Stronger correlation with myocardial ischemia of high-sensitivity troponin T than other biomarkers

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Background. **Acute myocardial infarction (AMI) is considered a major cause of death and disability. Myocardial perfusion scintigraphy (MPS) as a non-invasive diagnostic imaging procedure and certain biomarkers associated with myocardial ischemia (ISCH), such as ischemia-modified albumin (IMA), neuropeptide Y (NPY), *N*-terminal pro b-type natriuretic peptide (NT-proBNP), and high-sensitivity troponin T (hsTnT) could probably aid in the detection of myocardial infarction.**

Methods. **Between December 2011 and June 2012, we prospectively analyzed patients who underwent a MPS study with the clinical question of myocardial ISCH. An exercise test was performed along with a MPS. Blood was drawn from the patients before exercise and the within 3 minutes from achieving maximum load and was analyzed for the aforementioned biomarkers.**

Results. **A total of 71 patients (56 men and 15 women) were enrolled with a mean age of 61 ± 12 years. Twenty-six patients (36.6%) showed reduced uptake on stress MPS images that normalized at rest, a finding consistent with ISCH. Between ISCH and non-ISCH groups, only hsTnT levels showed a significant difference with the highest levels pertaining to the former group both before (0.0075 ng/ml vs 0.0050 ng/ml, $P = 0.023$) and after stress exercise (0.0085 vs 0.0050, $P = 0.015$). The most prominent differences were seen in higher stages of the Bruce protocol (stress duration > 9.05 minutes – $P < 0.017$). None of the IMA, NPY, and NP-pro BNP showed significant differences in time between the two groups.**

Conclusions. **Although IMA, NPY, and NT-pro BNP may not detect minor ischemic myocardial insults, serum hsTnT holds a greater ability of detecting not only myocardial infarction but also less severe ischemia. Further studies with larger cohorts of patients are warranted in order to better define the role of hsTnT as a screening tool for myocardial ischemia. (J Nucl Cardiol 2019;26:1674–83.)**

Key Words: Myocardial ischemia • hsTnT • myocardial perfusion scintigraphy

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Abbreviations	
AMI	Acute myocardial infarction
ISCH	Ischemia
MPS	Myocardial perfusion scintigraphy
IMA	Ischemia-modified albumin
NPY	Neuropeptide Y
NT-proBNP	*N*-terminal pro b-type natriuretic peptide
hsTnT	High-sensitivity troponin T
AUC	Area under the curve
PPV	Positive predictive value
NPV	Negative predictive value
PCI	Primary coronary intervention
PVD	Peripheral vascular disease
CHF	Congestive heart failure
STEMI	ST elevation myocardial infarction
NSTEMI	Non-ST elevation myocardial infarction
ACS	Acute coronary syndrome

See related editorial, pp. 1684–1687

INTRODUCTION

On a worldwide basis, acute myocardial infarction (AMI) is considered a major cause of death and disability. Initiation of effective evidence-based treatment primarily depends on the timely and accurate diagnosis, but this is still not always feasible.[1] Delayed interventions result in significant increases in morbidity and mortality rates.[2,3] Clinical examination, in-depth knowledge on the ECG, and cardiac troponin testing form the cornerstones of the early diagnosis of AMI.[2,3]

Myocardial perfusion scintigraphy (MPS) has been one of the most important and common non-invasive diagnostic imaging procedures that allows for assessing myocardial perfusion and in consequence the presence of myocardial ischemia (ISCH) and its severity[4–6]; it plays a key role in establishing prognosis and assessing the effectiveness of therapy.[7]

In recent years, there has been an increasing interest in the role of biomarkers and tracers associated with myocardial dysfunction produced by ischemia with a large number of studies in the literature assessing their significance and potential clinical value.[8–10] In the present study, we sought to evaluate the utility of four specific biomarkers in the detection of myocardial ischemia, including ischemia-modified albumin (IMA), neuropeptide Y (NPY), *N*-terminal pro b-type natriuretic peptide (NT-proBNP), and high-sensitivity troponin T (hsTnT). Specifically, we aimed to correlate the alterations of the above-mentioned serum biomarkers with the detection of ischemia, as characterized by MPS imaging.

MATERIALS AND METHODS

We prospectively included seventy-one (71) consecutive patients who underwent a MPS study in the Nuclear Medicine Department of the Onassis Cardiac Surgery Center between December 2011 and June 2012 with the clinical question of myocardial ISCH. Patients with a prior history of myocardial infarction were excluded from the study. All patients signed written consent form and the study protocol was approved by the ethical committee of the Onassis Cardiac Surgery Center.

Exercise test was performed in line with the Bruce protocol and was stopped when the pre-specified heart rate goal was reached or a specific event occurred as stated by the current exercise test guidelines (chest pain, hypotension, arrhythmia, etc.)

MPS was performed according to the EANM guidelines.[11] The tracer was Tc99m (myoview). Approximately 8 mCi were injected at peak stress and the study was continued for at least 1 minute for proper tracer uptake of the myocardium. Rest study was performed 3 hours later with injection of 20 mCi Tc99m tetrofosmin. The patient was imaged 40 minutes after stress tracer injection and 50 minutes after the rest infusion. Patients were imaged with Millennium VG Gamma Camera (GE Medical Systems; France). Images were evaluated by a very experienced nuclear medicine physician, blinded to patients' clinical history or the results of stress test. The study was interpreted positive for reversible ischemia when stress defect that corresponded to coronary artery distribution, showed improvement of tracer uptake in the rest study. Results were classified as follows: 1—ischemia, 2—normal (no ischemia).

Beta-blockers were withheld before the test, starting two days before. Venous blood was collected after overnight fasting. Blood was drawn from the patients in two time points; one before exercise and the other within 3 minutes from achieving maximum load according to the Bruce protocol.

The collected blood samples were immediately placed on ice and centrifuged at 3000 rpm for 10 minutes at 4 °C (Hettich Rotina 35R centrifuge; Hettich GmbH & Co. KG, Tuttlingen, Germany). Serum samples were isolated and immediately stored at − 80 °C until analysis of the serum biomarkers was performed in duplicate as described in the protocol of the datasheet. The following Elisa human kits were used for the biomarkers under investigation: IMA (CUSABIO, CSB-E09594h), NPY (PHOENIX PHARMACEUTICAL, CAT NO EK-049-03), NT-PROBNP (YH BIORESEARCH LABORATORY, CAT.NO YHB2178Hu). Samples were analyzed with an ELISA reader system (Chemwell Awareness analyzer machine, USA). Analysis of hsTnT was performed in an Elecsys 2010 system using a high-sensitivity TROPONIN T STAT immunoassay.

STATISTICAL ANALYSIS

Data are presented as median (lower quartile-upper quartile), percentages, or absolute values. The assumption of normality in our data was checked using the Shapiro-Wilk test. Regarding variables not following the

normal distribution, non-parametric tests were exclusively used. The Mann-Whitney's *U*-test and Wilcoxon-signed rank tests were used for unpaired and paired comparisons, respectively.

In order to determine cutoff values of hsTnT representing different sensitivities (50%, 60%, 70%, 95%) for ISCH, receiver-operating characteristic curves were constructed, and the area under the curve (AUC) was estimated. Specificity, positive predictive value (PPV), and negative predictive value (NPV) including 95% confidence intervals [CI] for ISCH were determined for each level of sensitivity. Statistical analyses were performed with the statistical program IBM SPSS version 20. All probability values were 2-sided, with a level of significance of < 0.05.

RESULTS

Our study sample comprised 56 men and 15 women with a mean age of 61 ± 12 years. Patient characteristics are presented in Table 1. Twenty-six (26) from the seventy-one (71) patients (36.6%) had myocardial regions showing reduced uptake on stress MPS images that normalized at rest, a finding consistent with ISCH, according to the established criteria of the test.[11] Compared to baseline, levels of IMA, NPY, NT-proBNP, and hsTnT were all significantly increased after the stress test ($P < 0.001$), as shown in Table 2 in all patients.

IMA

Pre- [9.66 IU/mL vs 9.34 IU/mL, $P = 0.616$] and post-test IMA plasma levels [16.26 IU/mL vs 13.31 IU/ml, $P = 0.081$] were higher in the non-ISCH group compared to the ISCH group, although these differences were not statistically significant. Accordingly, the test-induced increase in IMA plasma levels between the two groups did not reach statistical significance, as well ($P = 0.288$) (Tables 3, 4).

NPY

NPY plasma levels were comparable between ISCH and non-ISCH groups both at rest and after stress [median: 0.995 ng/mL vs 1.210 ng/mL, $P = 0.886$ and 3.30 ng/mL vs 3.15 ng/mL, $P = 0.863$, respectively]. As noted for IMA, the test-induced increase in NPY plasma levels was higher in the non-ISCH group but did not reach statistical significance ($P = 0.493$) (Tables 3, 4).

Table 1. Patient characteristics

Characteristic	ISCH (n = 26)	Non-ISCH (n = 45)	*P* value
Age, years	63 ± 11	61 ± 10	0.472
BMI, Kg/m^2	27.9 ± 3.5	28.2 ± 3.1	0.734
Male sex	26 (100.0)	30 (66.7)	**0.001**
DM	11 (3.42)	9 (20,0)	0.058
FH	18 (69.2)	15 (3,33)	**0.006**
SM	19 (73.1)	19 (42.2)	**0,015**
CAD	19 (73.1)	10 (22.2)	**< 0.001**
EF%	60 [59-65]	64 [60-65,5]	**0.038**
ST deviation	17 (65.4)	23 (51.1)	0.322
Prior symptoms			0.210
Angina	7 (26.9)	13 (28.9)	
Dyspnea	2 (7.7)	0 (0.0)	
Arrhythmia	4 (15.4)	4 (8.9)	
No symptoms	13 (50.0)	28 (62.2)	
Reason for termination			**< 0.001**
Angina	12 (46.2)	5 (11.1)	
Max HR achieved	9 (34.6)	39 (86.7)	
Dyspnea	3 (11.5)	0 (0.0)	
Hypertension response	2 (7.7)	1 (2.2)	

Bold values indicate statistical significance
Values are expressed as mean ± SD, median [lower-upper quartile], or n (%)
BMI body mass index, *DM* diabetes mellitus, *FH* familial hypercholesterolemia, *SM* smoking, *CAD* coronary artery disease, *EF* ejection fraction, *ISCH* ischemia, *HR* heart rate

Table 2. Levels of IMA, NPY, NT-proBNP, and hsTnT before and after Bruce exercise test

Biomarker	PRO	PEAK	*P* value[a]
IMA (IU/mL)	9.66 (6.12–13.22)	15.40 (11.43–19.32)	< 0.001
NPY (ng/mL)	1.03 (0.94–2.95)	3.23 (2.39–5.40)	< 0.001
NT-proBNP (ng/mL)	403.12 (326.50–496.02)	1024.20 (884.98–1155.14)	< 0.001
hsTnT (ng/mL)	0.006 (0.004–0.009)	0.007 (0.004–0.010)	< 0.001

There was a significant increase in the levels of all four biomarkers after stress test ($P < 0.001$)
Data are presented as median (lower-upper quartile)
[a]Wilcoxon-Signed Rank Tests

Table 3. Association between the levels of biomarkers before and after Bruce stress test and the presence of ischemia

	Ischemia		
Biomarker	Positive n = 26	Negative n = 45	*P* value*
IMApro (IU/mL)	9.34 (4.128–13.190)	9.66 (6.910–14.165)	0.616
IMApeak (IU/mL)	13.31 (10.280–17.413)	16.26 (11.745–19.690)	0.081
NPYpro (ng/mL)	0.995 (0.880–4.408)	1.210 (0.960–2.490)	0.886
NPYpeak (ng/mL)	3.30 (2.393–5.543)	3.15 (2.175–5.650)	0.863
NT-proBNP (ng/mL)	404.96 (346.463–482.528)	403.12 (312.675–508.790)	0.711
NT-proBNPpeak (ng/mL)	1032.13 (877.433–1156.053)	1023.77 (893.430–1148.075)	0.952
hsTnTpro (ng/mL)	0.0075 (0.0040–0.0110)	0.0050 (0.0040–0.0075)	**0.023**
hsTnTpeak(ng/mL)	0.0085 (0.0050–0.0123)	0.0050 (0.0040–0.0090)	**0.015**

Bold values indicate statistical significance
Only hSTnT levels were significantly higher before and after the stress test in the ISCH group, compared to the non-ISCH group
Data are presented as median (lower-upper quartile)
*Mann-Whitney *U*

NT-pro BNP

NT-pro BNP plasma levels were also comparable between the two study groups either before or after stress (median: 404.96 ng/mL vs 403.12 ng/mL, $P = 0.711$ and 1032.13 vs 1023.77, $P = 0.952$, respectively), showing no significant increase after stress test ($P = 0.445$)

hsTnT

In contrast to the above-mentioned biomarkers, patients in the ISCH group had significantly higher baseline plasma hsTnT levels compared to those in the non-ISCH group (median: 0.0075 ng/mL vs 0.0050 ng/mL, $P = 0.023$). Furthermore, hsTnT levels rose to a higher level in the ISCH group after completion of the

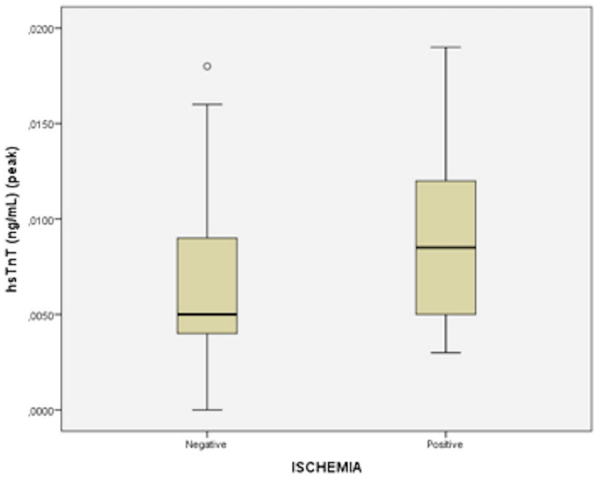

Fig. 1. Serum hsTnT levels between patients negative and positive for ISCH in the MPS before and after stress test. Median hsTnT levels were significantly higher in the ISCH group before ($P = 0.023$) and after the test ($P = 0.015$).

stress test (median: 0.0085 vs 0.0050, $P = 0.015$) (Figure 1) as compared to the non-ISCH group (Tables 3, 4)

Differences of Increase of Biomarkers and Stress Test Duration Between ISCH and Non-ISCH Groups

We also correlated the increase of biomarkers with the stress test duration. In that context, we performed separate analyses for all biomarkers under investigation, namely IMA, NPY, NP-pro BNP, and hsTnT in three different stages; a. duration $\leq$ 6.35 minutes, b. duration: 6.35 to 9.05 minutes, and c. duration $\geq$ 9.05 minutes. These time intervals correspond roughly to stage II, III, and IV of the Bruce protocol, respectively.

None of the IMA, NPY, and NP-pro BNP showed significant differences in time between the two groups, since alterations in both groups followed approximately the same patterns (Table 5). Prompted by the significantly increased hsTnT levels in ISCH group compared to the non-ISCH one, we further tried to determine the stage of Bruce protocol that had the strongest evidence of exercise-induced hsTnT elevation. Of note, elevations were not significantly different during the first two stages, namely from the beginning until 9.05 minutes. However, the difference in the increase of hsTnT levels was prominent in higher stages of the Bruce protocol (stress duration $>$ 9.05 minutes—$P < 0.017$), further enhancing the possible correlation between hsTnT increase and ISCH (Table 5).

Since hsTnT performed better that the 3 other biomarkers as regards detecting ISCH we measured sensitivity, negative, and positive predictive values of this biomarkers for assessing ISCH (Table 6, Figure 2).

DISCUSSION

In our study at treadmill exercise, Bruce protocol increased the plasma levels of all biomarkers, namely IMA, NPY, NT-pro BNP, and hsTnT. However, between ISCH and non-ISCH groups, only hsTnT levels showed a significant difference with the highest levels pertaining to the former group both before and after stress exercise.

IMA is thought to be associated with oxidative stress. Experimental and clinical studies have shown that IMA plasma rapidly increase during ischemia, including muscle ischemia.[12,13] Sinha et al. examined IMA plasma levels after primary coronary intervention (PCI), those were increased for at least 30 minutes after the procedure, indicating that IMA is a sensitive and early biomarker of significant ISCH.[14] IMA levels may represent a useful tool in an emergency base to rule out unstable angina in patients with chest pain.[15] Higher IMA levels are associated with acute coronary syndrome and acute ischemic stroke.[16]

Nevertheless, IMA levels may not always reflect the severity of ischemia since they can be influenced by factors such as serum albumin concentrations. In studies using the Bruce protocol that revealed lower IMA levels after stress compared to rest levels,[17] the decrease in IMA plasma levels was also attributed to hemoconcentration that led to protein plasma concentration changes and consequently to a decrease in free IMA levels.[17] Patients with peripheral vascular disease (PVD) undergoing stress test have been associated with a decrease in IMA levels immediately after test[18,19] raising concerns regarding the ability of IMA to detect myocardial ischemia in PVD patients. In our study, none of the patients enrolled had clinical features of intermittent claudication or other severe vascular disorders in the extremities.

Studies using pharmacological stress testing showed an increase in IMA plasma levels after stress without difference between groups with and without ISCH.[20] This is in line with our results that also showed an increase in IMA levels after stress in both ISCH and non-ISCH groups.

NPY is a 36-amino acid peptide found in the neurons of the sympathetic nervous system, especially in the brain and the heart.[21,22] In preclinical and clinical studies, stress increases NPY plasma levels[21–23] suggesting that ischemia activates the sympathetic nervous system leading to the elevated NPY plasma levels.[24]

Table 4. Biomarkers' increase before and after stress test for the patients with and without ISCH in the MPI

Value	Ischemia		*P* value*
	Positive n = 26	Negative n = 45	
IMA increase (IU/mL)	5.55 (1.853-7.733)	6.21 (4.415-9.245)	0.288
NPY increase (ng/mL)	1.45 (0.61-2.22)	1.57 (0.840-2.905)	0.493
hsTnT increase (ng/mL)	0.001 (0.00075-0.001)	0.001 (0.000-0.001)	**0.049**
NT-pro BNP increase (ng/mL)	581.63 (418.568-701.753)	598.46 (479.180-741.430)	0.445

Bold value indicates statistical significance
Statistically significant difference is found for hsTnT ($P = 0.049$)
Data are presented as median (lower-upper quartile)
*Mann-Whitney *U*

Increased NPY levels have been correlated with the severity of ST depression during ischemia.[25]

NPY levels may not always be correlated with the presence of ischemia.[26,27] Serum NPY increases in parallel with catecholamine levels during exercise,[28–30] as well as heart rate and blood pressure.[27] These exercise-induced alterations by themselves might increase NPY to such an extent that the additional increase due to ISCH is masked. In our study, no difference was found regarding its increase between the ISCH and the non-ISCH group.

NT-pro BNP is a widely used biomarker in the evaluation of left ventricle dysfunction and increased myocardial tension. It is derived from a pro-hormone that is mainly produced by the left ventricle myocytes.[31,32] Following a STEMI, NT-pro BNP levels are closely associated to the extent of myocardial injury as assessed by cardiac MRI.[33] Higher NT-pro BNP levels are found in patients with NSTEMI compared to STEMI patients on admission.[34–36] This suggests a larger ischemic insult in the NSTEMI patients.

It has been hypothesized that NT-pro BNP levels are associated with ISCH.[37] Studies using MPS as marker of ischemia, showed increased levels after exercise stress test. Similar to our findings, a previous study found no difference between the patients with ISCH and those with normal MPS.[37] In our study, resting values in patients showing ISCH were slightly higher compared to the non-ISCH group but not significantly different ($P = 0.711$).

The introduction of assay tests that can detect troponin T with high-sensitivity, has led to wide implementation of hsTnT measurements. The detection limit for hsTnT is extremely low, at the level of 0.00005 ng/mL that can also be detected at the serum of healthy controls.[38] A small fraction of hsTnT is considered to be located in the cytosol that can be released to the systematic circulation during ischemia, even though destruction of the cell is not present.[39] In preclinical studies with animal models undergoing stress test, increase in hsTnT levels correlated with the severity of ischemia.[40] Furthermore, clinical studies incorporating patients with stable coronary artery disease revealed that micro-ruptures of non-calcified plaques can lead to an increase in hsTnT levels and, therefore, hsTnT can serve as marker for vulnerable coronary lesions.[41] Both processes can be operable in our patients.

Studies using MPS as an indicator of ISCH revealed no difference in serum hsTnT between the group of patients with or without ischemia.[42] On the contrary, Sabatine et al. showed correlation between the increase in hsTnT levels and the presence and severity of ischemia on MPS imaging.[43] Our study indicated that patients with abnormal findings in MPS had significantly higher levels of hsTnT both at baseline or after stress exercise. We, however, measured TnT levels 3 minutes after achieving maximum load on stress test, whereas Sabatine et al. performed the measurements 4 hours after the stress test with similar results. Therefore, our study suggests a rapid increase of the hsTnT in stress test-induced myocardial ischemia, whereas the study by Sabatine et al indicates the maintenance of high hsTnT levels in the same setting.

Furthermore, Ahmed et al. found that patients with an abnormal scintigraphy had higher median levels of hsTnT when referred to the emergency department with acute chest pain.[44] Our findings are in line with these results (Figure 1). Patients with abnormal scintigraphy

Table 5. Alterations of biomarkers at different stages according to stress test duration and their correlation with the presence of ischemia in scintigraphy

	Ischemia		
	Positive	**Negative**	***P* value***
Stress test duration ≤ 6.35 minutes	n = 10	n =14	
IMA increase (IU/mL)	5.465 (3.263-6.533)	7.320 (4.485 to 10.225)	0.320
NPY increase (ng/mL)	1.680 (0.360-2.720)	1.675 (0.250 to 3.845)	0.682
NT-pro BNP increase (ng/mL)	535.995 (489.895-701.753)	633.475 (478.393 to 713.927)	0.558
hsTnT increase (ng/mL)	0.0010 (0-0.0010)	0.0010 (0 to 0.00125)	0.650
Stress test duration 6.35-9.05 minutes	n=7	n=17	
IMA increase (IU/mL)	5.69 (0.44-7.80)	5.71 (4.76 to 9.57)	0.546
NPY increase (ng/mL)	0.92 (0.30-2.06)	1.57 (0.90 to 2.83)	0.391
NT-pro BNP increase (ng/mL)	633.32 (372.30-680.10)	563.72 (335.52 to 758.84)	0.924
hsTnT increase (ng/mL)	0.0010 (0-0.0010)	0 (− 0.0005 to 0.0010)	0.229
Stress test duration > 9.05 min	n=9	n=14	
IMA increase (IU/mL)	5.190 (1.710-10.170)	6.105 (1.295 to 9.055)	0.900
NPY increase (ng/mL)	1.410 (1.000-2.720)	1.535 (0.985 to 2.425)	0.801
NT-pro BNP increase (ng/mL)	625.02 (359.87-731.94)	633.58 (562.02 to 754.28)	0.413
hsTnT increase (ng/mL)	0.0010 (0.0010-0.0025)	0 (0 to 0.0010)	**0.017**

Bold value indicates statistical significance
Among all biomarkers under investigation, significant increase is noted only for hsTnT and only in high stress levels (duration of the Bruce protocol > 9.05 min)

Table 6. Sensitivity, specificity, positive, and negative predictive value of hsTnT for predicting exercise ISCH

Target sensitivity (%)	Cut points for hsTnT (ng/mL)	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)
50	0.0075	50% (30-70)	76% (60-87)	54% (38-69)	72% (63-80)
60	0.0065	58% (37-77)	62% (47-76)	47% (35-59)	72% (61-81)
70	0.0045	73% (52-88)	40% (26-56)	41% (34-50)	72% (55-84)
95	0.0035	96% (80-100)	16% (6-29)	40% (36-43)	87% (48-98)

AUC (area under the curve) = 0.662, $P = 0.024$
95% confidence interval [CI] 0.525-0.798

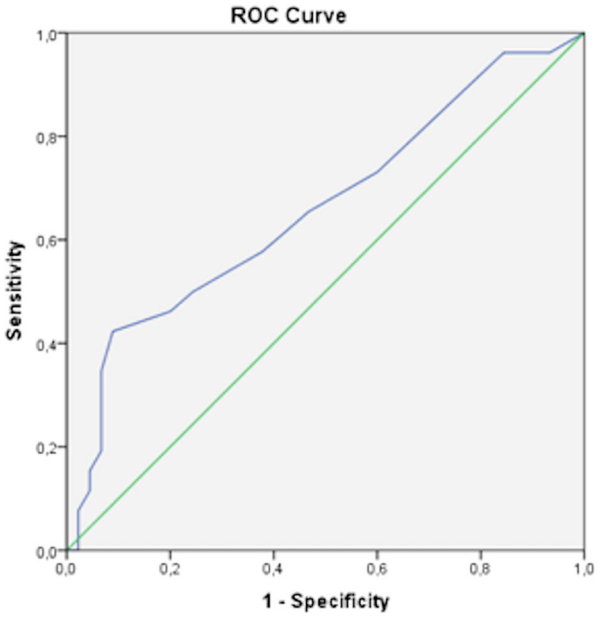

Fig. 2. ROC Curve for hsTnT levels before stress test and prediction of ISCH in the MPI. AUC (area under the curve) = 0.662, $P = 0.024$, 95% confidence interval [CI] 0.525–0.798. hsTnT do not seem to be able to serve as a screening test for ISCH.

had higher median resting hsTnT levels compared to those with no perfusion abnormalities (0.0075ng/dL vs 0.005ng/dL $P = 0.023$). The same pattern was followed for hsTnT levels at peak exercise (0.0085ng/dL vs 0.005ng/dL, $P = 0.015$).

The increase of hsTnT between the two groups before the test and at peak exercise was statistically significant ($P < 0.049$), indicating a correlation of hsTnT levels with the presence of ISCH. In addition, we noticed that the difference in the increase of hsTnT levels was more prominent in higher stages of the Bruce protocol (stress duration > 9.05 minutes—$P < 0.017$), further enhancing the possible correlation between hsTnT increase and ISCH (Table 5), although Ahmed et al. suggested that even in non-obstructive coronary artery disease, TnT is released to the circulation due to altered myocardial membrane permeability or micronecrosis.[44] The first mechanism could be responsible for the rapid onset increase detected in our study and the second mechanism for the chronic baseline higher levels in patients that eventually developed ISCH in MPS. Another possibility has recently been advanced is that hsTnT also reflects myocardial fibrosis.[45] In our study, the Area Under the Curve (AUC) was not high enough to render the measurement of hsTnT clinically useful as a screening test for ISCH and does not seem to be able to substitute MPS.

We only found an increase in hsTnT in patients undergoing exercise longer than 9 minutes. Actually, as already discussed, the increase of TnT after exercise is not completely understood.[46] It has been found even in pulmonary hypertension.[47] Since our patients did not have any other confounding factors (renal, pulmonary or skeletal muscle disease), we can postulate that myocardial ischemia was the factor responsible for this difference.

Our study is not without limitations. It is possible that a larger sample would provide stronger evidence and probably different results, especially regarding the NT-pro BNP levels. Another major drawback in our study is that alterations in the levels of biomarkers are linked to the level of ISCH induced by Bruce protocol stress study. It is possible that greater ischemia (such as in coronary artery occlusion during PCI) may increase the biomarker levels to a greater extent. In fact, this hypothesis is supported by the fact that increase in hsTnT was significantly different between the two groups (ISCH and no ISCH) only at the higher exercise levels (Table 5). However, higher ISCH can overlap with cardiomyocyte death which would further confound findings. Another point is that circulating autoantibodies may interfere with the detection of circulating troponins by available assays and this may positively or negatively affect the results in some occasions.[48]

NEW KNOWLEDGE GAINED

This study shows that hsTnT levels are elevated at rest in patients with ISCH findings on MPS imaging and that progression of ISCH further increases hsTnT levels. This rise is not only associated with myocardial infarction but also with less severe ischemia, underlining the significance of this biomarker as a valuable rule out test.

CONCLUSIONS

Although IMA, NPY, and NT-pro BNP may not detect minor ischemic myocardial insults, serum hsTnT holds a greater ability of detecting not only myocardial infarction but also less severe ischemia and consequently the presence of CAD. Further studies with larger cohorts of patients are warranted in order to better define the role of hsTnT as a screening tool for myocardial ischemia. Moreover, larger patient numbers may give more meaningful data as regards NT-proBNP, since it may represent myocardial dysfunction caused by exercise-induced ischemia.

Author contributions

Conception and design or analysis and interpretation of data or both: TP, YF, MP, MK, AT, DVC. Active involvement in collecting data or performing experiments with subsequent participation in data analysis: TP, AK, DIT, AT, ANP, CK, MK. Drafting of the manuscript or revising it critically for important intellectual content: AK, DIT, CK, DVC. Final approval of the manuscript submitted: All authors.

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