Original Article

Using Incremental High-Sensitive Cardiac Troponin T to Increase the Diagnostic Accuracy of Exercise Stress Test

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Background: Exercise stress test (EST) is the most practical method to diagnose coronary artery disease (CAD). Although it has a high negative predictive value (NPV), the positive predictive value (PPV) is low.

Objective: To increase the diagnostic accuracy of EST by combining the results with the delta change of high-sensitive cardiac troponin T (hs-cTnT) levels during stress exercise.

Materials and Methods: The authors conducted a diagnostic study in patients presenting with chest pain and having intermediate pretest probability of CAD who underwent EST at Queen Sirikit Heart Center of the Northeast in Khon Kaen, Thailand, between July 2018 and January 2019. Two blood samples were collected to measure hs-cTnT at 5-minute before and at 1-hour after exercise. The diagnosis of CAD was made from the coronary angiography (CAG) or coronary computed tomography angiography (CCTA) result. The authors created a ROC curve from the hs-cTnT delta change, selected a value that had high sensitivity, and combined it with EST results to enhance the PPV predicting CAD.

Results: Eighty-one patients were included in the present study. Thirty-one (38.3%) had positive EST, 47 (58.0%) had negative EST, and three (3.7%) had inconclusive results. To confirm the diagnosis of significant CAD, CAG was performed in 33 (40.7%) patients, and CCTA was performed in seven (8.6%) patients. Forty-two (51.8%) patients were determined not to have significant CAD based solely on negative EST results. Sixteen (19.8%) patients were in the CAD group and 65 (80.2%) in the non-CAD group. The average hs-cTnT at baseline, at 1-hour after EST, and delta change of patients in the CAD group were greater than those in the non-CAD group (7.81±3.62 ng/L and 4.83±2.97 ng/L, p<0.001, 9.21±4.41 ng/L and 4.94±2.92 ng/L, p<0.001, 17.99% and 9.18%, p=0.09, respectively). When the authors used a hs-cTnT delta-change of 3% as a cutoff point and combined this with the EST results, the PPV increased from 48% when using the EST alone to 63.2%.

Conclusion: Combining hs-cTnT delta change during an EST with EST results could raise the PPV of CAD diagnosis in patients with chest pain who had intermediate CAD pretest probability.

Keywords: Exercise stress test, Coronary artery disease, High-sensitive cardiac troponin T

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Coronary artery disease (CAD) is a global health problem with a high rate of morbidity and mortality. Early detection and treatment are key steps in improving outcomes but diagnosing CAD can be difficult due to its misleading clinical presentations. Thus, the current guideline suggests performing non-invasive tests in patients with an intermediate pretest probability (PTP) to make the diagnosis and stratify risk of CAD[1].

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The most practical non-invasive test in physically active patients is the exercise stress test (EST), which is widely available in secondary care hospitals[2]. It helps detect myocardial ischemia by comparing ST-segment deviation at baseline and during exercise using an electrocardiogram (ECG). However, if the baseline or exercise EGG images was ambiguous, the results may be difficult to interpret. Previous studies and a meta-analysis showed that sensitivity and positive predictive value (PPV) of the EST in diagnosing CAD were relatively low at 68% and 36%, respectively, but that specificity and negative predictive value (NPV) were high at 77% and 90%, respectively[3-5].

Cardiac troponin, a biomarker representing myocardial necrosis, is useful in diagnosing acute myocardial infarction. Nowadays, high-sensitive cardiac troponin T (hs-cTnT) assay is widely available and has a stronger sensitivity to detect myocardial injury not only in patients with acute myocardial infarction but also in 98% of patients with stable

CAD[6]. Myocardial ischemia during exercise can cause damage to cardiac myocytes, which may release cardiac troponin into the circulation. Thus, combining changes in hs-cTnT during the EST to the ST-segment deviation result may improve the accuracy of CAD diagnosis.

Objective

The authors aimed to raise the diagnostic accuracy for CAD by incorporating hs-cTnT delta changes during EST.

Materials and Methods

Study design

The present research was a cross-sectional diagnostic study aimed at enhancing the diagnostic yield of the EST for CAD by incorporating the delta change between pre- and post-exercise hs-cTnT. The authors examined patients who presented with chest pain and were scheduled to undergo EST at Queen Sirikit Heart Center of the Northeast in Khon Kaen, Thailand, between July 1, 2018 and January 31, 2019.

Study population

The authors enrolled consecutive patients who presented with chest pain and had intermediate PTP for CAD according to the 2013 ESC guidelines on the management of stable CAD in whom baseline ECG was appropriate to perform EST[1]. The main exclusion criteria were contraindication for the EST based on the ACC/AHA 2002 guideline update for exercise testing[5], supraventricular tachycardia (SVT) or sustained ventricular tachycardia (VT) during EST, or inability to achieve 85% of maximum predicted heart rate (MHR) without significant changes in the ST-segment of the ECG.

Study procedures and outcomes

All enrolled patients performed EST using the Bruce protocol and two venous blood samples were collected from each patient, first at 5-minutes before beginning EST and at 60-minutes after finishing the test. Hs-cTnT levels were measured using the fifth-generation Roche Elecsys hs-cTnT assay[7]. Two independent cardiologists, who did not know the hs-cTnT results, would interpret the EST results as either positive, negative, or unclear. In cases of the EST results were positive, invasive coronary angiography (CAG) would be performed. No further investigation was conducted in patients with negative EST results. If the EST results were unclear, the patient would undergo coronary computed tomography angiography (CCTA). If the CCTA revealed significant coronary stenosis, additional CAG would be conducted. Finally, the study population were divided into two groups, the CAD and non-CAD, the latter included patients with negative EST results, insignificant stenosis on CCTA, and insignificant stenosis on CAG[8].

Diagnosis of CAD

The diagnosis of CAD was made if there was more than 70% luminal narrowing of one or more major epicardial arteries or above 50% luminal narrowing of the left main coronary artery according to the results from CAG or CCTA, interpreted by an attending interventional cardiologist or radiologist who was unaware of the delta troponin T results.

Statistical analysis

The sample size was calculated to be 82 patients based on an assumption of 85% sensitivity, 60% CAD prevalence, and 10% acceptable error[9]. To compare all continuous variables, the authors used a two-tailed Student's t-test, and categorical variables used either chi-square or Fisher's exact test. A receiver operating characteristic (ROC) curve was then constructed based on the hs-cTnT delta change. A cutoff value with high sensitivity was selected to be used in combination with the EST results to improve the PPV for CAD. All statistical analyses were performed using Stata, version 10.1 (StataCorp LP, College Station, TX, USA). A p-value of less than 0.05 was considered significant.

The Ethics Committee of Khon Kaen University approved the present study protocol on 12 June 2018 (reference number: HE611188).

Results

Study population

The present study screened 85 patients who underwent EST between July 2018 and January 2019, 81 of them met the criteria in the primary objective analysis. The baseline characteristics are presented in Table 1. The mean ± standard deviation (SD) age was 56.10±7.74 years. Fifty-one (62.96%) were men, and 43 (53.09%) had previous medical conditions, hypertension and type 2 diabetes mellitus were the two most common comorbid diseases with 29 (35.80%) and 17 (20.99%) patients, respectively. In addition, 79 patients (97.53%) had intermediate PTP for CAD.

EST results

EST results were positive in 31 (38.3%), negative in 47 (58.0%), and inconclusive in three (3.7%)

Table 1. Baseline characteristics of the overall population, CAD patients, and non-CAD patients

Variables	CAD (n=16); n (%)	No CAD (n=65); n (%)	Total (n=81); n (%)	p-value
Sex				0.004
Male	15 (93.75)	36 (55.38)	51 (62.96)	
Female	1 (6.25)	29 (44.62)	30 (37.04)	
Age (year); mean±SD	58.81±8.27	55.43±7.52	56.10±7.74	0.11
BMI (kg/m^2); mean±SD	25.76±4.08	24.77±3.43	25.57±3.96	0.37
Comorbidity				0.16
Yes	6 (37.50)	37 (56.92)	43 (53.09)	
No	10 (62.50)	28 (43.08)	38 (46.91)	
Comorbidity				
DM	6 (37.50)	11 (16.92)	17 (20.99)	0.09
HTN	11 (68.75)	18 (27.69)	29 (35.80)	0.002
DLD	3 (18.75)	9 (13.85)	12 (14.81)	0.69
Prior CAD	1 (6.25)	3 (4.62)	4 (4.94)	1.00
PCI	0 (0.00)	1 (1.54)	1 (1.23)	1.00
Stroke	2 (12.50)	3 (4.62)	5 (6.17)	0.25
AF	0 (0.00)	1 (1.54)	1 (1.23)	0.99
Smoking				0.029
No	6 (37.50)	46 (70.77)	52 (64.20)	
Former	5 (31.25)	11 (16.92)	16 (19.75)	
Current	5 (31.25)	8 (12.31)	13 (16.05)	
Angina type				<0.001
Typical	0 (0.00)	18 (27.69)	18 (22.22)	
Atypical	3 (18.75)	34 (52.31)	37 (45.68)	
Non cardiac	13 (81.25)	13 (20.00)	26 (32.10)	
Pretest probability of CAD				<0.001
Low	0 (0.00)	2 (3.08)	2 (2.47)	
Intermediate low	4 (25.00)	56 (86.15)	60 (74.07)	
Intermediate high	12 (75.00)	7 (10.77)	19 (23.46)	
Creatinine (mg/dL); mean±SD	0.97±0.22	0.88±0.18	0.90±0.19	0.10

CAD=coronary artery disease; BMI=body mass index; DM=diabetes mellitus; HTN=hypertension; DLD=dyslipidemia; PCI=percutaneous coronary intervention; AF=atrial fibrillation; SD=standard deviation

patients. To confirm the diagnosis of significant CAD, CAG was performed in 33 (40.7%) patients, and CCTA was conducted in seven (8.6%) patients. Forty-two (51.8%) patients were determined not to have significant CAD based solely on negative EST results. Therefore, 16 (19.8%) patients were in the CAD group and 65 (80.2%) in the non-CAD group (Figure 1). The sensitivity, specificity, PPV, and NPV of EST alone in the present study were 93.8%, 75.4%, 48.4%, and 98.0%, respectively.

Troponin T results

The average baseline hs-cTnT levels of patients in the CAD group were significantly higher than those in the non-CAD group (7.81±3.62 and 4.83±2.97 ng/L, p<0.001). Mean hs-cTnT at 1-hour after the EST of patients in the CAD group was also higher than that of those in the non-CAD group (9.21±4.41 and 4.94±2.92 ng/L, p<0.001). Patients in the CAD group also exhibited greater hs-cTnT delta change from baseline to 1-hour after EST than those in the non-CAD group, but this difference was not statistically significant (17.99% and 9.18%, p=0.09) (Figure 2).

Combination of EST and troponin T results

The authors created a ROC curve based on the hs-cTnT delta change results and identified the hs-cTnT cutoff points, sensitivity, and specificity for

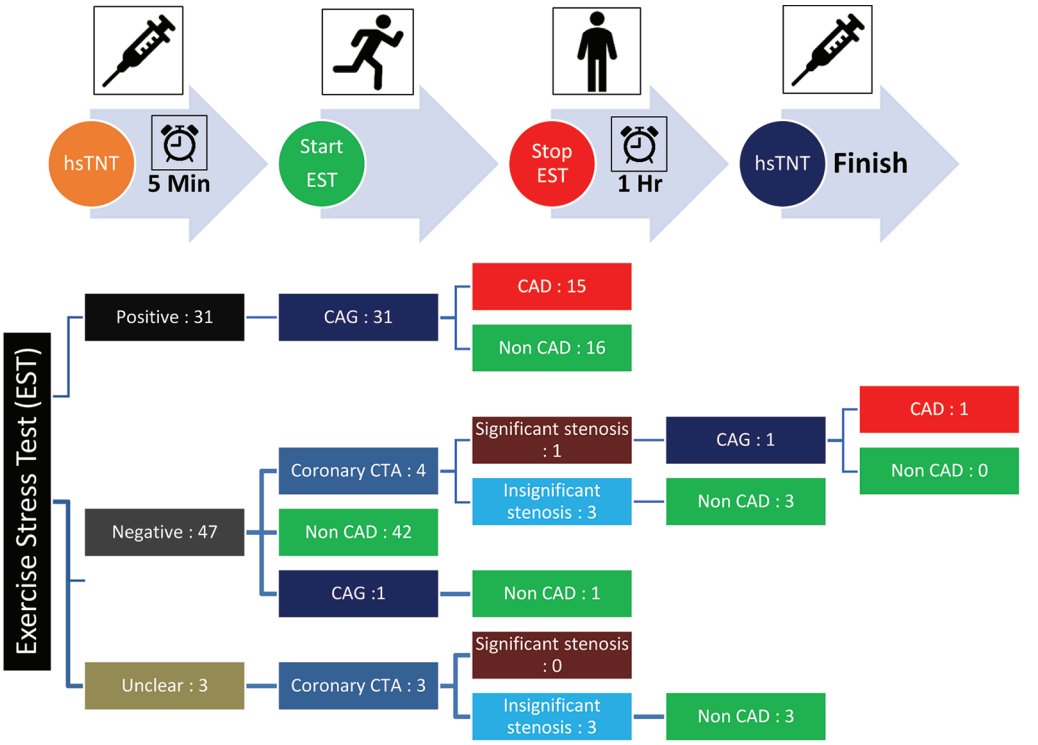
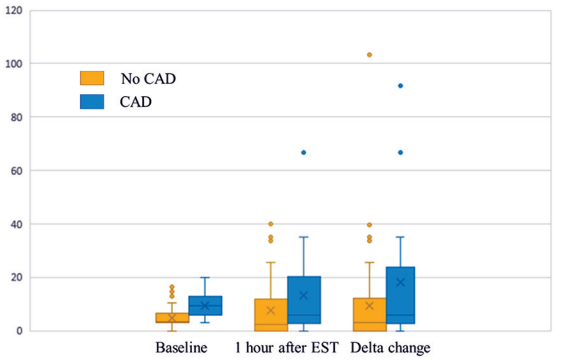


Figure 1. Study flow diagram.

Hs-TNT=high-sensitive cardiac troponin T; EST=exercise stress test; CAG=invasive coronary angiography; CAD=coronary artery disease; CTA=computed tomography angiography



High sensitivity cardiac troponin T levels	CAD (n=16)	Non-CAD (n=65)	Total (n=81)	p-value
hs-cTnT at baseline; mean±SD	7.81±3.62	4.83±2.97	5.42±3.31	<0.001
hs-cTnT at 1-hour after EST; mean±SD	9.21±4.41	4.94±2.92	5.79±3.67	<0.001
Delta change; % (95% CI)	17.99 (4.02 to 31.97)	9.18 (5.2 to 13.15)	10.93 (6.81 to 15.04)	0.09

Figure 2. High sensitive cardiac troponin T (hs-cTnT) levels.

CAD=coronary artery disease; EST=exercise stress test

the CAD diagnosis. The authors selected a cutoff value with high sensitivity and combined it with the

Table 2. Cutoff point of 3% hs-cTnT delta change during the EST combined with EST results for the diagnosis of CAD

	CAD	No CAD	Total
Combination with ≥3% hs-cTnT delta change plus positive EST results	12	7	19
Other results	4	58	62
Total	16	65	81

CAD=coronary artery disease; EST=exercise stress test; Hs-cTnT=high-sensitive cardiac troponin T

EST results to improve the PPV for CAD and chose 3% as the delta-change cutoff point and constructed a 2×2 table depicting the final CAD diagnosis and hs-cTnT delta change combined with EST to identify the diagnostic accuracy (Table 2). The sensitivity and specificity of the diagnostic test were 75% and 89.2%, respectively. The positive and negative likelihood ratios were 6.96 (95% CI 3.27 to 14.8) and 0.28 (95% CI 0.119 to 0.657), respectively. The PPV of the EST results increased from 48.4% (95% CI 30.2 to 66.9) to 63.2% (95% CI 38.4 to 83.7) after being combined with hs-cTnT delta change results with a 3% cutoff point (Table 3).

Table 3. Diagnostic accuracy after combined 3% hs-cTnT delta change during EST with EST results for the diagnosis of CAD

Parameter	Value	95% confidence interval
Sensitivity (%)	75.0	47.6 to 92.7
Specificity (%)	89.2	79.1 to 95.6
ROC area	0.821	0.71 to 0.94
Likelihood ratio (+)	6.96	3.27 to 14.8
Likelihood ratio (–)	0.28	0.119 to 0.657
Odds ratio	24.9	6.5 to 94.7
Positive predictive value (%)	63.2	38.4 to 83.7
Negative predictive value (%)	93.5	84.3 to 98.2

CAD=coronary artery disease; EST=exercise stress test; Hs-cTnT=high-sensitive cardiac troponin T; ROC=receiver operating characteristic

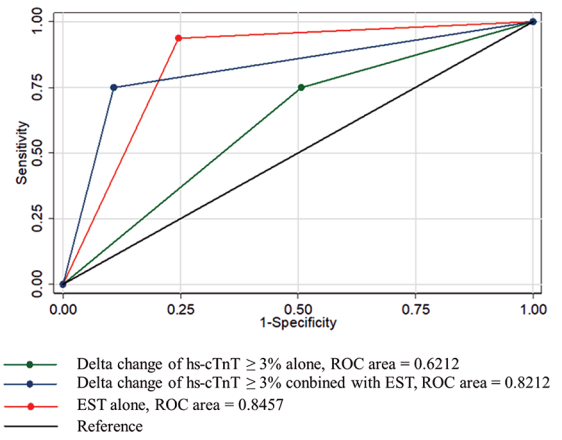


Figure 3. ROC curves of the tests for CAD diagnosis.

CAD=coronary artery disease; EST=exercise stress test; Hs-cTnT=high-sensitive cardiac troponin T; ROC=receiver operating characteristic

The area under the ROC curve increased from 0.62 (95% CI 0.49 to 0.75) when utilizing three-percent delta-change alone to 0.82 (95% CI 0.71 to 0.94) when interpreted three-percent delta-change of hs-cTnT as a cut point with the EST result, as shown in Figure 3.

Discussion

The authors conducted a diagnostic study to assess whether hs-cTnT measurements pre- and post-exercise could enhance the diagnostic accuracy of the EST for CAD in stable, intermediate-PTP patients with chest pain. The present study showed that hs-cTnT was significantly higher in the CAD group than in the non-CAD group, both at baseline and 1-hour after the EST. The hs-cTnT delta change was also greater in CAD patients, but no statistical significance. In addition, combining EST results and hs-cTnT delta change (3% cutoff) raised the PPV for CAD from 48.4% (EST alone) to 63.2%.

Previous studies tried to determine the changing pattern of cardiac troponin during exercise and pharmacologic stress tests in stable patients. Eryol et al found that cardiac troponin T was detectable after EST in stable-angina-pectoris patients with CAD, but undetectable in those without CAD[10]. Blood samples in that study were taken 6 and 24 hours after EST, which was different from the present research. The authors collected the blood samples at just one hour after the test because the version of the troponin T assay the present study used was more sensitive than in their study.

Several studies of high-sensitive cardiac troponin assays were conducted to further clarify the releasing pattern of ischemic markers during multimodal cardiac stress tests. Sou et al directly compared high-sensitive cardiac troponin I (hs-cTnI) and hs-cTnT levels, measured before, immediately after, two hours after, and four hours after maximal stress of exercise myocardial perfusion single-photon emission computed tomography in subjects with suspected CAD[11]. Similar to the present study, hs-cTnI and hs-cTnT levels were both significantly higher at all-time points in patients with exercise-induced myocardial ischemia compared to those without myocardial ischemia (all $p<0.001$). Furthermore, the increasing pattern of high-sensitive cardiac troponin was not only detected in the stress exercise test but also appeared in the pharmacologic stress test. Wongpraparut et al found that hs-cTnT levels were significantly higher in patients who had moderate to severe myocardial ischemia at baseline, one hour after, and three hours after pharmacological stress magnetic resonance imaging compared with those who had no or mild myocardial ischemia[12]. These results were comparable to the findings in the present study.

However, there were some conflicting data regarding the response pattern of cardiac troponin for helping in the diagnosis of CAD during cardiac stress tests. Orsini et al and Samaha et al found that significant increments in hs-cTnT were detected after both negative and positive stress tests[13,14]. These findings differed from the present study, which the delta change of hs-cTnT had a higher trend in patients with CAD compared with those without CAD. There were two possibilities to explain these unparalleled results. First, the hs-cTnT assays in that study were taken six hours after the stress tests. Blood sampling at a different time point might bring different result. Second, their results were based on

the ischemic pattern of the stress tests, not the definite CAD, diagnosed by CAG or CCTA. Therefore, some patients who had negative stress tests might be a false-negative and led to an increase of hs-cTnT in the stress test negative group.

Although EST is widely available for diagnosing CAD, it has limited diagnostic accuracy. Several studies showed that the sensitivity and PPV of the EST in the diagnosis of CAD were relatively low at 68% and 36%, respectively, but that the specificity and NPV were high at 77% and 90%, respectively[3-5]. From these findings, the present study was not only to determine the pattern of cardiac troponin during stress exercise but also tried to improve the diagnostic accuracy of EST. Thus, the authors constructed a ROC curve and chose a hs-cTnT delta change of 3% at baseline and 1-hour after exercise combined with EST results, which raised the PPV to 63.2%. This combination should be useful in clinical application to select intermediate-risk chest pain patients more effectually to perform invasive CAG.

The present study had some limitations. First, the prevalence of CAD was lower than expected. The authors initially estimated that CAD would be detected in 60% of the cases but found in only 20%. This finding suggested that a larger sample size may have been necessary. Second, CAG were done in only 40.7% and CCTA in only 8.6% of the study population. Initially the authors planned to perform CCTA in all patients with negative EST results, but because of the long waiting list, 51.8% of patients were determined not to have significant CAD based solely on negative EST results. This limitation may have led to over sensitivity and false-negative EST results.

Conclusion

Combining the hs-cTnT delta change levels during EST with EST results could raise the PPV for CAD diagnosis in patients with chest pain who had intermediate CAD PTP.

What is already known on this topic?

EST is the most practical non-invasive test in CAD diagnosis with a high NPV but low PPV. Cardiac troponin can rise and be detected in the circulation after the EST, especially in CAD patients.

What this study adds?

Combining the hs-cTnT delta change levels during EST with EST results can raise the PPV for CAD diagnosis in patients with chest pain who had intermediate CAD PTP.

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Conflicts of interest

The authors declare no conflict of interest.

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