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Application of stress-only myocardial perfusion imaging

Michał Włodarczyk[1], Jacek Kuśmierek[2], Małgorzata Bieńkiewicz[2], Krzysztof Filipczak[1], Anna Płachcińska[1]
[1]Department of Quality Control and Radiological Protection, Medical University of Łódź, Poland
[2]Department of Nuclear Medicine, Medical University of Łódź, Poland

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Abstract

BACKGROUND: Single-photon emission computed tomography myocardial perfusion study is usually a sequence of stress and rest part. In case of a normal stress study rest part can be given up.
The objective of this study was to examine factors affecting concordance of results of stress-only (SO) and stress-rest (SR) studies.
MATERIAL AND METHODS: SO and SR studies without and with attenuation correction (AC) of 212 selected patients (without cardiomyopathy, history of myocardial infarction or coronary artery bypass grafting) were analyzed visually. Influence of percutaneous coronary intervention (PCI) in the past, type of stress (physical/pharmacological) and application of AC (in form of combined method of non-corrected and corrected images — CM), patient body mass index (BMI) and gender on concordance rates of SO and SR studies were examined.
RESULTS: Neither a history of PCI, nor a type of stress affected concordance rate. AC (in form of CM) improved concordance rate significantly, from 60% to 68% ($p = 0.018$). Patient BMI affected concordance rates — 72% in non-obese and 59% in obese patients ($p = 0.05$). In the whole group, risk of overlooking patients with abnormal perfusion in SO study was small (< 2%), but it grew significantly with patient BMI. Rest study was necessary in about 20% of non-obese and in about 50% of obese patients.
CONCLUSION: MPS can be limited to stress part in appropriately selected, especially non-obese, patients provided that AC is applied, due to a low risk of overlooking patients with abnormal perfusion. In case of obese patients, careful analysis of exercise images for their normality is particularly important.

KEY words: myocardial perfusion study, stress-only, attenuation correction

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Introduction

Single-photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI) is a recognized diagnostic method allowing detection of coronary artery disease, prognosis of its course and assessment of treatment effectiveness. There are several protocols of this study, recommended by nuclear medicine societies in Europe [1] and in the world [2, 3], using technetium-99m-labeled radiopharmaceuticals (99mTc-sestamibi, 99mTc-tetrofosmin) or, less frequently, thallium-201 isotope. The most widely used protocol in Poland is a two-day study, after exercise or its pharmacological equivalent, and at rest (stress-rest, SR), using 99mTc-sestamibi. This procedure involves a double administration of a radiopharmaceutical, with an effective dose of radiation for a standard patient of about 10 mSv [1].

Correspondence to: Michał Włodarczyk, MD
Department of Quality Control and Radiological Protection
ul. Czechosłowacka 8/10, 92–213 Łódź, Poland
Tel/fax: +48 42 675 72 85
e-mail: michal.wlodarczyk@stud.umed.lodz.pl

It is assumed that when a stress study is normal, it is possible to resign from a rest part of it (stress-only, SO method) [4–6]. The use of SO is of particular importance in view of the fact that an ever lower proportion of studies show abnormal perfusion of the myocardium. In 2012 Duvall et al. [7] estimated frequency of abnormal MPI studies in two academic centers in United States to be about 34%. According to Rozanski et al. [8], this percentage may be even lower than 10% — data for the US from 2009. The benefits of this type of procedure, in addition to reduction of the effective radiation dose to approximately 5mSv [1], also include: lower cost of studies (shortening of acquisition time, reducing activity of a radiopharmaceutical), increasing the number of studies performed at a facility and increasing satisfaction and convenience of patients due to a shorter time spent on examination. Despite many years that have passed since the first application of SO study [9] and 10 years from the time when the possibility of resigning from a rest study was included in the recommendations of the European Association of Nuclear

Medicine (EANM) and the European Society of Cardiology [10], this protocol is not widely used [11, 12]. The main limitations of its use seem to be logistic problems related to planning the number of studies performed and financing of the examinations dependent not only on the number of patients, but also on whether both or only one part of the study have been performed [12]. The decision to do (or not) an additional rest study is made after the analysis of stress perfusion, and its outcome is difficult to predict. A great simplification in planning the schedule would be to find a group of patients with uncommon necessity of additional rest examination. According to literature data, patients without a history of myocardial infarction (MI) and coronary artery bypass graft (CABG), without cardiomyopathy or significant valvular heart disease should be included in this group [13].

The aim of this study was therefore to examine factors related to patients (gender, body mass index — BMI, history of angioplasty) or a study methodology (type of stress, correction for radiation attenuated inside a patient body referred to as attenuation correction — AC) that affect the concordance of results of SO study and the complete set of SR images. At the same time, different groups of patients were analyzed in terms of frequency of abnormal results and associated with it number of cases with necessary rest study.

Material and methods

A study included 241 patients without history of MI, CABG and without cardiomyopathy who underwent a two-day MPI using a Gated SPECT/CT method in the Department of Nuclear Medicine of the Medical University of Lodz. On one day, the study was performed after stress and on another day — at rest. The most common (in 81%) was exercise stress; less commonly (in 19%) the pharmacological stress test with dipyridamole was performed. Exercise tests on the treadmill were carried out in accordance with the Bruce protocol. Dipyridamole was administered intravenously over 4 minutes at a dose of 0.56 mg/kg. Beta blockers, long-acting nitrates and calcium channel blockers were suspended for 2 days, and trimetazidine for 7 days before the stress test. A radiopharmaceutical, ^{99m}Tc-sestamibi (10 MBq/kg) was administered intravenously at the time of maximum physical stress on the treadmill or within the first 3–5 minutes after administration of pharmacological stressor. After administration of the radiotracer, patients continued their effort for about 1 minute. Image acquisition was started 45–60 minutes after administration of the radiopharmaceutical. Images were recorded using a dual-head hybrid Infinia Hawkeye 4 gamma camera (by GE) equipped with low energy high resolution collimators. Gated SPECT acquisition (8 time intervals) consisted of 60 projections, in a 64x64 matrix (zoom of 1.28). After SPECT images were recorded, a low-dose CT scan of the chest (140 kV, 2.5 mA) was performed to enable attenuation correction during SPECT study reconstruction. Studies were reconstructed with ordered subset expectation maximization (OSEM) iterative method (2 iterations, 10 subsets) without (NC) and with attenuation correction (AC).

Reconstructed images of the left ventricular myocardium (sets of slices in three planes) were visually evaluated by two experienced specialists (a consensus). Myocardial perfusion was assessed using a 4-point scale: n — normal; pn — probably normal; pa — probably abnormal; a — abnormal. Perfusion defects were assigned to areas of vascularization of three main coronary arteries: left anterior descending (LAD), left circumflex (LCx) and right coronary artery (RCA). Initially, only stress images were analyzed (first NC, then AC). After a few days, stress together with rest analysis took place — first NC, then AC. Additionally, NC together with AC images were analyzed in accordance with EANM procedural guidelines for radionuclide MPI [1] and specialists assigned a rate on a 4-point scale based on a set of NC and AC studies. This combined method (CM) was considered optimal and was further used as the one applying attenuation correction. The order of assessed patients was random, and the specialists knew only their gender. Gated data (including left ventricular ejection fraction — LVEF) were available, as the global contractility of the left ventricle was also analyzed. At this stage, patients with abnormal global left ventricular contraction (LVEF < 50%) were discarded because results of such studies should not be considered normal.

For comparison of perfusion assessments in SO and SR studies, total concordance rates of assessments (percentages of patients with the same visual assessment) and kappa Cohen's coefficients were calculated. The analysis was performed separately for NC, AC and CM studies, and the impact on the concordance of such factors as: percutaneous coronary intervention (PCI), type of stress test (exercise/pharmacological), BMI and patient's gender were evaluated by comparing concordance rates in respective subgroups of patients.

The study was approved by the Medical University Bioethics Committee.

Statistical analysis

Significance of percentage differences in concordance rates in independent subgroups of patients (gender, BMI, PCI, type of stress) was assessed using the chi-square test or exact Fisher test, and in the case of the same group (NC, AC and CM) — the McNemar test. The significance of differences between kappa coefficients was estimated on the basis of their 95% confidence intervals. The adopted significance threshold was 0.05. Statistical analysis was performed using the Statistica 10.0 software.

Results

The final number of patients whose studies were subject to further analysis amounted to 212. Clinical and demographic characteristics of the group are presented in Table 1. Concordance

Table 1. Clinical and demographic characteristics of a studied group of patients

Parameter	Number
Number of patients	212
Males	111
Females	101
Hypertension	163
Diabetes mellitus	46
Hyperlipidemia	153
Smokers (past and present)	59
Number of patients after PCI	53
Mean age [years]	62 ± 8
Mean BMI [kg/m2]	28 ± 4

BMI — body mass index,
PCI — percutaneous coronary intervention

rates of SO and SR perfusion assessments in the group of all 212 patients grew statistically significantly with application of AC, especially with a separate evaluation of images (Tab. 2). Application of CM reduced this effect to some degree, although a concordance rate remained statistically significantly higher than in NC studies. Based on the SO study, perfusion was rated as either normal or abnormal in 51% (NC) or 73% (CM) patients.

Table 3 presents the comparison of locations of perfusion defects detected with CM method (evaluation of images performed on the basis of observation of both NC and AC images) in SO and SR studies. A tendency to detect more defects in the SR than in SO method is visible. This applies mostly to the RCA area (13 vs 2) and the LAD area (9 vs 2). Of 13 patients who had a perfusion defect detected in the RCA area only in the SR studies (invisible in the previous SO assessment), the majority (92%) were men, while among 9 patients with perfusion defects in the area of LAD detected during the assessment of SR images (invisible in SO study), the majority (56%) were women.

A greater impact of attenuation correction (in form of CM) on the increase in concordance rates was observed in men than in women. A similar trend was revealed by Cohen's kappa coefficients (Tab. 4).

Neither PCI nor type of stress applied (exercise/pharmacological) had a significant effect on the concordance of SO and SR examinations (Tab. 5).

Regarding the impact of BMI (Tab. 6), concordance rates fell statistically significantly with the increase in BMI even if attenuation correction in the form of CM was applied. Additional patient division by gender also showed decrease, although non-significant, in concordance rates in men as well as women with increase in BMI. The same trend was revealed by Cohen's kappa coefficients.

Table 2. Stress-only (SO) versus stress-rest (SR) perfusion rates in the whole study group
a) without attenuation correction (NC)
b) with attenuation correction (AC)
c) with combined method (CM)

a) NC		SR			N = 212
		n	pn	pa	a
SO	n	**56**	16	4	2
	pn	12	**36**	18	9
	pa		7	**10**	11
	a		1	4	**26**
kappa:	0.45		**concordance rate:**		**60%**
b) AC		**SR**			**N = 212**
		n	pn	pa	a
SO	n	**115**	12	4	1
	pn	9	**16**	7	5
	pa	1	2	**3**	8
	a			3	**26**
kappa:	0.58		**concordance rate:**		**75%**
c) CM		**SR**			**N = 212**
		n	pn	pa	a
SO	n	**90**	28	4	2
	pn	6	**23**	8	5
	pa		2	**4**	10
	a			3	**27**
kappa:	0.51		**concordance rate:**		**68%**

A four category scale was applied:
n — normal perfusion
pn — probably normal perfusion
pa — probably abnormal perfusion
a — abnormal perfusion
N — number of patients

Values in table present numbers of patients

Significance levels of differences between concordance rates:
NC vs AC: p = 0.0001;
NC vs CM: p = 0.018

Table 3. Comparison of locations of perfusion defects detected with CM method in SO and SR studies

		SR			
		No defect	LAD	RCA	LCx
SO	No defect	147	9	13	2
	LAD	2	18		
	RCA	2	1	22	1
	LCx				4

LAD — left anterior descending coronary artery
LCx — left circumflex coronary artery
RCA — right coronary artery
Values in table present numbers of patients

Table 4. Concordance rates between stress-only and stress-rest studies in subgroups of men and women

	Number	NC	p	CM
		concordance rate (kappa)		concordance rate (kappa)
Males	111	51%* (0.35)	0.05	61%** (0.44)
Females	101	70%* (0.56)	0.3	75%** (0.59)

CM — combined method using attenuation correction
NC — no attenuation correction
p — significance level of a difference between concordance rates of NC and CM
*p = 0.005; **p = 0.029

Table 5. Concordance rates between stress-only and stress-rest studies in subgroups of patients after and without PCI, and after two forms of stress

	Number	NC			CM		
		concordance rate	p	kappa	concordance rate	p	kappa
Patients after PCI	53	60%	p = 0.94	0.47	67%	p = 0.73	0.48
Patients without PCI	159	60%		0.44	70%		0.56
Physical stress	172	62%	p = 0.26	0.48	69%	p = 0.66	0.52
Pharmacological stress	40	53%		0.35	65%		0.46

Abbreviations: see Table 4
PCI — percutaneous coronary intervention
p — significance level of a difference between concordance rates in respective subgroups of patients

Table 6. Concordance rates between stress-only and stress-rest studies evaluated with CM in subgroups of patients divided according to BMI and gender

	BMI < 30		p	BMI ≥ 30	
All patients (N = 212)	N = 141	CR = 72% (0.55)	0.05	N = 71	CR = 59% (0.42)
Males (N = 111)	N = 68	CR = 66% (0.49)	0.18	N = 43	CR = 53% (0.35)
Females (N = 101)	N = 73	CR = 78% (0.61)	0.29	N = 28	CR = 68% (0.52)

BMI — body mass index
CR — concordance rate (kappa value in brackets)
N — number of patients
p — significance level of differences between concordance rates in two BMI subgroups

Table 7. Comparison of SO and SR study assessments in patient subgroups divided according to BMI (BMI < 30 and BMI ≥ 30), in CM method

BMI < 30		SR			N = 141
		n	pn	pa	a
SO	n	**67**	17	3	
	pn	4	**14**	5	2
	pa		1	**2**	7
	a				**19**
kappa:	0.55	**concordance rate:**			**72%**
BMI ≥ 30		**SR**			**N = 71**
		n	pn	pa	a
SO	n	**23**	11	1	2
	pn	2	**9**	3	3
	pa		1	**2**	3
	a			3	**8**
kappa:	0.42	**concordance rate:**			**59%**

Abbreviations — see Table 2
BMI — body mass index

Table 8. Frequencies of missing abnormal perfusion if study was finished after a) normal or b) normal or probably normal stress images evaluated with CM, with additional division into subgroups according to BMI

All patients (N = 212)		BMI < 30 (N = 141)		BMI ≥ 30 (N = 71)	
a	b	a	b	a	b
Below 2% (2*/124)	4% (7/166)	0% (0/87)	2%** (2/112)	5% (2/37)	9%** (5/54)

Abbreviations: see Table 6
*2 obese patients: 1 male and 1 female
**p = 0.04

More detailed data on assessments in SO and SR studies with CM method and their concordance rates in subgroups of patients divided according to BMI are presented in Table 7. Two patients with the greatest change in the assessment of perfusion between SO and SR (normal perfusion in the study SO, abnormal in SR) belonged to the subgroup with BMI ≥ 30.

Table 8 shows how frequently specialists reading SO images would miss abnormal perfusion if rest study was given up after normal and also normal or probably normal stress images evaluated with CM, with additional division into subgroups according to BMI. These results were obtained from data presented in Table 7. Although in the whole group of patients the risk of missing an abnormal perfusion was low in both of these situations (2% and 4%, respectively), these risks differed in the subgroups of patients divided by BMI. In the subgroup of non-obese patients, even a stress examination considered to be probably normal allows to give up the rest study, as the risk of overlooking abnormal perfusion does not exceed 2%. However, in the case of obese patients, the risk is significantly higher (about 9%) and, therefore, in such patients the resignation from the rest study can only take place if an unquestionably normal result of the stress examination is obtained.

After the SO study, perfusion in non-obese patients was assessed with CM method as abnormal or probably abnormal in 21% (29/141). In these patients it would be necessary to perform an additional rest study for a reliable assessment of the complete set of images. In obese patients, however, definitely normal results were obtained in 52% (37/71), so in this subgroup of patients rest studies could not be avoided in about 48% of patients.

In patients with different SO and SR study results assessed with CM (N = 68), perfusion in most cases (57/68, 84%) was assessed as more abnormal in the SR than SO method (see Tab. 2c — greater numbers of patients above the main diagonal). It should be noted that with the exception of patients with switch of study results from normal or possibly normal to abnormal (N = 7) (example in Fig. 1), in all remaining cases perfusion defects were of small size and severity.

Discussion

Research on the SO method has been going on since the beginning of the 1990s. During that time, numerous publications appeared, in which the possibility of giving up the rest part of the study was considered and consequences of such proceedings were discussed. Publications from the 90s [9, 14] focused mainly on the visual evaluation of the same patients, initially the exercise part (SO) and later together with the resting part (SR). Quite a large percentage of normal stress studies (20–30%, up to 40% in the group without a history of myocardial infarction), with unchanged result after adding the rest part, encouraged further research. The qualification of patients without prior myocardial infarction or PCI, as well as without cardiomyopathy, valvular heart disease or left bundle branch block in the past made the percentage of normal SO studies even higher, to about 55% [13]. Milan et al. [13] examined the concordance between visual assessments of SPECT MPI studies (SO and SR) without AC in 200 patients, dividing the results into normal and abnormal. Of the 112 patients presenting with a normal result in SO, only in 6 (5%) a change to an abnormal SR was obtained. The concordance rate of SO and SR results at the level of 85% is similar to the agreement obtained in the current

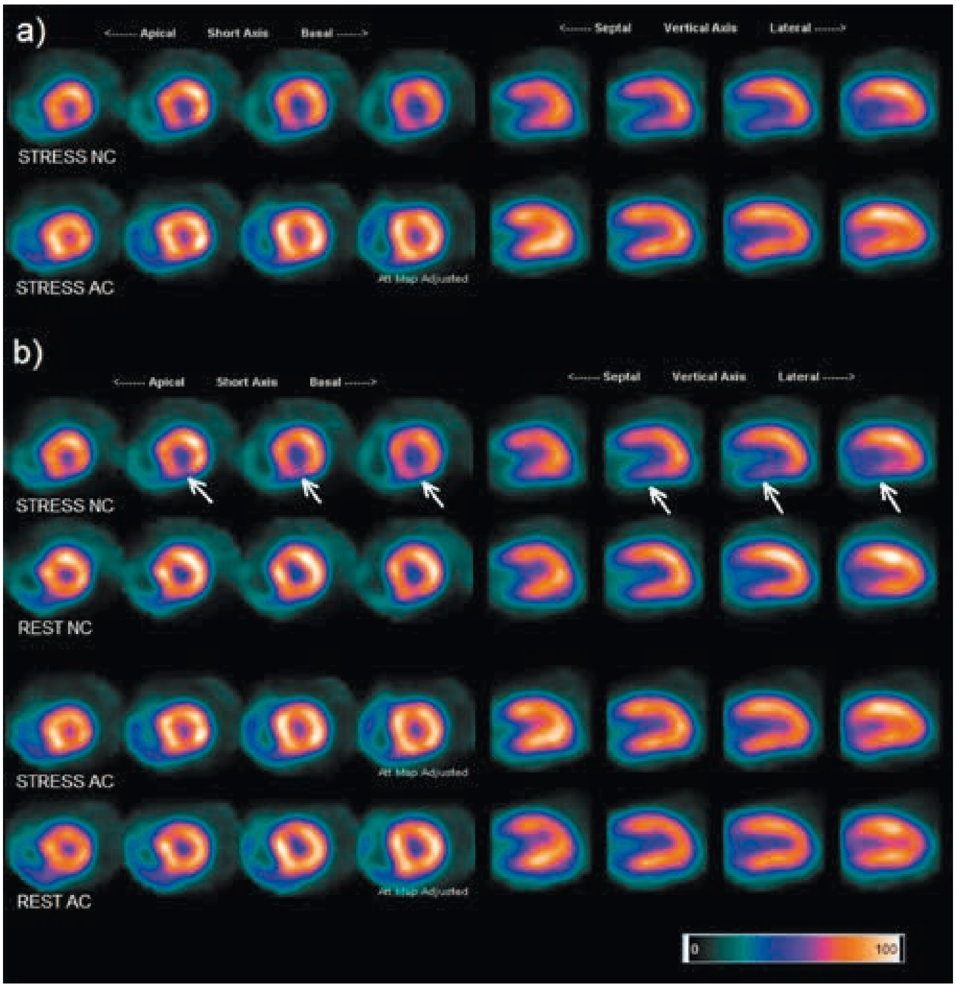

Figure 1. a) Comparison of images from the stress-only study without correction (NC, upper row) and with attenuation correction (AC, lower row) in a male patient whose perfusion was assessed to be probably normal in the NC, AC and CM studies; **b)** Comparison of stress + rest images without correction (NC, upper rows) and with attenuation correction (AC, lower rows) in the same patient. Stress perfusion was assessed as abnormal in the NC study (stress and rest), probably abnormal in AC and eventually abnormal in CM. A stress perfusion defect visible in the inferior wall (indicated by arrows)

study after the division of results into normal (n + pn) and abnormal (pa + a), without AC — 81%.

As noted earlier, in the above publication there was no question of using any form of AC, which, in the absence of proper patient selection, resulted very often in the need to perform a rest study. The use of AC allowed authors of subsequent research to reduce the percentage of studies with uncertain result and number of necessary rest studies. Trägårdh et al. [15], after examining 1261 patients, found that use of AC reduced number of rest studies by 17% (from 49% to 32%). An even greater influence of AC was noted by Mathur et al. [6] — rest imaging was necessary in 49% of 1383 studied patients without AC and only in 6% with AC. Piszczek et al. [16] performed a research on a modern CZT camera and replaced the classical attenuation correction with a projection in a prone position. One year follow-up revealed no sudden cardiac incidences in both, stress-only and stress-rest groups with normal perfusion. In the present study, SO perfusion assessments appeared as definitely normal or abnormal in 51% of patients without AC and 73% after attenuation correction, in the form of CM. Additional rest examination was necessary in about 20% of non-obese patients and about 50% of obese ones. It is worth noticing that differences in the above-mentioned percentages of studies assessed as uncertain as well as the necessity to acquire a rest study, in addition to the methodology used, resulted also from the selection of patients.

Evaluation of studies based on both sets of images: NC and AC, complies with the EANM recommendations for visual evaluation of the study [1]. This is justified by cases of overcorrection of left ventricular inferior wall due to high sub-diaphragmatic activity, which may result in the artificial filling of true perfusion defects in this wall. For this reason, specialists evaluating images decided not to take into account attenuation corrected images with excessive correction of the inferior wall, especially when in non-corrected images stress induced defects could be observed.

The greater number of perfusion defects observed in SR than SO studies was due to the recognition of typically lower image values in inferior wall in men (RCA blood supply area) and antero-septal wall in women (LAD blood supply area) in SO method as normal. When those images were compared with rest part of the study, lower image values were in some cases recognized as true perfusion defects.

In addition to increasing the reliability of the result and reduction of the frequency of the necessary rest studies, attenuation correction also had a significant impact on the concordance rate of the SO and SR studies, higher in men than in women. This fact is associated with more effective correction of artifacts resulting from diaphragmatic absorption of radiation, occurring more often in men than those associated with the absorption of radiation by breasts in women.

Regarding the type of applied stress, the difference in concordance rates in patients after physical and pharmacological stress was not statistically significant. Milan et al. [13] did not observe statistically significant difference in concordance in relation to applied type of stress either.

Remaining factors, this time patient-related (history of PCI, BMI, gender) should also be discussed. Division against the history of PCI did not reveal a significant difference in concordance rates. A statistically significantly higher concordance rate of SO and SR studies was found in subgroup of females than in males. Moreover, the BMI coefficient had an evident effect on concordance rates of SO and SR perfusion assessments. There was a significantly lower agreement in obese than in non-obese patients. After additional division of patients by gender, even with CM, concordance rates in obese men and women remained quite low, and in patients without obesity of both genders, agreement rates were higher. Despite the lack of statistical significance in the subgroups of men and women, a trend revealing lower concordance rates in obese patients of both genders could be observed. This result suggests caution when giving up a rest study in obese patients, especially men. Limitation to exercise part of the study can only take place if images are unquestionably normal. If there are doubts about them, this study should be supplemented with a rest part, because the lower concordance rate between the assessment of SO and SR in obese patients suggests more frequent errors in the assessment of SO studies. This fact has been explicitly confirmed by results presented in Table 8. The clear dependence of the concordance rate of SO and SR methods on patient BMI has not been demonstrated so far.

Lower concordance rate in obese patients should not obscure the value of SO protocol when using attenuation correction. Appropriate patient selection provides a high concordance rate between SO and SR study assessments and the risk of overlooking patients with abnormal perfusion is small, especially in non-obese patients. These results, pointing to high usefulness of SO MPI, are in line with the current trend also seen in large (several-dozen-thousand) studies groups of patients [4, 17–19], in whom usefulness of a stress-only study protocol was confirmed by a good prognosis in patients with a normal stress perfusion.

Study limitations

The results of the stress-only study have not been verified by comparison with results of coronary angiography or observation of patients. Verification of normal stress-only study results, by patient observation, is intended to be performed in the second stage of the project.

Conclusions

The possibility of omitting the rest part of the MPI study in appropriately selected patients should be emphasized, provided that attenuation correction is applied. In patients without obesity a high percentage of normal stress studies is obtained.

Giving up a rest part of the study is possible due to a low risk of overlooking patients with abnormal myocardial perfusion. In case of obese patients, careful analysis of exercise images for their normality is particularly important.

Conflict of interest:

none declared

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