

Original Article**Relationship between serum N-terminal Pro Brain Natriuretic Peptide (NT-Pro BNP) level and the severity of coronary artery involvements**

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Abstract

BACKGROUND: Rapid measuring of B-type natriuretic peptide (BNP) in the emergency departments effectively results in evaluating patients with acute cardiac attacks and has appeared to be a useful prognostic marker of cardiovascular risk. A current study came to address the association between plasma N-terminal pro BNP level and severity of coronary vessels' defects based on Gensini score in patients with stable angina pectoris candidate for coronary angiography.

METHODS: The study population consisted of 92 consecutive patients with appearance of stable angina and candidate for coronary angiography. All participants underwent selective left and right coronary angiography. For BNP measurement and just before the catheterization of left coronary, 5cc blood samples were drawn from coronary.

RESULTS: With respect to the role of N terminal pro BNP for predicting severity of CAD based on Gensini scoring, linear regression analysis confirmed that plasma BNP level was a strong predictor for CAD severity ($p = 0.009$) in the presence of study cofounders. A significant correlation was also observed between N terminal pro BNP and left ventricular ejection fraction, so that all patients with left ventricular dysfunction ($EF < 40\%$) had plasma N terminal pro BNP level higher than 100 pg/ml.

CONCLUSIONS: NT-pro BNP can be a good parameter for predicting the severity of coronary vessels' involvement besides other diagnostic tools. In all patients with left ventricular ejection fraction less than 40%, plasma NT-pro BNP level was higher than 100 pg/ml.

KEYWORDS: Coronary Artery Disease, Natriuretic Peptides

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Coronary artery disease (CAD) as the most common form of heart disease is the main cause of mortality and morbidity, particularly in the developed countries.^{1,2} More than 95% of coronary defects are mainly related to coronary artery stenosis caused by atherosclerosis. Coronary artery stenosis leads to reduced myocardial blood supply that can be presented as stable angina, unstable angina, myocardial infarction and heart failure. Benefits of appropriate invasive

approaches for diagnosis of acute coronary syndromes have been proved.¹ In stable angina, chest pain with typical features occurring at predictable levels of exertion, various forms of cardiac stress tests may be used to induce both symptoms and detect changes by way of stress echocardiography or myocardial scintigraphy.¹ If part of the heart seems to receive an insufficient blood supply, coronary angiography may be used to identify stenosis of the coronary arteries for revascularization by

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coronary intervention or bypass surgery. Following appearance of myocardial ischemia, various biomarkers can be released into the blood and elevate the plasma levels.³ Critical role of these markers as promising prognostic indicators for patients with acute coronary syndrome is identified. Brain natriuretic peptide or B-type natriuretic peptide (BNP) is a polypeptide secreted by the ventricles of the heart in response to excessive stretching of heart muscle cells or cardiomyocytes. It has been shown that rapid measuring BNP in the emergency departments effectively results in evaluating patients with acute cardiac attacks and has appeared to be a useful prognostic marker of cardiovascular risk.⁴⁻⁷ In some trials, the role of BNP for predicting severity of CAD as well as its related long-term mortality has been identified. Yeşil et al,⁸ Ndrepepa et al,⁹ and Sahinarslan¹⁰ revealed the beneficial effects of NT pro BNP as a prognostic marker for predicting CAD severity based on angiography findings. Furthermore, predictive role of this peptide for assessing long-term mortality of patients with CAD was demonstrated in researches by Omland et al¹¹ and Märs et al.¹² In addition, relationship between the severity of LAD involvement and plasma NT pro BNP level has been suggested.^{13,14} Current study came to address the association between plasma NT pro BNP level and severity of coronary vessels defects based on Gensini score and its relationship with left ventricular end-diastolic pressure (LVEDP) and systolic heart failure in patients with stable angina pectoris candidate for coronary angiography.

Methods

The study population consisted of 92 consecutive patients with appearance of stable angina candidate for coronary angiography and admitted to angiography units in the city of Kerman. Angina pectoris was defined according to the last definition of Braunwald's textbook of cardiovascular medicine¹³ as a deep poorly localized chest or arm discomfort reproducibly precipitated by physical exertion or emotional stress, and relieved within 5 to 15

minutes, by rest and/or sublingual nitroglycerine. Patients with the signs of myocardial infarction within the last two weeks were excluded. All participants underwent selective left and right coronary angiography. The catheter was introduced percutaneously through the right femoral artery by the Jud-Kinz technique. Pigtail catheter was also used for measuring LVEDP, and left ventricular injection was performed for those with LVEDP < 25 mmHg or without evidences of left main artery. The Ethical Committee of Kerman University of Medical Sciences approved the study and a written consent for the participation in the scientific study was obtained from all patients.

For BNP measurement and just before the catheterization of left coronary, 5 cc blood samples were drawn from coronary into a chilled ethylenediaminetetraacetic acid Vacutainer test tube. Samples were placed immediately on ice and plasma separation was performed at -4°C. Plasma samples were frozen at -80°C until assay. Serum NT pro BNP level was also quantified using an electrochemiluminescence immunoassay (ECLIA) method (Nt pro-BNP, Roche, Germany) with a Roche modular analytics E170 immunoassay analyzer. The participants underwent coronary angiography and evidences of coronary vessels involvement were interpreted by the two attending cardiologists blinded to subject data. Severity of CAD was determined based on the Gensini score. The patients underwent ventriculography and echocardiography (if LVEDP > 25 mmHg) for measuring ejection fraction.

Continuous data were shown as mean and standard deviation (SD) and categorical variables were presented as percentages. Multi-variable linear logistic regression analysis were used for determining relationships between Serum NT pro BNP level and Gensini score as dependent variable in the presence of co-founders such as gender, age and history of CAD risk factors. P values of 0.05 or less were considered statistically significant. All the sta-

tistical analyses were performed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

In the present cross-sectional study on 92 participants candidate for coronary angiography, the mean age of patients was 54.73 ± 8.24 ; 27.2% were women and 72.8% were men with the mean ages of 56.60 ± 8.80 and 45.03 ± 8.24 , respectively. Regarding prevalence of CAD risk factors, the most common risk factors were dyslipidemia, followed by opium addiction and hypertension (Table 1). Moreover, only 10 patients (10.7%) had LV ejection fraction less than 40.0%.

Table 1. Baseline characteristics and medical history in study population

Male gender	67 (72.8)
Age (year)	54.73 ± 8.24
Diabetes mellitus	22 (24.4)
Hypertension	32 (35.6)
Dyslipidemia	45 (51.1)
Family history of CAD	27 (32.1)
Cigarette smoking	27 (30.7)
Opium addiction	40 (45.5)
LVEDP	16.35 ± 7.31
Gensini score	40.65 ± 33.46
N Terminal pro BNP	394.63 ± 602.92

Data are presented as mean \pm SD or number (%)

With respect to the role of N terminal pro BNP for predicting severity of CAD based on Gensini scoring, linear regression analysis confirmed that plasma BNP level was a strong predictor for CAD severity ($p = 0.009$) in the presence of study cofounders (Table 2). Furthermore, regarding relationships between N terminal pro BNP and LVEDP, regression analysis could not demonstrate the significance of this relationship (Table 3).

A significant correlation was observed between N terminal pro BNP and left ventricular ejection fraction so that all patients with left ventricular dysfunction ($EF < 40\%$) had plasma N terminal pro BNP level higher than 100 pg/ml (Figure 1).

Table 2. The role of N terminal pro BNP for predicting CAD severity based on Gensini score in a linear regression model

Item	Standardized beta	P value
N terminal pro BNP	1.001	0.009
Male gender	1.253	0.420
Age (year)	1.009	0.529
Diabetes mellitus	1.050	0.841
Hypertension	1.565	0.070
Dyslipidemia	1.259	0.879
Family history of CAD	1.550	0.071
Cigarette smoking	1.040	0.875
Opium addiction	1.521	0.078

Table 3. The role of N terminal pro BNP for predicting LVEDP in a linear regression model

Item	Standardized beta	P value
N terminal pro BNP	1.000	0.467
Male gender	1.050	0.722
Age (year)	1.002	0.825
Diabetes mellitus	1.063	0.655
Hypertension	1.044	0.720
Dyslipidemia	1.062	0.562
Family history of CAD	1.065	0.635
Cigarette smoking	1.200	0.184
Opium addiction	1.181	0.189

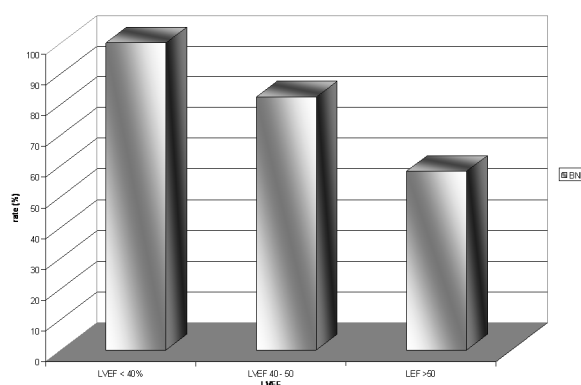


Figure 1. Relationship between left ventricular ejection fraction and plasma BNP level

Discussion

A current study assessed the predictive role of N terminal pro BNP for determining severity of coronary artery stenosis (based on coronary angiography findings), LVEDP and left ventricular ejection fraction in the presence of other general risk factors for CAD. The results of the present study showed a strong independently causative relationship between N

terminal pro BNP and the severity of coronary stenosis in multivariable model. Also, plasma pro BNP level was significantly higher than 100 pg/ml in all study patients with left ventricular ejection fraction less than 40%. However, we found no correlation between this chemical biomarker and LVEDP. Therefore, it is suggested that the measurement of N terminal pro BNP can be an acceptable marker for prediction of the severity of coronary stenosis as well as the heart failure. In fact, elevated BNP may be associated with a greater severity and extent of myocardial ischemic territory and may partly explain the association between elevated BNP and adverse outcomes of ischemic heart diseases. Recent studies focused on association between the severity of CAD and N terminal pro BNP level. In a similar study by Weber et al serum BNP level could effectively predict coronary involvement based on the number of defected coronary vessels in patients with angina pectoris.¹ Similar finding was observed in another study by Palazzuoli et al on subjects with non-ST segment elevation myocardial infarction.¹⁴ They demonstrated that BNP was also associated with a larger extent and greater severity of myocardial ischemia. Also, Sadanandan et al¹⁵ showed that the patients with BNP > 80 pg/ml had tighter culprit vessel stenosis on quantitative coronary angiography and a higher culprit vessel compared to the cases with lower plasma BNP level. Furthermore, Hamishayev et al found a significant correlation between NT-pro BNP levels in unstable angina and NT-pro BNP levels on admission in the patients with ST segment elevation MI with Gensini score and number of affected vessels.¹⁶ Another study in Japan confirmed usefulness of this biomarker for predicting the extent of CAD with considerable discrimination power.¹⁷ In contrast, in a logistic regression analysis by Nishikimi et al, it was revealed that N-terminal pro ANP, but not BNP, was independently associated with coronary artery stenosis after adjusting for clinical and demographic variables, however, the sensitivity, specificity, and positive and negative predictive values of each peptide

were not sufficiently high to be used for prediction. In their study, the patients with no evidences of CAD were compared to those with CAD and the severity of coronary defects was not quantitatively determined.⁴ In general, according to the results of the present study and previous similar studies, it seems that the NT-pro BNP is an appropriate marker for determining defected coronary vessels and higher levels of this marker can be probably associated with more severe coronary artery involvements.

In our study, there was no significant correlation between NT-pro BNP level and LVEDP adjusted for study cofounders. Similar previous studies had different results. In a study by Maeda, plasma BNP was known as a predictor of high LVEDP, however this result was shown only in those with symptomatic left ventricular dysfunction.¹⁸ This positive relationship between BNP and LVEDP in heart failure patients was also confirmed by other studies.^{5,19} Besides, other studies could not indicate this relationship adjusting other patients' characteristics as confounders.²⁰ Most of the recent studies were focused on patients with heart failure, whereas the sample of the present study mainly included those with stable angina candidate for angiography and therefore differences in study findings can be due to this subject.

Another important finding in the present study was direct association between NT-pro BNP level and ejection fraction. As shown in figure 1, in all cases with ejection fraction less than 40%, serum NT-pro BNP level was higher than 100 pg/ml, while most of the patients with normal ventricular function had NT-pro BNP less than 100 pg/ml. This result was also supported by other studies. According to findings of Emdin et al study, NT-pro BNP had an acceptable accuracy for identifying heart failure due to left ventricular dysfunction.²¹ Also, in Grewal study, BNP was identified as the strongest predictor of diastolic dysfunction as determined by Doppler-echocardiography.²²

In the present study, other known CAD risk factors were not associated with Gensini score.

Appearance of these factors may be only due to the CAD, but not to be risk profiles for the severity of coronary stenosis. Additionally, the main goal of this study was to determine role of BNP for prognosticating coronary stenosis. Therefore, it seems that the roles of these factors should be assessed with a greater sample size and a new study setting and further studies for determining prognostic value of these risk factors are recommended.

Conclusions

In summary, NT-pro BNP can be a good parameter for predicting the severity of coronary vessels involvement besides other diagnostic

tools. In all patients with left ventricular ejection fraction less than 40%, plasma NT-pro BNP level was higher than 100 pg/ml, but there was no significant correlation between NT-pro BNP and LVEDP in patients with confirmed CAD.

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Conflict of Interests

Authors have no conflict of interests.

Authors' Contributions

VS, MM and BSA carried out the design and coordinated the study, participated in most of the experiments and prepared the manuscript. HN and RMA provided assistance in the design of the study, coordinated and carried out all the experiments and participated in manuscript preparation. AS provided assistance for statistical analysis. HR managed and structured all steps of the study. All authors have read and approved the content of the manuscript.

References

1. Weber M, Dill T, Arnold R, Rau M, Ekinici O, Müller KD, et al. N-terminal B-type natriuretic peptide predicts extent of coronary artery disease and ischemia in patients with stable angina pectoris. *Am Heart J* 2004; 148(4): 612-20.
2. Bogavac-Stanojević N, Jelić-Ivanović Z, Spasojević-Kalimanovska V, Spasić S, Kalimanovska-Ostrić D. Lipid and inflammatory markers for the prediction of coronary artery disease: a multi-marker approach. *Clin Biochem* 2007; 40(13-14): 1000-6.
3. Manenti ER, Bodanese LC, Camay SA, Polanczyk CA. Prognostic value of serum biomarkers in association with TIMI risk score for acute coronary syndromes. *Clin Cardiol* 2006; 29(9): 405-10.
4. Nishikimi T, Mori Y, Ishimura K, Tadokoro K, Yagi H, Yabe A, et al. Association of plasma atrial natriuretic peptide, N-terminal proatrial natriuretic peptide, and brain natriuretic peptide levels with coronary artery stenosis in patients with normal left ventricular systolic function. *Am J Med* 2004; 116(8): 517-23.
5. Scardovi A, Coletta C, Aspromonte N, Sestili A, Di Giacomo T, Romano M, et al. Can BNP be a useful tool for predicting severe diastolic dysfunction in patients with chronic heart failure? *Eur J Echocardiography* 2003; 4(Suppl 1): S9.
6. Richards M, Nicholls MG, Espiner EA, Lainchbury JG, Troughton RW, Elliott J, et al. Comparison of B-type natriuretic peptides for assessment of cardiac function and prognosis in stable ischemic heart disease. *J Am Coll Cardiol* 2006; 47(1): 52-60.
7. Ogawa A, Seino Y, Yamashita T, Ogata K, Takano T. Difference in elevation of N-terminal pro-BNP and conventional cardiac markers between patients with ST elevation vs. non-ST elevation acute coronary syndrome. *Circ J* 2006; 70(11): 1372-8.
8. Yeşil M, Postacı N, Arikan E, Ceylan O, Bayata S, Köseoğlu M. Can we predict the severity of coronary artery disease in patients with stable angina using NT-ProBNP? *Anadolu Kardiyol Derg* 2006; 6(3): 235-8.

9. Ndrepepa G, Braun S, Mehilli J, von Beckerath N, Vogt W, Schömig A, et al. Plasma levels of N-terminal pro-brain natriuretic peptide in patients with coronary artery disease and relation to clinical presentation, angiographic severity, and left ventricular ejection fraction. *Am J Cardiol* 2005; 95(5): 553-7.
10. Sahinarslan A, Cengel A, Okay K, Yazici HU, Elbey S, Cemri M, et al. B-type natriuretic peptide and extent of lesion on coronary angiography in stable coronary artery disease. *Coron Artery Dis* 2005; 16(4): 225-9.
11. Omland T, Persson A, Ng L, O'Brien R, Karlsson T, Herlitz J, et al. N-terminal pro-B-type natriuretic peptide and long-term mortality in acute coronary syndromes. *Circulation* 2002; 106(23): 2913-8.
12. März W, Tiran B, Seelhorst U, Wellnitz B, Bauersachs J, Winkelmann BR, et al. N-terminal pro-B-type natriuretic peptide predicts total and cardiovascular mortality in individuals with or without stable coronary artery disease: the Ludwigshafen Risk and Cardiovascular Health Study. *Clin Chem* 2007; 53(6): 1075-83.
13. Libby P, Bonow RO, Mann DL, Zipes DP. Braunwald's heart disease: a textbook of cardiovascular medicine. 8th ed. New York: WB. Saunders; 2007.
14. Palazzuoli A, Gennari L, Calabria P, Quatrini I, Vecchiato L, De Paola V, et al. Relation of plasma brain natriuretic peptide levels in non-ST-elevation coronary disease and preserved systolic function to number of narrowed coronary arteries. *Am J Cardiol* 2005; 96(12): 1705-10.
15. Sadanandan S, Cannon CP, Chekuri K, Murphy SA, Dibattiste PM, Morrow DA, et al. Association of elevated B-type natriuretic peptide levels with angiographic findings among patients with unstable angina and non-ST-segment elevation myocardial infarction. *J Am Coll Cardiol* 2004; 44(3): 564-8.
16. Hamishayev JZ. Can NT-pro BNP together with Doppler tissue imaging predict severity of coronary artery disease in patients with acute coronary syndrome? *Atherosclerosis Suppl* 2008; 9(1): 174-5.
17. Niizuma S, Iwanaga Y, Yahata T, Goto Y, Kita T, Miyazaki S, et al. Plasma B-type natriuretic peptide levels reflect the presence and severity of stable coronary artery disease in chronic haemodialysis patients. *Nephrol Dial Transplant* 2009; 24(2): 597-603.
18. Maeda K, Tsutamoto T, Wada A, Hisanaga T, Kinoshita M. Plasma brain natriuretic peptide as a biochemical marker of high left ventricular end-diastolic pressure in patients with symptomatic left ventricular dysfunction. *Am Heart J* 1998; 135(5 Pt 1): 825-32.
19. Tanaka T, Hasegawa K, Fujita M, Tamaki SI, Yamazato A, Kihara Y, et al. Marked elevation of brain natriuretic peptide levels in pericardial fluid is closely associated with left ventricular dysfunction. *J Am Coll Cardiol* 1998; 31(2): 399-403.
20. Sakata K, Iida K, Mochiduki N, Nakaya Y. Brain natriuretic peptide (BNP) level is closely related to the extent of left ventricular sympathetic overactivity in chronic ischemic heart failure. *Intern Med* 2009; 48(6): 393-400.
21. Emdin M, Passino C, Prontera C, Fontana M, Poletti R, Gabutti A, et al. Comparison of brain natriuretic peptide (BNP) and amino-terminal ProBNP for early diagnosis of heart failure. *Clin Chem* 2007; 53(7): 1289-97.
22. Grewal J, McKelvie R, Lonn E, Tait P, Carlsson J, Gianni M, et al. BNP and NT-proBNP predict echocardiographic severity of diastolic dysfunction. *Eur J Heart Fail* 2008; 10(3): 252-9.