with coronary artery disease severity calculated by GENSINI scores.

### KEYWORDS :

#### INTRODUCTION

Chronic stable angina is a common clinical condition encountered in our day today practice. It is associated with symptomatic discomfort to the patient as well as increased cardiovascular event rates depending on the severity of the coronary artery disease. Risk stratification based on non invasive and invasive investigations are the key to management of the condition.

Coronary angiogram is the gold standard test to detect the severity of coronary atherosclerosis in patients with chronic stable angina. This being an invasive test has its own limitations. We need simple and accurate non invasive tests for risk stratification of these patients.

N terminal-pro brain natriuretic peptide (NT-pro BNP) a biomaker, has been extensively studied as a prognostic marker in acute clinical settings as acute coronary syndrome and heart failure. In this study we plan to evaluate the value of NT-pro BNP a non invasive marker to predict the severity of the coronary atherosclerosis in chronic stable angina with preserved left ventricular systolic function.

More recently, NT-pro BNP has been shown to be an important predictor of long term mortality independent of age, ventricular ejection fraction (EF), and conventional risk factors.[1] This is an area of interest of our study that the correlation of NT pro BNP and correlation of the coronary artery disease in stable angina with preserved left ventricular function.

Plasma N-terminal pro BNP also has prognostic value after an MI or unstable angina [2, 3]. The largest study of NT pro BNP in ACS comes from an analysis of data on 6809 patients from the GUSTO IV ACS trial [2]. Blood samples obtained within 24 hours of symptom onset in patients with a non-ST elevation ACS were retrospectively assayed for NT pro BNP. Patients in the lowest decile of NT pro BNP (98 ng/L) has a significantly lower mortality rate at one year than those in the highest decile (> 4634 ng/L) (0.4 versus 27.1 percent). NT pro BNP had a stronger correlation with mortality than any other marker studied, including cTnT and CRP. Elevated BNP levels obtained 4 months after hospitalization for acute coronary syndromes were strongly predictive of future deaths and heart failure hospitalizations (4).

In one of the large scale initial studies the predictive value of NT pro BNP in patients with stable angina was evaluated in report of 1034

patients who were referred for coronary angiography and then followed for nine years (5) and at follow up, 288 patients (28 %) had died. The patients who died had significant higher NT pro BNP values at presentation (386 vs 120 pg/ml). In another study involving 1059 patients with chronic stable angina [6] at median follow up of 3.6 years, the five year mortality progressively increased from 4.7 percent in patients in the lowest quartile of NT pro BNP to 7.8 percent, 11.4 percent, and 32.7 percent in the second, third, and highest quartiles, respectively.

The association between BNP levels at baseline and the composite end point has been evaluated in a German cohort of 1072 patients with stable angina and angiographically documented CAD (7). A strong and graded association with the primary outcome was observed independently of conventional risk markers.

1. In a sub-study of the Heart Outcomes Prevention Evaluation (HOPE) study, the association between NT pro BNP levels at baseline and the incidence of myocardial infarction, stroke or cardiovascular death was examined (8). A total of 3199 patients, of whom approximately 86% had a prior diagnosis of CAD, were included and followed for a median period of time of 4.5 years. During this period 501 patients experienced at least one of the three components of the primary composite outcome. NT pro BNP provided strong and independent prognostic information concerning the primary outcome after adjustment for conventional risk factors. When individual morbidity end points were considered. NT pro BNP provided significant prognostic information concerning the incidence of myocardial infarction (HR: 2.6; 95% CI: 1.9-3.4) but not stroke.
2. The Heart and Soul study is a prospective cohort study that included 987 subjects from California (USA) with stable CAD during the period 2000-2002 (9). Conventional echocardiography, an exercise treadmill test followed by echocardiographic assessment of wall motion abnormalities and blood samples for biomarker measurements were performed at baseline. During a median follow up of 3.7 years, a total of 256 participants had a cardiovascular event or died. A strong and graded association between NT pro BNP levels at baseline and the incidence of cardiovascular events or death was observed. When individual end points were considered. NT pro BNP independently predicted the incidence of cardiovascular death and heart failure.

**Objectives of the study**

1. To record the clinical profile of enrolled patients of chronic stable angina with regards to history, investigations and risk factors and echocardiographic findings.
2. Correlation of level of NT pro BNP in patients with and without significant coronary artery disease in the study population.
3. Correlation of level of NT pro BNP with severity of coronary atherosclerosis by angiography in the study population with chronic stable angina with preserved left ventricular systolic function.

**METHODS**

This is a two years prospective observational, non interventional study carried out on patients of chronic stable angina who were admitted for diagnostic coronary angiography in the Department of cardiology, SCBMCH Cuttack, a tertiary care referral centre. Patients who fulfilled the inclusion and exclusion criteria were finally enrolled in the study.

**Inclusion criteria:** 1. Patients admitted with chronic stable angina for diagnostic coronary angiogram. 2. Patients with preserved LV systolic function (EF > 55%) 3. Age > 18 years

**Exclusion criteria:** 1. Renal failure (S.creatinine > 2) 2. LV systolic dysfunction (EF < 55%) 3. Age ≤ 18 years 4. Pregnancy 5. Cardiomyopathy, valvular heart disease, pericardial disease, congenital heart diseases.

Additional a scoring system called Gensini scoring system was used to calculate the coronary artery disease severity. This scoring system involves specific scores for specific coronary segment and percentage narrowing of the epicardial vessels and additive value gives a comprehensive picture of the coronary artery disease severity.

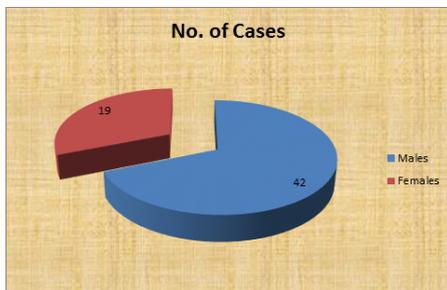
**Statistical analysis**

The following analysis methods were used to compare the results: Frequencies, Descirtive statistics, One way ANOVA Analysis , Two sample T Test, Pearson correlation test, Bi-variate correlations. All the statistical analysis was done using SPSS 22 inc. software.

**RESULTS**

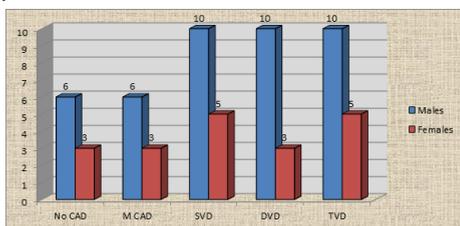
**Patient details**

There were 61 patients who qualified the inclusion criteria were enrolled during the study period. Out of which 42 were Males (69%) and 19 were Female patients (31%). Male to female ratio was almost 2:1.



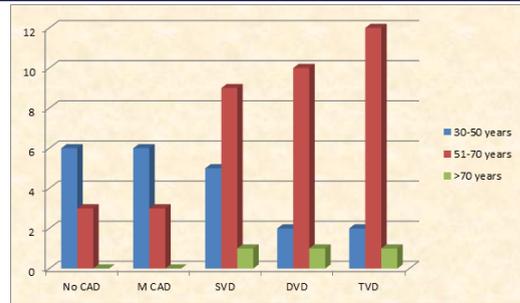
**Chart 1. Sex distribution in the study**

The sex distribution in different study groups is also been shown in the Chart 2.



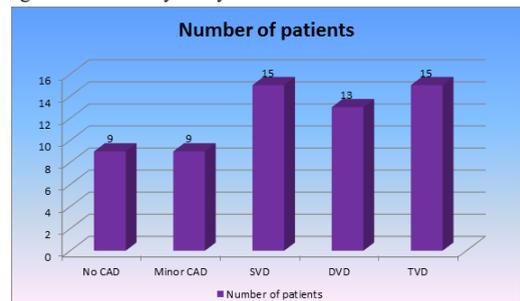
**Chart 2- Sex distribution among different study groups**

(CAD- coronary artery disease, MCAD – minor coronary artery disease, SVD-single vessel disease, DVD-double vessel disease, TVD-Triple vessel disease).



**Chart 4- Age wise distribution in different groups of coronary artery disease Angiography findings**

All patients underwent diagnostic coronary angiography (CAG). 45 patients (73.7%) underwent CAG through femoral artery approach and 16 patients (22.3%) underwent CAG through radial artery approach. No major complications were noted during coronary angiography. 9 patients had non-significant coronary artery disease and 43 patients had significant coronary artery disease.



**Chart-5: Number of patients in different groups based on CAG**

Study group	Number of patients
No CAD	9 (14.3%)
Non-significant CAD	9(14.3%)
Significant CAD	43(70.4%)

**Echo-cardiographic variables**

All the patients underwent 2D echocardiography and color Doppler. Mean ejection fraction noted in study population was 60.06 ± 3.11%. 9 patients in the study population had left ventricular (LV) regional wall motion abnormality (RWMA). Table Below shows mean ejection fraction in different study groups.

Study group	LV ejection fraction (Mean standard deviation)	Number of patients with LV RWMA
NO CAD	60.88±3.91%	0
Minor CAD	60.55±3.77%	0
SVD	59.89±2.03%	3
DVD	59.76±3.91%	3
TVD	59.73±3.33%	3

**Blood NT pro-BNP levels**

All patients had undergone blood NT pro BNP level assay. Mean NT pro BNP level in patients with non significant coronary artery disease was 87.88 ± 19.41 pg/ml and significant coronary artery disease was 166.72 ± 82.86 pg/ml. Highest level of NT pro BNP was 420 pg/ml noted in patient with triple vessel disease. The mean levels of NT pro BNP in different study groups are as shown in table below.

Study group	NT pro BNP levels (pg/ml) (mean standard deviation)
No CAD	79.88±18.38
Minor CAD	87.88±19.41
SVD	100.86±28.25
DVD	191.23±71.57
TVD	211.33±89.84

Gensini scores were calculated in every case and mean Gensini score of the study was 23.44 ± 21.56. Highest Gensini score noted was 94. Mean Gensini score in different study groups are shown in the table below.

**Table – Mean Gensini score in different study groups**

Study group	Number of patients	Gensini score (mean±standard deviation)
No CAD	9	0
Minor CAD	9	4.77±2.81
SVD	15	18.93±15.28
DVD	13	38.61±23.99
TVD	15	40.06±9.8

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum value	Maximum value
					Lower bound	Upper bound		
No CAD	9	75.888	18.3810	6.127	61.7600	90.017	65.00	120.00
Minor CAD	9	87.888	19.4129	6.470	72.9668	102.81	60.00	120.00
SVD	15	100.86	28.2510	7.294	85.2217	116.51	60.00	160.00
DVD	13	191.23	71.5741	19.85	147.9789	234.48	102.00	320.00
TVD	15	211.33	89.8440	23.19	161.5794	261.08	120.00	420.00
Total	61	141.68	80.2131	10.27	121.1450	162.23	60.00	420.00

NT pro BNP levels in the 3 groups (no CAD, minor CAD and significant CAD) were analyzed first. As the sample values for 3 groups are not same so correlation tests couldn't have been very accurate, so tests for variation namely One-Way ANOVA test was applied between 3 groups. **From One-Way ANOVA it is clear that there is some significant variation between groups** (table 2) so individual group analysis was done between the groups.

**A. Table 2 : ANOVA group analysis of 3 groups**

	Sum of Squares	Mean Square	F	Significance
Between groups	91960.653	4598.327	9.068	0.001
Within groups	294088.42	5070.490		
Total	386049.08			

- Two-Sample T-Test was applied between no CAD and minor CAD group: P-Value of the test was 0.198 implies there is no difference between mean of No CAD and mean of Minor CAD group.
- Two-Sample T-Test was applied between no CAD and Significant CAD group: P-Value of the test was 0.001 implies there is significant statistical difference between mean of No CAD and mean of significant CAD group.
- Two Sample T-Test was applied between minor CAD and significant CAD group: P-Value of the test was 0.001 implies there is significant statistical difference between mean of minor CAD and mean of significant CAD.

Group-cat1	Group-cat2	Mean Difference	Std. Error	Sig.
No. CAD	Minor CAD	-12.00000	27.55753	.665
	SVD	-24.97778	24.64820	.315
	DVD	-115.34188*	25.34924	.000
	TVD	-135.44444*	24.64820	.000
Minor CAD	No CAD	12.00000	27.55753	.665
	SVD	-12.97778	24.64820	.601
	DVD	-103.34188*	25.34924	.000
	TVD	-123.44444*	24.64820	.000
SVD	No CAD	24.97778	24.64820	.315
	Minor CAD	12.97778	24.64820	.601
	DVD	-90.36410*	22.15176	.000
	TVD	-110.46667*	21.34597	.000
DVD	No CAD	115.34188*	25.34924	.000
	Minor CAD	103.34188*	25.34924	.000
	SVD	90.36410	22.15176	.000
	TVD	-20.10256	22.15176	.368
TVD	No CAD	135.44444*	24.64820	.000
	Minor CAD	123.44444*	24.64820	.000
	SVD	110.46667*	21.34597	.000
	DVD	20.10256	22.15176	.368

So further individual analysis to test the significance of mean between the groups were done and the results are as follows (T-test was used)

- Two-Sample T-Test was applied to examine difference of mean between no CAD and SVD, DVD and TVD individually. P-Value of the test between no CAD and SVD was 0.16, no CAD and DVD was 0.001 and no CAD and TVD was 0.001 implies there is significant statistical difference between mean of No CAD and mean of 2 groups (DVD, TVD) however there was no statistical difference between mean of no CAD and mean of SVD group.
- Two-Sample T-Test was applied to examine difference of mean

**DISCUSSION**

**Correlation of NT pro BNP with severity of coronary artery disease**

The patients enrolled were initially divided into 3 groups namely no CAD (coronary artery disease), minor CAD and significant CAD. Further significant CAD group was divided into 3 groups SVD, DVD, TVD.

between minor CAD and SVD, DVD and TVD individually. P-Value of the test between minor CAD and SVD was 0.197, minor CAD and DVD was 0.001 and minor CAD and TVD was 0.001 implies there is significant statistical difference between mean of minor CAD and mean of 2 groups (DVD, TVD) however there was no statistical difference between mean of minor CAD and mean of SVD group.

- Two-Sample T-Test was applied to examine difference of mean between SVD group and DVD and TVD individually. P-Value of the test between SVD and DVD was 0.002, SVD and TVD was 0.001, implies there is significant statistical difference between mean of SVD and mean of 2 groups (DVD, TVD).
- Two-Sample T-Test was applied to examine difference of mean between DVD group and TVD: P-Value of the test was 0.66, implies there is no significant statistical difference between mean of DVD and TVD groups.

Finally the inference was that there was statistically significant difference between 0-2, 0-3, 1-2, 1-3 vessels involvement, but no significant difference between 0-1, 2-3 vessels involvement (0-minor CAD, 1-SVD, 2-DVD, 3-TVD). The results of the study are in accordance with some studies, where a good correlation of NT Pro BNP levels was observe with number vessels involved (10,11).

Pearson Correlation test was applied to see if any correlation exists between Gensini score and NT Pro BNP levels. We found that there was strong correlation between the groups thus implying good correlation of NT Pro BNP levels with higher Gensini values.

**LIMITATION OF THE STUDY**

- Some confounding factors for NT pro BNP like diastolic dysfunction, are being matches in study groups, though other factors which can influence NT pro BNP levels in minor levels like obesity, sex are not being matched.
- It's a study to correlate only the severity of coronary atherosclerosis, and the patients are not followed up and event rates in the following periods not done. So need good long term large scale studies to look for prognostic ability of NT pro BNP to determine the future event rate.

**CONCLUSIONS**

According our study NT pro BNP may be useful to predict the presence of angiographically determined significant coronary artery disease in patients with chronic stable angina with preserved left ventricular systolic function, though its value in differentiating patients with no coronary artery disease and minor non significant coronary artery disease may be limited.

The NT pro BNP levels were positively correlated with the number of coronary vessels involved. NT pro BNP may be of particular valuable to predict the presence of more severe coronary artery disease (double and triple vessel disease) than single vessel disease in patients with chronic stable angina with preserved left ventricular systolic function. The NT pro BNP has a good correlation with angiographically determined coronary artery severity calculated by Gensini scores.

**REFERENCES**

- Bergler-Klein J, Mundigler G, Pibarot P, et al. B type natriuretic peptide in low flow, low gradient aortic stenosis relationship to hemodynamics and clinical outcome results from the Multicenter Truly or Pseudo-Severe Aortic Stenosis (TOPAS) study. Circulation 2007; 115:2848.

2. Richards AM, Nicholls MG, Yandle TG, et al. Plasma N-terminal pro-brain natriuretic peptide and adrenomedullin, new neurohormonal predictors of left ventricular function and prognosis after myocardial infarction. *Circulation* 1998; 97:1921
3. James SK, Lindahl B, Siegbahn A, et al. N-terminal pro-brain natriuretic peptide and other risk markers for the separate prediction of mortality and subsequent myocardial infarction in patients with unstable coronary artery disease; a Global Utilization of Strategies To Open occluded arteries (GUSTO)-IV substudy. *Circulation* 2003;108:275.
4. Morrow DA, de Lemos JA, Blazing MA et al. Prognostic value of serial B type natriuretic peptide testing during follow up of patients with unstable coronary artery disease. *JAMA* 294(22), 2866-2871 (2005).
5. Kragelund C, Gronning B, Kober L, et al. N-terminal pro B-type natriuretic peptide and long term mortality in stable coronary heart disease. *N Engl J Med* 2005; 352:666.
6. Ndrepepa G, Braun S, Niemoller K, et al. Prognostic value of N-terminal pro-brain natriuretic peptide in patients with chronic stable angina. *Circulation* 2005; 112:2012.
7. Schnable R, Lubos E, Rupprecht HJ et al. B-type natriuretic peptide and the risk of cardiovascular events and death in patients with stable angina: results from the Athero Gene Study. *J. Am. Coll. Cardiol.* 47(3), 552-558 (2006).
8. Blankenberg S, McQueen MJ, Smieja M et al. Comparative impact of multiple biomarkers and N-terminal pro-brain natriuretic peptide and N-terminal pro-brain natriuretic peptide in the context of conventional risk factors for the prediction of recurrent cardiovascular events in the Heart Outcomes Prevention Evaluation (HOPE) Study. *Circulation* 114(3), 201-208 (2006).
9. Poutanen T, Tikanoja T, Riikonen P, et al. Long term prospective follow up study of cardiac function after cardiotoxic therapy for malignancy in children. *J Clin Oncol* 2003;107:2440.
10. Yesil M, Postaci N, Arikan E, Ceylan O, Bayata S, Koseoglu M; Can we predict the severity of coronary artery disease in patients with stable angina using NT-pro BNP ; *Anadolu Kardiyol Derg.* 2006 Sep; 6(3): 235-8.
11. Weber M, Dill T, Arnold R, Rau M, Ekinci O, Muller KD, Berkovitsch A, Mitrovic H, Hamm C; N-terminal B type natriuretic peptide predicts extent of coronary artery disease and ischemia in patients with stable angina pectoris; *Am Heart J.* 2004 Oct; 148(4):612-20.