Initial and delayed stress phase imaging in a single-injection double-acquisition SPECT

The potential value of early ^{99m}Tc-MIBI redistribution in assessment of myocardial perfusion reversibility in patients with coronary artery disease

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Keywords
^{99m}Tc-MIBI, redistribution, dobutamine, myocardial perfusion SPECT, partial volume effect

Summary
Some studies reported that ^{99m}Tc-MIBI may redistribute in ischaemic myocardium and this phenomenon may have potential role for better assessment of viability by delayed ^{99m}Tc-MIBI imaging. Some studies also suggested that infusion of low dose dobutamine during delayed imaging may enhance the value of ^{99m}Tc-MIBI imaging for evaluation of viability. The aim of this study is to determine whether the observed changes of perfusion defects on delayed images are caused by early radiotracer redistribution or as a result of reversal partial volume effect secondary to inotropic stimulation. Patients, methods: 89 patients with angiographically proven coronary artery disease (CAD) were enrolled in this randomized clinical trial study. In all cases, gated-SPECT images were obtained 60 minutes after stress with dipyridamole injection. Subsequently the patients were randomly allocated in two groups and the second imaging was performed at 120th minute during low dose dobutamine (dobutamine group; 45 cases) or placebo infusion (placebo group; 44 cases). Difference between summed stress score of the first (SSS_1) and second (SSS_2) stress images (ΔSSS) was considered as a marker of reversibility in single-injection double-acquisition (SIDA) protocol. Also summed difference score (SDS) was recorded as a marker of reversibility in standard stress/rest, double-injection double-acquisition (DIDA) protocol. ΔSSS of the two studied groups were compared. Also the correlation and agreement between ΔSSS and SDS were analyzed. Results: A significant difference was found between SSS_1 (median 15, range 0–48) and SSS_2 (median 11, range 0–42) in total patients ($p < 0.0001$). A significant correlation was noted between ΔSSS and SDS in dobutamine group ($r = 0.58$, $p = 0.002$) as well as in placebo group ($r = 0.57$, $p < 0.0001$). Considering DIDA protocol as a standard reference method, the influence of dobutamine infusion was not shown to be significantly different from the placebo effect on the magnitude of fixed or reversible perfusion defects in SIDA protocol. Conclusion: The changes in the magnitude of the perfusion defects may occur in the first hours of ^{99m}Tc-MIBI injection in the stress phase imaging. These changes correlate well and are in agreement with perfusion improvement on the rest images. This phenomenon may be independent of improvement in myocardial function, in more delayed imaging or following inotropic augmentation, and thus is likely due to ^{99m}Tc-MIBI redistribution. This may open new technical and clinical aspects and potentials for ^{99m}Tc-MIBI imaging.

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Frühe und späte SPECT-Aufnahmen nach Belastung (single-injection double-acquisition SPECT) – Potenzieller Nutzen einer frühen ^{99m}Tc-MIBI Umverteilung für die Beurteilung reversibler Perfusionsstörungen bei KHK-Patienten
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Schlüsselwörter
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Zusammenfassung
Einige Studien geben Hinweise, dass sich ^{99m}Tc-MIBI in ischämischem Myokard umverteilt und späte ^{99m}-Tc-MIBI-Aufnahmen eine genauere Vitalitätsdiagnostik liefern. Darüber hinaus konnte nachgewiesen werden, dass eine Low-dose-Dobutamin-Infusion während der Spätaufnahmen die Vitalitätsdiagnostik mit ^{99m}Tc-MIBI verbessert. Ziel dieser Studie ist nachzuweisen, ob die beobachtbaren Veränderungen von Perfusionsdefekten auf den Spätaufnahmen durch eine frühe Umverteilung des Radiopharmakons verursacht werden oder Folge eines (reversiblen), durch eine inotrope Stimulation hervorgerufenen Partialvolumeneffektes sind. Patienten und Methodik: 89 Patienten mit angiographisch nachgewiesener koronarer Herzkrankheit (KHK) wurden in diese randomisierte Studie eingeschlossen. 60 min nach einer Dipyridamol-Belastung wurden gated-SPECT-Aufnahmen erstellt. Anschließend wurden die Patienten randomisiert zwei Gruppen zugewiesen. Die Spätaufnahme erfolgte nach 120 min unter Low-dose-Dobutamin-Infusion (Dobutamin-Gruppe; 45 Patienten) oder unter Placebo-Infusion (Placebo-Gruppe; 44 Patienten). Die Differenz des Summed Stress

Scores (SSS_1) zwischen erster und zweiter Aufnahme (SSS_2) nach Belastung (ΔSSS) wurde als Reversibilitätsmarker des SIDA-Protokolls (single-injection double-acquisition) verwendet. Der SDS (summed difference score) wurde als Reversibilitätsmarker beim Standard-DIDA-Protokoll (double-injection double-acquisition) mit Aufnahmen nach Belastung und in Ruhe geführt. Verglichen wurde der ΔSSS-Wert in beiden Gruppen. Außerdem wurden Korrelation und Übereinstimmung zwischen ΔSSS und SDS analysiert. Ergebnisse: Für das Gesamtkollektiv ergab sich ein signifikanter Unterschied zwischen SSS_1 (Median 15, Bereich 0–48) und SSS_2 (Median 11, Bereich 0–42; $p < 0{,}0001$). Eine signifikante Korrelation zwischen ΔSSS und SDS zeigte sich in der Dobutamin-Gruppe ($r = 0{,}58$, $p = 0{,}002$) und in der Placebo-Gruppe ($r = 0{,}57$, $p < 0{,}0001$). Beim DIDA-Protokoll (Standard-Referenz-Protokoll) fand sich kein Unterschied im Ausmaß reversibler und nicht-reversibler Perfusionsdefekte zwischen der Low-dose-Dobutamin-Infusion und der Placebo-Infusion. Schlussfolgerung: Veränderungen von Perfusionsdefekten bei Belastungsaufnahmen können in den ersten Stunden nach Injektion von ^{99m}Tc-MIBI auftreten. Es besteht hierin eine gute Korrelation und Übereinstimmung mit den Ruheaufnahmen. Dieser Effekt zeigte sich unabhängig von einer Erholung der Myokardfunktion oder einer Low-dose-Dobutamin-Infusion in den Spätaufnahmen, und ist wahrscheinlich auf eine Umverteilung von ^{99m}Tc-MIBI zurückzuführen. Hiermit eröffnen sich neue technische und klinische Aspekte für ^{99m}Tc-MIBI Myokard-Perfusions-SPECT.

Technetium-99m methoxyisobutyl isonitrile (^{99m}Tc-MIBI) is a lipophilic cationic imaging agent that distributes throughout the myocardium proportional to coronary blood flow (1). Some previous studies suggested that ^{99m}Tc-MIBI does not show significant redistribution (9). However, some other studies have revealed evidences in favour of ^{99m}Tc-MIBI redistribution in animal models and human studies (2, 4, 7, 13, 15). Although some preliminary reports have suggested a potential value of ^{99m}Tc-MIBI to show viability using delayed images, the importance of ^{99m}Tc-MIBI redistribution for showing viability after stress injection has not yet been widely evaluated.

In some studies, evidence for redistribution is seen on more delayed images obtained after three hours of injection (2, 8). Some other studies revealed that in addition to slower washout and redistribution of ^{99m}Tc-MIBI in ischaemic areas, a reversal of partial volume effect may have an additive role in enhancement of activity in ischaemic areas. This may be due to improvement of systolic thickening and motion on more delayed images or after dobutamine-induced augmentation (12, 14). Also in our previous study, we reported that ^{99m}Tc-MIBI with a single-injection double-acquisition (SIDA) method, before and during low dose dobutamine infusion may have a potential value for showing more reversibility of the viable ischaemic myocardium as compared with standard stress/rest protocol (3). This finding may be explained by reversal of partial volume effect during improvement of systolic thickening and motion after inotropic stimulation with dobutamine or ^{99m}Tc-MIBI redistribution during the time period between the first and second images or combination of both.

The influence of different factors such as radiotracer redistribution or functional recovery (during a period of time and/or inotropic stimulation of dobutamine) on apparently improved perfusion defects is still unclear. Considering this fact, the true reversibility may not be assessed by a SIDA method. This limitation has also been pointed out by van der Wall et al. as an appraising comment (16). Indeed, without considering the possibility of early ^{99m}Tc-MIBI redistribution, SIDA method has to be relied on a reversibility equivalent defined based on both radiotracer uptake and systolic thickening/motion. To determine the net effect of ^{99m}Tc-MIBI redistribution on the perfusion defect magnitude during a short period of time, we designed a study with random allocation of the patients in two groups; one with low dose dobutamine and the other with placebo infusion.

Patients, material, methods

The study protocol was approved by ethics committee of Tehran University of Medical Sciences. 89 patients consisting of 55 men (61.8%) and 34 women (38.2%); mean age 57.7 ± 10.7 years (range: 34–77 years) with known coronary artery disease (CAD) according to angiography report (at least 50% stenosis in one or more main coronary arteries or their major branches) and with no arrhythmias interfering with gated acquisition were prospectively studied. After obtaining written informed consent, clinical history and the physical examination findings were recorded.

The patients were instructed to withdraw β-blockers and calcium blocking agents 48 hours before study. Patients were asked to fast 4 hours and discontinue caffeine containing drugs or foods and long-acting aminophylline 24 hours before the stress phase of the study.

All patients underwent a standard pharmacological stress phase imaging using ^{99m}Tc-MIBI controlled for labeling efficiency according the manufacturer's instructions. For pharmacological stress, 0.56 mg/kg body weight dipyridamole was slowly injected intravenously over a 4-minute period and 3–5 minutes later, 740–925 MBq ^{99m}Tc-MIBI was injected intravenously. Thirty minutes after injection of ^{99m}Tc-MIBI, the patients were encouraged to eat a waterless fat-rich snack to accelerate elimination of radiotracer from hepatobiliary system.

Post-stress acquisition with gated SPECT was performed 60 minutes after pharmacologic stress using a rotating, dual head gamma camera (Solus, ADAC, Milpitas, CA) equipped with a low-energy high-resolution parallel-hole collimator. A 20% window around the photo-peak energy of ^{99m}Tc-MIBI (140 keV) was used. Patients were in a supine position during the image acquisition. Thirty-two projections (60 seconds/projections) were obtained in a 180-degree circular orbit, beginning from 45 degrees right anterior oblique to 135 degrees left posterior oblique with step/shoot acquisition. A 64×64×16 matrix and 38.5 cm detector mask (1.22 zoom) were used. Gated mode acquisition with prefixed R-R interval at a rate of eight frames per cardiac cycle and beat acceptance window of 40% was carried out for each patient. Cine-display images of the rotating planar projections were reviewed on the monitor screen

to assess the sub-diaphragmatic activities, attenuations and patient motion.

After completion of the initial stress-phase imaging, the patients were randomly allocated into two groups:

- Group A (dobutamine group): 45 patients including 29 men (64.4%) and 16 women (35.6%); mean age 58.3 ± 11.2 years),
- group B (control or placebo group): 44 patients including 27 men (61.4%) and 17 women (38.6%); mean age 57.4 ± 10.6 years).

Group A (dobutamine group): A low dose dobutamine (LDD) was intravenously infused 30 minutes after the end of the first acquisition at a constant rate of about 7.5 µg/kg/min. The patient's heart rate following infusion was allowed to become stable with less than 15% variability compared to base heart rate and was not permitted to exceed 100 beats/min to prevent demand/supply impairment in the myocardium.

The second imaging was started in the same manner about one-hour after termination of the first imaging without any additional radiotracer injection (3). LDD infusion was continued during the second acquisition under continuous electrocardiographic and blood pressure monitoring. Criteria for early interruption included hypotension, angina, and significant ventricular arrhythmias.

Group B (control): The sequential steps as in group A were carried out in group B with the only exception that saline was used as a placebo (instead of LDD). To keep double blindness of the study, patients as well as nuclear medicine technologists were not informed about the content of infusion sets.

For both groups, the standard rest phase imaging was carried out 60 minutes after intravenous injection of 740–925 MBq ^{99m}Tc-MIBI on the following day. To better differentiate fixed from reversible defects, three pearls of sublingual trinitroglycerin (TNG) with three minutes intervals were administered prior to rest injection (11). The rest images were considered as a reference to detect uptake enhancement in stable asymptomatic state and to differentiate fixed from true reversible defects.

Image analysis

The raw data from initial and second stress acquisitions were reconstructed using ramp and Butterworth filters with a window frequency cut-off of 0.45 and order of 9 for gated frames and composite images without attenuation correction. Filtered back-projected images were displayed in short-axis, vertical long-axis and horizontal long-axis slices. The images were subsequently analyzed using an automatic quantifying software package for quantitative perfusion SPECT and quantitative gated SPECT (QPS/QGS/AutoQUANT; ADAC Laboratories) based on Cedars-Sinai 20-segment, 5-point scoring model (i.e. 0–4 from normal to absent perfusion for each segment). Summed stress scores (SSS) for the first (SSS_1) and for the second (SSS_2) stress phase imaging in both groups (group A with LDD and group B with placebo) were obtained. Summed difference score (SDS), as a marker of reversibility, and summed rest score (SRS), as a marker for the magnitude of non-reversible defects, in DIDA standard protocol were calculated by selecting the initial stress and rest phase images. Correspondingly, in SIDA protocol, SSS_2 and ΔSSS (SSS_1 minus SSS_2) were considered as the markers of fixed and reversible perfusion defect magnitude, respectively. As an extra step, to answer whether the changes in delayed images are function- dependent or not, the end-systolic and end-diastolic images were separately analyzed to detect the degree of reversibility. For this reason, the frames 1 and 4 as the representatives of end-diastole and end-systole were respectively selected from 8-frame gated images and reconstructed separately. The automatic pixel-based perfusion analysis for each specified frame was performed using the raw polar map menu of QPS application of the AutoQUANT software. On one-frame reconstructed images, the preset grid of three separate vascular territories including left anterior descending (LAD), left circumflex (LCx) and right coronary artery (RCA) was applied to obtain the perfusion (P) in percent of each territory on the initial and delayed stress images. The so-called reversibility percentage (R) on each vascular territory, for the two separate frames, was automatically calculated by Auto-quant software based on the following formula:

$$R = \frac{[P_{\text{delayed stress}} - P_{\text{initial stress}}]}{P_{\text{initial stress}}} \times 100$$

Statistical analysis

Statistical analysis was done using SPSS 11.5 for Windows (SPSS Inc., Chicago, Illinois). Distribution of sex, age and past history of diabetes mellitus were compared between two groups (A and B) using Chi square, t-student and Fisher exact tests, respectively. Since the distribution function of SSS_1 and SSS_2 was not fitted to a normal distribution, a non-parametric related-sample test (Wilcoxon signed ranks test) was used to compare SSS_1 and SSS_2 in total as well as separate group of patients. The Spearman Rho test was used to analyze the correlation between ΔSSS and SDS or between SSS_2 and SRS in each group, separately. The difference between SRS and SSS_2 (SRS minus SSS_2) was applied as a marker of difference between SIDA and DIDA protocols for indicating the magnitude of persistent defects. Also the difference between SDS and ΔSSS (SDS minus ΔSSS) represents the difference between these two protocols for showing the magnitude of reversible defects. Bland-Altman plot was used to compare the new SIDA technique with already established DIDA protocol for measurement of reversible defect magnitude (ΔSSS vs. SDS). The later two parameters were also compared between two groups (dobutamine and placebo) using Mann-Whitney U test. Using a paired t-test and regression analysis, end-systolic reversibility percentage for each territory was compared to end-diastolic reversibility percentage in the corresponding territory. A p value of < 0.05 was considered as statistically significant.

Results

Ten from 45 cases in group A (22.2%) and 9 from 44 patients in group B (20.5%) had a past history of myocardial infarction (MI). No differences were noted between two groups with respect to age ($p = 0.780$), gender ($p = 0.804$), past history of diabetes mellitus ($p = 0.628$) or MI ($p = 0.850$).

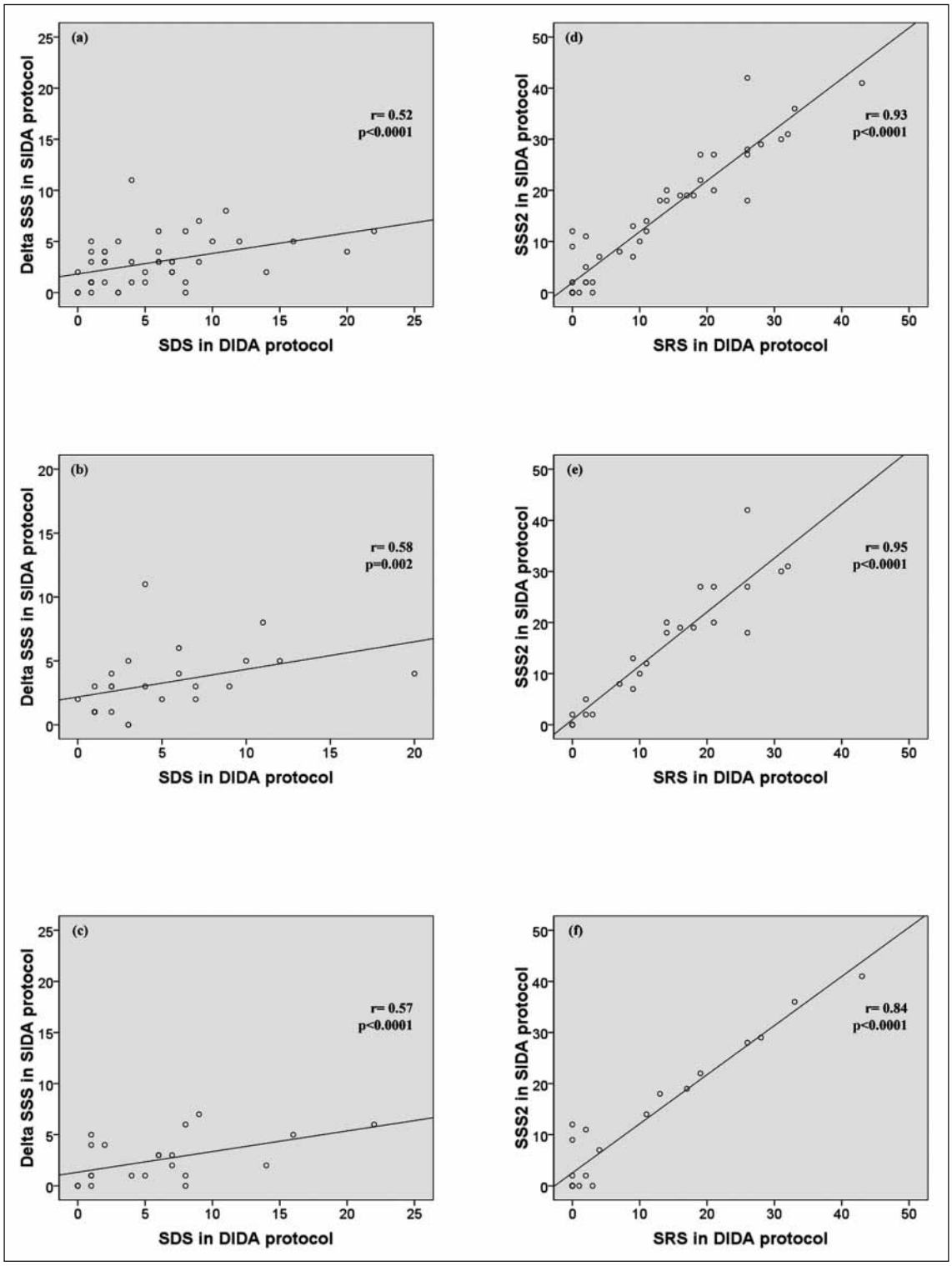

Fig. 1
Correlation between ΔSSS (as a marker of reversibility in single-injection double-acquisition protocol) and SDS (as a marker of reversibility in double-injection double-acquisition two-day protocol) and between SSS_2 and SRS (d–f) **a, d)** total patients; **b, e)** dobutamine cases; **c, f)** placebo group

A significant difference was found between SSS_1 (median:15, range: 0–48) and SSS_2 (median: 11, range: 40–42) in total patients ($p < 0.0001$). These significant differences were also observed in dobutamine group (SSS_1: median: 19, range: 1–48 vs. SSS_2: median: 13, range: 0–42; $p < 0.0001$) as well as placebo group (SSS_1: median: 11, range: 0–46 vs. SSS_2: median: 8, range: 1–41; $p < 0.0001$), separately. A significant correlation was noted between ΔSSS (as a marker of reversibility in SIDA protocol) and SDS (as a marker of reversibility in DIDA stress/rest protocol) in total patients (▶Fig. 1a). A significant correlation was also noted between SSS_2 and SRS (▶Fig. 1d). Bland-Altman plots (▶Fig. 2) were applied to compare the DIDA and SIDA protocols for

measurement of reversible defect magnitude (SDS vs. ΔSSS, respectively). When the score of reversible perfusion defects as measured by standard protocol (SDS) was less than 8, the magnitudes of the differences between two parameters (SDS and ΔSSS) in more than 95% of patients were constantly less than 5 throughout the range of measurement (▶Fig. 2a). However, in the special cases with more extensive reversible defects (SDS>8), the magnitude of differences between two protocols was progressively more increased with increasing the magnitude of reversible perfusion defects (▶Fig. 2b). On the whole, from 42 patients with SDS<4, 32 (76.2%) revealed also a ΔSSS<4, while only 21 of 47 patients (44.7%) with SDS equal or more than 4 represented a ΔSSS more than 4 as well.

The correlation between two protocols was also observed following analyses performed separately in dobutamine (▶Fig. 1b and 1e) and placebo (▶Fig. 1c and 1f) groups. The difference between SSS_2 and SRS (as a marker of difference between two protocols – SIDA & DIDA – for showing the magnitude of fixed defects) as well as the difference between ΔSSS and SDS (as a marker of difference between two protocols -SIDA & DIDA- for showing the magnitude of reversible perfusion defects) have been compared between dobutamine and placebo groups in ▶Figure 3. This figure revealed that, when the DIDA protocol was considered as a standard reference study, the influence of dobutamine infusion on the magnitude of fixed or reversible perfusion de-

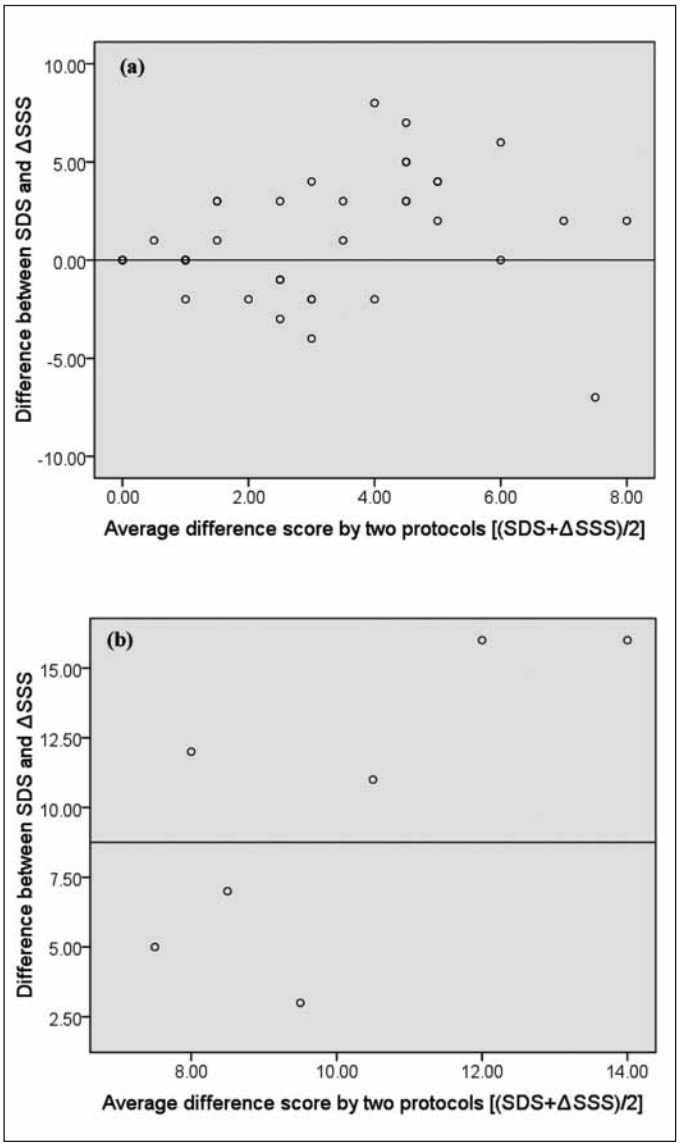

Fig. 2
Bland-Altman plot
a) patients with SDS < 10: Differences between reversible defect magnitudes measured by two methods are near 0 and in the neighborhood of ± 5. The two protocols show sufficient agreement to be used interchangeably in a wide range of SDS (1–10).
b) patients with SDS ≥ 10: An apparent lack of agreement is shown between two protocols in special cases with more extensive reversible defects and this disagreement may be progressively increased with rising SDS.

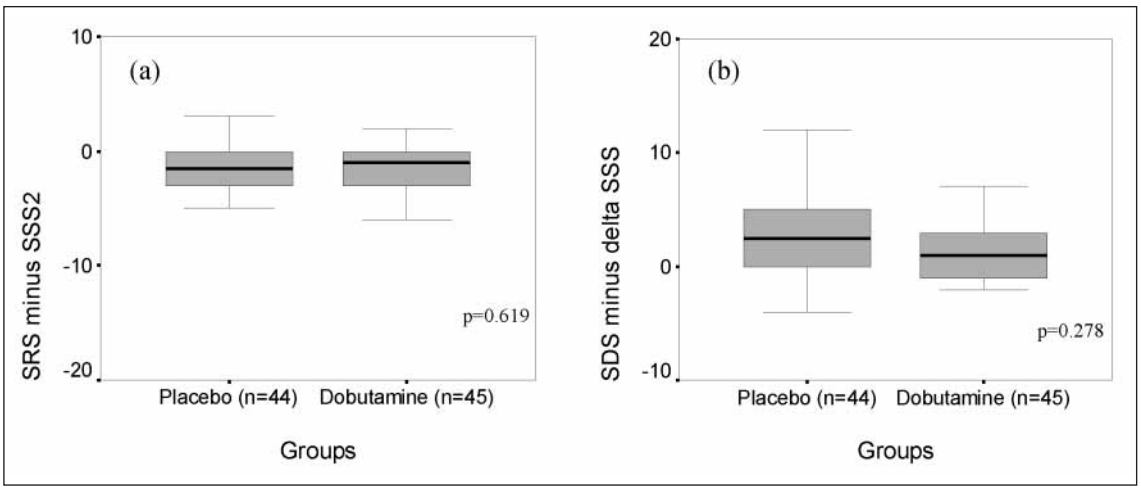

Fig. 3
Marker of difference between the protocols SIDA & DIDA have been compared between dobutamine and placebo groups concerning the magnitude of
a) fixed defects: SSS_2 and SRS
b) reversible perfusion defects: ΔSSS and SDS

Tab. 1 Comparison of end-systolic and end-diastolic reversibility percentage in each myocardial territory in single-injection double-acquisition method

vascular territories	reversibility percentage in two phases of cardiac cycle										
	end-diastolic (%)		end-systolic (%)		significance* of difference	correlation**		significance of regression#		regression coefficients##	
	mean	SD	mean	SD	p-value	r	p-value	F	p-value	Y-intercept	slope
LAD	2.73	13.95	1.31	10.82	0.241 NS	0.61	<0.0001	50.46	<0.0001	0.02 NS	0.47 S
LCX	0.47	9.48	1.03	8.55	0.375 NS	0.79	<0.0001	142	<0.0001	0.70 NS	0.71 S
RCA	4.11	11.97	3.44	12.48	0.455 NS	0.76	<0.0001	119	<0.0001	0.18 NS	0.79 S

SD: standard deviation; NS: not significant; S: significant ($p < 0.001$); *paired sample T-test analysis; **Pearson correlation coefficient analysis;
#F to test if the independent variable (X) accounts for a significant amount of variability in the criterion variable (Y). In this regression model, X is the end-diastolic and Y is the end-systolic reversibility percentages.
##Regression equation is Y (i. e. end-systolic reversibility percentage) = Y-intercept + slope × X (i. e. end-diastolic reversibility percentage)

fects in SIDA protocol was not significantly different from placebo effect. Accordingly, the end-systolic and end-diastolic reversibility percentages (obtained by initial and delayed stress images) were compared in each myocardial territory (▶Tab. 1). No difference was seen between end-systolic and end-diastolic reversibility percentages but a significant correlation was noted between systolic and diastolic phases. In addition, regarding the statistical significance of the regression model (▶Tab. 1), the variability in end-diastolic reversibility accounts for a significant amount of variability in end-systolic reversibility. This indicates the reversibility at different levels of myocardial thickening pursues the same pattern of variability from the phase of maximal myocardial relaxation to the phase of maximal contraction.

Thus, the reversibility is mostly independent to the myocardial function variability.

Discussion

Time dependent changes in ^{99m}Tc-MIBI distribution has been reported in the initially detected myocardial perfusion defects (2, 8, 12, 14). However, the exact origin of these observed changes has not been described yet. The degree of time dependent changes on extremely delayed images (4 hours) has been shown to be somewhat related to myocardial viability as identified by thallium-201 (2), but these changes have been presumed to be observable in only extremely delayed images and have been suggested to be due to a very slow and delayed redistribution. Therefore, the potential clinical contribution of ^{99m}Tc-MIBI redistribution to evaluate true perfusion defect reversibility using a protocol with single-injection and double-acquisition has not yet been evaluated.

Our research is the first clinical study evaluating the effect of early ^{99m}Tc-MIBI redistribution isolated from the other factors such as the changes caused by myocardial thickening improvement during post-stress recovery period. Another special feature of our study is to deal with the new aspect of ^{99m}Tc-MIBI redistribution for diagnosis of reversibility, using a single-injection double-acquisition imaging method in comparison with conventional double-injection techniques.

Some studies (6, 9) reported that ^{99m}Tc-MIBI does not show significant or rapid myocardial redistribution following intravenous injection at stress. However, early or delayed ^{99m}Tc-MIBI redistribution has been observed by other investigators under certain experimental conditions (4, 7, 13) and in certain clinical situations (2, 15).

Taillefer et al. (1991) found significantly lower ischaemic/normal wall ratios at one hour as compared with three hours stress phase imaging with ^{99m}Tc-MIBI representing a faster myocardial washout from normal walls (15). This finding was confirmed by others (2, 8). Dilsizian et al. (1994) studied both ^{99m}Tc-MIBI and ^{201}Tl images in a series of patients (2). They reported that when an additional 4-hour redistribution image in rest phase ^{99m}Tc-MIBI study was acquired, the concordance between ^{201}Tl and ^{99m}Tc-MIBI studies was increasing from 75% to 82% (2). Maurea et al. also showed that acquisition of delayed 5-hour ^{99m}Tc-MIBI images (compared with 1-hour images) enhances the differentiation between viable hypoperfused myocardium from scar tissue in chronic CAD and LV dysfunction. They suggest that resting ^{99m}Tc-MIBI imaging should be more delayed when assessing myocardial viability (8). The findings of the mentioned clinical studies may confirm that some degree of detectable reversibility by ^{99m}Tc-MIBI imaging is due to delayed 3 to 4-hour redistribution of this radiotracer.

Despite these evidences in favour of delayed 3 to 4-hour redistribution of ^{99m}Tc-MIBI, the earlier redistribution (at less than 3 hours interval from time of injection) is controversial. While some researchers have reported an earlier redistribution for this radiotracer (4, 7, 13), others found no sign of redistribution in the first hours of injection (5).

In an animal model research, Li et al. indicated that following transient ischaemia and reperfusion ^{99m}Tc-MIBI clearly undergoes early (2-hour) myocardial redistribution, but more slowly and less completely than ^{201}Tl (7). Sinusas et al. (1994) showed that under conditions of sustained low flow, there was detectable 2.5-hour rest "redistribution" of ^{99m}Tc-MIBI verified by both gamma well counting and high-resolution postmortem imaging of myocardial slices in an experimental model (13). However, another study by Glover et al. revealed that under ideal conditions, sestambi is

redistributed into reperfused viable myocardium but the amount of this redistribution is small and can not be perceived by visual image analysis (4).

Whether or not ^{99m}Tc-MIBI rest redistribution will be detectable by serial clinical imaging remains uncertain. Additionally, the clinical significance of redistribution in the first hours of injection was evaluated by Richter et al. (10). In their research, global myocardial ^{99m}Tc-MIBI washout was registered within the first 120 min after injection. A fill-in of initial defects as well as an early tracer loss could be detected in a relevant number of patients with chronic CAD during the first two hours post injection at maximal exercise stress test (10). These investigators concluded that the difference between the immediate and 2-hour myocardial images is the resultant of the two different processes; one is the tracer washout which is faster in normal as compared with ischaemic tissue, and the other is redistribution with an unknown mechanism. In this study, an apparent detectable difference was noted between the images obtained immediately and the images acquired by the second hour (10).

Discordant findings have been found in an experimental evaluation by Kaltoft et al. on ten pigs following induction of acute MI and subsequent revascularization (5). In this study, no evidence of ^{99m}Tc-MIBI redistribution was seen in the reperfused areas in serial images from 30 minutes to 4 hours (5). In our study, a significant difference in distribution of radiotracer between the images obtained by one hour and the images acquired one hour later (as an improvement of defects regarding the SRS and SDS values) was observed.

> This finding verified that the improvement of defects in delayed stress images with ^{99m}Tc-MIBI may occur even in one or two hours post injection.

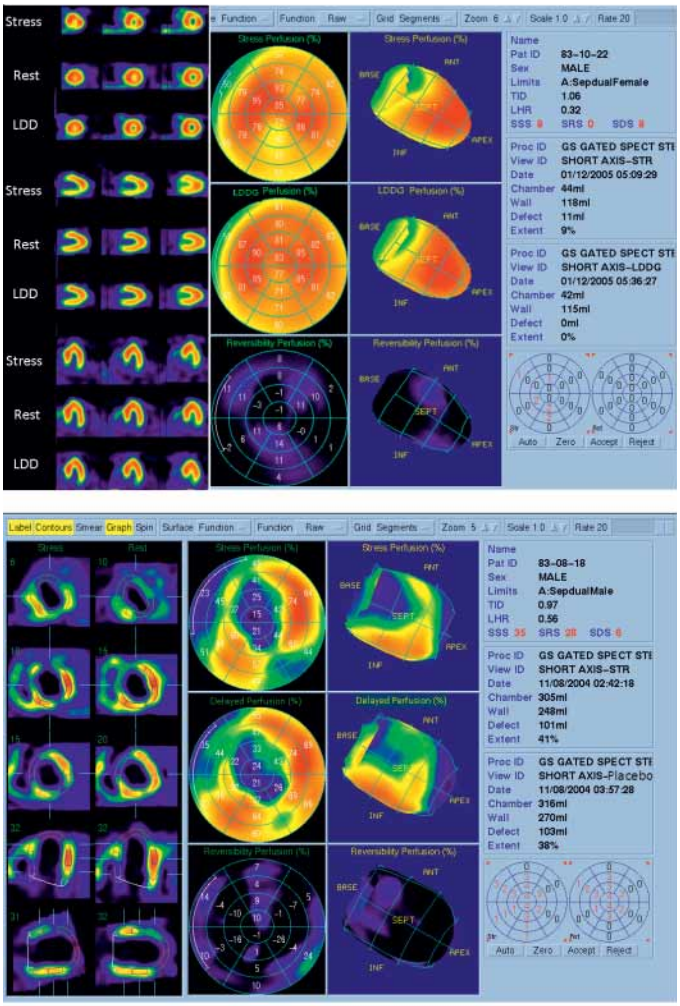

Fig. 4 Reversibility of the perfusion defects between the early and delayed post-stress images resulting from ^{99m}Tc-MIBI redistribution within a time interval of about 1-hour duration (LDD: low dose dobutamine).
The upper image shows the reversibility of the perfusion in the inferior and to a lesser degree in the anterior walls of the myocardium in a patient with early and delayed post-stress imaging before and during dobutamine inotropic augmentation. The rest phase images are also shown for comparison between two methods of reversibility evaluation (i.e. single-injection double-acquisition method vs. double-injection double-acquisition).
The lower image reveals the corresponding reversibility perfusion (%) in a patient with infusion of placebo during the second stress phase imaging indicating true early redistribution of the ^{99m}Tc-MIBI in the basal segments of the inferior, inferoseptal, inferolateral and to a lesser degree in the anteroseptal walls. The quantitative data in the right side of both images are derived from reconstruction and processing of the two early and late stress images. In fact, SDS values which are shown in both images are the representative of ΔSSS. The true SDS values (not shown) are almost the same as the ΔSSS values for both patients.

The degree of reversibility between initial and late stress phase (ΔSSS) (as the representative of delayed improvement of ^{99m}Tc-MIBI uptake in ischaemic areas) is fairly correlated with SDS (as the degree of improvement of radiotracer uptake in the corresponding areas at rest). Also SSS_2 (as the magnitude of persistent defects on delayed stress phase) is strongly correlated with SRS (as the magnitude of fixed defects at rest phase). In addition to slower washout and redistribution of ^{99m}Tc-MIBI in ischemic areas, some studies have suggested that a reversal of partial volume effect after improvement of dysfunction in delayed images and in dobutamine induced augmentation, resulting from improvement of systolic thickening and motion, are also partly responsible for enhancement of activity in ischaemic areas (12, 14).

Sansoy et al. (12) reported that ^{99m}Tc-MIBI defect magnitude became slightly but

significantly smaller when repeated images were acquired after releasing the LAD stenosis in dogs, even though no additional dose of the radionuclide was administered. Further reduction in defect magnitude occurred when images were again acquired during dobutamine infusion after stenosis release. In dogs that did not have the stenoses removed before dobutamine infusion, ^{99m}Tc-MIBI defect magnitude remained unaltered. They concluded that the improvement in defect magnitude after inotropic stimulation is presumably due to a reversal of the partial volume effect. These findings are consistent with those of Sinusas et al who found a reduction in ^{99m}Tc-MIBI defect size with resolution of ischemic dysfunction and dobutamine-induced augmentation of regional wall motion (14). Also in our study, the inotropic effect on the magnitude of stress perfusion defects was evaluated based on the one-hour and two-hour images obtained in two comparable groups (one with infusion of dobutamine and the other with infusion of placebo). In both groups, in stress studies, the magnitude of perfusion defects was significantly reduced from one-hour early phase to two-hour late phase images (during only 1 hour time difference). Despite slightly more improving effect of dobutamine, as compared with placebo, the between-group difference was not statistically significant. We concluded that the changes between initial and delayed stress phases and the reduction in the magnitude of perfusion defect with time seem to be a time dependent phenomenon rather than the inotropic effect of dobutamine. This time-dependent effect might be due to real redistribution and/or time-dependent functional recovery. Subsequently, to differentiate between real redistribution and time-dependent functional recovery, that may in turn result in reversal of partial volume effect mimicking redistribution, we analyzed the degree of perfusion improvement (i. e. reversibility percentage) in different phases of cardiac cycle (i. e. end-systolic phase, when the thickening of the myocardium is in its maximum limit, and end-diastolic phase, when the thickening is in its minimum limit). A similar pattern of reversibility in end-systolic and end-diastolic phases reinforces the theory that the reversal of partial volume effect would be less likely than the real redistribution to be the main cause of apparent reversibility with time. To address evidence in favor of this theory, we compared end-systolic and end-diastolic reversibility percentage between initial and delayed stress phases (▶Tab. 1). No difference was noted between end-systolic and end-diastolic reversibility percentage. Also, regarding the regression analysis of the data between two phases of the cardiac cycle (▶Tab. 1), the reversibility at the end of systole, when the myocardium is in its maximal thickening, pursues a pattern of variability near to the model that is evident by the end of diastole (i. e. at the beginning of thickening), pointing to the fact that the changes in the magnitude of the defects are in-dependent to the function of the myocardium and the apparent reversibility is more in favor of real redistribution phenomenon rather than reversal of partial volume effect. Both groups showed a minimal average variation between ΔSSS obtained with stress 1st/2nd phases and SDS obtained with stress/rest phases (the amount of SDS minus ΔSSS is within a limit around zero; ▶Fig. 3b). In addition, significant correlations between these two parameters were obtained in total and each separate group. This means that considering the initial stress images, the changes in the magnitude of defects on delayed stress and the changes on the rest phase images are both in a same direction but the correlation coefficient values were not tight enough to support the substitution of the SIDA for the DIDA protocol to exactly estimate the extent of reversibility for all patients. We tried to check the precision of correlations and to judge about actual agreement between two protocols using Bland-Altman plot analysis (▶Fig. 2). On the basis of this analysis, the improvement of the defects between initial and delayed stress images (ΔSSS in SIDA method) is closely comparable with the true reversibility between stress and rest study (SDS in DIDA method) in a relatively wide range of measurements in the presence of small to moderate sized reversible defects (SDS < 8). However, increasing disagreement between two protocols was seen in especial cases with more extensive reversible defects (SDS > 8). This fact may result in some underestimation of reversibility in a few numbers of patients. Indeed, about 75% of patients with SDS < 4, revealed a ΔSSS < 4 while only about one-half of the cases with SDS ≥ 4 revealed also a ΔSSS ≥ 4. Thus, the SIDA protocol may underestimate the extent of reversible defects.

In summary, the SIDA protocol may serve to reveal reversibility (▶Fig. 4). However, it cannot exactly estimate the extent of reversibility and should not be used for risk stratification into low, intermediate or high risk groups. The clinical impact of this shortcoming should be analyzed by further studies. In addition, more delayed images (i. e. more than one hour), may provide a chance for more redistribution leading to better estimate SDS on the basis of ΔSSS. This would also be a topic of future studies.

Limitations

Regarding the possible underestimation of reversibility with ^{99m}Tc-MIBI, lack of a standard method such as ^{201}Tl or ^{18}F-FDG imaging for more precise estimation of true reversibility/viability may be a drawback of this study that may to some extent be compensated with TNG-enhanced ^{99m}Tc-MIBI rest phase images as a reference for detecting the true reversibility.

Another limitation is represented by the lack of earlier post stress acquisition (e. g. 15 to 30 minutes after injection) due to higher frequency of sub-diaphragmatic uptake in dipyridamole stress imaging resulting in suboptimal scan in most of our studied cases. Also, in spite of the randomization an undesirable difference was noted between the studied groups concerning the SSS_1 (i. e. 19 vs. 11 in group A and B, respectively). However, this drawback is due to an inherently unavoidable random error in the process of randomization.

Conclusion

The changes in the magnitude of the defects in ^{99m}Tc-MIBI uptake between initial (1 h) and delayed (2 h) images are most likely due to true redistribution in ischaemic areas even in a time as short as one hour. This finding is not related to re-

versal of partial volume effect caused by inotropic effect of dobutamine or delayed post-stress recovery.

Regarding this fact, more delay in imaging after ^{99m}Tc-MIBI injection at rest phase may provide an opportunity for better reversibility in viable myocardium. On the other hand, by postponing the image acquisition following stress-phase ^{99m}Tc-MIBI injection, the magnitude of stress perfusion defects may be underestimated. These topics are investigated in a study which is currently underway at our institution.

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Conflict of interest

The authors declare, that there is no conflict of interest.

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