Direct comparison of cardiac Troponin I and cardiac Troponin T in the detection of exercise-induced myocardial ischemia

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ABSTRACT

Background: It is unknown, whether cardiac troponin (cTn) I or cTnT is the preferred biomarker in the detection of exercise-induced myocardial ischemia.

Methods: We investigated patients with suspected myocardial ischemia referred for exercise or pharmacological rest/stress myocardial perfusion single-photon emission computed tomography (SPECT) to directly compare the diagnostic accuracy of high-sensitivity cTnI (hs-cTnI) and hs-cTnT. Diagnostic performance were analyzed separately according to stress modality. Hs-cTnI and hs-cTnT were measured before, immediately after, as well as 2h and 4h after maximal exercise in a blinded fashion. Further, all clinical information available to the treating cardiologist was used to quantify the clinical judgment regarding the presence of myocardial ischemia using a visual analogue scale twice: once prior and once after stress-testing. The presence of stress-induced myocardial ischemia was adjudicated using SPECT combined with coronary angiography findings.

Result: A total of 403 consecutive patients were enrolled in our study, of which 229 underwent exercise stress and 174 patients pharmacological stress. Exercise-stress-induced myocardial ischemia was detected in 90 patients (39.3% of 229). Levels of hs-cTnI and hs-cTnT were both significantly higher at all time-points examined in patients with exercise-induced myocardial ischemia as compared to patients without myocardial ischemia (all $p < 0.001$). Correlation of hs-cTnI and hs-cTnT was high in direct comparison of time-points (Spearman's ρ all ≥ 0.7). The AUC for baseline/peak/2h/4h for hs-cTnI and hs-cTnT were 0.71/0.71/0.72/0.69 vs. 0.74/0.73/0.71/0.72, respectively (all $p = \text{ns}$ for hs-cTnI versus hs-cTnT). In patients undergoing pharmacological stress, the AUC for baseline/peak/2h/4h for hs-cTnI and hs-cTnT were 0.66/0.66/0.68/0.67 and 0.61/0.62/0.64/0.59, respectively (all $p = \text{ns}$ for

hs-cTnI versus hs-cTnT). Also the combinations including clinical judgment or changes during serial sampling were similar for hs-cTnI and hs-cTnT (all $p=ns$).

Conclusions: Hs-cTnI and hs-cTnT provide comparable diagnostic information regarding exercise-induced myocardial ischemia. Overall, their diagnostic accuracy seems moderate.

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INTRODUCTION

Ischemic heart disease (IHD) is the main cause of mortality and morbidity in the United States and Europe.[1,2] Accurate and early diagnosis of IHD is one of the most important tasks in medicine, as cardiovascular events including death can be prevented effectively by starting behavioral and pharmacological treatment in symptomatic as well as in asymptomatic patients at an early stage.[3] The detection of myocardial ischemia usually requires imaging techniques.[4,5] However, the use of imaging techniques has recently come under scrutiny: While they are very valuable clinical tools, they unfortunately have important limitations, are associated with high costs and inherent risks, and seem to be used increasingly inappropriately also in patients with very low pre-test probability. Further, most of them provide anatomical, but no functional information. For clinical practice, functional information differentiating coronary lesions that cause exercise-induced myocardial ischemia from functionally irrelevant lesions is critical.[6–8]

In contrast to the early diagnosis of acute myocardial infarction (AMI), in current clinical practice cardiac biomarkers do not have a role in the detection of stable IHD and exercise-induced myocardial ischemia. Cardiac troponin (cTn) is a protein complex which consists of three subunits, cTnI (inhibitory; molecular weight approximately 23 kDa), cTnT (tropomyosin-binding; molecular weight approximately

35 kDa) and TnC (Ca^{2+} -binding; molecular weight approximately 18 kDa). These subunits are crucial in regulation of cardiac muscle contraction.[9] CTnI and cTnT are unique to cardiomyocytes and are specific and sensitive biomarkers of myocardial injury.[10–12] Due to irreversible cardiomyocyte necrosis cTnI and cTnT are released as both intact proteins and their degraded products.[13] Hence high-sensitivity (hs) cTn assays are widely used in the diagnostic pathways for AMI.[14–16] Substantial biochemical differences between intact cTnI and T and their degraded products could result in different diagnostic performance.[9,17] Previous studies indicate that cTn can also be used for detecting reversible myocardial ischemia. Which analyte (cTnI or cTnT) would be preferable for this novel indication is poorly known.[18–20]

Therefore, the aim of this study was to directly compare hs-cTnI and hs-cTnT using two clinically-used hs-assays for the detection of stress-induced myocardial ischemia.

METHODS

Patient population

Biochemical And Electrocardiographic Signatures in the Detection of Exercise-induced MyocardiaL Ischemia (BASEL VIII) is an ongoing prospective observational study designed and coordinated by the University Hospital Basel, Switzerland.

From January 2010 to August 2010, consecutive patients referred for IHD evaluation by rest/stress myocardial perfusion SPECT at the University Hospital Basel were eligible for this study. This cohort included patients with suspected stable IHD as well as patients with suspected unstable IHD after initial stabilization on medical therapy. Patients with one of both biomarker measurements missing were excluded from analysis (n=113). The diagnostic performance of hs-cTnI and hs-cTnT was analyzed separately according to stress modality (exercise (n=229) versus pharmacological (n=174)).

The study was conducted according to the principles of the Declaration of Helsinki and approved by the local ethics committee. Written informed consent was obtained from all participating patients.

Rest/stress myocardial perfusion SPECT protocol

All patients underwent routine rest/stress (bicycle ergometry or pharmacological stress) dual isotope (^{201}Tl rest/ $^{99\text{m}}\text{Tc}$ sestamibi) myocardial perfusion SPECT protocol as previously described.[21–23] Rest-SPECT was obtained 30 minutes after administration of 111 MBq ^{201}Tl . Bicycle ergometry exercise stress test using standard protocols was performed symptom limited with a 12-lead ECG recording continuous monitoring of the ECG throughout the test. If bicycle ergometry test was not possible or sufficient, pharmacological stress (adenosine 140 $\mu\text{g/kg}$ per minute for 6 minutes) was used, either combined with exercise on lowest physical load or

pharmacological only. Image acquisition was performed using standard protocols.[24–26]

Adjudicated final diagnosis and image interpretation

The final diagnosis of stress-induced myocardial ischemia was based on expert interpretation of perfusion images. If coronary angiography was performed, angiography findings were considered in adjudication. Although interpretation of MPI-SPECT images was used as the sole reference standard in previous studies[19,20,27,28], we chose to add data from coronary angiography to further improve the accuracy of perfusion images as the gold standard. Coronary angiography was used to overrule the interpretation of perfusion images only when its findings were contradictory to MPI-SPECT findings, for example, showing normal coronary arteries in patients with a perfusion scan indicating ischemia, or in case of a negative MPI-SPECT result, with coronary angiography, showing a high-grade lesion. Perfusion images were scored semiquantitatively using a 17-segments model with a 5-point scale (0=normal, 1=mildly reduced tracer uptake, 2 =moderately reduced uptake, 3=severely reduced uptake and 4 =no uptake). Summed stress score (SSS) and summed rest score (SRS) were calculated by adding the scores of the 17 segments in the stress and rest images, respectively. Summed difference score (SDS) was derived as the difference between stress and rest scores. According to previous work, for the degree of reversibility, SDS less than 2 was considered nonischemic, and 2 or more ischemic.[21–23] SSS and SRS were derived by visual assessment (2 readers) and compared to the software (QGSTM) result. Differences in the visual assessment by the two readers were resolved by finding consent. Perfusion images readings were blinded to hs-cTn levels.

Assessment of pre-test probability on a visual analogue scale

Pre-test probability for the presence of stress-induced ischemia estimated by the examining cardiologist was quantified using a visual analog scale with values between 0 and 100 percent (in steps of 5). Pre-test probability was determined twice: once before stress testing on the basis of age, gender, baseline ECG data, previous cardiac history and detailed evaluation of symptoms as described in previous work;^[4,29,30] a second time after stress testing but before SPECT imaging, at which the cardiologist added the findings of the stress testing including ST-segment changes during exercise ECG, achieved physical load and heart rate, drop of blood pressure, and patients symptoms. In pharmacologically stressed patients appropriate exercise findings were lacking. The cardiologist was blinded to hs-cTn levels as well as myocardial perfusion SPECT results at the time of the assessment.

Blood sampling and laboratory methods

Blood samples were taken from a peripheral venous catheter before, immediately after, as well as 2 h and 4 h after stress. Blood withdrawal was not possible at all times in all patients due to technical issues. Blood samples were placed in serum tubes for hs-cTnI and EDTA plasma tubes for hs-cTnT. After centrifugation, samples were frozen at -80°C for three years until assayed in a blinded fashion in a dedicated core laboratory. There were no freeze-thaw cycles, which ensures the stability of hs-cTnT and hs-cTnI under these conditions.^[31–33] The Roche hs-cTnT assay was measured on Modular® Analytics E170 (Roche Diagnostics). The limit of blank (LoB) and limit of detection (LoD) were determined to be 3ng/l and 5ng/l respectively. The 99th-percentile of a healthy reference population was reported at 14ng/l with an imprecision corresponding to 10% coefficient of variation (CV) at 13ng/l.^[34] The Abbott hs-cTnI assay used was the final pre-commercial release version of the ARCHITECT High Sensitive STAT Troponin I assay (Abbott Laboratories, Abbott Park, IL) blinded by laboratory technicians to patient data. Samples were thawed,

mixed, and centrifuged (for 30 minutes at 3,000 rcf and 4°C for serum samples or for 10 minutes, twice, at 3,000 rcf for plasma samples) prior to analysis and according to manufacturer's instructions. The hs-cTnI assay has a 99th percentile concentration of 26.2ng/l with a corresponding co-efficient of variation (CV) of <5% and a limit of detection of 1.9ng/l.[35]

Statistical analysis

Baseline characteristic were compared using Students t-test, Mann-Whitney-U test or Chi-square test as appropriate. Data are expressed as counts and percentages, mean $\pm$ standard deviation, or median and interquartile range as appropriate.

Distribution of levels of cTn was determined by Kolmogorow-Smirnoff test and then compared by Mann-Whitney U test. Correlation between biomarkers variables was made using Spearman's rank correlation coefficient. Receiver operating characteristics (ROC) curves were constructed to assess the sensitivity and specificity of both assays, to allow comparison of their diagnostic performance in exercise-induced and pharmacologically-induced myocardial ischemia. The comparison of AUC was performed as recommended by deLong et al.[36] Combination of pre-test probability with log-transformed high-sensitivity cardiac troponin I and T levels (because of non-normal distribution) was done using a binary logistic regression model to calculate mean predicted values.

Combination of delta change and the baseline value was done using a binary logistic regression model.

All hypothesis testing was two-tailed and p-value of less than 0.05 was considered statistically significant. All statistical analyses were performed using SPSS for Windows 21.0 (SPSS Inc, Chicago, IL) and MedCalc 9.6.4.0 (MedCalc software, Mariekerke, Belgium).

RESULTS

Patient characteristics

Baseline characteristics of 403 consecutive patients are listed in Table 1A/B. The exercise-stress group had 229 patients (56.8%), the pharmacological group had 174 patients (43.2%). Exercise-induced myocardial ischemia was detected in 90 patients (39.3%), pharmacologically induced myocardial ischemia was detected in 94 patients (54%).

Reclassified patients due to coronary angiography

A total of 160 patients (39.7%) underwent coronary angiography, 1 patient (0.2%) was reclassified to the ischemic group, and 8 patients (2%) were reclassified to the nonischemic group.

Hs-cTnI and Hs-cTnT are associated with myocardial ischemia

As shown in Figure 1A/B and Table 2, patients with exercise-induced myocardial ischemia had significantly higher levels of hs-cTnI and hs-cTnT at all time-points compared to patients without ischemia. Similarly, patients with pharmacologically induced myocardial ischemia also had higher levels of hs-cTnI and hs-cTnT at all time-points compared to patients without ischemia.

Diagnostic performance of hs-cTnI and T

Exercise stress test

Overall, AUC for exercise-induced myocardial ischemia were similar for both analytes. As shown in Figure 2A, AUC for hs-cTnI at rest was 0.72 (95% confidence interval (95%CI) 0.65-0.77), and AUC for hs-cTnT was 0.73 (95%CI 0.67-0.78, $p=0.73$). Immediately after exercise AUC for hs-cTnI was 0.72 (95%CI 0.66-0.78), and AUC for hs-cTnT was 0.71 (95%CI 0.65-0.77, $p=0.79$). 2 hours after exercise AUC for hs-cTnI was 0.73 (95%CI 0.67-0.79), and AUC for hs-cTnT was 0.71 (95%CI

0.64-0.77, $p=0.37$). 4 hours after exercise AUC for hs-cTnI was 0.72 (95%CI 0.62-0.8), and AUC for hs-cTnT was 0.69 (95%CI 0.6-0.78, $p=0.56$).

Pharmacologic stress test

Overall, AUC for pharmacologically-induced myocardial ischemia were also similar for both analytes. As shown in Figure 2B, AUC for hs-cTnI at rest was 0.66 (95%CI 0.58-0.73), and AUC for hs-cTnT was 0.61 (95%CI 0.53-0.68, $p=0.15$). Immediately after stress AUC for hs-cTnI was 0.66 (95%CI 0.58-0.73), and AUC for hs-cTnT was 0.62 (95%CI 0.54-0.69, $p=0.3$). 2 hours after stress AUC for hs-cTnI was 0.68 (95%CI 0.6-0.75), and AUC for hs-cTnT was 0.64 (95%CI 0.56-0.71, $p=0.26$). 4 hours after stress AUC for hs-cTnI was 0.67 (95%CI 0.56-0.77), and AUC for hs-cTnT was 0.59 (95%CI 0.47-0.72, $p=0.11$).

Incremental value of hs-cTnI and hs-cTnT to clinical assessment after stress

To evaluate whether hs-cTnI and hs-cTnT levels provide different incremental value for clinical practice, we compared hs-cTnI and hs-cTnT combined with clinical assessment after stress using ROC curves according to stress modality.

Hs-cTnI with exercise stress test

As shown in Figure 3A, the combination of hs-cTnI at rest and clinical assessment after exercise had an AUC of 0.77 (95%CI 0.71-0.82), which was significantly higher than the AUC for clinical assessment (0.72 (95%CI 0.65-0.77)) alone ($p=0.036$). Similar results were obtained for the time-points immediately after stress and 2h after stress. Combination of hs-cTnI 4h after stress and clinical assessment showed no significantly higher AUC compared to clinical assessment alone ($p=0.17$).

Hs-cTnT with exercise stress test

As shown in Figure 3B, the combination of hs-cTnT at rest and clinical assessment after exercise had an AUC of 0.78 (95%CI 0.72-0.84), which was significantly higher than the AUC for clinical assessment (0.72 (95%CI 0.65-0.77)) alone ($p=0.009$) and

AUC for hs-cTnT at rest, respectively (0.73 (95%CI 0.66-0.78), $p=0.034$). Similar results were obtained for hs-cTnT immediately after stress. Combination of hs-cTnT 2h after stress and clinical assessment after exercise had an AUC of 0.77 (95%CI 0.71-0.83), which was significantly higher as compared to the AUC for hs-cTnT (0.71 (95%CI 0.64-0.77)) alone ($p=0.024$). Combination of hs-cTnT 4h after stress and clinical assessment showed no significantly higher AUC compared to clinical assessment alone ($p=0.41$).

Hs-cTnI with pharmacologic stress test

As shown in Figure 4A, the combination of hs-cTnI at rest and clinical assessment after pharmacological stress test had an AUC of 0.75 (95%CI 0.68-0.82), which was only slightly and not statistically significant higher than the AUC for clinical assessment (0.72 (95%CI 0.64-0.79) only ($p=0.176$)). Similar results were obtained for the later time-points.

Hs-cTnT with pharmacologic stress test

As shown in Figure 4B, the combination of hs-cTnT at rest and clinical assessment after pharmacological stress had an AUC of 0.74 (95%CI 0.67-0.81), which was only slightly and not statistically significant higher than the AUC for clinical assessment (0.72 (95%CI 0.64-0.79) only ($p=0.268$)). Similar results were obtained for the later time-points.

Diagnostic performance of delta values in hs-cTnI and hs-cTnT

We compared the baseline value of hs-TnI and the baseline value of hs-cTnT with the delta change and the combination of both using ROC curves according to stress modality.

Exercise stress: hs-cTnI, delta change and its combination

As shown in Figure 5A, during exercise stress combination of delta change in serial measurements and baseline hs-cTnI showed comparable diagnostic performances, respectively (all p=ns).

Similar results were obtained with hs-cTnT.

Pharmacological stress

As shown in Figure 5B, during pharmacological stress similar results were obtained in comparison to exercise stress.

Correlation of hs-cTnI and hs-cTnT

As shown in Figure 6, in direct comparison of each time-point biomarkers showed high correlation (Spearman's $\rho \geq 0.7$, all P-values < 0.0001).

DISCUSSION

The aim of this prospective diagnostic study was to directly compare hs-cTnI and T for the detection of myocardial ischemia. We report six major findings: First, patients with myocardial ischemia had significantly higher levels of hs-cTnI and hs-cTnT at all time-points than patients without ischemia. Second, hs-cTnI and hs-cTnT provided comparable diagnostic accuracy with similar AUCs at all time-points. Third, in patients, in whom exercise could be used to induce myocardial ischemia, hs-cTnI and hs-cTnT provided higher diagnostic accuracy as compared to patients in whom pharmacological stress was used. Likely this reflects the higher prevalence of cardiac and non-cardiac comorbidities in patients undergoing pharmacological stress. Fourth, measurements of hs-cTnI and hs-cTnT during or after stress testing do not provide added value on top of measurements at rest. This suggests that myocardial ischemia during the exercise associated with daily physical activities is sufficient as trigger for the release of hs-cTn. Fifth, hs-cTnI and hs-cTnT provided statistically significant increment in diagnostic accuracy on top of clinical assessment after exercise testing (including exercise ECG-findings), but only a trend in patients undergoing pharmacological testing. Again, the increment was present for both hs-cTnI and hs-cTnT. Sixth, assessment of changes in hs-cTnI and hs-cTnT had no incremental diagnostic value versus the hs-cTn blood concentration at rest.

Our findings of comparable diagnostic accuracy of hs-cTnI and hs-cTnT are supported by a small pilot study with a very low prevalence of myocardial ischemia (<10%)[28]. These findings extend and corroborate previous studies examining the possible clinical use of cardiac biomarkers in the evaluation of patients with suspected myocardial ischemia [6,19,20,27,28]. Overall, these studies support the concept that not only irreversible cardiomyocyte necrosis, but also reversible cardiomyocyte injury such as exercise induced myocardial ischemia results in a

detectable release of cTn when using hs-cTn assays.[37–40]

Further research is necessary before the possible routine clinical use of hs-cTnI or hs-cTnT in this indication should be considered. Although we found strong evidence for a comparable accuracy of both analytes, the diagnostic accuracy of hs-cTn alone as well as the incremental value on top of clinical assessment including the exercise-ECG findings is moderate. Options for further improvements include their use in combination with other cardiovascular biomarkers as well as the use in patients without pre-existing IHD and with a low clinical probability of myocardial ischemia.[6,19,20,27,28]

Some limitations of this study should be considered. First, we cannot comment on the diagnostic accuracy of hs-cTnI and hs-cTnT in patients with terminal renal failure requiring dialysis as well as patients with baseline ECG abnormalities that were not interpretable for myocardial ischemia, as those patients were excluded from the study. Second, we used rest/ergometry stress MPI SPECT combined with coronary angiography and in some cases also coronary flow reserve as the gold standard to adjudicate the presence or absence of myocardial ischemia. However, as these coronary angiography and coronary flow reserve were only performed when clinically indicated, these were not available in addition to MPI-SPECT in all patients. Still, it seems fair to state that this study used the most accurate adjudication process ever performed in this setting.[6,19,20,27,28]

In conclusion, hs-cTnI and hs-cTnT seem to provide comparable diagnostic accuracy regarding the detection of exercise-induced myocardial ischemia. Overall, their diagnostic accuracy seems moderate.

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Table 1A Baseline characteristics of all patients in the different stress modalities

Patients characteristics	All patients (n=403)	Exercise (n=229)			Pharmacological (n=174)			Overall
		No ischemia (n=139)	Ischemia (n=90)	P-value	No ischemia (n=80)	Ischemia (n=94)	P-value	P-value ¹⁾
Age, years	66 (57-74)	62 (53-69)	66 (58-73)	0.011	68 (59-77)	69 (59-77)	0.825	<0.0001
Male sex (%)	285 (70.7)	89 (64.0)	70 (77.8)	0.027	44 (55.0)	82 (87.2)	<0.0001	0.515
BMI, kg/m ²	27.0 (24.5-30.4)	26.7 (24.5-30.3)	26.6 (24.5-29.4)	0.78	27 (23.9-30.8)	27.9 (25.2-30.5)	0.22	0.125
Comorbidities								
Diabetes mellitus (%)	96 (23.8)	21 (15.1)	22 (24.4)	0.077	24 (30.0)	29 (30.9)	0.903	0.006
Hypertension (%)	304 (75.4)	89 (64.0)	74 (82.2)	0.003	65 (81.3)	76 (80.9)	0.947	0.023
Hypercholesterolemia (%)	241 (59.8)	70 (50.4)	58 (64.4)	0.036	48 (60.0)	65 (69.1)	0.207	0.067
Former smoker (%)	167 (41.4)	55 (39.6)	44 (48.9)	0.164	29 (36.3)	39 (41.5)	0.480	0.402
Current smoker (%)	74 (18.4)	22 (15.8)	12 (13.3)	0.604	18 (22.5)	22 (23.4)	0.888	0.037
Family history of cardiovascular disease (%)	119 (29.5)	41 (29.5)	32 (35.6)	0.337	18 (22.5)	28 (29.8)	0.277	0.236
Known ischemic heart disease (%)	202 (50.1)	36 (25.9)	57 (63.3)	<0.0001	33 (41.3)	76 (80.9)	<0.0001	<0.0001
Prior myocardial infarction (%)	137 (34.0)	23 (16.5)	33 (36.7)	0.001	24 (30.0)	57 (60.6)	<0.0001	<0.0001
Prior percutaneous intervention (%)	150 (37.2)	30 (21.6)	45 (50.0)	<0.0001	18 (22.5)	57 (60.6)	<0.0001	0.033
Prior coronary bypass grafting (%)	60 (14.9)	7 (5.0)	13 (14.4)	0.014	11 (13.8)	29 (30.9)	0.008	<0.0001
Peripheral artery disease (%)	43 (10.7)	9 (6.5)	6 (6.7)	0.954	9 (11.3)	19 (20.2)	0.109	0.002
Cerebrovascular disease (%)	27 (6.7)	7 (5.0)	5 (5.6)	0.863	6 (7.5)	9 (9.6)	0.627	0.179
Chronic obstructive pulmonary disease (%)	45 (11.2)	10 (7.2)	9 (10.0)	0.452	14 (17.5)	12 (12.8)	0.383	0.036
Atrial fibrillation (%)	44 (10.9)	12 (8.6)	3 (3.3)	0.113	17 (21.3)	12 (12.8)	0.134	0.001
Medication								
ACE inhibitor (%)	133 (33.0)	31 (22.3)	26 (28.9)	0.260	29 (36.3)	47 (50.0)	0.068	0.294
Angiotensin receptor blocker (%)	121 (30.0)	34 (24.5)	32 (35.6)	0.070	33 (41.3)	22 (23.4)	0.012	0.856
Beta blocker (%)	247 (61.3)	60 (43.2)	59 (65.6)	0.001	49 (61.3)	79 (84.0)	0.001	<0.0001
Calcium antagonist (%)	92 (22.8)	16 (11.5)	22 (24.4)	0.010	21 (26.3)	33 (35.1)	0.208	0.014
Diuretic (%)	141 (35.0)	38 (27.3)	24 (26.7)	0.911	43 (53.8)	36 (38.3)	0.041	<0.0001
Nitrate (%)	60 (14.9)	10 (7.2)	12 (13.3)	0.124	10 (12.5)	28 (29.8)	0.006	0.545
Statin (%)	241 (59.8)	62 (44.6)	63 (70.0)	<0.0001	44 (55.0)	72 (76.6)	0.003	<0.0001
Aspirin (%)	250 (62.0)	64 (46.0)	73 (81.1)	<0.0001	40 (50.0)	73 (77.7)	<0.0001	0.001
Clopidogrel (%)	84 (20.8)	14 (10.1)	33 (36.7)	<0.0001	13 (16.3)	24 (25.5)	0.136	<0.0001
Oral anticoagulation (%)	50 (12.4)	14 (10.1)	1 (1.1)	0.007	20 (25.0)	15 (16.0)	0.138	0.001

Data are presented as number (percentage) or median (interquartile range). P-values were based on Mann-Whitney U tests or Chi-square tests. BMI = Body mass index, ACE = Angiotensin converting enzyme. 1) Overall p-value of all patients between exercise stressed and pharmacologically stressed patients

Table 1B Test characteristics of all patients in the different stress modalities

	All patients (n=403)	Exercise (n=229)			Pharmacological (n=174)			Overall
Exercise testing		No ischemia (n=139)	Ischemia (n=90)	P-value	No ischemia (n=80)	Ischemia (n=94)	P-value	P-value ¹⁾
Maximal work load, W	90 (35-140)	130 (100-170)	125 (100-155)	0.26	25 (0-40)	35 (0-55)	0.094	<0.0001
Maximal heart rate, bpm	130 (107-(148)	148 (135-159)	140 (130-149)	0.003	106 (91-120)	100 (84-111)	0.007	<0.0001
Maximal syst. blood pressure, mmHg	162 (143-(187)	176 (154-194)	178 (159-202)	0.149	148 (127-167)	143 (124-163)	0.286	<0.0001
Rate pressure product, mmHg*bpm	21798 (15680-26467)	25476 (22079-29073)	25088 (21971-28914)	0.491	15965 (11856-20241)	14445 (10087-17667)	0.019	<0.0001
Exercise time, m:ss	5:14 (4:13-6:00)	5:14 (4:14-6:03)	5:14 (4:04-6:00)	0.551	- -	- -	-	
Exercise on antianginal drugs (%)	102 (46,8)	59 (55.1)	18 (33.3)	0.009	18 (54.5)	7 (29,2)	0.057	0.606
Ischemic stress ECG (%)	69 (17,1)	11 (7.9)	34 (37.8)	<0.0001	4 (5.0)	20 (21,3)	0.002	0.122
Symptomatic bicycle ergometry (%)	74 (18,4)	15 (10.8)	22 (24.4)	0.006	11 (13.8)	26 (27,7)	0.025	0.190
Myocardial perfusion SPECT								
Summed rest score	2 (0-6)	0 (0-2)	4 (0-7)	<0.0001	0 (0-3)	7 (2-11)	<0.0001	<0.0001
Summed stress score	4 (0-11)	0 (0-3)	10 (6-15)	<0.0001	0 (0-4)	13 (6-20)	<0.0001	0.001
Summed difference score	1 (0-5)	0 (0-0)	5 (4-7)	<0.0001	0 (0-0)	5 (3-9)	<0.0001	0.035
Transient Ischemic Dilation (%)	29 (7,2)	1 (0.7)	13 (14.4)	<0.0001	1 (1.3)	14 (14.9)	0.001	0.335
End-diastolic volume, ml	94 (71-122)	86 (62-103)	93 (76-121)	0.009	90 (71-120)	131 (95-167)	<0.0001	<0.0001
End-systolic volume, ml	41 (27-61)	32 (22-46)	42 (28-61)	0.001	35 (26-59)	65 (42-103)	<0.0001	<0.0001
Post stress LVEF, %	57 (49-64)	61 (53-68)	55 (48-63)	<0.0001	58 (50-66)	50 (38-56)	<0.0001	<0.0001

Data are presented as number (percentage) or median (interquartile range). P-values were based on Mann-Whitney U tests or Chi-square tests.

1) Overall p-value of all patients between exercise stressed and pharmacologically stressed patients; W=watts, bpm=beats per minute, ECG=electrocardiogram, LVEF=Left ventricular ejection fraction

Table 2 Direct comparison of cardiac Troponin I and T in the different stress modalities

	Exercise				Pharmacological			All patients (n=403)	Overall <i>P</i> -value
	No ischemia	Ischemia	<i>P</i> -value		No ischemia	Ischemia	<i>P</i> -value		
Hs-cTnI levels in ng/l									
At Rest (n=229)	2.9 (1.9-5.0)	5.7 (3.0-14.5)	<0.0001	At Rest (n=174)	4,1 (2,7-8,0)	6,5 (4,0-16,3)	<0.0001	4,3 (2,6-8,7)	<0.0001
Immediately after exercise (n=223)	3.3 (2.0-5.4)	6.2 (3.6-15.3)	<0.0001	Immediately after exercise (n=171)	4,9 (2,9-8,5)	6,7 (4,2-16,8)	0.001	4,9 (2,9-9,8)	<0.0001
2h after exercise (n=202)	4.0 (2.4-6.5)	7.9 (4.7-17.7)	<0.0001	2h after exercise (n=161)	4,9 (2,8-9,1)	7,5 (4,2-17,1)	<0.0001	5,5 (3,1-11,3)	0.017
4h after exercise (n=105)	5.4 (3.0-7.6)	12.1 (5.3-31.3)	<0.0001	4h after exercise (n=80)	6,3 (2,5-10,7)	9,0 (4,8-16,9)	0.008	6,8 (3,6-13,1)	0.883
Hs-cTnT levels in ng/l									
At Rest (n=229)	5 (2.9-8)	10 (6-16)	<0.0001	At Rest (n=174)	9 (3,5-18)	12,5 (7-22)	0.017	8 (4-15)	<0.0001
Immediately after exercise (n=223)	5 (2.9-9)	10 (6-17)	<0.0001	Immediately after exercise (n=171)	10 (4-18)	13,0 (7-25)	0.009	8 (4-16)	<0.0001
2h after exercise (n=202)	6 (3-9)	11 (6-18)	<0.0001	2h after exercise (n=161)	9 (3-17)	12,5 (7-28)	0.002	8 (4-16)	<0.0001
4h after exercise (n=105)	6 (2.9-11)	11 (5-21)	<0.0001	4h after exercise (n=80)	12 (4-17)	12,0 (6-17)	0.273	10 (5-16)	0.013

Data are presented as median (interquartile range). *P*-values were based on Mann-Whitney U tests or Chi-square tests.

Fig. 1A Exercise stress

High-sensitivity Troponin I and high sensitivity Troponin T in exercise-induced ischemia

Fig 1B Pharmacological stress

High-sensitivity Troponin I and high-sensitivity Troponin T in pharmacologically induced ischemia

Fig. 2A Exercise

ROC of high-sensitivity Troponin I and high-sensitivity Troponin T during exercise stress

Fig. 2B Pharmacological

ROCs of high-sensitivity Troponin I and high-sensitivity Troponin T during pharmacological stress

Fig. 3A Exercise stress

ROCs of pre-test probability, hs Troponin I and its combination during exercise stress

Fig. 3B Exercise stress

ROCs of pre-test probability, hs Troponin T and its combination during exercise stress

Fig. 4A Pharmacological stress

ROCs of pre-test probability, hs Troponin I and its combination during pharmacological stress

Fig. 4B Pharmacological stress

ROCs of pre-test probability, hs Troponin T and its combination during pharmacological stress

Fig. 5A Exercise stress: Delta change

Fig. 5B Pharmacological stress: Delta change

Table 3 Spearman's rank correlation coefficient

		Spearman-Rho			
		Hs- TnT at rest	Hs-cTnT immediately after stress	Hs-cTnT 2h after stress	Hs-cTnT 4h after stress
Hs-cTnI at rest	correlation coefficient	0.700	0.709	0.669	0.652
	P-value	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	N	403	398	372	188
Hs-cTnI immediately after stress	correlation coefficient	0.692	0.714	0.675	0.653
	P-value	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	N	395	394	367	185
Hs-cTnI 2h after stress	correlation coefficient	0.643	0.654	0.732	0.743
	Sig. (2-seitig)	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	N	365	362	363	182
Hs-cTnI 4h after stress	correlation coefficient	0.555	0.566	0.694	0.733
	P-value	< 0.0001	< 0.0001	< 0.0001	< 0.0001
	N	187	185	182	185

Fig. 6 Spearman's rank correlation coefficient

Spearman's rho