Clinical Biochemistry 63 (2019) 18–23

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

High-sensitivity cardiac troponin T increases after stress echocardiography

Eslam Samaha[a], Jamie Brown[a], Frank Brown[a], Sara C. Martinez[b], Mitchell Scott[c], Allan S. Jaffe[d], Victor G. Davila-Roman[b], Peter Nagele[a,*]

[a] Department of Anesthesiology, 660 S. Euclid Ave., 63110 St. Louis, MO, United States
[b] Cardiovascular Imaging and Clinical Research Core Laboratory, Cardiovascular Division, 660 S. Euclid Ave., 63110 St. Louis, MO, United States
[c] Department of Pathology and Immunology, Washington University School of Medicine, 660 S. Euclid Ave., 63110 St. Louis, MO, United States
[d] Cardiovascular Division, Department of Internal Medicine and Division of Core Clinical Laboratory Services, Department of Laboratory Medicine and Pathology, Mayo Clinic and Medical School, 200 First St. SW, 55905 Rochester, MN, United States

ARTICLE INFO

Keywords:
Coronary artery disease
Myocardial ischemia
High-sensitivity cardiac troponin T
Stress echocardiography

ABSTRACT

Introduction: Exercise (ESE) and dobutamine stress echocardiography (DSE) have high sensitivity and specificity to detect inducible myocardial ischemia in patients with significant coronary artery disease (CAD). High-sensitivity cardiac troponin (hs-cTn) assays detect troponin concentrations in the ng/L range. The aim of this study was to determine the kinetics of hs-cTnT in patients undergoing ESE and DSE and possible association of hs-cTnT with inducible myocardial ischemia.

Methods: In this prospective study adult patients undergoing ESE/DSE were enrolled. Peripheral blood samples were obtained before, and 30 min, 1, 2, and 4–6 h after completion of ESE/DSE. Hs-cTnT was measured on a Roche Diagnostics Elecsys 2010 analyzer.

Results: We enrolled 48 patients (33 ESE and 15 DSE); 11 patients (23%) had elevated baseline hs-cTnT concentrations > 14 ng/L (99th percentile URL); 31/48 (65%) developed an hs-cTnT increase after ESE/DSE (peak 4–6 h post stress test), but only three patients (all in ESE group) had a positive stress test. Absolute and relative hs-cTnT increases were higher after DSE (median Δhs-cTnT +9.7 ng/L [IQR 4.5, 27.2]; +123% [IQR 49, 271]) compared to ESE (median Δhs-cTnT +2.3 ng/L [IQR 1, 4.9]; +37% [IQR 9.1, 221]).

Conclusions: One in four patients undergoing ESE/DSE had increased hs-cTnT values prior to stress testing. Hs-cTnT increased above the upper limit of normal occurred commonly after ESE/DSE but was more pronounced after DSE. Increases in hs-cTn did not appear to be associated with inducible myocardial ischemia. These findings may have important implications for the clinical use of hs-cTnT within 6 h after ESE/DSE.

1. Introduction

Coronary artery disease (CAD) is a leading cause of morbidity and mortality among adults, accounting for approximately 600,000 deaths in the United States every year [1,2]. The noninvasive evaluation of patients with CAD is frequently performed with stress testing, either with exercise or with pharmacologic agents such as dobutamine and imaging modalities such as echocardiography or myocardial perfusion imaging [3,4]. Stress echocardiography has high sensitivity and specificity to detect myocardial ischemia, manifested as new or worsening segmental wall motion abnormalities [5–9].

Cardiac troponin (cTn) is the standard biomarker for the diagnosis of myocardial infarction (MI) [10,11]. High-sensitivity cardiac troponin (hs-cTn) assays have lowered the limit of analytical detection by an order of magnitude (i.e. ng/L range) [12,13]. A potentially important advantage associated with the use of hs-cTn assays is the detection of circulating blood levels at rest and under different conditions such as exercise and/or pharmacologic stress [14–18]. In patients with acute chest pain not managed by an initial invasive strategy, pre-test hscTn values may identify patients with myocardial ischemia or infarction on subsequent stress testing [19]. Recent studies have shown conflicting results – some showing varying degrees of hs-cTn increase after stress, but other showing none [20–22]. For example, healthy adolescent and young adult athletes undergoing treadmill exercise, post-exercise hs-cTnT elevation occurred in all runners, peaked 3–4 h post-exercise, and the peak hs-cTnT concentration after prolonged exercise was higher in adolescents than adults [21]. Dobutamine administration also causes increases in hs-cTn, even in normal subjects [22]. Conversely, the best predictor of a normal stress test appears to be a very low pre-test hs-cTn value [23].

* Corresponding author at: Department of Anesthesia & Critical Care, 5841 S. Maryland Ave. MC-4028, Chicago, IL 60637, United States.
E-mail address: pnagele@dacc.uchicago.edu (P. Nagele).

https://doi.org/10.1016/j.clinbiochem.2018.11.013
Received 30 July 2018; Received in revised form 24 November 2018; Accepted 28 November 2018
Available online 28 November 2018

The purpose of this pilot study was to determine the hs-cTnT kinetics in hospitalized patients with a clinical indication for undergoing ESE and DSE. We focused on hospitalized patients as this allowed us to obtain hs-cTnT samples 4–6 h after stress test. Furthermore, we aimed to determine if post stress-test hs-cTnT values are higher in patients who develop inducible myocardial ischemia than in those who do not.

2. Methods

2.1. Study design and population

In this prospective study, adult patients who were scheduled to undergo stress echocardiography at Barnes-Jewish-Hospital/Washington University Medical Center in St. Louis, from April to August 2013 were approached for enrollment. The study coordinator approached consecutive patients one ½ day during the study period.

Inclusion criteria: a) 18 years of age or older; b) scheduled for stress echocardiography; c) normal baseline global/segmental LV function (see below). Exclusion criteria: a) acute coronary syndrome on admission to the hospital (i.e., ischemic changes on 12-lead electrocardiogram and/or any abnormal elevation of cardiac enzymes at the time of hospitalization); b) inability to provide informed consent; c) contraindication to stress testing. The study was approved by the IRB at Washington University of St. Louis, St. Louis, Missouri. Patients were approached for enrollment in the stress echocardiography suite; informed consent was obtained just prior to the start of the stress test.

2.2. Stress echocardiography

Patients underwent either exercise stress echocardiography (ESE) or pharmacologic stress with dobutamine (DSE) based on their ability to exercise on a treadmill; if unable to exercise, a DSE was performed. Before the stress test, all patients underwent a complete echocardiogram; those with a LVEF < 55% or segmental wall motion abnormalities were excluded from the study. The left ventricle was divided into 17 segments, and wall motion was scored on a 3-point scale (score: 1 = normal, 2 = hypokinesis, 3 = akinesis/dyskinesis). A normal response to either exercise or dobutamine consisted of increased global and segmental wall motion with increasing stress (increase exercise or increase dobutamine dose). The study was considered abnormal (i.e., myocardial ischemia) if wall motion in one or more segments increased (worsened) by one or more grades during stress testing.

Dobutamine echocardiography was performed as described previously [24]. Briefly, intravenous dobutamine was infused in a graded fashion (10–40 μg/kg/min) with two-dimensional digital echocardiographic monitoring of global and segmental left ventricular wall motion. Atropine was used if > 85% of maximal predicted heart rate was not achieved at the maximal dobutamine dose of 40 μg/kg/min. Exercise stress echocardiography was performed by a symptom-limited maximal exercise in a treadmill according to the Bruce protocol. Post-exercise images were obtained immediately after the discontinuation of exercise. Two expert echocardiographers reviewed all ESE/DSE studies independently; any disagreements were to be settled by consensus.

2.3. Measurements and laboratory evaluations

Peripheral blood samples were obtained before, and 30 min, 1-, 2-, and 4–6 h after completion of ESE/DSE. Blood drawn from the patient was immediately processed and spun down; plasma was stored in a freezer at −80 °C until further analyzed. All laboratory tests were performed for research purposes only and were analyzed in a batch of 20–25 samples. High-sensitivity cardiac troponin (hs-cTnT; Roche Diagnostics) were measured on a Roche Elecsys 2010 analyzer (limit of detection: 5.0 ng/L; 99th percentile: 14 ng/L; a 10% CV at 13 ng/L) [25].

Table 1
Baseline characteristics: ESE vs. DSE.

Variables	ESE *n* = 33 (%)	DSE *n* = 15 (%)
Male, n (%)	13 (39)	9 (60)
Age, mean (SD)	54 (11.3)	59 (10.9)
Caucasian	13 (39)	6 (40)
African American	20 (60)	9 (60)
BMI, mean (SD)	31.8 (8.4)	29.4 (10.1)
Comorbidities, n (%)		
Smoking History	20 (60)	14 (93)
Current Smoker	11 (33)	8 (53)
Arterial Hypertension	21 (64)	12 (80)
Hypercholesterolemia	14 (42)	3 (2)
Carotid Artery Disease	0 (0)	1 (7)
Peripheral Vascular Disease	0 (0)	1 (7)
Atrial Fibrillation	1 (3)	1 (7)
Left Ventricular Hypertrophy	7 (22)	7 (47)
Coronary Artery Disease	6 (18)	5 (33)
Myocardial Infarction	1 (3)	2 (13)
Cardiac Catheterization	3 (9)	3 (20)
CABG	3 (9)	1 (7)
Congestive Heart Failure	1 (3)	1 (7)
Diabetes	6 (18)	2 (13)
Insulin Dependent	1 (3)	0 (0)
Stroke	1 (3)	2 (13)
COPD	2 (6)	5 (33)
Chronic Kidney Disease	0 (0)	0 (0)
Creatinine (mg/dl)	0.81 (0.72–1.02)	0.93 (0.72–1.04)
Medications, n (%)		
ACE-Inhibitors	7 (21)	5 (33)
Beta-Blockers	9 (27)	5 (33)
Diuretics	12 (36)	4 (27)
Calcium-Blockers	10 (30)	0 (0)
Nitrates	0 (0)	1 (7)

ACE: angiotensin-converting enzyme, CABG: coronary artery bypass graft, CAD: coronary artery disease, COPD: chronic obstructive pulmonary disease, CVA: cerebrovascular accident, GFR: Glomerular filtration rate.

2.4. Statistical analysis

Cardiac troponin values are presented as median (interquartile range, IQR). One-way comparisons between the two stress test groups were done using non-parametric tests, such as the Mann-Whitney test, or two-sided unpaired *t*-test. Before and after comparisons within patients were analyzed with a paired t-test and simple repeated-measures ANOVA. A linear correlation was determined using least squares regression (r^2). Incidence rates of positive and negative stress test were calculated, as well as absolute and relative hs-cTnT change values by subtracting the peak hs-cTnT value from the baseline value. A particular emphasis was placed on hs-cTnT values > 14 ng/L (99th percentile URL). All tests were two-sided and a *p*-value of < 0.05 was considered statistically significant. Statistical analysis was performed using JMP 13.0 (SAS Institute, Cary, NC).

3. Results

Baseline characteristics of the study population (n = 48) are shown in Table 1 and Fig. 1. All patients were scheduled to undergo stress echocardiography (ESE: n = 33, DSE: n = 15) as part of their cardiac evaluation. Indications for ESE/DSE, listed on Table 2, were: chest pain (n = 18, 38%), preoperative cardiac evaluation (n = 20, 42%), and syncope, atrial fibrillation and shortness of breath (n = 10, 21%).

At baseline, all patients had normal global and segmental wall motion. Baseline median hs-cTnT levels were significantly higher in the DSE group vs. the ESE group (ESE: 4.4 ng/L [IQR 0, 11.9] vs. DSE: 8.2 ng/L [IQR 7.5, 17.5]; p = .02). Eleven patients (23%) had an elevated hs-cTnT concentration above the 99th percentile URL (14 ng/L) before the start of the stress test (ESE: 18% vs. DSE: 33%). Patients with left ventricular hypertrophy were more present in the DSE group (ESE:

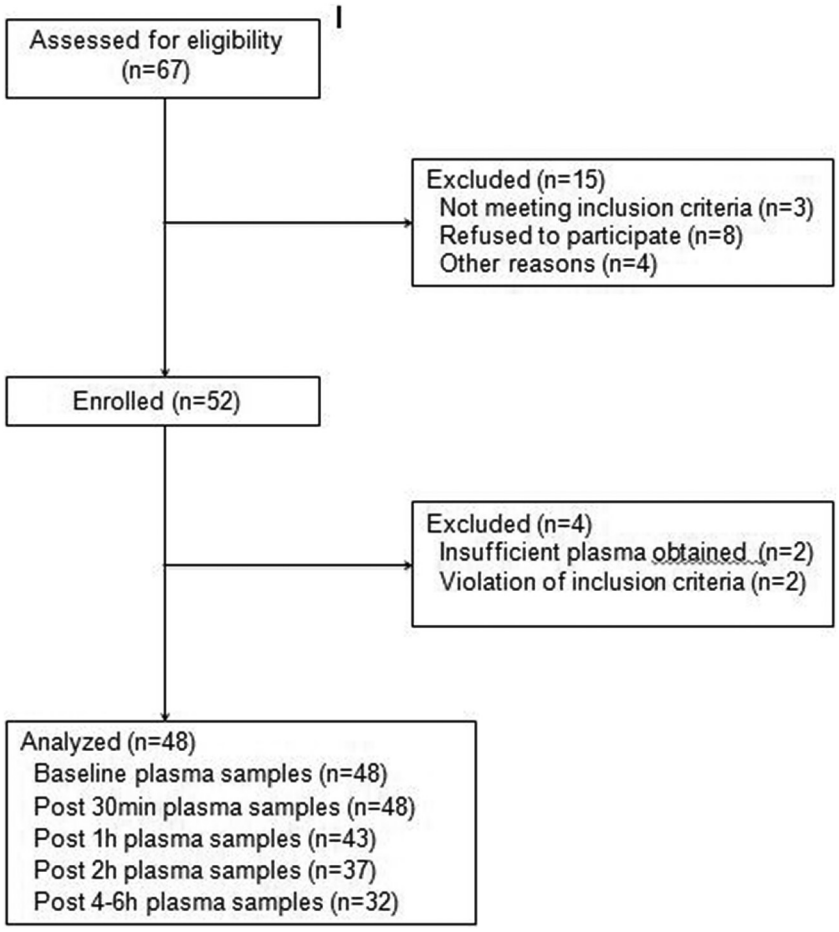

Fig. 1. Study flow diagram.

Table 2
Indications for stress echocardiography, ESE vs. DSE.

Indication	ESE n = 33 (%)	DSE n = 15 (%)
Chest Pain	13 (39.5)	5 (33)
Preoperative Evaluation	13 (39.5)	7 (47)
Syncope	3 (9)	3 (20)
Atrial Fibrillation	3 (9)	0 (0)
Shortness of Breath	1 (3)	0 (0)

22% vs. DSE: 47%) and had higher baseline median hs-cTnT levels (No LVH: 4.7 ng/L [IQR 0, 8] vs. LVH: 11.7 ng/L [IQR 5.6, 17.8]).

Sixteen patients (33%) were not able to provide blood samples at the 4–6 h timepoint; however, there was no difference in drop out rate between the two groups (ESE 12/36 (36.4%) vs. DSE 4/15 (26.7%), $P = .543$).

At baseline, the mean rate pressure product (heart rate x systolic blood pressure) was comparable between ESE and DSE patients (10,193 ± 2773 (SD) vs. 10,161 ± 2040, $p = .97$). After stress test, the rate pressure product increased by 132% in ESE patients to 23,671 ± 6902 and by 157% to 26,066 ± 6313 in DSE patients ($p < 0001$ for before-and-after comparison within each group; $p = .28$ for comparing ESE and DSE). Peak rate pressure product was not correlated with Δ hs-cTnT ($r^2 = 0.08$).

After ESE/DSE, the peak median hs-cTnT levels increased significantly more in the DSE group compared to the ESE group (peak levels: DSE: 25.8 ng/L [IQR, 15.9, 35.1] vs. ESE: 6.0 ng/L [4.9, 17.5]; $p < .001$); similarly, the relative median hs-cTnT increase was more pronounced after DSE vs. ESE (DSE: 123% increase [IQR 49, 271] vs. ESE: 37% increase [IQR 9.1, 221], $p = .03$). The median hs-cTnT absolute change was significantly higher in the DSE group vs. ESE group (absolute change, ESE: 2.3 ng/L [IQR 1, 4.9] vs. DSE: 9.7 ng/L [IQR 4.5, 27.2], p < .001, Table 3, Fig. 2). Within our observed period, hs-cTnT values peaked at 4–6 h after stress test. The median duration of the

Table 3
High-sensitivity cardiac troponin T changes after stress echocardiography, ESE vs. DSE.

	ESE N = 33	DSE N = 15	Positive test
Baseline hs-cTnT [ng/L] median, IQR	**4.4 [0, 11.9]**	**8.2 [7.5, 17.5]**	**6.1 [4.6, 14.5]**
Baseline hs-cTnT > 14 ng/L, n (%)	**6/33 (18)**	**5/15 (33)**	**1/3 (33)**
Peak hs-cTnT [ng/L], median, IQR	**6.0 [4.9, 17.5]**	**25.8 [15.9, 35.1]**	**18.4 [5.8, 19.6]**
Absolute hs-cTnT change [ng/L], median, IQR	**2.3 [1–4.9]**	**9.7 [4.5–27.2]**	**3.9 [1.2, 13.5]**
Relative Change hs-cTnT, % median, IQR	**+ 37% [9, 221]**	**+ 123% [49, 271]**	**+ 27% [26.1, 221]**
Any rise in hs-cTnT, n (%)	**19/33 (58)**	**12/15 (80)**	**3/3 (100)**
Myocardial ischemia, n (%)	**3/33 (9)**	**0**	**3**

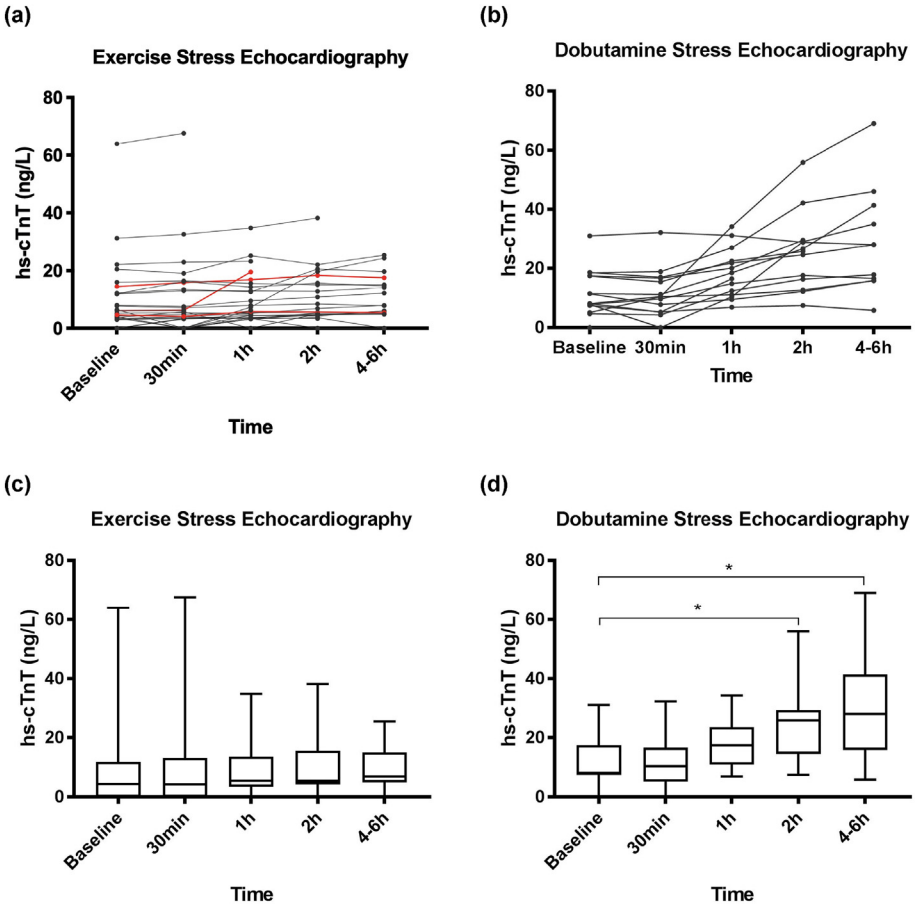

Fig. 2. a. Hs-cTnT values before and after stress echocardiography.
Fig. 2b. Hs-cTnT values (median, IQR) before and after stress echocardiography. Mann-Whitney-U Test was performed to determine significance.

exercise stress test was 537 s [IQR, 394, 567 s]. There was no linear correlation between duration of exercise and absolute Δ hs-cTnT ($r^2 = 0.07$) and a weak correlation with relative hs-cTnT ($r^2 = 0.20$).

Three patients in the ESE group (6.3%) exhibited myocardial ischemia during stress testing (none after DSE); two of these underwent subsequent coronary angiography and significant CAD (> 50% luminal stenosis) was identified in at least one major coronary artery on both. There was 100% agreement between the two echocardiographers in terms of the ESE/DSE studies considered normal (no myocardial ischemia) and those with myocardial ischemia. There was no apparent correlation between hs-cTnT baseline or change pattern and a positive cardiac stress test.

4. Discussion

The results of this study showed several findings: a) that approximately one fourth of patients undergoing ESE/DSE have increased hs-cTnT values prior to stress testing; b) that hs-cTnT increases (many above the 99th% URL) occur commonly for at least six hours after ESE/DSE; c) the increase in post-stress test hs-cTnT was significantly higher after DSE vs. ESE; and d) that increases in hs-cTn were not unique to patients with inducible myocardial ischemia. These findings may have important implications for the clinical use of hs-cTnT after ESE/DSE, particularly within 6 h after stress testing.

Studies have shown conflicting results regarding change in cardiac troponin levels in healthy and young exercising subjects. In a study of 13 healthy adolescent and 13 young adult athletes undergoing treadmill exercise, post-exercise hs-cTnT elevation occurred in all runners, peaked 3–4 h post-exercise, and the peak hs-cTnT concentration after prolonged exercise was higher in adolescents than adults [21]. Although substantial inter-individual variability was noted in peak hs-cTnT, particularly in the adolescent group, the peak hs-cTnT was followed by a rapid decrease in both groups, however the levels in adolescents had not returned to baseline at 24 h. Scherr showed increases in hs-cTnT immediately after a marathon race with normalization of within 72 h. of exercise [26]. Thus, studies in healthy, young individuals undergoing strenuous exercise show marked increases of cardiac troponin in the absence of myocardial ischemia or obstructive coronary artery disease, suggesting that exercise-induced cTnT release reflects a physiological rather than a pathological substrate [21,27,28].

Studies in patients undergoing exercise stress testing for evaluation of CAD have shown varying degrees of cardiac troponin increases. Sabatine studied 120 patients enrolled in the TIMI 35 who underwent exercise stress testing with myocardial perfusion imaging [20]. The hs-cTnI (Singulex Erenna System) was detectable in all patients before stress testing; by 4 h. after exercise troponin levels were unchanged in patients without ischemia, however, circulating levels increased by 24% in those with mild ischemia and by 40% in those with moderate-to-severe ischemia. However, the change in hs-cTnI was very small in absolute terms and not clearly above what might occur in some patients due to biological variation alone. When added to clinical factors, an increase in high-sensitive TnI was an independent predictor of ischemia (OR: 3.54, $P = .007$). Roysland used serial hs-cTnT measurements before and after exercise stress test and found, similar to our study, no association between inducible myocardial ischemia and hs-cTnT rise. However, in slight contrast to our study demonstrating a significant increase of hs-cTnT from dobutamine stress, they showed an overall trend for increased hs-cTnT from exercise-stress [29]. Sou showed that serial hscTn measurements during exercise stress testing has moderate accuracy for inducible exercise-induced myocardial ischemia [30].

Recently, Lee et al. showed that hs-cTnI concentrations at rest and after exercise provided improved clinical diagnosis after stress test [23]. Thus, varying hs-cTn increases were shown after exercise stress, with some but not all studies showing association between hs-cTn increases and severity of ischemia.

Studies measuring hs-cTn during dobutamine stress for evaluation of CAD have also shown variable findings. Siriwardena measured hs-cTnT before DSE and serially for 4 h in 16 patients with coronary artery disease (CAD) and in 10 healthy volunteers [22]. Mean hsTnT concentrations in healthy volunteers increased after DSE at 2 h. and peaked at 3 h. HsTnT concentrations in CAD patients without inducible ischemia started from a higher baseline and increased at 2 h. (with levels still increasing at the end of sampling period). This study showed DSE-induced stepwise increases in plasma hsTnT in healthy volunteers and in CAD patients. Those exhibiting inducible ischemia exhibited the highest increases in hsTnT; however, this group also received the highest dobutamine doses, suggesting a dobutamine-dose related effect. Wongpraparut showed that hscTnT increase after pharmacologic (dobutamine or adenosine) stress test is larger in patients who exhibit moderate-to-severe myocardial ischemia compared to those with mild ischemia [31]. In summary, studies in patients undergoing dobutamine stress testing for evaluation of CAD show consistent increases in hs-cTn; however as opposed to exercise stress, increases in post-stress hs-cTn levels seem to correlate better with presence of myocardial ischemia. As expected, higher levels of hs-cTnT at baseline presaged more marked changes irrespective of the presence or absence of ischemia. Interestingly, isolated atrial pacing also causes an increase in hs-cTn concentrations. [32]

However, a potential caveat regarding the interpretation of these different studies lies in the fact that these results may vary due to: 1) population (age, sex, comorbidities) which could differ due to the inclusion/exclusion criteria used in each study. 2) calibration of 4th generation assays and hs-cTnT assays, which are not standardized. 3) the assay method used, since contemporary assays show poor analytical performance at low cTn concentrations compared to high-sensitivity assays, especially in women. This could have a noticeable impact on the results as cTn can be under the 99th URL value of the method in pre-test condition [33–35].

The present study appears to be the first to compare changes in hs-cTn levels in patients undergoing ESE vs. DSE. We found that approximately one fourth of patients undergoing ESE/DSE have increased hs-cTnT values prior to stress testing and that the magnitude of hs-cTnT increase was higher for those undergoing DSE compared to ESE. The last finding was unexpected based on previous studies showing large increases in hs-cTn with exercise.

Serial post-stress hs-cTnT exhibited increased levels begin to plateau 2 h after completion of stress testing, but in some the peak may not occur for 4–6 h after completion of stress testing.

5. Limitations

This study has certain limitations. A potential caveat regarding the interpretation of the results lies in the fact that some patients may not have achieved maximum stress during exercise and that the stress level was not maximized.

We also observed that increases in hs-cTn did not appear to be significantly different in those with myocardial ischemia compared to those without. This could be due to the relatively low number of patients showing myocardial ischemia, as only three patients (all in ESE group) had myocardial ischemia.

Finally, it is important to recognize that the relatively small study sample size may limit conclusions and that this study should be more considered as a pilot study and warrants further study.

Funding

This work was supported by the Longer Life Foundation (St. Louis, Missouri) [grant number 2013-004].

Conflicts of interest

Samaha, Brown J, Brown F, Martinez, Davila-Roman: None

Scott: Research Support - Siemens Healthcare Diagnostic; Abbott Diagnostics, Instrumentation Laboratories;

Consulting - Instrumentation Laboratories; Becton-Dickinson, Alere; Speaker fees: Abbott.

Jaffe: Consultation: Beckman, Ortho, Abbott, Alere, Critical Diagnostics, Roche, Radiometer, Amgen and theHeart.org

Nagele: Research Support: Roche Diagnostics US; Abbott Diagnostics.

References

[1] H. Hemingway, A. McCallum, M. Shipley, K. Manderbacka, P. Martikainen, I. Keskimaki, Incidence and prognostic implications of stable angina pectoris among women and men, JAMA 295 (2006) 1404–1411.
[2] M. Heron, Deaths: leading causes for 2009, Natl Vital Stat Rep. 61 (2012) 1–94.
[3] G.F. Fletcher, P.A. Ades, P. Kligfield, R. Arena, G.J. Balady, V.A. Bittner, et al., Exercise standards for testing and training: a scientific statement from the American Heart Association, Circulation 128 (2013) 873–934.
[4] R. Sicari, P. Nihoyannopoulos, A. Evangelista, J. Kasprzak, P. Lancellotti, D. Poldermans, et al., Stress Echocardiography Expert Consensus Statement–Executive Summary: European Association of Echocardiography (EAE) (a registered branch of the ESC), Eur. Heart J. 30 (2009) 278–289.
[5] K. Fox, M.A. Garcia, D. Ardissino, P. Buszman, P.G. Camici, F. Crea, et al., Guidelines on the management of stable angina pectoris: executive summary: the Task Force on the Management of Stable Angina Pectoris of the European Society of Cardiology, Eur. Heart J. 27 (2006) 1341–1381.
[6] Y. Kwok, C. Kim, D. Grady, M. Segal, R. Redberg, Meta-analysis of exercise testing to detect coronary artery disease in women, Am. J. Cardiol. 83 (1999) 660–666.
[7] R.S. Gibson, The diagnostic and prognostic value of exercise electrocardiography in asymptomatic subjects and stable symptomatic patients, Curr. Opin. Cardiol. 6 (1991) 536–546.
[8] E.A. Ashley, J. Myers, V. Froelicher, Exercise testing in clinical medicine, Lancet 356 (2000) 1592–1597.
[9] R.J. Gibbons, G.J. Balady, J.T. Bricker, B.R. Chaitman, G.F. Fletcher, V.F. Froelicher, et al., ACC/AHA 2002 guideline update for exercise testing: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice guidelines (Committee to Update the 1997 Exercise Testing guidelines), Circulation 106 (2002) 1883–1892.
[10] J.E. Adams 3rd, G.S. Bodor, V.G. Davila-Roman, J.A. Delmez, F.S. Apple, J.H. Ladenson, et al., Cardiac troponin I. a marker with high specificity for cardiac injury, Circulation 88 (1993) 101–106.
[11] K. Thygesen, J.S. Alpert, A.S. Jaffe, M.L. Simoons, B.R. Chaitman, H.D. White, et al., Third universal definition of myocardial infarction, Circulation 126 (2012) 2020–2035.
[12] F.S. Apple, P.O. Collinson, Biomarkers ITFoCAoC, Analytical characteristics of high-sensitivity cardiac troponin assays, Clin. Chem. 58 (2012) 54–61.
[13] K. Thygesen, J. Mair, E. Giannitsis, C. Mueller, B. Lindahl, S. Blankenberg, et al., How to use high-sensitivity cardiac troponins in acute cardiac care, Eur. Heart J. 33 (2012) 2252–2257.
[14] F.S. Apple, R. Ler, M.M. Murakami, Determination of 19 cardiac troponin I and T assay 99th percentile values from a common presumably healthy population, Clin. Chem. 58 (2012) 1574–1581.
[15] J.A. de Lemos, M.H. Drazner, T. Omland, C.R. Ayers, A. Khera, A. Rohatgi, et al., Association of troponin T detected with a highly sensitive assay and cardiac structure and mortality risk in the general population, JAMA 304 (2010) 2503–2512.
[16] C.R. Defilippi, J.A. de Lemos, R.H. Christenson, J.S. Gottdiener, W.J. Kop, M. Zhan, et al., Association of serial measures of cardiac troponin T using a sensitive assay with incident heart failure and cardiovascular mortality in older adults, JAMA 304 (2010) 2494–2502.
[17] T. Omland, J.A. de Lemos, M.S. Sabatine, C.A. Christophi, M.M. Rice, K.A. Jablonski, et al., A sensitive cardiac troponin T assay in stable coronary artery disease, N. Engl. J. Med. 361 (2009) 2538–2547.
[18] J.T. Saunders, V. Nambi, J.A. de Lemos, L.E. Chambless, S.S. Virani, E. Boerwinkle, et al., Cardiac troponin T measured by a highly sensitive assay predicts coronary heart disease, heart failure, and mortality in the Atherosclerosis Risk in Communities Study, Circulation 123 (2011) 1367–1376.
[19] W. Ahmed, C.L. Schlett, S. Uthamalingam, Q.A. Truong, W. Koenig, I.S. Rogers, et al., Single resting hsTnT level predicts abnormal myocardial stress test in acute chest pain patients with normal initial standard troponin, J. Am. Coll. Cardiol. Img. 6 (2013) 72–82.
[20] M.S. Sabatine, D.A. Morrow, J.A. de Lemos, P. Jarolim, E. Braunwald, Detection of

acute changes in circulating troponin in the setting of transient stress test-induced myocardial ischaemia using an ultrasensitive assay: results from TIMI 35, Eur. Heart J. 30 (2009) 162–169.
[21] Y. Tian, J. Nie, C. Huang, K.P. George, The kinetics of highly sensitive cardiac troponin T release after prolonged treadmill exercise in adolescent and adult athletes, Journal of applied physiology Bethesda Md: 1985 113 (2012) 418–425.
[22] M. Siriwardena, V. Campbell, A.M. Richards, C.J. Pemberton, Cardiac biomarker responses to dobutamine stress echocardiography in healthy volunteers and patients with coronary artery disease, Clin. Chem. 58 (2012) 1492–1494.
[23] G. Lee, R. Twerenbold, Y. Tanglay, T. Reichlin, U. Honegger, M. Wagener, et al., Clinical benefit of high-sensitivity cardiac troponin I in the detection of exercise-induced myocardial ischemia, Am. Heart J. 173 (2016) 8–17.
[24] V.G. Davila-Roman, A.D. Waggoner, G.A. Sicard, E.M. Geltman, K.B. Schechtman, J.E. Perez, Dobutamine stress echocardiography predicts surgical outcome in patients with an aortic aneurysm and peripheral vascular disease, J. Am. Coll. Cardiol. 21 (1993) 957–963.
[25] E. Giannitsis, K. Kurz, K. Hallermayer, J. Jarausch, A.S. Jaffe, H.A. Katus, Analytical validation of a high-sensitivity cardiac troponin T assay, Clin. Chem. 56 (2010) 254–261.
[26] J. Scherr, S. Braun, T. Schuster, C. Hartmann, S. Moehlenkamp, B. Wolfarth, et al., 72-h kinetics of high-sensitive troponin T and inflammatory markers after marathon, Med. Sci. Sports Exerc. 43 (2011) 1819–1827.
[27] F. Sedaghat-Hamedani, E. Kayvanpour, L. Frankenstein, D. Mereles, A. Amr, S. Buss, et al., Biomarker changes after strenuous exercise can mimic pulmonary embolism and cardiac injury–a metaanalysis of 45 studies, Clin. Chem. 61 (2015) 1246–1255.
[28] A. Legaz-Arrese, I. Lopez-Laval, K. George, J.J. Puente-Lanzarote, C. Mayolas-Pi, E. Serrano-Ostariz, et al., Impact of an endurance training program on exercise-induced cardiac biomarker release, Am. J. Physiol. Heart Circ. Physiol. 308 (2015) H913–H920.
[29] R. Roysland, G. Kravdal, A.D. Hoiseth, S. Nygard, P. Badr, T.A. Hagve, et al., Cardiac troponin T levels and exercise stress testing in patients with suspected coronary artery disease: the Akershus Cardiac Examination (ACE) 1 study, Clin Sci (Lond). 122 (2012) 599–606.
[30] S.M. Sou, C. Puelacher, R. Twerenbold, M. Wagener, U. Honegger, T. Reichlin, et al., Direct comparison of cardiac troponin I and cardiac troponin T in the detection of exercise-induced myocardial ischemia, Clin. Biochem. 49 (2016) 421–432.
[31] N. Wongpraparut, S. Piyophirapong, A. Maneesai, K. Sribhen, R. Krittayaphong, R. Pongakasira, et al., High-sensitivity cardiac troponin T in stable patients undergoing pharmacological stress testing, Clin. Cardiol. 38 (2015) 293–299.
[32] A.T. Turer, T.A. Addo, J.L. Martin, M.S. Sabatine, G.D. Lewis, R.E. Gerszten, et al., Myocardial ischemia induced by rapid atrial pacing causes troponin T release detectable by a highly sensitive assay: insights from a coronary sinus sampling study, J Am Coll Cardiol. 57 (2011) 2398–2405.
[33] F.S. Apple, Y. Sandoval, A.S. Jaffe, J. Ordonez-Llanos, ITFoCAoC Bio-Markers, Cardiac Troponin Assays: Guide to Understanding Analytical Characteristics and their Impact on Clinical Care, Clin. Chem. 63 (2017) 73–81.
[34] F.S. Apple, A.S. Jaffe, P. Collinson, M. Mockel, J. Ordonez-Llanos, B. Lindahl, et al., IFCC educational materials on selected analytical and clinical applications of high sensitivity cardiac troponin assays, Clin. Biochem. 48 (2015) 201–203.
[35] A.H.B. Wu, R.H. Christenson, D.N. Greene, A.S. Jaffe, P.A. Kavsak, J. Ordonez-Llanos, et al., Clinical Laboratory Practice Recommendations for the use of Cardiac Troponin in Acute Coronary Syndrome: Expert Opinion from the Academy of the American Association for Clinical Chemistry and the Task Force on Clinical applications of Cardiac Bio-Markers of the International Federation of Clinical Chemistry and Laboratory Medicine, Clin. Chem. 64 (2018) 645–655.