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Original Article

The Relationship Between Coronary Artery Disease and High-Sensitive Troponin T Changes During the Exercise Stress Test

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ABSTRACT

Background The aim of this study was to investigate the relationship between coronary artery disease and changing of high sensitivity troponin T (hs-TnT) values during the exercise stress test (EST) in patients with suspected coronary artery disease (CAD).

Material and Methods We included 68 patients who underwent coronary angiography after positive EST. The hs-TnT values of all patients were measured before EST and at 4 hours after EST. Patients with coronary artery stenosis of 50% or more were divided into two groups (CAD [+]) and those without (CAD [-]). Hs-TnT values measured before and after EST were compared.

Results Among the 68 patients evaluated, 26 patients (39.3%) were identified as CAD (-) and 42 patients (61.7) as CAD (+). There was no significant difference between the two groups in the hs-TnT values before and after EST. There was a significant correlation between hs-TnT before exercise and pre-EST systolic blood pressure (SBP) (r=0.313, p=0.009) and hs-TnT before exercise and peak SBP during EST (r=0.241, p=0.038). There was a significant correlation between hs-TnT after EST and peak SBP during EST (r=0.398, p=0.001). Also, a strong negative correlation was found between the Duke treadmill score (DTS) calculated by the exercise test parameters and the Syntax score, which indicates the extent and severity of coronary artery disease (r=-0.521, p=0.0001).

Conclusions As a result of our study, it was observed that hs-TnT values did not contribute to the diagnosis of coronary artery disease. However, DTS evaluation performed before invasive coronary angiography can provide important information about coronary artery lesion complexity.

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Introduction

Cardiovascular diseases continue to be the most common cause of death in the world. Especially coronary artery disease (CAD) is shown as the most important factor for increased mortality in the adult population.[1] Therefore, the importance of early diagnosis and treatment of CAD has been discussed in more detail in recent years.[2,3] Early diagnosis is an essential factor in the treatment and prognosis of the disease. For the diagnosis of stable CAD, 12-lead electrocardiogram (ECG), exercise test, coronary computed tomography angiography, and myocardial perfusion scintigraphy are the most frequently used examination tools.[2] Among these diagnostic tests, the exercise stress test (EST) is the most frequently used method for applicability and cost. However, due to low sensitivity and specificity, false positive and negative results can be encountered. For this reason, there are studies to increase the diagnostic power of this test with new parameters to be added to the EST examination. One of these parameters is high sensitive-troponin T (hs-TnT).

Hs-TnT is a cardiac biomarker used to diagnose acute coronary syndromes, especially in emergency rooms.[4] In previous studies, hs-TnT has been shown to predict heart failure and cardiovascular death, independent of other risk factors.[5] In stable coronary artery patients, it has been shown that when hs-troponin is above normal reference values, it increases the potential risk.[6]

The aim of this study is to investigate the relationship between CAD and hs-TnT values measured before and after EST in individuals with suspected CAD.

Material and Methods

Sixty-eight patients with the complaint of chest pain and having positive EST were included in this study. The demographic and clinical characteristics of the patients were recorded from routine polyclinic examinations. Informed consent was obtained from all members of the patient group participating in the study. The Ethics Committee approved the study's compliance with the Declaration of Helsinki and ethical rules.

Patients with clinical heart failure, severe valve disease, a permanent pacemaker, left bundle branch block, atrial fibrillation, history of cardiac surgery, percutaneous coronary intervention, and acute coronary syndrome were excluded from the study.

Exercise Stress Test Procotol

Routine 12-lead ECG were obtained from all the patients . Heart rate, blood pressure, and ECG were recorded at the end of each stage. The formula, Maximum Heart Rate (beats/minute)=220-age (years) was used for the target heart rate. Chest pain, decrease in systolic blood pressure (SBP) by ten mmHg or more compared to the initial blood pressure, development of bradycardia, downsloping of the ST segment in 2 or more consecutive leads, or a horizontal depression of 1 mm or more after 80 ms from the J junction, and ST-segment elevation were taken as the positive criteria of the test. ST-segment depression in the upsloping type without typical chest pain was not considered a positive criterion.[7] The equation for calculating Duke treadmill score (DTS) is as follows: DTS=exercise time-(5 x ST deviation)-(4x exercise angina). Exercise angina was assessed as one of three levels: 0, none; 1, nonlimiting; and 2, exercise-limiting.

Coronary Angiography

Coronary angiography (CAG) was performed with standard techniques. Before CAG, an informed consent form was obtained from all patients. All coronary angiographies were recorded in DICOM format on compact discs and then examined off-line and visually. The presence and severity of CAD were evaluated using the SYNTAX scoring method, special computer software with previously proven prognostic value.[8]

High-Sensitive Troponin T Measurement

Approximately 5-10 cc of blood was drawn from the peripheral venous route at the fourth hour after the EST. These blood samples were described as post-exercise blood samples. The blood samples of the patients who came for CAG on the day of their appointment were taken before the angiography while lying in the ward while at rest. Blood samples taken during this period were described as basal or non-exercise blood samples.

Blood samples taken under both conditions were subjected to centrifugation, and their sera were distinguished. Serum samples were stored under suitable conditions. It was then mass analyzed using the hs-TnT Elecsys kit (Roche Diagnostics, Mannheim, Germany). Values above 14 ng/L in the healthy population was considered abnormal.

Statistical Analysis

Data analysis was carried out by the computer software Statistical Package for Social Sciences (IBM SPSS Statistics for Windows, version 15.0, Armonk, New York, USA). Data conforming to normal distribution are presented as mean (±) standard deviation and data not conforming to normal distribution are presented as median and quartiles. Categorical data was presented as frequency distribution and percentage. Yates corrected Chi-square test, and Fisher's exact test were used for comparison of categorical variables. Mann-Whitney U test was used to compare two independent groups that were not normally distributed. Student t-test was used to compare two groups that fit a normal distribution. Spearman correlation test was used for the relationship between the measurement and specified variables. The Kendall Tau correlation test was used for the relationship between categorical variables. Statistical significance value was accepted as p<0.05.

Results

The patients were divided into two groups as CAD (+) and CAD (-) according to their final coronary angiographical data (coronary artery stenosis of 50% or more). The main characteristics of both groups are summarized in Table 1. The CAD (+) group was older than the CAD (-) group (53.73±7.4 vs. 58.81±9.55, p=0.02). There was no statistically significant difference between the two groups in terms of gender, diabetes, hypertension, hyperlipidemia, family history of CAD, smoking, body mass index, LDL-HDL-total-cholesterol, triglyceride, creatinine, and glucose. with CAD (-) and CAD (+) were compared. CAD was detected in 42 of 68 patients whose EST was accepted as positive, and 26 patients did not have CAD. EST's positive predictive value was 61%. There was no statistically significant difference between the percentage increase hs-TnT, basal hs-TnT, post-EST hs-TnT, and Δh hs-TnT (ΔHs-Troponin T; after exercise hs-TnT - before exercise hs-TnT). There was no significant correlation between basal hs-TnT, post-EST hs-TnT, Δh hs-TnT, and SYNTAX score (*Table 2*). There was a significant correlation between hs-TnT before exercise and pre-EST SBP (r=0.313, p=0.009) and hs-TnT before exercise and peak SBP during EST (r=0.241, p=0.038).There was a significant correlation between hs-TnT after EST and peak SBP during EST (r=0.398, p=0.001) *(Table 3)*. Also, a strong negative correlation was found between the DTS and the Syntax score (r=-0.521, p=0.0001) *(Figure 1)*.

Figure 1. Corelation between duke treadmill score and syntax score.

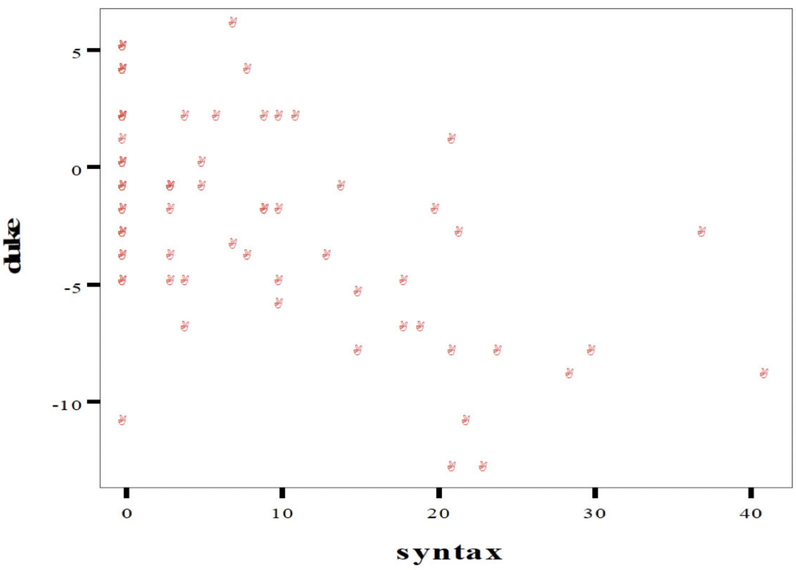

Table 1. Baseline characteristics of the study population

	CAD (-) (n=26)	CAD (+) (n=42)	p value
Gender, male (n%)	17 (65.4%)	36 (85.7%)	NS
Age (years)	53±7	58±9	0.024
BMI (kg/m²)	30±5	28.5±4	NS
Familial history (n%)	12 (46.2%)	17 (4.5%)	NS
Diabetes mellitus (n%)	8 (30.8%)	12 (28.6%)	NS
Hypertension (n%)	14 (53.8%)	26 (61.9%)	NS
Hyperlipidemia (n%)	10 (38.5%)	20 (47.6%)	NS
Smoking (n%)	3 (11.5%)	11 (26.2%)	NS
Biochemical parameters			
Total cholesterol (mg/dL)	197.4±59	210±35	NS
HDL-c (mg/dL)	41 (34/45)	40 (37/45)	NS
LDL-c (mg/dL)	141.4±41	145±31	NS
Triglyceride (mg/dL)	224±148	176±82	NS
Serum creatinine (mg/dL)	0.8 (0.67/1)	0.9 (0.8/1)	NS
Glucose (mg/dL)	106(96/121)	103 (95/118)	NS
Before exercise hs-TnT (ng/dL)	7 (5,10.2)	8 (6,12)	NS
After exercise hs-TnT (ng/dL)	10 (6,15.5)	11 (8,16.5)	NS
Delta hs-TnT (ng/dL)	1.5 (1,1.5)	2 (1,6)	NS
Percentage increase hs-TnT (ng/dL)	0.25 (0.09,0.48)	0.3 (0.1,0.5)	NS
Stress test parameters			
Heart Rate (beat/min)	86 (78,93)	82 (70,97.5)	NS
Before exercise SBP (mmHg±SD)	140 (130,150)	140 (130,15	NS
Before exercise DBP (mmHg±SD)	85 (80,90)	80 (75,90)	NS
Duration (minutes±SD)	7 (4.8,9)	7 (5.3,7.6)	NS
Maximum workload (METs±SD)	10 (7,10)	9 (7,10)	NS
Peak SBP (mmHg±SD)	181±25	180±29	NS
Heart rate recovery	30.2±13	27±9.1	NS
Duke treadmil score	-0.23±3.85	-3.67±4.4	0.002
Syntax score	-	10 (5.7,21)	-

BMI: body mass index, CAD: coronary artery disease, DBP: diastolic blood pressure, HDL-c: high-density lipoprotein cholesterol, METs: metabolic equivalent, LDL-c: low-density lipoprotein cholesterol, SBP: systolic blood presssure.

Table 2. Relation between hs-TnT values and Syntax score

	r	p
Before exercise hs-TnT (ng/dL)		
Syntax score	-0.073*	0.64
After exercise hs-TnT (ng/dL)		
Syntax score	0.029*	0.856
Δ hs-TnT (ng/L)		
Syntax score	0.097*	0.543
Before exercise hs-TnT (pg/dL) T ≥14 ng/L		
Syntax score	0.181**	0.167
After exercise hs-TnT (pg/dL) T ≥14 ng/L		
Syntax score	0.012**	0.928

hs-TnT: high sensitive troponin T.
*Spearman correlation test was used.
**Kendall tau correlation test was used.

Discussion

In this study, we investigated that the change in hs-TnT levels after EST and the use of stress test parameters together could be beneficial in identifying high-risk individuals and in the early diagnosis of CAD. In our study, CAD was detected in 42 of 68 patients whose EST was accepted as positive, and 26 patients did not have CAD. Similar to the literature, the limited role of EST positivity in determining the presence of CAD was found in our study. In our study, no significant relationship was found between CAD and the presence of diabetes, hypertension, smoking, and family history. In this study, we thought that the absence of a significant relationship between CAD and major clinical risk factors was due to the small number of our patients. However, many large angiographic studies have shown the relationship between CAD and risk factors. It has been demonstrated that it is useful to consider classical CAD risk factors in EST interpretation.

Early diagnosis of the acute coronary syndrome and prediction of prognosis based on a hs-TnT level have been clearly established in earlier studies; however, in the literature, there are not enough data for using change of hs-TnT during the EST as a diagnostic tool for CAD. In a study conducted by Omland *et al.*[9], a strong correlation was found between baseline hs-TnT value and prognosis in 3679 stable coronary artery patients at 5.2 years of follow-up. In the study conducted by Mingels *et al.*[10], the basal hs-TnT value of 1,088 patients with chest pain was examined, and cardiac events and cardiac mortality were significantly higher in the group with high hs-TnT group at 2.2 of follow-up. Ndrepepa *et al.*[11] showed a significant correlation was found between baseline hs-TnT levels and angiographic CAD in 904 stable coronary artery patients ($p<0.001$). The difference between our study and this study may be due to the difference in the number of patients and the patient population. Ndrepepa *et a*l.[11] hypothesized that the increase in basal hs-TnT levels in patients with stable CAD may be due to myocardial ischemia in myocardial microcirculation with the embolization of thrombotic material formed by the dysrussion of silent plaques with physical activity.

In our study, it was found that the post-EST hs-TnT levels increased significantly compared

Table 3. Relation between hs-TnT values and stress test parameters

	r*	P
Maximum workload, METs Before exercise hs-TnT (pg/dL)	1.0	0.398
Maximum workload, METs After exercise hs-TnT (pg/dL)	-0.086	0.464
Peak HR (beats/minute) Before exercise hs-TnT (pg/dL)	0.051	0.667
Peak HR (beats/minute) After exercise hs-TnT (pg/dL)	-0.027	0.819
Duration (minutes) After exercise hs-TnT (pg/dL)	-0.137	0.243
Before exercise hs-TnT (pg/dL) Peak SBP (mmHg)	0.241	0.038
Before exercise hs-TnT (pg/dL) Before exercise SBP (mmHg)	0.313	0.009
After exercise hs-TnT (pg/dL) Peak SBP (mmHg)	0.398	0.0001
After exercise hs-TnT (pg/dL) Peak DBP (mmHg)	0.146	0.213

DBP: diastolic blood pressure, HR: heart rate, hs-TnT: high sensitive troponin T, METs: metabolic equivalent, SBP: systolic blood pressure.
*Spearman correlation test was used.

to the basal values. An increase in troponin levels has been reported after heavy exercise in various previous studies and case reports.[12,13] In studies conducted so far, troponin levels that increase with exercise have not been elucidated to be physiological or pathological. Frank *et al*.[14] found that this increase may be due to reversible cardiomyocyte membrane leakage due to oxidative stress induced by exercise and the circulation of cytosolic cTnT. König *et al*.[15] designed to evaluate whether the troponin increase mechanism due to exercise-induced myocardial stress is related to oxidative stress and inflammation. They showed that there is no correlation between the levels of markers. They reported that hs-Troponin increase only correlated with the increase in myoglobin, CK and CK-MB released from skeletal muscle. Hs-TnT is the third generation troponin and does not show cross-reaction with skeletal muscle. For this reason, they thought that hs-TnT release from the myocardium and myoglobin and CK, CK-MB release from skeletal muscle maybe by the same mechanism. Kurz *et al*.[16] and Axelsson *et al*.[17] reported that similar to our study, post-EST troponin values increased compared to basal troponin. In our study, we thought that this increase may be due to the transfer of cytosolic troponin into the circulation due to the temporary and reversible permeability increase in myocyte membrane permeability due to exercise-related metabolic stress.

In our study, the DTS from the stress test data was significantly more negative in the group with CAD. There was a negative correlation between DTS and Syntax score. Previous studies reported that major cardiac events were more common in patients with high Syntax scores.[18,19] In Mark *et al*.[20], they reported that the cardiac events were significantly higher in patients with a more negative DTS. Previous studies revealed a relationship between the ST-segment depression occurring during the exercise test, the number of leads with collapse, and the ST segment depression pattern and the presence of CAD. However, there is no study in the literature comparing the DTS and the syntax score. EST can give an idea about DTS, the presence, prevalence, and severity of CAD.

There are some limitations of our study. Our most important limitation is related to the number of patients. The hypothetical relationship between the presence and complexity of CAD and hs-TnT elevation due to exercise may have been overlooked due to the limited number of patients. Another issue concerns our methodology. Since our main goal was to investigate the relationship between CAD and CAD complexity and exercise-induced hs-TnT elevation, we only included EST-positive and potentially undergoing CAG. Therefore, we initially excluded the patient population with a negative EST test. The main reason for this initial exclusion is that we could not recommend CAG to the EST-negative group for ethical reasons. For this reason, our study data are far from representative of the entire stress test patient population. This methodological limitation prevented us from taking blood for hs-TnT before exercise, since we did not know which patient would have a positive EST at the beginning. For this reason, we found it appropriate to use the hs-TnT value taken at rest at a later time instead of hs-TnT before EST for comparison.

Conclusions

In our study, data could not reveal the relationship between the increase of hs-TnT, which is a biochemical marker we recommend to be added to EST, and the presence of CAD and its complexity. This suggests that exercise-induced hs-TnT elevation, even in patients with CAD, maybe due to other potential mechanisms other than ischemia, such as increased left ventricular afterload and increased wall tension. It is thought that additional studies are needed that include a higher number of patients and use biochemical markers such as BNP that reflect wall tension. However, a strong negative correlation was found between DTS and the extent and severity of CAD. DTS evaluation performed before invasive CAG can provide important information about coronary artery lesion complexity.

Conflict of interest

The authors declared that there are no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contribution

Study Conception: IG, MTA, SC; Study Design: IG, MTA, SC; Supervision: IG, MTA, SC; Materials: MTA, IG; Data Collection and/or Processing: IG, MTA; Statistical Analysis and/or Data Interpretation: IG, SC; Literature Review: IG, MTA, SC; Manuscript Preparation: SC, IG; and Critical Review: MTA.

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