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The contribution of high-sensitivity troponin T on the diagnosis of coronary artery disease in patients undergoing exercise ECG test

Efor testi yapılan hastalarda yüksek duyarlıklı troponin T'nin koroner arter hastalığı tanısına katkısı

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ABSTRACT

The aim of the study was to investigate the contribution of high-sensitivity troponin T (hsTnT)whose levels increase with exercise test on the diagnosis of coronary artery disease in patients undergoing exercise test. The study included 45 patients (28 male, mean age 54.1±7.6 years), in whom coronary angiography (CAG) was performed. HsTnT levels were measured before and after six hours of exercise test. The change in hsTnT was taken as the difference between hsTnT level before and after exercise. Noncritical coronary stenosis (n=30; 66.7%), and critical coronary stenosis (n=15; 33.3%) were detected in respective number of patients. Among 15 patients who had critical coronary stenosis, 11 (24.4%) had positive hsTnT after exercise. Blood urea nitrogen (BUN) (p=0.005), creatinine (Cr) (p=0.023), hsTnT values (p<0.001) before, and, after exercise tests (p=0.001) in critical CAD group were higher when compared with the non-critical CAD group. HsTnT levels before (OR: 4.863, 95%CI: 2.342-7.384, p<0.001), and after exercise (OR: 6.859, 95%CI: 1.554-12.165, p=0.012), Δ hsTnT (OR: 6.768, 95% CI: 1.409-12.127, p=0.015) and BUN (OR: 1.083, 95%CI: 0.109-2.059, p=0.03) were detected as independent predictors for critical CAD in multiple logistic regression analysis. The specificity of exercise test combined with hsTnT was 93.3%, while the sensitivity of exercise test combined with hsTnT was 73.3%. Elevated hsTnT after exercise test is a significant independent factor, and has higher sensitivity and specificity than exercise test. We may use hsTnT together with the exercise test and myocardial perfusion scintigraphy.

Keywords: *hsTnT, exercise test, coronary*

ÖZ

Bu çalışmanın amacı efor testi ile artan high sensitivity troponin T'nin (hsTnT) koroner arter hastalığı tanısına katkısını araştırmaktı. Koroner anjiyografi (KAG) yapılan 45 hastayı (28 erkek, 17 kadın ve ortalama yaş 54.1±7.6 yıl) kapsamaktadır. Egzersiz testinden önce ve 6 saat sonra hsTnT ölçüldü. Egzersiz sonrası hsTnT değeri ile öncesinde ölçülenin arasındaki fark değişim hsTnT olarak hesaplandı. Otuz hastada (%66.7) kritik olmayan darlık, 15 hastada (%33.3) kritik darlık mevcuttu. Kritik darlığı olan 15 hastanın (%33.3) 11'inde (%24.4) hsTnT pozitifti. Kritik KAG grubunda kan üre nitrojeni (BUN) (p=0.005), kreatinin (Cr) (p=0.023), egzersiz öncesi hsTnT (p<0.001), egzersiz sonrası hsTnT (p<0.001) ve delta hsTnT (p=0.001), kritik olmayan KAG grubuna göre daha yüksekti. Kritik KAG'ı belirlemede multiple lojistik regresyon analizi ile, egzersiz öncesi hsTnT (OR: 4.863, %95 CI:, 2.342-7.384, p<0.001), egzersiz sonrası hsTnT (OR: 6.859, %95 CI: 1.554-12.165, p=0.012), delta hsTnT (OR: 6.768, %95 CI: 1.409-12.127, p=0.015) ve BUN (OR: 1.083, %95 CI: 0.109-2.059, p=0.03) bağımsız belirteç olarak tespit edildi. Egzersiz testi ile beraber hsTnT'nin özgüllüğü %93,3, duyarlılığı ise 73,3 % idi. Sonuç olarak, egzersiz testinden sonra artmış hsTnT, kritik KAH için önemli bir belirleyici ve yüksek özgüllüğe ve duyarlılığa sahiptir. Egzersiz testine ve miyokart perfüzyon sintigrafisine ek test olarak hsTnT'yi kullanabiliriz.

Anahtar kelimeler: *hsTnT, egzersiz test, koroner*

INTRODUCTION

Coronary artery disease (CAD) has high mortality and morbidity rates, and its incidence is increasing at an alarming rate. There are some non-invasive methods that can detect the presence of obstructive CAD in patients with stable angina pectoris (SAP). Exercise stress test is most commonly used in patients with stable angina pectoris. Due to the low specificity and sensitivity of exercise stress test, false positive and

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negative results are often produced. Recently, a new assay based on high-sensitivity troponin T (hsTnT) level has been developed, which can measure even small amounts of troponin. This study was aimed to investigate whether additional evaluation of hsTnT level could add to the diagnosis by the exercise stress test in patients with suspect CAD.

MATERIAL and METHODS

Our study included 45 patients, (28 male, 17 female and mean age 54.1±7.6 years) who underwent coronary angiography (CAG). The exclusion criteria were contraindications of exercise stress test including clinical heart failure, valve problems, congenital heart disease, permanent pacemaker, chronic kidney disease, chronic liver disease, and severe pulmonary hypertension. All patients were examined by written clinical history, and underwent EKG. Complete blood count, serum lipid, and hsTnT levels, kidney, and liver functions were measured from venous blood samples before the exercise. HsTnT level was again measured in venous blood samples after six hours of exercise test. An hsTnT level of 0.014 pg/L was accepted as a cut-off value. ΔhsTnT was calculated as the difference between the hsTnT level before and after exercise. CAG was performed with Siemens Axiom Sensis XP and Toshiba Infinix devices in our clinic. Written permission was obtained as a routine procedure before CAG from all patients. Coronary lesions were assessed by two cardiologists. Critical coronary lesions were defined as more than 50% occlusion in the left main coronary artery and/or more than 70% occlusion in major epicardial arteries. The study was conducted according to the recommendations set forth by the declaration of Helsinki on biomedical research involving human subjects, and the study protocol was approved by the Institutional Ethics Committee. Each participant signed a written informed consent.

Statistical Analysis

Demographics, laboratory parameters, exercise test, and angiographic findings were expressed as continuous and categorical variables. Continuous variables were tested for normality with the Kolmogorov–Smirnov test. Normal variables were recorded as mean and standard deviation. Independent sample t-test was used to make comparisons between the critical CAD-positive and negative patients. Categorical data were compared with chi-square test. Significant variables were analyzed to detect independent predictors for critical CAD with multiple logistic regression analysis. P-value <0.05 was accepted as statistically significant. The statistical analyses were performed by using SPSS for Windows, version 20.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

Thirty (66.7%) patients had noncritical, and 15 (33.3%) had critical coronary stenosis. Among patients (n=15) with critical coronary stenosis, 11 (24.4 %) had positive hsTnT test results after exercise. Eleven (24.4 %) patients in the same group had positive exercise test results. Seven patients (15.6%) with critical coronary

Table 1. Demographic, biochemistry and exercise findings of critical and non-critical CAD patients.

	Critical CAD (+) n=15	Critical CAD (-) n=30	p
Age (years)	52.0 ± 9.7	52.7±5.4	0.065
Gender (M/F)	12/3	16/14	0.077
Diabetes mellitus (%)	5 (33.3)	10 (33.3)	0.635
Hypertension (%)	8 (53.3)	15 (50.0)	0.542
Hyperlipidemia (%)	3 (20.0)	14 (46.6)	0.077
Smoking (%)	2 (13.3)	6 (20.0)	0.458
Familial history (%)	2 (13.3)	5 (16.6)	0.571
Hemoglobine (gr/dL)	14.5±1.4	15.0±4.6	0.668
Hematokrit (%)	40.5±4.0	41.8±3.3	0.275
BUN (mg/dL)	38.4±12.6	29.1±8.5	0.005
Creatinin (mg/dL)	1.0±0.2	0.8±0.2	0.023
Total colesterol (mg/dL)	189.5±45.4	201.0±58.0	0.505
LDL (mg/dL)	112.4±33.6	115.0±44.2	0.842
HDL (mg/dl)	42.7±9.7	43.9±10.3	0.707
Trigliserid (mg/dL)	193.0±78.3	151.2±81.7	0.109
Positive exercise test (%)	10 (66.7)	20 (66.7)	0.626
Before exercise hsTnT (pg/dl)	0.008±0.004	0.004±0.002	<0.001
After exercise hsTnT (pg/dl)	0.159±0.279	0.006±0.004	<0.001
Delta hsTnT (pg/dl)	0.151±0.278	0.002±0.003	0.001

BUN: Blood urea nitrogen, LDL: Low density lipoprotien, HDL: High density lipoprotien, CAD: Coronary arterial disease, hs-TnT: High sensitive troponin T

stenosis had negative exercise test results. Six patients (13.3 %), with positive exercise test and positive hsTnT test results had critical coronary stenosis. Seven (15.5%) patients with negative exercise test and negative hsTnT (cut-off level 0.014 pg/dL) test results had noncritical coronary stenosis. Blood urea nitrogen (BUN) (p=0.005), creatinine (Cr) (p=0.023), hsTnT values before (p<0.001), and after exercise (p<0.001) and ΔhsTnT (p=0.001) in critical CAD group were higher than non-critical CAD group. The other findings were similar (Table 1) as shown by multiple logistic regression analysis. HsTnT levels before (OR: 4.863, 95%CI: 2.342-7.384, p<0.001), and after exercise (OR: 6.859, 95% CI: 1.554-12.165, p=0.012), ΔhsTnT levels (OR: 6.768, 95% CI: 1.409-12.127, p=0.015) and BUN (OR: 1.083, 95%CI: 0.109-2.059, p=0.03) were detected as independent predictors for critical CAD with multiple logistic regression analysis (Table 2). The specificity, and sensitivity of the exercise test were 33.3, and 66.7%, respectively. The specificity, and sensitivity of the exercise test combined with hsTnT were 93.3, and 73.3%, respectively.

Table 2. Independent markers to determine citical CAD.

	Odds ratio	% 95 confidence interval	p
Before exercise hsTnT (every 0.01 pg/L)	4.863	2.342-7.384	<0.001
After exercise hsTnT (every 0.01 pg/L)	6.859.	1.554-12.165	0.012
Delta hsTnT (pg/dl)	6.768	1.409-12.127	0.015
BUN (mg/dl)	1.083	0.109-2.059	0.03
Cr	19.796	-24.537-64.129	0.373

HsTnT: High sensitive troponin T, BUN: Blood urea nitrogen, Cr:creatinin

DISCUSSION

BUN, Cr, hsTnT levels before, and after exercise test and ΔhsTnT in critical CAD group were higher than those in noncritical CAD group. BUN, hsTnT levels, before, and, after hsTnT, and ΔhsTnT were detected as independent predictors for critical CAD. Positive hsTnT with positive exercise test showed 93.3% specificity and 73.3% sensitivity.

Early diagnosis of acute coronary syndrome and prediction of prognosis based on hsTnT level have been clearly established in earlier studies; however, in the literature, there are not enough data for using hsTnT as a diagnostic tool for stable angina pectoris[1,2]. According to recent studies, hsTnT is more useful and ten-times more sensitive than traditional troponins. The measurement of hsTnT may be useful during rest and after exercise in the diagnosis of cardiovascular disease[3,4]. Hsieh et al.[5] determined hsTnT cut-off level as 58% high in 987 patients who had stable angina pectoris. Elevated hsTnT level was correlated with increasing frequency of cardiovascular event during a long-term follow up. HsTnT level was found to be elevated by 92% in heart failure disease which was correlated with bad prognosis[6]. Another study determined the cut-off hsTnT level as 11.1% higher than normal levels in 3679 stable CAD patients; herein it was shown as an independent factor to predict cardiovascular death and heart failure[6]. Resting hsTnT level can be considered in the diagnosis of CAD in moderately suspected CAD patients as observed by us and in earlier studies. As reported earlier, myocardial ischemia activates caspase-3 enzyme. This enzyme releases troponins, which go into systemic circulation, and extremely small amounts of troponins can be detected in plasma[7]. In our study, hsTnT level before exercise was lower than the cut-off level, but after exercise hsTnT level was detected to be higher than cut-off level in 14 patients. Critical coronary stenosis was detected in 11 patients, among them. Exercise stress test, which is noninvasive and inexpensive, is commonly used for diagnosis of moderate risk CAD patients. However, exercise test demonstrates higher rates of false positive and negative results. The sensitivity and specificity of exercise test have been reported as 67% and 72%, respectively[8]. Therefore, an additional test needs to be incorporated to increase specificity and sensitivity. In our study, the specificity and sensitivity of hsTnT test performed after exercise were 93.3% and 73.3%, respectively. According to an earlier study, hsTnT levels in critical CAD were higher than non-critical CAD patients. Patients with more critical coronary artery stenosis have elevated hsTnT level. This relation has been shown to be sta-

tistically significant. HsTnT level was found to be an independent risk factor to determine severe CAD patients[9]. HsTnT and NT-proBNP were measured in 378 patients with stable angina. Median hsTnT level was measured as 6.17 pg/l. HsTnT concentrations significantly increased in patients with CAD with or without myocardial ischemia but only NT-proBNP levels in CAD group were higher than those detected in the non-CAD group. Even in the absence of ischemia, hsTnT levels can increase by an ischemia-independent mechanism[10]. HsTnT levels were measured only once in this study without stress test. If stress test was performed, hsTnT could have risen.

Exercise-induced myocardial ischemia was detected in 278 patients. High-sensitivity cTnI levels were significantly higher at all time points in the patients with myocardial ischemia. Exercise test and baseline hs-cTnI levels were shown to enhance diagnostic accuracy in an earlier study[11]. These findings are similar with our study.

HsTnT levels were compared between moderate to severe myocardial ischemia group (Group A) and no to mild myocardial ischemia group (Group B). The blood sample were collected twice, after 1 and 3 h. HsTnT levels in Group A were higher than Group B. There was a trend toward a higher incidence of myocardial infarction in patients with baseline hsTnT levels of ≥14 pg/mL[12]. After exercise hsTnT levels were higher than before exercise and hsTnT levelswdere relatively higher in critical CAD patients in our study.

LIMITATIONS

The number of patients in our study was very low and we did not follow up our patients, thus we do not have any information about the role of elevated hsTnT levels in the long-term prognosis. We did not correlate ischemia with perfusion scintigraphy. We did not consider other parameters that might be associated with CAD such as Hs-CRP, homocysteine, cystatin-C, H-FABP, fibrinogen, and BNP.

CONCLUSION

Elevated hsTnT after exercise test was found to be a significant independent factor for the diagnosis of CAD and showed higher sensitivity and specificity than exercise test alone. We may use hsTnT level in addition to exercise test and myocardial perfusion scintigraphy.

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