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Safety of patients diagnosed with myocardial perfusion scintigraphy with dipyridamole stress — drawing the issue to the attention

Bezpieczeństwo pacjentów poddawanych badaniu scyntygrafii perfuzyjnej mięśnia sercowego po obciążeniu dipirydamolem

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Abstract

Introduction. Myocardial perfusion scintigraphy (MPS) with dipyridamole is an accepted method for assessment of ischaemic heart disease, in case of contraindication to exercise testing. However, very often we observe clinical symptoms and changes in ECG while monitoring patients during the study with pharmacologic stress with dipyridamole. The aim of this study was to investigate the safety of patients diagnosed with MPS with dipyridamole.

Material and methods. Twenty-five patients with stable coronary artery disease participated in a 2-day protocol (0.56 mg/kg dipyridamole i.v. and then rest) using Tc-MIBI imaging. Continuous clinical monitoring and 12-lead serial ECG has been used since the beginning of the MPS up to 20 minutes after the examination. High-sensitive cardiac troponin I (hscTnI) concentration was measured before, four hours and the next day after stress test. Primary endpoint included hscTnI concentration above 99th percentile of the upper reference limit in second or third measurement or new persistent ST-T segment changes. Secondary endpoints were: new persistent or transient ECG changes (ST-T segment elevation or depression or negative T waves, prolongation of QRS complex, PR interval or QTc), or any drug-related adverse event.

Results. The concentrations of hscTnI were below 99th percentile of the upper limit among all the patients. Primary and secondary endpoint were observed in 6 (24%) and 23 (92%) patients, respectively. Transient ST-T segment elevation occurred in 4 (16%) patients, transient ST-T segment depression or negative T wave — in 7 (25%) patients, QRS complex prolongation — in 11 (44%) patients, PR interval prolongation — in 18 (75%) patients, QTc prolongation — in 22 (88%) patients, any clinical adverse event related to dipyridamole — in 16 (64%) patients. Following endpoints were correlated with positive MPS results: ST-T segment changes, RP interval prolongation, and with a history of chest pain: ST-T segment changes, QRS complex and QTc prolongation.

Conclusions. MPS with dipyridamole stress is relatively safe, as hscTnI concentration remains within normal in prolonged observation after the examination. While there is a significant risk of minor clinical and electrocardiographic adverse events it is not related with a myocardial necrosis.

Key words: myocardial perfusion scintigraphy, ischaemic heart disease, dipyridamole, safety

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Introduction

Myocardial perfusion scintigraphy (MPS) is one of the most important and commonly performed non-invasive imaging test in diagnosis of ischemic heart disease [1]. European Association of Nuclear Medicine and European Society of Cardiology guidelines emphasizes high sensitivity (about 90%) and specificity (about 80%) of MPS in detecting haemodynamic obstructive coronary artery disease (CAD) [2, 3]. The prognostic power of MPS has been extensively evaluated, and several studies have demonstrated that myocardial perfusion imaging has an independent relationship with subsequent major adverse cardiac events [4, 5]. Moreover, it adds incremental prognostic value to the information obtained from patient clinical variables, stress test and angiographic findings [4–6].

There are several different protocols for performing a MPS. Usually MPS is a two-step examination: a 'stress' part and a 'rest' part, to allow comparison of blood flow during stress and rest [2, 3]. During the stress part of the test, the heart is made to work either with exercise testing on a treadmill [7], or alternatively with infusion of a drug. Pharmacological vasodilatation with e.g. dipyridamole is indicated for patients who are unable to exercise or unable to increase their heart rate, patients with left bundle branch block or paced ventricular rhythm [2].

In everyday practice, we observe both clinical symptoms and electrocardiography (ECG) changes during pharmacological stress study. With a high sensitivity cardiac troponin I (hscTnI) we may reliably evaluate the risk of myocardial necrosis related to the study. Thus, the aim of this study was to assess the safety of dipyridamole testing in patients undergoing MPS.

Material and methods

Study population

We performed a single-center, prospective study of 25 consecutive patients with stable CAD (SCAD), who underwent MPS. The analysis excluded those patients hscTnI concentration above 99th percentile of the upper reference limit.

The ethical approval before initiation of the study was obtained and all patients provided informed consent.

Myocardial perfusion scintigraphy protocol

The MPS studies were performed using a 2-day stress/rest Tc-99m-MIBI protocol, with injection of 740 MBq Tc-99m-MIBI (NCBJ or POLATOM, Poland) at stress and rest study. Stress and rest acquisition began about 50–60 min after the end of the injection of Tc-99m-MIBI. Images were obtained according to established clinical protocols, using gated hybrid SPECT/computed tomography (CT) with a dual-head gamma camera (Symbia T6 Siemens, Erlangen, Germany). Patients were imaged in the supine position. Low energy high-resolution collimator and a zoom factor of 1.0 were used. We obtained 32 projections in a 128 × 128 matrix, with an acquisition time of 25 s per projection. The energy window width for scatter correction was centered at 140 keV and with width of 15%. At the end, a low-dose CT attenuation correction (CTCA) was performed using imaging settings: 130 ke, 13 mAs/slice (slice thickness of 5 mm).

Patients were stressed using pharmacological test with dipyridamole. Medications that contain methylxanthines or caffeine and food beverage with caffeine have been withdrawn 12–24 hours prior to procedure. Dipyridamole was infused over a 4-min period at a dose of 0.56 mg/kg diluted in normal saline solution. Radiopharmaceutical was injected at the 7th–8th minute of the infusion.

Normal MPS was defined as visually homogeneous and quantitative analysis presenting no perfusion defect, with all parameters obtained from the gated-SPECT within normal.

Positive MPS was defined as a perfusion defect reversion over 10% of left ventricle mass during the rest examination.

Clinical assessment and follow-up

Patients were assessed for clinical signs and symptoms of angina by a physician. The concentration of hscTnI (ADVIA Centaur TnI-Ultra® Assay, Siemens, Germany) was measured two hours before MPS (first assessment), four hours after pharmacological stress with dipyridamole (second assessment) and the next day after examination (third assessment). According to the product characteristics, 99th percentile upper normal limit is 40 ng/L (pg/mL).

Continuous clinical monitoring and 12-lead serial ECG examination have been used since the beginning of the MPS up to 20 min after the examination. ECG was performed every three minutes and analyzed for significant ST segment elevation or depression or negative T waves in any lead and prolongation of PR interval, QRS complex or QTc by a second physician. Every new ST-T segment change was classified as transient or persistent due to its presence 20 min after the end of MPS.

Study endpoints

Primary endpoint was a composite of hscTnI concentration above 99th percentile of upper normal limit in second or third assessment or new persistent ST-T changes.

Secondary endpoints were:

- hscTnI concentration four hours after pharmacological stress (in the second assessment) higher than before MPS (in the first assessment);
- new ECG changes (transient ST segment elevation or depression or negative T waves, prolongation of QRS complex, PR interval or QTc) during an examination;
- any drug-related adverse event (AE).

Statistical analysis

Statistical analysis was performed using Statistica v. 12. Quantitative variables are expressed as mean ± standard deviation and median (first and third quartile value). Categorical variables are presented as an exact number and percentage of patients. Differences between two groups for continuous variables were tested by Mann-Whitney U-test. The comparisons of categorical variables were analyzed using χ^2 independence test. Two-way tables were assessed with the χ^2 test with double-sided Fisher's exact test due to limited number of patients. A P value < 0.05 was defined as statistically significant.

Results

The study group included 25 patients (mean age 68.5 ± 8.9 years; women, 52%. Primary endpoint was observed in 6 (24%) patients due to ECG permanent ST-T segment changes. Concentration of hscTnI remained within normal range among every patient during the study. We observed differences between compared groups, however large-scale data could provide greater statistical reliability. Detailed characteristics of patients that reached and did not reach primary endpoint was presented in Table 1.

Secondary endpoint was observed in 23 (92%) patients and the most frequent items were as follows: QTc prolongation in 22 (88%) patients and PR interval prolongation in 18 (72%) patients. Increased hscTnI concentration (within normal range) was observed in about half of patients four hours after pharmacological stress. Clinical AE related to dipyridamole were rather often — 16 (64%) patients experienced at least one AE. The frequency of secondary endpoints was presented in Table 2.

Additional analysis was performed to assess correlations between reported AE and clinical factors. More than 80% of patients with QTc prolongation reported chest pain. New transient or persistent ST segment depression or negative T waves were present only among patients without a history of chest pain (p = 0.01) and correlated with positive MPS (p = 0.04). History of chest pain was present in 10 per 11 patients with QRS complex prolongation (p = 0.0001). PR interval prolongation was present in 13 and 5 patients without and with a positive MPS, respectively (p = 0.056).

Discussion

Dipyridamole prevents the intracellular reuptake and deamination of adenosine [8]. It is an indirect coronary artery dilatator increasing myocardial blood flow during stress on the order of three to five times [7–10]. Stimulating adenosine 2A receptors (A2A) dipyridamole induce myocardial hyperaemia [8]. But diseased coronary artery has a reduced perfusion reserve. Thus, the drug provokes perfusion heterogeneity or even ischemia of myocardium supplied by diseased coronary artery due to coronary steal [2, 3]. However, besides A2A receptors adenosine stimulates A1, A2B and A3 receptors too, resulting in various clinical adverse effects [11, 12].

Clinical and ECG monitoring extended up to 20 minutes after the MPS, is a result of clinical observations of patients who underwent the examination at our center. In the

Table 1. Characteristic of study group and subgroups per met primary endpoint*

	All patients (N = 25)	Primary endpoint positive (N = 6)	Primary endpoint negative (N = 19)	p
Females	13 (52)	2 (33.3)	11 (57.9)	0.3782
Age (years)	68.5 ± 8.9	69.83 + 7.57	68.05 + 9.46	0.7739
Diabetes	5 (20)	2 (33.3)	3 (15.8)	0.5622
SCAD symptomes:				
• chest pain	19 (76)	5 (83.3)	14 (73.7)	1.0
• *angina pectoris*	14 (56)	4 (66.7)	10 (52)	0.6608
MPS:				
• within normal	5 (20)	1 (16.7)	4 (21.1)	1.0
• possitive	8 (32)	3 (50)	5 (26.3)	0.3441
hscTnI concentration (ng/L):				
• 1st assessment	5.28 ± 6.88	6.67 ± 8.38	4.84 ± 6.53	0.6928
• 2nd assessment	6.04 ± 8.89	8.5 ± 7.06	5.26 ± 9.43	0.3237
• 3rd assessment	5.68 ± 8.07	2.33 ± 3.2	6.74 ± 8.89	0.3397

*Continuous variables were presented as median (interquartile range) and categorical variables are presented as absolute numbers (percentages). P values are given for differences between the patients who met and did not meet primary endpoint; N — number of patients; SCAD — stable coronary disease; MPS — myocardial perfusion scintigraphy; hscTnI — high-sensitivity cardiac troponin I

Table 2. Prevalence of adverse events in studied group

Primary endpoint	Value
Positive hscTnI assessment*	0 (0)
New persistent ST segment elevation or depression	6 (25)
Secondary endpoint	
Increased hscTnI concentration**	12 (48)
New transient or persistent ST segment elevation	4 (16)
New transient or persistent ST segment depression or negative T waves	7 (28)
QRS complex prolongation	11 (44)
PR interval prolongation	18 (72)
QTc prolongation	22 (88)
Any dipyridamole-related adverse event:	16 (64)
• headache	15 (60)
• dizziness	1 (4)
• chest pain	4 (16)
• *angina pectoris*	3 (12)
• dyspnoea	5 (20)
• heat	1 (4)
• excessive sweatting	6 (24)
• fatigue	1 (4)
• palpitations	1 (4)

*hscTnI concentration above 99th percentile of the upper normal limit in second or third assessment; **hscTnI concentration in the second assessment higher than in the first one; categorical variables are presented as absolute numbers (percentages); hscTnI — high-sensitivity cardiac troponin I

study, we assessed the biochemical markers of ischemia (with high sensitivity), ECG changes and clinical adverse events related to the drug. Dynamic changes in collected data allows to conclude about patients' safety.

The study showed no increased hscTnI levels above 99th percentile of upper reference limit. We observed increased hscTnI concentration four hours after MPS from baseline in 12 (48%) patients, but it was below 99th percentile of upper reference limit. Clinical symptoms and ECG changes (even permanent) are insufficient to diagnose myocardial infarction per current definition [13]. However, within patients who met primary endpoint, the hscTnI levels were higher (6.7 ± 8.4 mg/L vs 4.8 ± 6.5 ng/L, p = 0.69). Lack of statistical significance is comprehensible due to low number of patients. However, it is well known, that among patients with SCAD hscTnI concentration (even within normal) is an efficient tool to stratify the risk of poor prognosis in short- and long-term observation [14–16]. To the best of our knowledge this is one of the first announcements of possible negative influence of dipyridamole pharmacologic stress test on hscTnI concentration and multiple ECG changes in stable patients.

Ischaemic changes in ECG were observed in the study group after pharmacological stress. Especially alarming were persistent changes of the ST-T segment. New persistent elevation or depression of ST segment were observed in 25% of patients and correlated with the positive MPS and history of chest pain. It is a crucial observation as the clinical meaning of new changes in ECG during MPS study was never assessed. Nevertheless, we may reject the hypothesis of myocardial necrosis as the hscTnI concentration remains within normal in prolonged observation.

Recent analyzes regarding the safety of dipyridamole do not differentiate between persistent and transient ST-T segment changes. In the paper published by Doumas A et al [17], new ST-T changes were observed in 5 out of 41 (12%) patients after dipyridamole administration. Out of 125 patients evaluated in the Zaman et al. study, 78 (68.4%) had some form of minor adverse reactions *e.g.* chest pain was experienced by 39 cases (31%) and ST-T changes occurred in 36 (29%) patients who underwent dipyridamole perfusion imaging [18]. Compared to mentioned studies, this study is distinguished by the stratification method of ST-T segment changes considering their dynamics during and after the pharmacologic stress test. There are also no publications validating ST-T changes during MPS as a risk factor for significant cardiovascular events.

Among other changes in the ECG, QTc prolongation and PR prolongation were observed most frequently. In Guideri et al. [19] study, twenty-five patients admitted for evaluation of chest pain of suspected myocardial origin after discontinuation of antianginal treatment underwent an echocardiographic stress test. Of these patients, 10 underwent an echocardiographic adenosine stress test and 15 underwent an echocardiographic dipyridamole stress test. After dipyridamole and adenosine administration, a significant prolongation of the QTc interval was observed only in those patients who had positive test results [19]. Interestingly, in our study over 80% of patients with QTc prolongation reported chest pain and about 60% of patients had typical angina before the examination. Although, we have shown no correlation between QTc prolongation and the MPS, our results confirms Guideri's suggestions that QTc interval prolongation during pharmacological stress tests might be considered as a marker of myocardial ischemia.

The relatively frequent occurrence of clinical AE (64% of patients) is noteworthy. The authors reported all AEs regardless of their severity. In the literature, we found reports of the occurrence of AE after intravenous administration of dipyridamole in 40 to nearly 70% of patients [19, 20].

The main limitation of our study is the limited number of patients. It is a single-center pilot study designed to assess the safety of the dipyridamole administration during the MPS with a modern study protocol. Per authors' knowledge and experience this is an observation worth to

highlight to make further studies, including a larger study population, that confirm our findings.

Conclusions

MPS with dipyridamole stress is related to significant risk of clinical and electrocardiographic adverse events. There is a considerable number of ECG changes with undetermined clinical implication (especially QRS complex and QTc prolongations) related to dipyridamole infusion.

Conflict(s) of interest

The authors declare no conflict of interest.

Streszczenie

Wstęp. Scyntygrafia perfuzyjna mięśnia sercowego (MPS) z obciążeniem dipirydamolem jest szeroko akceptowaną metodą oceny niedokrwienia mięśnia sercowego, szczególnie u pacjentów z przeciwwskazaniami do elektrokardiograficznego testu wysiłkowego. Jednak podczas obciążenia dipirydomolem często obserwuje się objawy kliniczne i zmiany w badaniu elektrokardiograficznym (EKG). Celem badania jest określenie bezpieczeństwa badań MPS z obciążeniem dipirydamolem.

Materiał i metody. Do badania włączono kolejnych 25 pacjentów, u których wykonywano badanie MPS w celu diagnostyki niedokrwienia mięśnia sercowego w protokole dwudniowym (po obciążeniu dipirydamolem w dawce 0,56 mg/kg mc. *i.v.* i w spoczynku). Badania wykonywano z wykorzystaniem Tc-MIBI. W trakcie badania pacjenci byli monitorowani za pomocą 12-odprowadzeniowaego EKG. U wszystkich pacjentów oznaczono stężenie troponiny I metodą wysokoczułą (hscTnI) przed badaniem, 4 godziny po obciążeniu dipirydamolem i następnego dnia. Pierwszorzędowym punktem końcowym było stężenie hscTnI ponad 99. percentyla górnej granicy wartości referencyjnej w 2. lub 3. oznaczeniu albo nowe i utrzymujące się zmiany odcinka ST-T. Drugorzędowym punktem końcowym były nowe przemijające lub utrzymujące się zmiany w zapisie EKG (uniesienie lub obniżenie odcinka ST-T, wydłużenie czasu trwania zespołu QRS, odstępu PR lub skorygowanego czasu QT [QTc]) lub jakiekolwiek zdarzenie niepożądane związane z dipirydamolem.

Wyniki. Stężenia troponiny w kolejnych pomiarach mieściły się w wartościach referencyjnych u wszystkich pacjentów. Pierwszorzędowy i drugorzędowy punkt końcowy obserwowano u odpowiednio 6 (24%) i 23 (92%) badanych. Przemijające uniesienie odcinka ST-T wystąpiło u 4 (16%) badanych, przemijające obniżenie odcinka ST lub ujemne załamki T u 7 (25%) badanych, wydłużenie zespołu QRS u 11 (44%) badanych, odstępu PR u 18 (75%) badanych, QTc u 22 (88%) badanych, a jakiekolwiek zdarzenie niepożądane związane z lekiem u 16 (64%) badanych. Obecność punktów końcowych korelowała z dodatnim wynikiem badania MPS (zmiany odcinka ST-T, wydłużenie odstępu PR) i wywiadem dolegliwości dławicowych (zmiany odcinka ST-T, wydłużenie zespołu QRS i QTc).

Wnioski. Stężenie hscTnI w granicy normy w przedłużonej obserwacji pacjentów po badaniu MPS z obciążeniem dipirydamolem wskazuje na to, że jest to względnie bezpieczna procedura diagnostyczna. W trakcie badania obserwuje się zmiany elektrokardiograficzne i kliniczne zdarzenia niepożądane niezwiązane z martwicą miokardium.

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