## ORIGINAL RESEARCH ARTICLE

# 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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### A B S T R A C T

**Introduction:** The aim of the study was to evaluate correlation between a noninvasive biomarker N terminal-pro brain natriuretic peptide (NT Pro BNP) and severity of coronary atherosclerosis in patients with chronic stable angina with preserved left ventricular systolic function.

**Material and Methods**: 61 adult patients were included. The history regarding grade and duration of the anginal pain, risk factors, previous coronary revascularization, use of antiplatelets, antianginals, antihypertensives and other cardiovascular drugs were taken. Blood investigations namely fasting lipid profile and NT-Pro BNP level were done. A 2D echocardiography with colour Doppler was done to note left ventricular ejection fraction, Regional wall motion abnormality, Grade of left ventricular diastolic dysfunction and bilateral, common carotid artery intima media thickness. Angiography was done to evaluate coronary artery.

**Results:** Male to female ratio was almost 2:1. Mean age of patients was 54.54 ± 8.89 years. Mean ejection fraction was 60.06 ± 3.11%. Mean Carotid intima and medial thickness (CIMT) was more in patients with significant coronary artery disease than patients with non significant coronary artery disease (0.93±0.12 mm versus 0.91 ± 0.13 mm). 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 which is statistically significant (p=0.0001). Highest level of NT PRO BNP was 420 pg/ml noted in patient with triple vessel disease.

**Conclusion:** non invasive NT-Pro BNP can be a good alternative of invasive angiography for assessment of severity of coronary artery disease.

**Key words:** Angina Stable; Coronary Artery Disease; Brain Natriuretic Peptide

## INTRODUCTION

Chronic stable angina is one of the most common manifestations of obstructive coronary artery disease (CAD). 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. N terminal–pro brain natriuretic peptide (NT-pro BNP*)* a biomarker, has been extensively studied as a prognostic marker for acute coronary syndrome and heart failure. We plan to evaluate the value of NT-pro BNP a noninvasive marker to predict the severity of the coronary atherosclerosis in chronic stable angina with preserved left ventricular systolic function.

## MATERIAL AND METHODS

Present prospective observational study was conducted in Department of cardiology, Meenakshi Medical College and Research Institute, Kanchipuram and Burdwan Medical College, both tertiary care referral centre on 61 patients from Jan 2013 to Dec 2014.

### Inclusion criteria
1. Patients admitted with chronic stable angina for diagnostic coronary angiogram
2. Patients with preserved Left Ventricular systolic function (LVEF >55%)
3. Age >18 years

### Exclusion criteria
1. LV systolic dysfunction (LVEF <55%)
2. Age <18 years
3. Cardiomyopathy, valvular heart disease, pericardial disease, congenital heart diseases

**Method of data collection:** This study was done after getting approval from the Institutional Ethics Committee of our

institution and an informed consent.

## Methodology

Enrolled patient's demographic data, detailed history of grade and duration of the angina pain, risk factors and drugs were taken. Clinical examination and blood investigations including NT-Pro BNP were done. The following parameters were noted with 2D echocardiography with colour Doppler

1. Left ventricular ejection fraction (LVEF)
2. Regional wall motion abnormality (RWMA)
3. Grade of left ventricular diastolic dysfunction (LVDD)
4. Doppler evaluation of the bilateral common carotid artery is done and carotid intima media thickness (CIMT) was noted by Gray scale ultrasound and high resolution B-mode color Doppler ultrasound system (Siemens acuson cv70 machine) equipped with a L10-5 vascular probe with 5-10 MHz. The mean IMT value was calculated from 3 measurements.

## NT Pro BNP Assay

NT PRO BNP assay was done before coronary angiogram with 2 ml of the venous blood and assay was done by radiometer aqt90 analyzer by immune-chromatographic method using gold labeled optically read immunoassay (GLORIA) format.

## Coronary angiography

Angiographically significant coronary artery disease (CAD) was defined as at least 70% lumen diameter reduction of major epicardial coronary arteries at visual estimation. A stenosis >50% of the left main artery was defined as significant CAD. Patients was classified into 5 major groups based on angiographic findings as

1. NO CAD (no lumen irregularities)
2. NON-significant CAD (defined as lumen irregularities < 70% lumen diameter reduction)
3. Significant CAD which were further divided into
   a) Single vessel disease (SVD)
   b) Double vessel disease (DVD)
   c) Triple vessel disease (TVD)

In case of post stenting patients same angiographic significance criteria was used. In patients with previous history of coronary artery bypass grafts additional graft angiography were performed and significance was estimated. Additional scoring system called Gensini scoring system was used to calculate the coronary artery disease severity.

## RESULTS

**Patient details:** 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. Mean age of patients in the present study was 54.54 ± 8.89 years. Minimum age noted in the present study was 40 years and the maximum

| Age distribution | | | | |
|---|---|---|---|---|
| **Age in years** | **No.** | **Percentage (%)** | **Mean age** | |
| 30-50 | 21 | 34.4 | 54.54 ± 8.89 years | |
| 50-70 | 37 | 60.6 | | |
| >70 | 3 | 4.9 | | |
| **Baseline lipid profile in different groups and comparison among them** | | | | |
| **Investigations** | **No CAD** | **Minor CAD** | **Significant CAD** | **p- value** |
| LDL (mg/dl) | 110.77±22.86 | 99.11±12.72 | 99.41±19.72 | 0.27 |
| HDL (mg/dl) | 37.11±7.0 | 40.11±2.2 | 36.53±0.9 | 0.33 |
| Triglyceride (mg/dl) | 167.44±61.5 | 194.77±25.87 | 173.04±31.28 | 0.214 |
| **Table-1:** Age and baseline lipid profile of the patients | | | | |

| Study groups | Left ventricular ejection fraction (mean±standard deviation) | p-value 0.56 | No of patients with LV RWMA | CIMT mean ± standard deviation |
|---|---|---|---|---|
| No CAD | 60.88 ± 3.91% | | 0 | 0.88 ± 0.1 |
| Minor CAD | 60.55 ± 3.77% | | 0 | 0.91 ± 0.13 |
| SVD | 59.86 ± 2.03% | | 3 | 0.92 ± 0.13 |
| DVD | 59.76 ± 3.91% | | 3 | 0.94 ± 0.14 |
| TVD | 59.73 ± 3.33% | | 3 | 0.95 ±0.09 |
| **Table-2:** mean left ventricular ejection fraction and mean value of CIMT | | | | |

| Study group | No DD | Grade 1 DD | Grade 2 DD | Percentage (%) | P value = 0.9 |
|---|---|---|---|---|---|
| No CAD | 4 | 4 | 1 | 55.5 | |
| Minor CAD | 4 | 3 | 2 | 55.5 | |
| SVD | 6 | 6 | 3 | 60 | |
| DVD | 6 | 4 | 3 | 53.8 | |
| TVD | 7 | 5 | 3 | 53.3 | |
| **Table-3:** grades of diastolic dysfunction in different study group | | | | | |

| Descriptive of NT PRO BNP levels in different groups (pg/ml) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Different group | No. | Mean | Standard Deviation | Standard error | 95% confidence interval of 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 |
| Multiple Comparisons between 5 groups | | | | | | | | |
| Group_cat1 | Group_cat2 | | Mean difference | | Standard error | | Significance | |
| NO CAD | Minor CAD | | -12.00000 | | 27.55753 | | 0.665 | |
| | SVD | | -24.97778 | | 24.64820 | | 0.315 | |
| | DVD | | -115.34188 | | 25.34924 | | 0.000 | |
| | TVD | | -135.44444 | | 24.64820 | | 0.000 | |
| Minor CAD | No CAD | | 12.00000 | | 27.55753 | | 0.665 | |
| | SVD | | -12.97778 | | 24.64820 | | 0.601 | |
| | DVD | | -103.34188 | | 25.34924 | | 0.000 | |
| | TVD | | -123.44444 | | 24.64820 | | 0.000 | |
| SVD | No CAD | | 24.97778 | | 24.64820 | | 0.315 | |
| | Minor CAD | | 12.97778 | | 24.64820 | | 0.601 | |
| | DVD | | -90.36410 | | 22.15176 | | 0.000 | |
| | TVD | | -110.46667 | | 21.34597 | | 0.000 | |

**Table-4:** NT PRO BNP Levels and their multiple comparison

| Severity of CAD in different study group based on CAG with Gensini score | | | |
|---|---|---|---|
| Study group | No of patients (%) | | Gensini score (Mean ±standard deviation) |
| No CAD | 9 (14.3%) | | 0 |
| minor CAD | 9 (14.3%) | | 4.77±2.81 |
| Significant | 43 (70.4%) | | |
| SVD | 15 (24.5%) | | 18.93±15.28 |
| DVD | 13 (21.3%) | | 38.61±23.99 |
| TVD | 15 (24.5%) | | 40.06±9.8 |
| Data of the NT pro BNP in different groups based on Gensini score | | | |
| Gemini Score group | | Statistic of BNP(pg/ml) | Standard error |
| ≤20 | Mean | 91.7273 | 6.10308 |
| | Std. Deviation | 28.62597 | |
| | Minimum | 60.00 | |
| | Maximum | 160.00 | |
| 21-40 | Mean | 155.9444 | 21.32697 |
| | Std. Deviation | 90.48267 | |
| | Minimum | 60.00 | |
| | Maximum | 420.00 | |
| >40 | Mean | 182.4000 | 26.76988 |
| | Std. Deviation | 84.65380 | |
| | Minimum | 100.00 | |
| | Maximum | 320.00 | |

**Table-5:** severity of CAD and in different study group based on CAG with Gensini score and NT pro BNP in different groups based on Gensini score

age was 83 years. The age distribution was shown in table 1. 23(37.7%) patients from class 1 angina, 24 (39.3%) patients from class 2 and 14 (22.9%) patients were suffering from class 3 angina according to Canadian Cardiovascular Society Angina Grading Scale.

**Medication history:** 59(96.9%) patients were on antiplatelets (asprin or clopidogrel) and 23 (37%) were on dual antiplatelts. All the patients were on one of the antianginals. Nitrates were the most common antianginal used in 52 (83%) patients. 24 patients were on single antianginal, 18 were on 2 antianginals, 12 were on 3 antianginals and 7 were on more than 3 antianginals. Mean number of antianginal was 2.06 ± 1.1 per person.

**Risk factor evaluation:** Most common risk factor associated was smoking, documented in 23(37.7%). 20(32.7%) patients were hypertensive and 19(31.1%) were diabetic. 15 out of 20 hypertensive and 14 out of 19 diabetic patients had significant CAD. Among patients with significant CAD 3 had coronary angioplasty and stenting 1 had cerebrovascular accident and 1 had peripheral artery disease. 9 of them (significant CAD) had post coronary artery syndrome.

Lipid profile of the patients was also shown in table 1. By group analysis of variance these values were statistically insignificant, implying that all the groups were comparable in these variables.

**Echocardiographic variables:** Mean ejection fraction noted in study population was 60.06 ± 3.11%. By group analysis of variance values of left ventricular ejection fraction (LVEF) were statistically insignificant, implying that all the groups were comparable in these variables. 9 patients had left ventricular regional wall motion abnormality. Mean CIMT seen in the study population was 0.91 ± 0.12 mm. Mean CIMT measured in patients with non significant coronary artery disease was 0.91±0.13 mm and in patients with significant coronary artery disease was 0.93±0.12 mm. Table 2 shows mean ejection fraction and mean CIMT measurements in different study groups.

34 patients (55.7%) in the present study had some grade of left ventricular diastolic dysfunction (DD), amongst 5 patients with non significant coronary artery disease 24 of them with significant coronary artery disease. None of them had grade 3 or 4 grade DD. In subgroup analysis it was found in 55.5% of patients each in no CAD and minor CAD group, 60% in SVD, 53.3% in DVD, 55.8% in TVD groups respectively. The degree of diastolic dysfunction in specific study groups were shown in the table 3. By applying chi-square test to compare the groups, there was no statistical difference (p=0.9) between the study groups. Diastolic dysfunction in this study was equally present in all groups, so the different groups were comparable in this variable.

**Blood NT Pro BNP levels:** 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 descriptive of NT PRO BNP levels in different study groups were shown in table 4.

**Correlation of NT PRO BNP with severity of coronary artery disease:** The patients enrolled were initially divided into 3 groups namely no CAD, minor CAD and significant CAD. Further significant CAD group was divided into 3 groups SVD, DVD, TVD. 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 was clear that there was some significant variation between Groups, so individual group analysis was done between the groups. From the results of One-Way ANOVA it was also clear that there

was some significant variation between the study subgroups. In all three methods LSD, Bonferroni, Tamhane it was clear that DVD and TVD had no significant difference between them and minor CAD, No CAD and SVD, and were all of same significance.

So further individual analysis to test the significance of mean between the groups were done and the results are as follows

1. P-Value of the test between no CAD and SVD, no CAD and DVD, and no CAD and TVD imply that 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

2. P-Value of the test between minor CAD and SVD, minor CAD and DVD, and minor CAD and TVD imply that 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

3. P-Value of the test between SVD and DVD, and SVD and TVD imply that there is significant statistical difference between mean of SVD and mean of a 2 groups (DVD, TVD)

4. P-Value of the test 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, 1-3,1-2 vessels involvement, but no significant difference between 0-1, 2-3 vessels involvement (0- minor CAD, 1- SVD,2-DVD, 3-TVD. Table 4 is also showing multiple comparison between 5 groups of CAD.

**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 redial 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. Further patients were reassigned into 5 study groups as mentioned in the study methods. 9 of the Patients had normal coronaries, 9 patients had minor CAD, 15 patients had single vessel disease, 13 patients had double vessel disease and 15 patients had triple vessel disease. 3 patients had in-stent restenosis and 3 patients had significant left main coronary artery disease. 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. Severity of CAD based on CAG and Mean Gensini score in different study groups were shown in the table 5. An effort was also done to examine if any correlation exists between NT Pro BNP levels and calculated Gensini score (score to measure severity of coronary artery disease). The patients were divided into 3 groups based on Gensini scores (≥20, 21-40, >40). Correlation between Gemini score and NT-Pro BNP was shown in Table 5.

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.

**Correlation of carotid intima and media thickness (CIMT) with CAD:** CIMT was measured in all groups and was then compared. From One-Way ANOVA it was clear that there is no significant variation between Groups.

On testing the difference in mean between 3 groups, results are as follows

1. Two-Sample T-Test was applied to examine difference of mean between no CAD group minor CAD group. P-value of the test was 0.18, implies there is no significant statistical difference between mean of no CAD and mean of a minor CAD group.

2. Two-Sample T-Test was applied to examine difference of mean between no CAD group significant CAD group. P-value of the test between 0.018, implies there is significant statistical difference between mean of no CAD and mean of a significant CAD group.

3. Two-Sample T-Test was applied to examine difference of mean between minor CAD group significant CAD group. P-value of the test was 0.608, implies there is no significant statistical difference between mean of minor CAD and mean of a significant CAD group.

## DISCUSSION

**Patient details:** Sex ratio in our study was almost 2:1 with male predominance. There was a female under-representation in all the groups and the sex ratio was almost equal in all groups. The results are in tune with the incidence rates seen in most referral hospitals data from western countries. But a recent large general population study from Finland showed an age-standardized annual incidence per 100 population of all cases of angina was 2.03 in men and 1.89 in women, with a sex ratio of 1.07.[1] Theses gender difference in the referral tertiary centers may be due to the referral bias. Data from the Euro Heart Survey of Stable Angina conducted in 2003 suggest that significant bias exists against the use, not just of arteriography but also of exercise testing in women, even after adjustment for factors such as age, co-morbidity. And in the same study it was also found that women were less likely to receive revascularization and were less likely to receive effective secondary preventive medical therapy. So this gender difference noted in the study may just be because of under investigation and under referral. Mean age of patients in the present study was 54.54 ± 8.89 years which is higher than some Indian study.[2-4] Common pre-morbid illnesses associated in study population were smoking, hypertension, diabetes dyslipidemia which are similar to interheart study.[5] Hypertension was seen (32%), which is higher compared to Indian data (from centre for chronic disease control) on risk factors in coronary artery disease where hypertension was seen in 17-22% of patients with coronary artery disease. Diabetes was seen in 19 out of 61 patients ((31%) which was comparable with data from centre for chronic disease control, where diabetes was documented in 30- 40% of patients with coronary artery disease (depending on the various groups based on socioeconomic strata) but higher than ROW. We also noted that 23 out of 61 (37.7%) were

smokers which was again comparable to data from centre for chronic disease control, where smoking was seen in 32-40% of patients with coronary artery disease. 59 patients were on one of the antiplatelets and all the patients were on one of the antianginals. The most common antianginal used was nitrates, in 51 patients. Mean number of antianginal medication used was 2.06 ± 1.1 tablets per person. The average number of antianginals used in triple vessel disease group was much higher compared double vessel disease group and single vessel disease group (2.9 ±1.0, 2.3 ±1.1 and 2.1±1.0 respectively). Our 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 which is independent of systolic dysfunction.[6-9] In presence of normal systolic and diastolic function NT pro BNP is useful to predict the angiographic severity of CAD.[10] The finding of the transcardiac increase of plasma NT-pro BNP was significantly increased with the severity of coronary artery stenosis seen in one study.[11] Another study showed a strong independently causative relationship between N terminal pro BNP and the severity of coronary stenosis in multivariable model.[12,13] BNP levels rose significantly with increasing number of vessels involved. Gensini Score showed a strong correlation with BNP levels.[13]

According to our study CIMT was more in patients with significant CAD which is also a finding in a large number of study where surrogate marker CIMT was shown to be intimately related with severity of CAD, that points toward the fact that atherosclerosis affects not only cardiac artery but also carotid artery. Some studies have also shown that non invasive CIMT measurement might be substitute of invasive angiographic assessment of coronary artery.[14-19] Conclusion Although majority studies over a long period of time showed correlation between CIMT and severity of CAD but one study found that severity of CAD did not correlate with CIMT. Risk factors like diabetes, hypertension could be related to increased CIMT.

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