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Predictive value of N-terminal-Pro brain natriuretic peptide in the detection of coronary artery disease in patients with positive myocardial perfusion imaging

Reza Rahmani[1], Akbar Shafiee[2], Kambiz Parazaran*[1], Najmeh Reshadati[1]

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Abstract

Background: N-terminal pro-brain natriuretic peptide (NT-ProBNP) increases during myocardial ischemia and has a potential for the diagnosis of patients with coronary artery disease (CAD). We aimed to determine the incremental diagnostic value of NT-ProBNP in the selection of patients with positive myocardial perfusion imaging (MPI) for coronary angiography. We also tested the association between the level of NT-ProBNP and severity of CAD based on the vessel score and Gensini score.

Methods: In this cross-sectional study, stable angina patients with positive MPI who were assessed by coronary angiography in Imam Khomeini Hospitalwere enrolled. After the collection of demographic and clinical data, NT-ProBNP was measured in all patients on the day of coronary angiography, and its association with the presence of CAD, vessel score and Gensini score was tested.

Results: We enrolled 170 patients (mean age61.2±10.1 years, 86 males (50.6%)). Seventy-two (42.3%) patients had at least one stenotic vessel. NT-Pro BNP was significantly higher in the CAD-positive group (OR=1.01, 95% CI: 1.00-1.02; p=0.008) and could independently predict the presence of CAD at a cut-off point of 69.5, with a sensitivity of 55.6%, specificity of 82.5% and diagnostic accuracy of 61.7%. The Gensini score had a modest correlation with NT-Pro BNP (r=0.60, p<0.001). The combination of MPI result and NT-Pro BNP could predict the presence of CAD (OR=14.57, 95% CI: 4.28, 49.56; p<0.001).

Conclusion: Serum level of NT-Pro BNP alone and its combination with the results of MPI can significantly predict the presence of CAD and therefore, highlights the need for performing coronary angiography.

Keywords: Coronary artery disease, NT-Pro brain natriuretic peptide, Myocardial perfusion imaging, Coronary angiography, Diagnosis

Conflicts of Interest: *None declared*
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Introduction

Coronary artery disease (CAD) is the most prevalent cardiovascular disease worldwide and thereby its early diagnosis and management can save thousands of lives annually (1). Currently, conventional coronary angiography is the gold standard for the diagnosis of CAD (2). Due to its invasive nature, selection of the patients for coronary angiography is still a challenge for the clinicians. Based on the current guidelines, patients with symptomat-

Corresponding author: *Dr Kambiz Parazaran, kambizparazaran@yahoo.com*

1. Department of Cardiology, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran
2. Department of Cardiovascular Research, Tehran Heart Center, Tehran University of Medical Sciences, Tehran, Iran

↑What is "already known" in this topic:
Several biomarkers are currently used for the diagnosis, risk stratification, and management of cardiovascular diseases. Current evidence suggests that NT-ProBNP rises during myocardial ischemia and therefore it has a potential for the diagnosis of patients with CAD.

→What this article adds:
NT-Pro BNP could independently predict the presence of CAD at a cut-off point of 69.5, with a sensitivity of 55.6%, specificity of 82.5% and diagnostic accuracy of 61.7%. The combination of MPI result and NT-Pro BNP can predict the presence of CAD.

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ic chest pain and positive non-invasive tests, such as exercise tolerance test of myocardial perfusion imaging (MPI) are potential candidates for coronary angiography (2). However, there is still a noticeable rate of unnecessary tests due to the patients with false positive non-invasive test results (3). Therefore, there is a need to improve the precision of the selection process for coronary angiography.

Several biomarkers are currently used for the diagnosis, risk stratification, and management of cardiovascular disease (4, 5). Among them, N-terminal Pro B-type natriuretic peptide (NT-ProBNP) can help to diagnose heart failure and acute coronary syndromes as well as to determine the prognosis of such patients (6-8). Current evidence suggests that NT-ProBNP rises during myocardial ischemia and therefore it has a potential for the diagnosis of patients with CAD (9). However, its clinical implication in the selection of patients for coronary angiography is not well-studied.

In the present study, we aimed to determine the diagnostic value of NT-ProBNP in the selection of patients for coronary angiography who had positive MPI as well as its additive diagnostic value with the certainty of MPI results in our center. Moreover, we wanted to find out the association between the level of NT-ProBNP and the severity of CAD based on the vessel score and Gensini score.

Methods

In this cross-sectional study, stable angina patients with positive MPI who were assessed in the cardiology department of Imam Khomeini Hospital, Tehran, Iran, between March 2016 and February 2017 were enrolled. The study inclusion criteria were positive MPI, sinus heart rhythm, ejection fraction>50% based on the echocardiography before coronary angiography, and age>18 years. The exclusion criteria were the presence of valvular disease, sepsis, malignancy, renal or hepatic failure, and history of pulmonary emboli or pulmonary hypertension. The study protocol was approved by the research board of the cardiology department and committee of medical ethics at Tehran University of Medical Sciences. Informed consents were given from all patients before enrolment to the study. The study protocol conforms to the declaration of Helsinki.

In the first step, demographic and clinical data of the patients, including age, sex, height, weight, history of cardiovascular risk factors (diabetes mellitus, dyslipidemia, hypertension, cigarette smoking and family history of CAD) were asked from the patients and recorded in the study forms.

On the day of coronary angiography, a venous blood sample was obtained from the patients to measure blood cell counts, creatinine, sodium, potassium, blood urea nitrogen and NT-ProBNP at our hospital laboratory. NT-ProBNP was measured by RAMP® test (Response Biomedical Corp., Vancouver, Canada).

Then patients underwent conventional coronary angiography via femoral accessin our catheterization laboratory and the results were reported as the presence or absence of CAD, vessel score as well as Gensini score. CAD was defined as ≥50% narrowing in the luminal diameter of the left main artery or ≥70% narrowing in other coronary artery branches. In the next step, the study variables were compared between the patients with and without CAD. Association of NT-pro-BNP with CAD and its severity as well as its cut-off points for the detection of CAD were evaluated. Its sensitivity and specificity were also determined.

Finally, we combined the result of MPI (either definite or indefinite) and dichotomized level of NT-Pro BNP around the cut-off point to assess the predictive value for the presence of CAD.

Statistical analysis

We described continuous variables with mean and standard deviation (SD) or with median and interquartile range for skewed data and compared them between CAD and non-CAD groups using the Student's t or Mann-Whitney U test where appropriate. We expressed categorical variables as frequency and percentage and compared them between the two groups using the Chi-square test. The area under the receiver operating characteristic (ROC) curve with 95% confidence interval (CI) was applied to measure the discrimination power of NT-ProBNP. Variables which were simultaneously associated with CAD and NT-proBNP with p-values less than 0.2 were considered potential extraneous variables. A multiple logistic regression model was applied to evaluate the association of NT-proBNP and CAD adjusted for detected potential extraneous variables. We reported the adjusted effect through odds ratio (OR) with 95% CI. P-values less than 0.05 were considered statistically significant. The statistical analysis was performed using IBM SPSS version 24.0 (IBM, USA).

Results

In the present study, we enrolled 170 stable angina patients (mean age 61.2±10.1 years, 86 males (50.6%)). Seventy-two (42.3%) patients had at least one stenotic vessel in the coronary angiography and were classified as the coronary angiography positive group. Patients in the coronary angiography positive group were significantly different from their coronary angiography negative peers regarding age, body mass index, the presence of diabetes, and white blood cell count. Moreover, the serum level of NT-ProBNP was significantly higher in the coronary angiography positive group (Table 1). Moreover, there was a significant rise in the level of NT-Pro BNP by the increase in the vessel score (Figure-1). Also, the Gensini score had a modest correlation with NT-Pro BNP in our patients (r=0.60, p<0.001).

The multivariate analysis of the predictors for CAD showed that NT-Pro BNP could independently predict the presence of CAD (OR=1.01, 95% CI: 1.00-1.02; p=0.008), as shown in Table 2.

At a cut-off point of 69.5, NT-proBNP could predict the presence of CAD with a sensitivity of 55.6% and specificity of 82.5% (Area under the ROC curve 71.3%, 95% confidence interval (CI): 63.5-79.1; p<0.001). The negative predictive value was 71.6 (95%CI: 65.8-76.9). The diag-

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Table 1. Univariate analysis of the study variables and their comparison between the study groups based on the results of the coronary angiography

Characteristic*	Total population (n=170)	CAG negative (n=98)	CAG positive (n=72)	Odds ratio	95% confidence interval	p†
Age, year	61.2±10.1	58.9±10.3	64.4±8.9	1.06	1.02, 1.09	0.001
Male gender, n (%)	86 (50.6)	43 (43.9)	43 (59.7)	1.89	1.02, 3.51	0.42
BMI, kg/m2	27.5±5.2	28.3±5.8	26.5±4.1	0.93	0.87, 0.99	0.037
Hypertension, n (%)	85 (50.0)	47 (48.0)	38 (52.8)	0.82	0.44, 1.51	0.535
Diabetes, n (%)	60 (35.3)	24 (24.5)	36 (50.0)	0.32	0.16, 0.62	0.001
Dyslipidemia, n (%)	46 (27.1)	25 (25.5)	21 (29.2)	0.83	0.42, 1.64	0.596
Smoking, n (%)	17 (10.0)	10 (10.2)	7 (9.7)	1.05	0.38, 2.91	0.918
WBC, 1/mm3	7574±2443	6976±2154	8388±2589	1	1.00,1.00	<0.001
Hemoglobin, mg/dl	13.4±1.7	13.5±1.7	13.3±1.8	0.93	0.78, 1.11	0.469
Platelets, 1/mm3	253664±79350	245193±79740	265194±77888	1	1.00, 1.00	0.107
Creatinine, mg/dl	0.97±0.37	0.93±0.37	1.01±0.37	1.73	0.70, 4.27	0.235
Na, mg/dl	137.4±10.9	136.5±14.0	138.6±3.8	1.05	0.97, 1.13	0.21
K, mg/dl	4.3±0.5	4.2±0.5	4.3±0.4	1.67	0.86, 3.23	0.126
BUN, mg/dl	27.2±14.2	25.9±13.4	29.0±15.1	1.02	0.99, 1.03	0.169
NT-ProBNP, pg/ml	43.0 [17.0, 85.5]	27 [13.5, 64.0]	72.0 [28.0, 108.5]	1.01	1.00, 1.02	<0.001

BMI: Body mass index; BNP: Brain natriuretic peptide; BUN: Blood urea nitrogen; CAG: coronary angiography; WBC: White blood cell
* Variables are shown as frequency (percentage), mean ± standard deviation and median [interquartile range] where appropriate.
† P-value less than 0.05 was considered as statistically significant.

nostic accuracy of NT-Pro BNP for predicting a positive coronary angiography was 71.2%.

In the multivariable regression model of the combination of MPI result and NT-Pro BNP subgroups, we observed a significant predictive value for the combination of both variables in predicting the presence of CAD (OR=14.57, 95% CI: 4.28, 49.56; p<0.001) (Table 3). The area under the curve for this combination was 84.6% (95% CI: 78.8, 90.3; p<0.001).

Discussion

In this study, we observed that NT-ProBNP was a predictor for the presence of CAD and thereby it can be used as a marker in decision making for coronary angiography. Besides, it was also associated with the severity of CAD based on the vessel score and Gensini score. Additionally, combining the positive result of MPI with the level of NT-ProBNP could increase the predictive value for the presence of CAD.

In comparison with other biomarkers such as high sensitive C-reactive protein and Gamma glutamyltransferase, NT-ProBNP proved to be a better predictor for the presence of CAD (10, 11). Several other studies have also confirmed that NT-ProBNP is a useful marker in the prediction and assessment of the severity of CAD. In Radwan et al. study on 132 consecutive patients with acute coronary syndrome, NT-ProBNP level was associated with the number of affected vessels and TIMI flow grade (12). Rajabiani et all suggested that NT-ProBNP was associated with the severity of coronary lesions in angiographyof acute coronary syndrome patients, both with Gensini score and vessel score (13). Similar to our study, Ribiero et al. showed that NT-ProBNP levels above 250pg/ml could independently predict CAD as well as diabetes mellitus, increased monocyte number and fibrinogen plasma concentration (14). Weber et al. study showed that NT-ProBNP level is elevated in patients with stable angina and has a positive correlation with the severity of atherosclerosis (15). All of the findings of the abovementioned studies are in line with our study. However, only

Table 2. Multivariable model of the predictors for positive coronary angiography

Characteristic	Odds ratio	95% confidence interval	p*
NT-ProBNP	1.01	1.00, 1.02	0.008
Age	1.05	1.01, 1.09	0.023
Male gender	1.37	0.60, 3.13	0.455
BMI	0.94	0.86, 1.03	0.162
WBC	1	1.00, 1.00	0.001
Diabetes	2.43	1.08, 5.5	0.031
Definite MPI result	4.3	1.70, 10.97	0.001

BMI: Body mass index; BNP: Brain natriuretic peptide; WBC: White blood cell
* P-value less than 0.05 was considered as statistically significant.

Table 3. Multivariable model of the predictors for positive coronary angiography using the combination of NT-pro BNP and MPI subgroups

Characteristic	Odds ratio	95% confidence interval	p*
Both Negative	Ref	Ref	Ref
Elevated NT-proBNP alone†	2.38	0.48, 12.1	0.295
Definite MPI alone‡	2.89	0.97-8.57	0.056
Both present	14.57	4.28, 49.56	<0.001
Age	1.05	1.01, 1.10	0.012
Male gender	1.3	0.56, 3.01	0.536
BMI	0.95	0.87, 1.04	0.255
Diabetes	2.49	1.09, 5.70	0.03

BMI: Body mass index; BNP: Brain natriuretic peptide; MPI: Myocardial perfusion imaging
* A P-value less than 0.05 was considered as statistically significant.
† Defined as NT-ProBNP<69.5 pg/ml
‡ MPI results definitely showing ischemic heart disease.

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one study did not find NT-ProBNP as an independent predictor of CAD based on exercise tolerance test (16).

In specific groups of patients, NT-ProBNP was also a good predictor for CAD. In diabetic patients, silent CAD is a prevalent condition particularly, and NT-ProBNP has proved itself as a useful biomarker in its diagnosis(17). In another study on asymptomatic hypertensive patients, NT-ProBNP was a marker for preclinical CAD (18).

NT-ProBNP was also helpful in the diagnosis of CAD in unstable angina patients with a normal electrocardiogram, echocardiogram and cardiac enzyme levels (9). These authors also showed a positive correlation between NT-ProBNP levels and Gensini score. In a similar study on stable angina patients, the presence and severity of CAD – based on the computed tomographic angiography score – was significantly associated with the serum level of NT-ProBNP (19). A study in Turkey investigated the association of NT-ProBNP with the extent of the CAD as assessed by SYNTAX score and found that NT-ProBNP could independently predict the burden of CAD in patients with acute coronary syndrome (20).

The incremental predictive effect of NT-proBNP to other non-invasive diagnostic tests has also been investigated in some studies. Wolber et al. could successfully develop a diagnostic score by the use of clinical data, results of exercise tolerance test and BNP to improve the prediction of CAD by non-invasive tests (21). In their study, BNP level≥50 pg/ml could predict the presence of CAD along with other factors in the model (sensitivity=66%, specificity=97%, and diagnostic accuracy=83%). Lee et al. also showed that combining the clinical evidence of CAD based on exercise tolerance test with BNP levels could increase the diagnostic accuracyfor the presence of myocardial ischemia (22). A similar finding was also observed in another study, where the authors could differentiate the severity of CAD based on the changes in BNP before and after the exercise test (23). In a recent study, combination of BNPlevels with Duke clinical score could successfully predict the presence of CAD in patients who underwent computed tomographic angiography (24). The cut-off point of BNP in the abovementioned study was 20.3pg/ml.

Limitations

There are some limitations to our study. First, this was a single center study performed in a university hospital, so the results of our study cannot be easily generalized. It is probable that unforeseen confounders such as socioeconomic status, other morbidities and medications influence our results, which demands further studies. Due to the differences in the level of NT-Pro-BNP in various studies, we presume that its level is center-dependant and reaching a consensus on its cut-off level seems to be difficult. Therefore, performing a multi-center study and finally, a meta-analysis could help to reach a unique cut-off point for NT-ProBNP.

Conclusion

In the present study, we observed that the level of NT-Pro BNP alone and its combination with the results of MPI can significantly predict the presence of CAD and therefore the need for performing coronary angiography. Due to the invasive nature of the coronary angiography, the results of our study can assist the clinician to decide more incisively about the need for performing coronary angiography in an individual patient. Future larger studies can help to approve our findings.

Conflict of Interests

The authors declare that they have no competing interests.

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