

Can we predict the severity of coronary artery disease in patients with stable angina using NT-ProBNP?

Stabil angina pektorisli hastalarda NT-ProBNP'yi kullanarak koroner arter hastalığı ciddiyetini öngörebilir miyiz?

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ABSTRACT

Objective: We aimed to investigate the value of N-terminal pro-Brain Natriuretic Peptide (NT-proBNP) in combination with tissue Doppler imaging (TDI) to predict the presence of significant coronary artery (CAD) in patients with conventionally normal systolic and diastolic function .

Methods: Plasma NT-proBNP concentrations were measured in 87 patients who had been referred to coronary angiography with stable anginal symptoms, and preserved systolic and diastolic LV function in conventional echocardiography. Regional diastolic function was additionally assessed by TDI in all patients. Patients were then divided into 2 groups according to having normal or abnormal diastolic function with TDI. Group 1 had preserved diastolic function with conventional and TDI methods. Group 2 had conventionally normal function and abnormal regional function with TDI. Groups were divided into 2 subgroups according to the cut-off NT-proBNP value of 100pg/ml. Coronary artery disease was classified as 0 (absence of >70% diameter stenosis in any coronary artery), 1, 2 or 3 vessel disease (with lesions >70%).

Results: The NT-proBNP levels were positively correlated with the number of coronary vessels involved. There was statistically significant difference between 0-2, 0-3, 1-3 vessels involvement, but no significant difference between 0-1, 1-2, 2-3 vessels involvement. In group 1 all patients with plasma NT-proBNP levels >100 pg/ml had severe CAD (p=0.003). But in group 2 only 60% of patients with NT-proBNP>100 pg/ml had severe CAD.

Conclusion: In patients with stable angina who have normal systolic and diastolic function, NT-proBNP is useful to predict the angiographic severity of CAD. In patients with unimpaired regional diastolic function, NT-proBNP may be valuable to predict the presence of severe CAD in stable angina. (*Anadolu Kardiyol Derg 2006; 6: 235-8*)

Key words: BNP, coronary artery disease, tissue Doppler imaging, stable angina pectoris

ÖZET

Amaç: Konvansiyonel olarak sistolik ve diyastolik fonksiyonları normal olan olgularda doku Doppler (TDI) tetkikinin sonuçlarına göre koroner arter hastalığı (KAH) mevcudiyetini öngörmeye N-terminal Pro-Beyin Natriüretik Peptid'in (NT-proBNP) değerini araştırmayı amaçladık.

Yöntemler: Koroner anjiyografi için başvuran stabil anginalı, sistolik fonksiyonu korunmuş ve konvansiyonel yöntemle normal diyastolik işleve sahip 87 hastada plazma NT-proBNP düzeyleri ölçüldü. Ayrıca bütün hastalarda doku Doppler (TDI) kullanılarak bölgesel diyastolik disfonksiyon araştırıldı. Hastalar TDI sonuçlarına göre iki gruba ayrıldı. Grup 1 konvansiyonel yöntemle ve TDI ile normal diyastolik fonksiyona sahipti. Grup 2 konvansiyonel olarak normal diyastolik fonksiyona sahipken TDI ile bölgesel diyastolik disfonksiyon tespit edilen hastaları kapsıyordu. Gruplar NT-proBNP "cut-off" değeri 100 pg/ml kabul edilerek kendi içinde ikiye ayrıldı.

Bulgular: Plazma NT-proBNP seviyesi hastalıklı damar sayısı ile pozitif olarak korele bulundu. Plazma NT-ProBNP seviyeleri açısından 0-2, 0-3, 1-3 damar hastalığı arasında anlamlı fark bulundu, fakat 0-1, 1-2, 2-3 damar hastalığında anlamlı fark bulunmadı. Grup 1'de plazma NT-proBNP seviyeleri > 100 pg/ml bütün hastalarda ciddi koroner arter hastalığı (KAH) tespit edilirken (p=0.003) grup 2'de NT-proBNP değeri > 100 pg/ml olan hastaların %60'ında ciddi KAH tespit edildi.

Sonuçlar: Stabil anginalı, sistolik ve diyastolik fonksiyonu korunmuş hastalarda NT-proBNP KAH ciddiyetini saptamada yararlıdır. Doku Doppler ile bölgesel diyastolik disfonksiyonu olan gruba kıyasla olmayanlarda NT-proBNP'nin KAH ciddiyetini öngörücü değeri daha fazladır. (*Anadolu Kardiyol Derg 2006; 6: 235-8*)

Anahtar kelimeler: BNP, koroner arter hastalığı, doku Doppler görüntüleme, stabil angina pektoris

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Introduction

The natriuretic peptides, atrial natriuretic peptide (ANP) and especially brain natriuretic peptide (BNP) have been promising markers for biochemical measurement of cardiac performance. They are often increased in patients with heart failure, and BNP has been studied extensively as a marker of asymptomatic LV dysfunction or early heart failure. Brain natriuretic peptide is synthesized by the ventricles and released to the circulation in response to ventricular stretch as a prohormone, proBNP, which is immediately split in the physiologically active form BNP, and the inactive form N-Terminal pro-BNP (NT-proBNP). Both BNP and NT-proBNP have been shown to identify patients with congestive heart failure (CHF). In general, a BNP level less than 100 pg/mL has strong negative predictive value for CHF (1).

On the other hand, BNP has been shown to be released in response to cardiac ischemia. Transient myocardial ischemia induced by exercise testing was associated with an immediate increase in circulating BNP levels, and the magnitude of this increase was proportional to the severity of ischemia (2). Elevated levels of BNP are independently associated with inducible ischemia in patients with stable coronary artery disease (CAD), particularly among those with a history of myocardial infarction (3). Additionally, NT-proBNP is a powerful indicator of long-term mortality in patients with acute coronary syndrome and provides prognostic information above and beyond conventional risk markers (4). There is also evidence that BNP reflects the remodeling process in hypertension. Plasma BNP levels in patients with left ventricular hypertrophy and echocardiographic signs of diastolic dysfunction were greater than those in patients without hypertrophy and normal diastolic parameters on echocardiography (5). Other conditions with elevated NT-proBNP levels are acute pulmonary embolism (6), atrial fibrillation (7) and left ventricular hypertrophy in end-stage renal disease independent of CHF (8).

As our knowledge on the implications of BNP in different patient groups, particularly ischemic syndromes is still growing, we sought to investigate whether there is an association between NT-proBNP levels and the extent of significant stenosis in the coronary tree. Our target population was patients with stable coronary symptoms or evidence for ischemia who were referred to coronary angiography. Regional diastolic function of these patients were also determined echocardiographically in combination with NT-proBNP levels in order to predict the presence of severe CAD more accurately before proceeding with the invasive imaging procedure.

Methods

Eighty-seven patients (62 men, mean age 57.0 ± 8.5 years) with symptoms of stable angina pectoris, or objective evidence of ischemia (positive exercise electrocardiogram or nuclear test) and normal conventional systolic and diastolic left ventricular (LV) function were included. All patients had class 2 or 3 angina according to Canadian classification and underwent coronary angiography. Blood samples were obtained for NT-proBNP from all patients early morning on the day of angiography. Elecsys NT-

proBNP kits (Roche diagnostics, Mannheim, Germany) were used for the assay. The lower limit of detection was 5 pg/ml. Levels above 100 pg/ml were considered to be increased. Standard coronary angiography with left ventriculography was performed. Two experienced cardiologists who were blinded to the NT-proBNP levels evaluated the angiograms. Diameter stenosis $\geq 70\%$ with quantitative angiography was accepted as significant. Regardless of the number of significant lesions on each vessel, patients were classified as having 0, 1, 2, 3 vessel disease.

Patients were evaluated echocardiographically the day before angiography. Echocardiography was performed by a single operator using a G.E. Vivid 3 imaging system. Transmitral flow velocities were obtained by placing the cursor at the level of mitral leaflet tips at diastole. Tissue Doppler patterns were recorded in all patients at rest from the apical 4-chamber view. Measurements were made by placing the sample volume on the mitral annulus at lateral and medial sites, and on mid-lateral and mid-septal myocardium. Color flow Doppler recordings from the parasternal, apical four-chamber and the apical long-axis views enabled semi-quantitative assessment of the severity of mitral, tricuspid and aortic regurgitation. Echocardiographically 32 of 87 patients showed normal transmitral E and A velocities, and normal tissue Doppler (TDI) patterns which indicate 'totally' normal diastolic function (Group 1). On the other hand, the rest 55 of 87 patients showed normal transmitral flow velocities hence normal global diastolic function, but showed regional diastolic dysfunction with TDI in at least one segment (Group 2).

Statistical Analysis: Statistical assessment was made by using SPSS 14.0 for Windows. Continuous data was expressed as median, minimum, maximum and interquartile ranges (IQR). Categorical parameters were given as number and percentage. Comparisons of data between the study groups were assessed by Kruskal Wallis, Mann Whitney U, Chi-square tests and ROC (receiver operator curve) curve was drawn. P value less than 0.05 was accepted as significant.

Results

There was no statistically significant difference between the NT-proBNP values of men and women ($p=0.46$). Median values for men and women were 89.9 and 79.7 where interquartile ranges were 105.6 pg/ml and 142.61 pg/ml respectively (Fig 1). In the whole study population, NT-ProBNP levels were positively correlated with the number of vessels involved ($p=0.001$). The area under the receiver operating characteristic (ROC) curve was 0.71 (95% CI 0.60-0.82) ($p=0.001$). Median, (minimum-maximum) values and IQR of NT-proBNP for 0 vessel disease are 70.16 pg/ml (12.9-494.7 pg/ml) IQR=79.1 pg/ml, for 1 vessel disease - 89.12 pg/ml (21.2-311.5 pg/ml) IQR=124.0 pg/ml, for 2 vessel disease - 150.85 pg/ml (51.76-769.2 pg/ml) IQR=79.9 pg/ml and for 3 vessel disease - 278.8 pg/ml (76.48-662.2 pg/ml) IQR=291.98 pg/ml, respectively (Fig 2). There were statistically significant differences between 0-2 vessel ($p=0.003$), 0-3 vessel ($p=0.000$), 1-3 vessel ($p=0.012$) diseases, but no significant differences between 0-1 vessel ($p=0.22$), 1-2 vessel ($p=0.121$) and 2-3 vessel ($p=0.19$) involvement (Fig 2). The NT-ProBNP was <100 pg/ml in the majority ($n=36$, 72%) of 50 patients with normal or noncritical lesions ($p < 0.001$).

On the other hand, NT-ProBNP was >100 pg/ml in the majority (n=10, 83%) of 12 patients with two vessel (p=0.021), and 7 (87%) of 8 patients with 3 vessel disease (p=0.034). The NT-ProBNP values did not reach adequate strength to indicate 1 vessel disease (p=0.637) (Table 1)

Subgroup analyses were also done according to TDI results and CAD. In group 1 (n=32) all patients with NT-proBNP levels >100 pg/ml (7/7) had severe CAD (p=0.003). But in group 2 (n=55) only 15 of 25 pts (60%) with NT-proBNP>100 pg/ml had severe CAD (p=0.125) (Table 2). A cut-off value of 100 pg/ml for NT-proBNP has a modest positive and better negative predictive value (%63 and %73 respectively) for the prediction of coronary artery disease. Also for this cut-off value, sensitivity of NT-pro BNP to detect CAD is 65% while specificity is 72%. In an effort to increase specificity, at a higher calculated cut-off level of 120 pg/ml, specificity slightly improved to 74% at the cost of significant loss in sensitivity (54%).

Discussion

In the present study, in patients with normal coronaries or 1 vessel disease, median NT-proBNP levels were under the cut-off value of 100 pg/ml. In spite of the fact that none of these patients

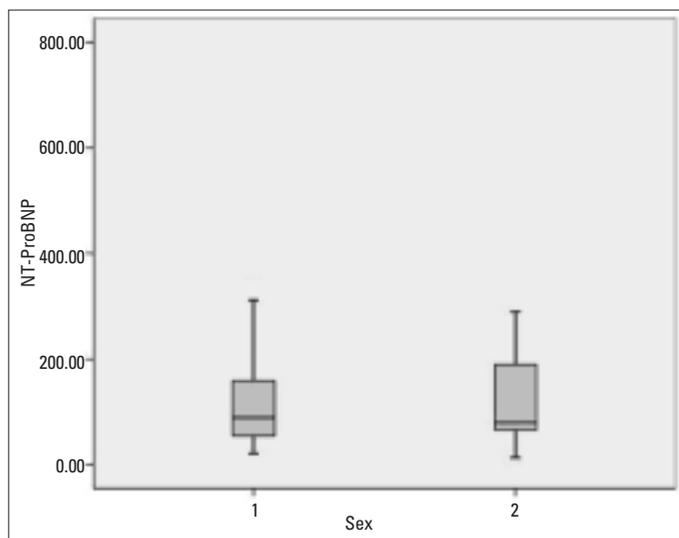


Figure 1. The NT-ProBNP values in men and women (1=men, 2=women). Median values for men and women were 89.9 pg/ml and 79.7 pg/ml, where interquartile ranges were 105.6 pg/ml and 142.61 pg/ml, respectively
NT-ProBNP- N-terminal pro-Brain Natriuretic Peptide

Table 1. Correlation of NT-proBNP with number of diseased vessels

Number of vessels involved	NT-proBNP		p
	≤ 100 pg/ml n (%)	> 100 pg/ml n (%)	
0	36 (72. 0)	14 (28)	<0. 001*
1	10 (20. 0)	7 (21. 6)	0. 637
2	2 (16. 6)	10 (83. 3)	0. 021*
3	1 (12.5)	7 (87.5)	0. 034*

*P<0.05 is statistically significant
NT-ProBNP- N-terminal pro-Brain Natriuretic Peptide

had heart failure, NT-proBNP showed direct correlation with severe CAD and the number of vessels involved, indicating that NT-proBNP is directly related with the extent of cardiac ischemia. Another support for this was the statistically significant difference between 0-2, 0-3, 1-3 vessel disease. The association between the extent of ischemia and NT-proBNP levels may help us explain the prognostic importance of natriuretic peptides. One explanation may be that bouts of ischemia cause change in regional wall stress and probably trigger the release of NT-proBNP in direct relation to extent of affected territory (9).

Hence, the findings of this study support previous reports which suggest that elevated levels of BNP are associated with coronary heart disease (2, 4, 10) although our major limitation was the relatively small number of patients with CAD (37 of 87 patients, 42%)

In a larger study by Kragelund et. al.(10) the investigators reported that NT-proBNP predicted the severity of angiographic coronary disease and myocardial area at risk independently of traditional risk factors, and in consistent with our data, the ability of NT-proBNP to identify clinically significant angiographic lesions was modest if not poor. Our study confirms and extends this information by using an additional parameter of regional diastolic function with tissue Doppler imaging despite a smaller number of patients.

All of our patients had normal systolic function with no abnormal segmental wall motion. Their diastolic functions were also reported normal as indicated by normal transmitral velocity patterns (E>A). But 55 of 87 patients who were evaluated with TDI had regional diastolic dysfunction at rest. We combined regional diastolic function by TDI and NT-proBNP to predict CAD. Previous studies showed that TDI at rest alone was not adequate to predict the presence of severe CAD. Pharmacological stress with dobutamine was used in most of these studies. Changes that have been documented during ischemia include reduced and delayed peak systolic velocities, reduced myocardial velocity gradients, and impaired diastolic relaxation (11).

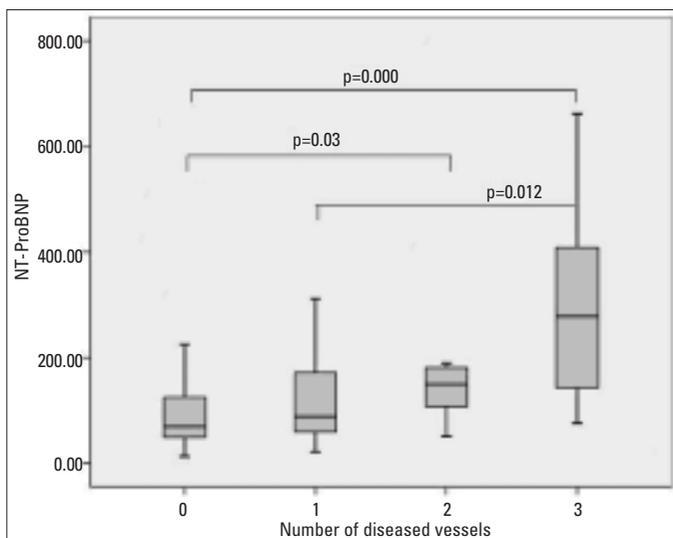


Figure 2. Box plots according to the number of coronary vessels involved. Statistically significant p values are also shown.

NT-ProBNP - N-terminal pro-Brain Natriuretic Peptide

Table 2. Relationship between NT-proBNP and CAD in patients with and without diastolic dysfunction by TDI

Coronary Angiogram	Group 1 (TDI Normal)		Group 2 (TDI Abnormal)	
	NT-proBNP ≤ 100 pg/ml	NT-proBNP > 100 pg/ml	NT-proBNP ≤ 100 pg/ml	NT-proBNP > 100 pg/ml
	n (%)	n (%)	n (%)	n (%)
Normal	20 (80)	0	21 (70)	10 (40)
≥1 vessel disease	5 (20)	7 (100)*	9 (30)	15(60)
TOTAL	25 (100)	7 (100)	30 (100)	25 (100)

*- differences are significant-p<0.003, CAD- coronary artery disease,
NT-ProBNP-N- terminal Pro-Brain Natriuretic Peptide, TDI- tissue Doppler imaging

In patients with normal diastolic function, NT-proBNP values were low in patients with normal coronary arteries, whereas it was significantly high in those with severe CAD ($p = 0.003$). It seems that in the presence of normal diastolic function by TDI, the finding of high NT-proBNP values may strongly suggest the presence of CAD. On the other hand, in patients with diastolic dysfunction (Group 2), NT-proBNP did not differ significantly in patients with and without CAD ($p = 0.125$). One possible explanation is that NT-proBNP values may have been affected by diastolic dysfunction due to causes other than ischemia in that subset of patients.

In an other large prospective study by Schnabel et al. (12) demonstrated high baseline BNP values (cut-off value of 100 pg/ml)- independent of LV systolic function- increased the risk of future myocardial infarction and death in stable CAD patients. Until its pathophysiological background is entirely understood, this and similar studies provide promise for risk stratification in stable CAD which may improve prognosis assessment.

Lastly, among patients with unstable angina/non ST elevation myocardial infarction, which were not included in this study, elevated BNP levels are associated with tighter culprit stenosis, higher TIMI (Thrombolysis in Myocardial Infarction) frame count, and left anterior descending coronary artery (LAD) involvement. These findings also suggest that elevated BNP may be associated with a greater severity and extent of myocardial ischemic territory during the index event and may partly explain the association between elevated BNP and adverse outcomes (13).

Conclusion: In patients with stable angina who have normal systolic and diastolic function, NT-proBNP is useful to predict the angiographic severity of CAD. In patients with unimpaired regional diastolic function, NT-proBNP may be valuable to predict the presence of severe CAD in stable angina.

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