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Association Between Serum NT-proBNP and Coronary Artery Ectasia

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ABSTRACT

Objective: Coronary artery ectasia is defined as the dilation of at least one coronary artery 1.5 times or more than the adjacent normal coronary artery segment. Coronary ectasias, the most common cause of which is atherosclerosis, are mostly seen together with coronary artery disease (CAD), but can also be detected in isolation. The relationship between coronary artery ectasia (CAE) and N-terminal pro B-type natriuretic peptide (NT-pro BNP) is unknown. In this study, it was aimed to investigate whether there is a relationship between NT-proBNP level and CAE.

Material and Methods: A total of 126 patients who underwent coronary angiography between January 2018 and August 2019 and had NT-proBNP value in their blood samples were included in the study. Sixty-six patients with coronary ectasia, coronary ectasia group and 60 age-sex matched patients without coronary ectasia were included in the study as the control group. Patients with acute coronary syndrome, significant coronary artery stenosis, history of coronary intervention, mild or significant valve dysfunction, heart failure,chronic kidney or liver disease, any inflammatory or autoimmune disease, malignancy, anemia and patients without NT-proBNP value were excluded from study.

Results: Mean age of the study population was 60.2 ± 8.8 years (34.1%, n= 43, female). Mean systolic, diastolic blood pressures and smoking were significantly higher in the CAE group compared to the control subjects. Mean NT-proBNP levels were statistically significantly higher in the CAE patients than the control subjects (111.32 ± 17 ng/ml vs. 98.89 ± 8.6 ng/ml, p< 0.001). In receiver operating characteristic (ROC) analysis, a cut-off value of NT-proBNP ≥95 ng/ml had 85.3% sensitivity and 58.8% specificity for predicting CAE (area under the curve: 0.772, p< 0.001). Multivariate analysis showed that smoking (OR= 1.799; p= 0.024) and NT-ProBNP (OR= 1.094; p< 0.001) were independently associated with CAE.

Conclusion: Coronary ectasia may cause angina pectoris as a result of turbulent flow and microvascular perfusion impairment. Relative increase of NT-proBNP may be associated with CAE. In this study, it was determined that serum NT-proBNP levels were increased significantly in patients with CAE and increased serum NT-proBNP levels were independently associated with CAE.

Keywords: N-terminal pro b-type natriuretic peptide, coronary artery ectasia, myocardial ischemia

ÖZ

Serum NT-proBNP ve Koroner Arter Ektazisi Arasındaki İlişki

Giriş: Koroner arter ektazisi, en az bir koroner arterin komşu normal koroner arter segmentinin 1.5 katı veya daha fazla genişlemesi olarak tanımlanmıştır. En sık nedeni ateroskleroz olan koroner ektaziler büyük bir oranda koroner arter hastalığı (KAH) ile birlikte görülmekle beraber izole olarak da saptanabilmektedirler. Koroner arter ektazisi (KAE) ile N-terminal pro b-tipi natriüretik peptit (NT-proBNP) arasındaki ilişkili bilinmemektedir. Bu çalışmada NT-proBNP düzeyi ile KAE arasında bir ilişki olup olmadığını araştırmayı amaçladık.

Gereç ve Yöntemler: Ocak 2018 ve Ağustos 2019 tarihleri arasında koroner anjiyografi yapılan ve kan örneklerinde NT-proBNP değeri olan 126 hasta çalışmaya dahil edildi. Koroner ektazisi bulunan 66 hasta, koroner ektazi grubu ve koroner ektazisi olmayan, yaş-cinsiyet uyumlu 60 hasta, kontrol grubu olarak çalışmaya dahil edildi. Akut koroner sendrom, belirgin koroner arter darlığı, koroner girişim öyküsü, hafif veya önemli kapak disfonksiyonu, kalp yetmezliği, kronik böbrek veya karaciğer hastalığı, herhangi bir enflamatuvar, otoimmün hastalık, malignite, anemi olan hastalar ve NT-proBNP değeri olmayan hastalar çalışma dışı bırakıldı.

Bulgular: Çalışma popülasyonunun ortalama yaşı 60.2 ± 8.8 yıl (%34.1, n= 43, kadın) idi. Ortalama sistolik, diyastolik kan basınçları sigara içiciliği KAE grubunda kontrol grubuna göre anlamlı derecede yüksekti. Ortalama NT-proBNP seviyeleri KAE hastalarında kontrol grubuna göre istatistiksel olarak anlamlı derecede yüksekti (111.32 ± 17 ng/ml'ye karşı 98.89 ± 8.6 ng/ml, p< 0.001). ROC analizinde Pro-BNP ≥95 ng/ml üzeri değerler KAE'yi tahmin etmede %85.3 duyarlılık ve %58.8 özgüllüğe sahipti (eğri altındaki alan: 0.772, p< 0.001). Çok değişkenli analizde de sigara içiciliği (OR= 1.799; p= 0.024) ve NT-proBNP (OR= 1.094; p< 0.001) KAE ile bağımsız olarak ilişkili saptanmıştır.

Sonuç: Koroner ektazi, türbülan akım ve mikrovasküler perfüzyon bozukluğu sonucunda anjina pektorise neden olabilir. Rölatif NT-proBNP artışı KAE'si ile ilişkili olabilir. Bu çalışmada, KAE hastalarında serum NT-proBNP seviyelerinin anlamlı şekilde arttığını ve artmış serum NT-proBNP seviyelerinin KAE ile bağımsız olarak ilişkili olduğu belirlenmiştir.

Anahtar Kelimeler: N-terminal pro b-tipi natriüretik peptit, koroner arter ektazi, miyokardiyal iskemi

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INTRODUCTION

Coronary artery ectasia (CAE) is characterized by localized or diffuse dilatation of the coronary arteries. CAE is determined as the ratio of the dilated segment of coronary artery to the adjacent normal segment >1.5. The prevalence of CAE is reported between 1.2% to 4.9% in different studies (1-3). The exact mechanism underlying CAE is not clear; however, atherosclerosis, inflammation, and endothelial dysfunction have been suggested to be possible mechanisms (4-6). The most frequently observed etiologic factor is atherosclerosis (6). Previous studies have shown that CAE can cause myocardial ischemia and the most frequent symptom is stable angina pectoris (7,8). Nowadays, many biomarkers are used to diagnose cardiovascular diseases, to classify risk and to determine their treatment (9,10). N-terminal pro B-type natriuretic peptide (NT-ProBNP) has an important role in the diagnosis and prognosis of heart failure (11). Elevated Pro-BNP is associated with increased risk of cardiovascular and all-cause mortality in the general population (12,13). Mitchell et al. have shown that Pro-BNP may reflect subclinical myocardial microvascular dysfunction in patients with overt coronary artery disease (14). Similarly, Torbjørn et al. have shown that the NT-ProBNP level was strongly related to the incidence of cardiovascular mortality, heart failure and stroke in patients with stable coronary artery disease (15).

Since atherosclerosis is an important etiology of CAE and CAE can lead to myocardial ischemia, it was aimed to evaluate whether CAE was associated with an elevated serum NT-proBNP level.

MATERIALS and METHODS

Between January 2018 and August 2019, all consecutive patients who underwent elective coronary angiography in our center were evaluated retrospectively. Of these patients, 126 patients with CAE without significant stenosis (<50% stenosis) in epicardial coronary arteries. Patients diagnosed as acute coronary syndrome, who had significant coronary artery stenosis of at least one epicardial coronary artery or previous history of coronary intervention, had mild or significant valve dysfunction, a history of heart failure, had chronic kidney and liver disease, any inflammatory or autoimmune disease or malignancy, and had anemia were excluded from study. Also, if the patients' NT-proBNP level was not evaluated at the time of CAG or hospitalization, they were excluded from the analysis. For measuring the NT-pro BNP levels, NT-pro BNP ELİSA (enzyme-linked Immunoassay technology and time resolued fluorometric determination) kit (Radiometer QAT90 FLEX immunoassay Denmark) used. The Limit of detection was determined to be ≤20 ng/L, the reportable range of the assay is 70-35000 ng/L, and the results were given as ng/ml Finally, the study population consisted of 66 CAE patients with stable angina pectoris and 60 subjects with normal coronary angiogram who were age and sex matched to the CAE patients, which was determined as the control group.

Baseline characteristics, medical history, laboratory parameters and echocardiography of the patients and control subjects were recorded from patients' files and the hospital digital information system. Hypertension was defined as systolic and diastolic blood pressure >140/90 mmHg or using antihypertensive medications. Type 2 diabetes mellitus (DM) was defined as fasting blood glucose of 126 mg/dl and over or having a previous diagnosis. Dyslipidemia was defined as total cholesterol level ≥200 mg/dl or use of lipid-lowering drugs. Cigarette smoking was defined as smoking ≥1 cigarettes a day for at least one year, without an attempt to quit. Family history was defined as the presence of cardiovascular disease in a male first-degree relative aged <55 years or in a female first-degree relative aged <65 years.

The study was approved by the local Clinical Research Ethics Committee of our hospital (Date: 28.08.2019, Decision number: 537). The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Coronary Angiography

All patients underwent elective coronary angiography (CAG) with the presence of angina or a positive noninvasive stress test, such as treadmill test, myocardial perfusion scintigraphy or dobutamine stress echocardiography. All CAG was performed by standard Judkins techniques through the femoral artery. Coronary angiograms were evaluated by two experienced cardiologists with digitized CAG equipment (Siemens, Munchen, Germany). CAE was defined as a segment or diffuse dilatation of the coronary artery being more than 1.5 times the diameter of the adjacent normal segment, or the diameter of the patient's largest coronary artery without stenosis (16).

Statistical Analysis

Continuous variables were defined as mean (± standard deviation) and categorical variables were defined as numbers and percentages. Continuous variables with normal distributions were compared with Student's t-test and those without normal distribution were compared with the Mann-Whitney U test. Distribution of variables were tested with the Kolmogorov-Smirnov test. In order to compare categorical variables were analyzed with Chi-square test or the Fishers Exact test were used. Receiver operating characteristics (ROC) curve was used to demonstrate the sensitivity and specificity of NT-proBNP cut-off values for CAE. In order to determine independent predictors of CAE, binary logistic regression analysis was performed. Variables with a p value

<0.1 in univariate analysis were included in the multivariate analysis. Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS 20.0) for Windows (SPSS Inc., Chicago, Illinois, USA). A p value <0.05 was considered statistically significant.

RESULTS

Mean age of the study population was 60.2 ± 8.8 years (34.1%, n= 43, female). Baseline demographic characteristics of the groups are presented in Table 1. There was no statistically significant difference between the two groups in terms of HT, DM, HPL, chronic obstructive pulmonary disease and left ventricular ejection fraction. Mean systolic, diastolic blood pressures and smoking were significantly higher in the CAE group when compared to the control subjects (Table 1). Laboratory variables are summarized in Table 2. There was no significant difference between the groups in terms of routine

Table 1. Comparison of baseline characteristics of study groups

Variables	CAE group (n= 66)	Control group (n= 60)	p
Age, years	60.4 ± 9.9	59.9 ± 7.0	0.670
BMI (kg/m^2)	24.3 ± 5.9	25.1 ± 5.5	0.315
Female, % (n)	35.8 (73)	34.6 (53)	0.823
Diabetes mellitus, % (n)	33.3 (69)	32.0 (49)	0.795
Hypertension, % (n)	66.2 (135)	58.2 (89)	0.122
Hyperlipidemia, % (n)	57.8 (118)	64.7 (99)	0.189
Smoking, % (n)	42.6 (87)	30.7 (47)	**0.021**
Pulmonary disease, % (n)	9.3 (13)	11.8 (18)	0.452
Systolic blood pressure (mmHg)	123 ± 21.1	117 ± 13	**<0.001**
Diastolic blood pressure (mmHg)	78 ± 11	74 ± 12	**<0.001**
Left ventricular EF, %	59.9 ± 3.1	60.4 ± 4.7	0.415

CAE: Coronary artery ectasia, BMI: Body mass index, EF: Ejection fraction.

Table 2. Comparison of laboratory parameters of study groups

Variables	CAE group (n= 66)	Control group (n= 60)	p
Hemoglobin, g/dl	13.6 ± 1.6	13.5 ± 1.5	0.341
Hematocrit, %	39.9 ± 5.2	39.1 ± 3.9	0.406
White blood cell count, ×10^3/ml	7.3 ± 2.2	7.4 ± 2.9	0.960
Platelet count, ×10^3/ml	244 ± 61	254 ± 53	0.514
Lymphocyte count, ×10^3/ml	2.4 ± 1.0	2.5 ± 1.1	0.752
Neutrophil count, ×10^3/ml	4.4 ± 1.4	4.5 ± 1.3	0.667
Neutrophil/lymphocyte ratio	1.99 ± 1.1	1.89 ± 0.9	0.725
Fasting glucose (mg/dl)	132 ± 37	1395 ± 46	0.568
Creatine (mg/dl)	0.84 ± 0.2	0.75 ± 0.1	0.421
C-reactive protein (mg/L)	2.9 ± 2.1	2.1 ± 1.6	0.235
Hs-Troponin (ng/ml)	7.7 ± 3.1	6.7 ± 2.4	0.378
Total Cholesterol (mg/dl)	209 ± 47.8	212 ± 34	0.744
HDL-Cholesterol (mg/dl)	44 ± 10.0	45 ± 8.1	0.396
LDL-Cholesterol (mg/dl)	144 ± 34	141 ± 36	0.546
Triglyceride (mg/dl)	190 ± 94	184 ± 97	0.780
NT-proBNP (pg/ml)	111.32 ± 17	98.89 ± 8.6	**<0.001**

NT-proBNP: N-terminal pro b-type natriuretic peptide.

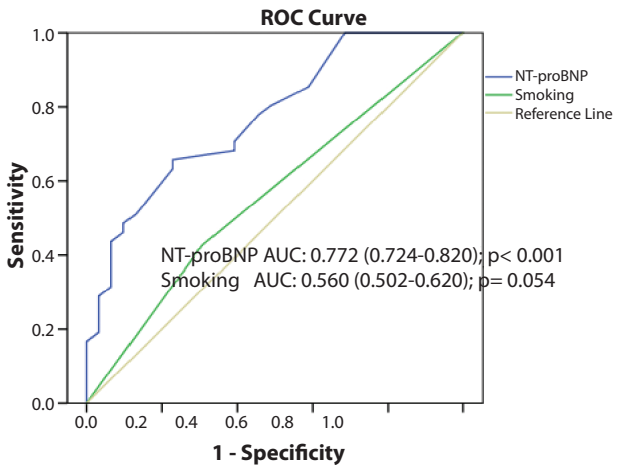

Figure 1. Receiver operating characteristic analysis for smoking and NT-ProBNP levels.

blood parameters, lipid parameters, fasting blood glucose, C-reactive protein, and Hs-Troponin. However, the mean NT-proBNP level was statistically significantly higher in the CAE patients than the control subjects (111.32 ± 17 ng/ml vs. 98.89 ± 8.6 ng/ml, p< 0.001). In receiver operating characteristic (ROC) analysis, a cut-off value of NT-proBNP ≥95 ng/ml had 85.3% sensitivity and 58.8% specificity for predicting CAE [area under the curve: 0.772, 95% CI= 0.724-0.820; p<0.001] (Figure 1). Univariate and multivariate logistic regression analyses results are summarized in Table 3. The multivariate analysis that included smoking, systolic blood pressure, diastolic blood pressure, and NT-proBNP showed that smoking (OR= 1.799, 95% confidence interval (CI)= 1.082-2.993; p= 0.024) and NT-proBNP (OR= 1.094, 95% CI= 1.088-1.125; p< 0.001) were independently associated with CAE.

DISCUSSION

In the present study, we demonstrated that serum NT-proBNP level was significantly increased in patients with CAE compared to the control subjects with normal coronary arteries. We also found that increased serum NT-proBNP levels remained as an independently associated factor with CAE. Similarly, we have shown that increased smoking was independent predictor of CAE.

Coronary artery ectasia (CAE) is defined as a 1.5 to 2-fold locally or diffusely increased dilatation of the coronary arteries compared to normal coronary artery segments (17). Previous studies have reported a CAE prevalence of 1.2% to 4.9%. In our study, the incidence of CAE was 1.7% and was similar to the literature. CAE is considered to be a variant of atherosclerosis, mainly characterized by an extensive exaggerated positive remodeling of the coronary artery. CAE can be congenital or may occur later. Although the etiology is not fully elucidated, it is frequently associated with atherosclerosis and in about 50% of patients, the etiology is atherosclerosis. Other etiological causes include congenital CAE, Kawasaki disease, mycotic and infective septic emboli such as syphilis and borreliosis, connective tissue diseases, arthritis such as Marfan syndrome, Takayasu and polyarthritis nodosa (18). Although a number of previously published studies have demonstrated a positive correlation between various inflammatory markers and CAE, a conventional risk factor for CAE has not been identified (19). While some studies have found a positive correlation between hyperlipidemia, hypertension and smoking, which are the traditional risk factors for atherosclerosis, with CAE, no relationship was found or an inverse relationship was found between diabetes mellitus and CAE (20,21). In our study, smoking, a well-defined atherosclerosis risk factor, was found to be an independent risk factor for CAE. Although there was no significant difference between the CAE group and the control group in terms of HT, both mean systolic and diastolic blood pressures were high in the CAE group.

Previous studies have shown that coronary artery ectasia leads to myocardial ischemia, but the mechanism of coronary ischemia in these patients is not fully understood. Studies have shown that slow or turbulent flow in the en-

Table 3. Univariate and multivariate logistic regression analysis of possible predictors of coronary artery ectasia

Analysis	Univariate		Multivariate	
Variables	**p**	**OR [95% CI]**	**p**	**OR [95% CI]**
Hypertension	0.122	1.407 (0.913-2.169)		
Hyperlipidemia	0.189	0.748 (0.486-1.154)		
Smoking	0.022	1.677 (1.078-2.608)	**0.024**	1.799 (1.082-2.993)
Systolic blood pressure	<0.001	1.021 (1.009-1.034)	0.704	0.995 (0.972-1.019)
Diastolic blood pressure	<0.001	1.032 (1.013-1.051)	0.105	1.029 (0.994-1.066)
NT-proBNP	<0.001	1.093 (1.063-1.123)	**<0.001**	1.094 (1.088-1.125)

NT-proBNP: N-terminal pro b-type natriuretic peptide.

larged coronary arteries causes thrombus formation in the ectasic segment or embolization in the distal coronary artery (22). In another study, 17 out of 33 patients with coronary artery ectasia without concomitant clogging coronary artery disease were found to have a positive stress test result and it was concluded that coronary artery ectasia caused ischemia (7). It has been shown that epicardial and microvascular perfusion is impaired in patients with isolated coronary artery ectasia (23). In another study, coronary flow velocity was measured and coronary flow velocity was significantly decreased in the ectasic segment and in normal segments (24). In two previous studies using tissue Doppler, a relation was found between coronary ectasia and left ventricular diastolic dysfunction, and it was suggested that this relationship might be caused by microvascular dysfunction and/or ischemia (25).

NT-proBNP is a biomarker which has an important role in the diagnosis, follow-up and prognosis of cardiovascular diseases such as heart failure and acute coronary syndrome. However, there are studies showing that NT-proBNP is also elevated in other coronary anomalies leading to stable angina pectoris and myocardial ischemia. NT-proBNP was found to be high in patients with stable angina pectoris and correlated closely with the severity of coronary artery disease (26). In low-risk patients with stable coronary artery disease and preserved ventricular function, BNP and NT-proBNP have been shown to provide additional prognostic information in addition to traditional risk factors (14). In another study, decreased myocardial perfusion reserve has been inversely related to serum NT-proBNP levels in asymptomatic individuals without significant coronary artery disease, and higher NT-proBNP levels have been associated with subclinical myocardial microvascular dysfunction (12). In this study, we found that serum NT-proBNP level was significantly higher in patients with CAE. Furthermore, we found an independent association between increased NT-proBNP and CAE. Similar to the aforementioned studies, the increased NT-proBNP level in CAE patients in our study may be due to subclinical myocardial microvascular dysfunction in these patients.

Limitations

Our study has more than one limitations. First, it was a single center study with a small number of patients and retrospectively performed. Second, because all NT-proBNP patients were screened and only NT-proBNP patients were included in the study, methodological "selection bias" could have been performed. However, this situation can be clarified with a prospective study. The third limitation, as mentioned before, was that the relationship between NT-proBNP and any inflammatory marker that had previously been associated with CAE could not be evaluated, due to the study's retrospective nature.

CONCLUSION

In the present study, we demonstrated that NT-proBNP levels were significantly increased in patients with CAE, and increased serum NT-proBNP levels were an independently associated with CAE.

Ethics Committee Approval: The study was approved by the Local Clinical Research Ethics Committee of our hospital (Decision Number: 537, Date: 28.08.2019).

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Conflict of Interest: There is no conflict of interest.

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