**Myocardial injury in stress echocardiography: comparison of dobutamine, dipyridamole and dynamic stressors - single center study**

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The authors declare that there are no conflicts of interest related to this study.

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**Abstract**

**Objectives**

In stress echocardiography (SE), dipyridamole (DIP) and dynamic stress (ExSE) are reported as safer than dobutamine stress (DSE). We investigated whether commonly used stressors cause myocardial injury, measured by high sensitivity troponin T (hsTnT).

**Methods**

135 patients (DSE n=46, ExsE n=46, DIP n=43) with negative SE were studied. Exclusion criteria were known ischemic heart disease (IHD), baseline wall motion abnormalities, left ventricle systolic dysfunction/regional wall motion abnormalities, septum/posterior wall ≥13 mm, diabetes, baseline hsTnT level ≥14 ng/L, baseline blood pressure ≥160/100 mmHg, peak pulmonary pressure ≥45mmHg, eGFR <1mL/s/1.73m2, more than mild to moderate valvular disease and dobutamine side effects. HsTnT was measured before and 180 minutes after the test.

**Results**

All patients had low pre-test probability of IHD. HsTnT increased in DSE, less so in ExSE, and unchanged in DIP group [9.4 (1.5–58.6), 1.1 (-0.9–15.7), -0.1 (-1.4–2.1) ng/L, p<0.001]. In DSE, hsTnT change was associated with peak dobutamine dose (r=0.30, p= 0.045), test length (r=0.43, p=0.003) and atropine use (p<0001). In ExSE, hsTnT rise was more likely in females (p=0.012) and elderly (>65 years) (r=0.32, p=0.03), no association was found between atropine use (p=0.786) or test length and hsTnT rise (r=0.10, p=0.530).

**Conclusions**

DSE is associated with myocardial injury in patients with negative SE, no injury was observed in DIP and only mild one in ExSE. Whether myocardial injury is causative of the higher reported adverse event rates in DSE remains to be determined.

**Key words**

negative stress echocardiography, myocardial injury, hsTnT

**Introduction**

Use of stress echocardiography (SE) dates to 1979, when the first paper on exercise stress echocardiography (ExSE) in clinical practice was published.1 Introduction of dobutamine (DES) and dipyridamole stress echocardiography (DIP) followed shortly.2,3 Since then, SE became established tool in investigation of patients with suspected ischemic heart disease (IHD). All three modalities are considered to have equal diagnostic performance in clinical practice, with similar sensitivity and specificity, although ExSE is recommended as the first line method in patients who can exercise.4,5 One of the reasons is the higher adverse event rate reported in DSE compared to ExSE and DIP, usually attributed to the dobutamine pharmacological effect.6-8

Results of studies evaluating troponin kinetics in patients undergoing SE are controversial.In one study, no change of high sensitivity troponin T (hsTnT) in dynamic exercise stress testing was observed, regardless of presence of ischemia, whereas another similar size study showed increase in hsTnT levels in patients undergoing exercise stress, blunted in patients with evidence of reversible ischemia.9,10  In DSE, the hsTnT rise was found in healthy volunteers, but higher hsTnT response was observed in patients with inducible ischemia.11 Another studies showed rise of hsTnT in DSE, but no association with ischemia. 12,13 Blatt et al demonstrated no TnT rise in DSE patients with or without ischemia.14 Studies on DIP mostly show no or mild hsTnT rise.15,16 However, patients´ characteristics in most of these studies were not homogeneous with inclusion of patients with known ischemic heart disease (IHD), heart failure, diabetes or increased baseline hsTnT level in various proportions. 9,10,12,13,16 The authors of recent meta-analysis concluded that hsTnT rise after exercise and pharmacological stress testing appeared inconsistent and comparably small and did not appear to be correlated with inducible ischemia.17

The aim of this study was to investigate myocardial injury associated with the most common stressors used in SE for investigating chest pain, as measured by hsTnT release, in a selected defined population sample with negative result of SE for myocardial ischemia.

**Methods**

**Study Population**

A total of 135 patients undergoing SE (DSE n=46, ExsE n=46, Dip n=43) for chest pain suspicious of angina or shortness of breath (as its equivalent), with negative SE result, were enrolled in the study. The choice of stressor was left at the discretion of the medical team depending on availability and patient features such as likelihood to exercise till target heart rate. Patients with the following baseline and stress criteria were excluded from study enrolment: previous acute coronary syndrome and/or revascularisation, known epicardial coronary artery stenosis >50%, baseline regional wall motion abnormalities, left ventricle (LV) systolic dysfunction (EF ≤50%), diabetes or prediabetes (fasting glycemia > 5,6 mmol/l from the baseline blood sample), baseline elevated hsTnT level (≥14 ng/L), more than mild LV hypertrophy (septum/posterior wall ≥13 mm), uncontrolled hypertension (baseline blood pressure ≥160/100 mmHg), estimated peak pulmonary pressure ≥45mmHg at baseline echocardiogram, eGFR <1mL/s/1.73m2, moderate and severe valvular disease, and patients who experienced dobutamine side effect (hypotension, atrial fibrillation) or did not achieve target heart rate (HR > 85% of maximal predicted HR defined as 220-age in years).

**Study protocol**

All patients were instructed to fast but allowed to drink plain fluids for four hours prior to the test. β blocker or non-dihydropyridine calcium channel blocker therapy was stopped 48 hours prior to the test irrespective of the stressor used. Patients scheduled for DIP were instructed to refrain from caffeine/decaffeinated food products and beverages for 24 hours prior to the test.

Patients´ baseline characteristics were obtained before start of the test. Pre-test probability (PTP) of IHD was calculated as recommended.18 All patients underwent SE using standard protocols.4,19 Briefly, in DSE, intravenous dobutamine was infused starting at 10ug/kg/min and increased at 3-minute intervals to 20, 30 and 40 ug/kg/min. shall needed. Handgrip was used at a dobutamine dose of 30 ug/kg/min. if target HR was not achieved, with the optional addition of intravenous atropine at 100-200 ug increments up to the total dose 1000 ug. Intravenous β blocker (metoprolol up to 5 mg in 1 mg increments) was routinely used to reverse the effect of dobutamine provided blood pressure was not low (systolic BP < 110 mmHg) at the end of the test. For ExSE, dedicated echocardiography bicycle ergometer (eBike EL© by GE) was used. The workload was increased by 25W at 2-minute intervals. Handgrip and/or intravenous atropine in 200ug increments up to 1000ug could be used to achieve target HR should patient fail to achieve it by exercise alone. In DIP, dipyridamole 0.84mg/kg was administered over 6 minutes, terminated in 10 minute by an intravenous bolus of aminophylline 120-240 mg. The test length was determined as the time interval between start and termination of dobutamine infusion (DSE) or start and termination of pedalling (ExSE). An ultrasound enhancing agent (0.3-0.6 ml boluses of Sonovue© by Bracco) using a very low MI contrast pre-set was used if > one segment of the left ventricle was not reliably visualised. For all stress modalities baseline, low, intermediate, peak and recovery images were digitally acquired on an echocardiography scanner equipped with stress protocol (IE 33© by Philips or Vivid 9© by General Electrics). Images were analysed at the end of the study in the machine and/or off-line (Intellispace Cardiovascular©, Philips). Only patients with negative stress study were enrolled; patients with segmental hypokinesia, lack of hyperkinesia or tardokinesia during stress/in recovery were excluded. All studies were reported by an experienced cardiologist holding British Society of Echocardiography Stress Echocardiography accreditation. Blood samples were obtained immediately before and at 180 +/- 10 minutes following termination of SE. Plasma and serum were separated into aliquots and stored at -70 ̊C for analysis. HsTnT was analysed by electroluminiscent imunoanalysis (Cobas 8000©, Troponin T hs STAT kit, Roche). All assays were performed by personnel blinded to the stressor used and result of SE. Haemolytic index was measured, if exceeded 120 in baseline or 180 min. sample, patient was also excluded from the study.

**Statistical analysis**

Quantitative data were expressed as median and interquartile range. Comparison of categorical variables was performed using Pearson’s chi-square or Fisher‑exact tests. Continuous data were tested using Mann‑Whitney U test, Kruskal‑Wallis test was used for multiple comparisons. Correlation between two continuous variables was assessed using Spearman’s rank correlation coefficient. P-values less than 0.05 were considered statistically significant (all tests two-sided). The distribution of continuous variables across different patient groups was graphically represented using box and whisker plots. Whiskers were drawn to represent the numerically smallest and largest values of observations that are not outliers (ie observations with value > 1.5 times larger or lower than the 75th and 25th percentile, respectively). The same definition was used to identify outliers in change of hsTnT from baseline to three hours after the test. Analysis was performed using SPSS software (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) and software R version 4.0.3 ([www.r-project.org](http://www.r-project.org)).

**Results**

Patients in all groups had comparable baseline characteristics; however, higher eGFR (p=0.017), more frequent positive family history of IHD (p=0.048) and transpulmonary contrast use (p=0.004) were observed in DIP group. PTP of obstructive IHD was low in all groups. (*Table 1*)

Baseline hsTnT was similar across all groups [DSE 5.1 (3.0–13.0), ExSE 5.4 (3.0–9.5), DIP 5.5 (3.6–9.2) ng/l, p=0.575, *Table 1*]. In early stage of the study we observed continuous rise in hsTnT following termination of DSE (*Figure 1*) and decided to compare hsTnT values in 180 min. only. There was an increase in hsTnT after both DSE and ExSE, although the rise was significantly higher in DSE group [∆hsTnT 9.4 (1.5–58.6) ng/L and 1,1 (-0.9–15.7 ng/L, respectively, p< 0.001]. In contrast, no rise was observed in DIP [∆hsTnT -0.1 (-1.4–2.1) ng/L, p<0.001, *Figure 2*]. Similarly, peak hsTnT values were highest in DSE group [DSE 16.0 (4.2-154.4), ExSE 7.5 (3.0-136.2), DIP 5.7 (3.0-20.8), p< 0.001]. In DSE, hsTnT change was related to peak dobutamine dose (r=0.30, p=0.045), test length (r=0.43, p=0.003) and atropine use (p<0.001); atropine use was associated with longer test and tendency to higher peak dobutamine dose. (*Table 2*) In ExSE, hsTnT rise was associated with female gender (p=0.012) and age (r=0.32, p=0.030), no link was found between atropine use (p=0.786) or length of the test (r=0.10, p=0.530) and hsTnT release. (*Table 3*). In ExSE group hsTnT dropped in 17%, in 43% rose by ≤2 ng/L and in 20% increased ≥ 14ng/l at 180 min. in comparison to the baseline value. In DSE group hsTnT dropped only in one patient (2%) and increased ≥ 14ng/l in majority (54%) of the patients. 89% of patients with very high hsTnT rise recruited from DSE group. (*Table 4, Figure 3*). Lastly, no relationship was found between number of risk factors and baseline hsTnT or its change (*Table 5, Figure 4*).

**Discussion**

This study compared hsTnT release in dynamic, dobutamine and dipyridamole challenge in patients with negative SE result. The main findings are as follows (i) DSE leads to significant hsTnT release related to the test length/atropine use (ii) ExSE causes minimal myocardial injury expressed in terms of hsTnT rise (iii) DIP causes no measurable effect on this parameter.

HsTnT reflects not only ischemia, but any kind of myocardial injury.20 It also serves as a marker of cardiovascular risk in general and is increased in the presence of stable IHD, left ventricle hypertrophy (LVH) or diabetes, and predicts outcome in patients with heart failure.21-26 Increased hsTnT level, which might be explained by repetitive peripheral microembolisations, is also a marker of vulnerable atherosclerotic plaque and predictive of ischemia.27-29  Similarly to our findings, Samaha in the study on 48 patients (33 ExSE, 15 DSE) demonstrated continuous rise in hsTnT in DSE/ExSE following termination of the test and higher hsTnT rise in DSE in comparison to ExSE [9.7 (4.5–27.2) vs 2.3 (1.0–4.9) ng/L].12 However, 23% patients in his cohort had elevated baseline hsTnT ≥14ng/l, which was one of the exclusion criterions in our study, as was diabetes, LV hypertrophy or known IHD. Our study therefore confirms that hsTnT rise during DSE/ExSE is independent to elevated baseline hsTnT levels or presence of structural heart disease.

Whether troponin can be released from myocyte without its necrosis remains controversial.30 Most of troponin is bound to myofibrils, and about 5% is free-cytosolic. This latter portion seems to be responsible for early troponin rise and fall within 24 hours.20,31,32 The mechanisms for troponin release apart from necrosis might include apoptosis, increased by β adrenergic stimulation, normal myocyte turnover, cellular release of proteolytic troponin degradation products, increased cellular wall permeability and formation/release of membranous blebs.33-35

It is recognised that excessive increase of systemic or myocardial catecholamine levels can induce myocyte injury.36,37 During the dynamic exercise plasma epinephrine and norepinephrine demonstrate an exponential relationship with increasing workload.38 We observed mild hsTnT increase in our ExSE group, findings similar to previously published data.39 Higher hsTnT release was demonstrated in our study ExSE group in older females, i.e. in the group where ExSE might have represented extra strenuous activity due to lower fitness.

In DSE high dose of dobutamine up to 40ug/kg/minute is used. In animal models on healthy rats, epinephrine administered aiming to increase blood pressure and correspondingly LV end-diastolic pressure (LVEDP) led to troponin I (TnI) release which was significantly reduced by β blocker pre-treatment. Pathological analysis demonstrated myocyte apoptosis, but no necrosis.40,41 Interestingly, our DSE group exhibited much higher hsTnT release compared to ExSE despite lower peak heart rate and maximum systolic blood pressure i.e. likely lower peak LVEDP. (*Table 1).* β adrenoreceptors density is greatest at the left ventricular apex which is the most sensitive area of the myocardium to catecholamines.42 Apical transient microcirculatory dysfunction and catecholamine adrenoreceptor overstimulation, in addition to left ventricular tract obstruction, might be responsible for myocyte injury in DSE induced cardiomyopathy.43,44 We therefore postulate that high hsTnT release in DSE group was likely due to direct β adrenoreceptor effect of dobutamine on myocyte, correlating with the length of dobutamine infusion i.e. cumulative dobutamine dose, as previously observed.11

HsTnT rise was higher in the subgroup of DSE patients with atropine use. Published data suggest that vagal stimulation is having cardioprotective effect in reperfusion injury, likely by stabilising mitochondrial membrane, mechanism independent on bradycardia, and this effect is abolished by atropine.45-47 However, atropine administration was in our study associated with longer DSE test and importantly, atropine did not affect hsTnT rise in ExSE group. In our opinion it is therefore more likely that the atropine effect on hsTnT rise only reflects longer dobutamine infusion/higher cumulative dobutamine dose in patients who could not achieve target heart rate on dobutamine only.

Whereas exercise and dobutamine acts mainly by increased oxygen demand, the major stress mechanism during dipyridamole SE along with modest increase of oxygen demand is horizontal and vertical steal phenomena. It leads to impaired subendocardial flow and decreased oxygen supply as the consequence.48 Our findings in DIP group are consistent with previously published studies showing no hsTnT release following dipyridamole challenge, which is probably due to the absence of adrenergic stimulation and resulting increased wall stress observed in ExSE and DSE.15,16,49, 50

**Study limitations**

Our study lacks randomization in assigning patients to different stress tests. However, most of the patients were assigned to a given stress modality depending on logistics and other patient characteristics such as the ability to exercise reflecting clinical practice. Nevertheless, all three SE groups were balanced in their baseline characteristics with non-significantly higher proportion of females in DSE and ExSE in comparison to DIP. However, there was a tendency of male, not female, for higher hsTnT response in DSE group. (*Table 3*)

Also, calculated PTP of obstructive IHD in all groups was low but the variation of the upper range among the groups was observed. However, the lowest variation was exhibited in DSE group, which showed the highest hsTnT rise during SE (*Table 1)*. Another limitation is the lack of definite proof of the absence of obstructive IHD. On the other hand all stress echo modalities are reported to have similar accuracy and sensitivity4, suggesting that possible false-negative SE results were evenly distributed across all the studied SE groups.

Patients assigned to DSE had wider baseline hsTnT 95%CI with possibility of a certain degree of baseline bias toward this group. Left ventricular outflow tract obstruction in the DSE group, a potential mechanism behind hsTnT rise, was not systematically studied. Also, we used a shorter DSE protocol starting with 10 ug/kg/min of dobutamine. However, as total administered dose of dobutamine is closely related to the test length, hsTnT increase would have been likely even higher if standard protocol starting with 5ug/kg/min. had been used.

Lastly, our study population is small to moderate only, but similar to previously published studies.

**Conclusion**

In patients with no evidence of inducible ischemia on stress echocardiography, DSE caused significant hsTnT release which correlated with the length of the test, peak dobutamine dose and atropine administration. In contrast, ExsE caused only mild hsTnT rise, while DIP did not result in any significant hsTnT change. Whether myocardial injury is related to the higher reported adverse event rates in DSE remains to be determined.

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