

# Single Tc99m Sestamibi injection, double acquisition gated SPECT after stress and during low-dose dobutamine infusion: a new suggested protocol for evaluation of myocardial perfusion

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**Abstract** *Background* The ability of low dose dobutamine (LDD) has been established in exploiting the reserved contractility of ischemic myocardium. This study was designed to assess the value of a new protocol, with an additional stress imaging during LDD infusion instead of the rest images, for evaluation of coronary artery disease (CAD) and perfusion reversibility. *Methods* A total of 51 patients (42 men, 9 women;  $57.2 \pm 11.3$  years) were included in the study and underwent three sequential steps of imaging; the first step-stress gated SPECT with Tc-99m sestamibi, immediately followed by the second step-gated SPECT during constant infusion of  $7.5 \mu\text{g/kg/min}$  dobutamine and finally the third step-rest phase scan following trinitroglycerine administration in the next day. The findings were interpreted using the images in three sets of display; first vs. second step-single injection-double acquisition gated SPECT before and during LDD (*SIDAGS-LDD*), first vs. third step-*standard stress/rest* protocol, and only first step-gated *stress-only* SPECT. In all cases, the *Visual perfusion index* of each protocols were calculated by

summing the premeditated 5-point scale (5: normal, 4: completely reversible, 3: partially reversible, 2: nontransmural fixed and 1: transmural fixed defects) of 17 standard myocardial segments. The accuracy as well as the correlation and agreement of protocols for detecting perfusion abnormality and corresponding reversibility were statistically analyzed. *Results* Calculated sensitivity, specificity, positive predictive value, negative predictive value and accuracy regarding the presence of CAD in both *SIDAGS-LDD* and *standard* protocols were 90.9% (40/44), 71.4% (5/7), 95.2% (40/42), 55.6% (5/9) and 88.2% (45/51), respectively. The extent and localization of perfusion abnormality with the new protocol were correlated well with standard method. The estimation of reversibility, however, was considerably improved by *SIDAGS-LDD*, especially in those with history of previous myocardial infarction (MI). *Conclusion* Our proposed protocol demonstrates good correlation and agreement with standard method and even is superior in some cases especially for estimation of viability after MI. Regarding no need for the rest phase radiotracer injection and imaging, this protocol can be more convenient (except the need for close monitoring of the patient during LDD infusion), less time-consuming, less expensive and moreover with less radiation burden to the patients and personnel.

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## Introduction

There are numerous modalities for the evaluation of ischemic heart disease. At the present time, myocardial perfusion scintigraphy and echocardiography are among the most commonly used methods of cardiac investigation [1]. However, nowadays many investigators are interested to introduce some procedures as “one-stop-shop” assessments to evaluate multiple parameters in one test, simultaneously [1]. Current diagnostic approaches to assess myocardial perfusion abnormality are complex and involve multiple tests. Clinicians await a single diagnostic modality that accurately rules in or out any myocardial perfusion and function disturbances. It is also important to modify the standard protocols aiming to reduce the cost, duration and side effects of diagnostic procedure [2]. Electrocardiographic gated single-photon emission computed tomography (ECG-gated SPECT) provides assessment of both myocardial perfusion and function abnormalities induced by pharmacological or exertional stress. Although in some previous reports the nuclear physicians have used wall thickening on stress ECG-gated SPECT to predict reversibility or non-reversibility of myocardial perfusion abnormalities [2–5], some other studies revealed considerable discordance in detecting reversibility [6, 7] and therefore this protocol of single injection ECG-gated SPECT did not achieve global acceptance for routine use in daily practice of nuclear medicine. Despite inherent advantages of *gated stress-only SPECT*, modification of this method seems to be necessary to eliminate drawbacks and improve accuracy.

In many studies, the ability of low-dose dobutamine (LDD) has been established in exploiting the reserved contractility in the cases of hibernated viable myocardium [8]. In fact, it is a long time that cardiac stimulation with LDD infusion during echocardiography has been incorporated to the routine echocardiography to provoke functional myocardial reserve and hence to detect myocardial viability [9]. It has been confirmed that viable myocardium may functionally improve in response to inotropic stimulation, and contractile reserve elicited by LDD is a predictor of functional recovery in patients with chronic coronary artery disease [9]. Furthermore, on the basis of a previous study, addition of the wall motion response to dobutamine seems to yield

better predictive values of gated-SPECT concerning myocardial viability [10].

Based on the above evidences, our study was designed to investigate the potential value of a specifically-designed protocol with single-injection double-acquisition  $^{99m}\text{Tc}$ -sestamibi ECG-gated SPECT, before and during LDD infusion (*SIDAGS-LDD*), comparing its results with those of *gated stress-only SPECT* and *standard stress/rest SPECT*, for the diagnosis of reversible and non-reversible myocardial perfusion abnormalities.

## Methods

### Study population

From December 2004 to May 2005, 51 consecutive patients (42 men and 9 women; mean age:  $57.2 \pm 11.3$  years, range: 34–80 years) who were referred to our nuclear medicine department for myocardial perfusion imaging were prospectively studied. A Total of 34 patients (group A) had a recent history of hospitalization with clinical suspicion of unstable angina or myocardial infarction (MI), and 17 others (group B) were out-patients with intermediate pretest probability of coronary artery disease (CAD) [11]. After obtaining written informed consent, all patients underwent systematic history taking, physical examination and review of the past medical records. The presence of atrial fibrillation or other significant arrhythmias interfering with gated acquisition was considered as exclusion criteria.

### Patient preparation

Patients were instructed to fast for at least 4 h before the study. All  $\beta$ -blocking medications, diltiazem and verapamil were stopped 48 h before the stress phase. Also caffeine containing drugs or foods and long-acting aminophylline were discontinued for 24 h before the dipyridamole pharmacological stress.

### Image acquisition sequence

A commercial sestamibi kit (AEOI, Tehran, Iran) was used and the labeling and quality control procedures were performed according to the manufacturer's

instructions. Our study was designed to include three steps of image acquisition on the following order:

**Step 1. Post-stress image acquisition:** The first gated SPECT was performed after the injection of 740–925 MBq  $^{99m}\text{Tc}$ -sestamibi at peak treadmill exercise (18 patients, 35.3%) or following dipyridamole infusion (33 patients, 64.7%). For treadmill exercise, the Bruce protocol was used and continued for a minimum of 60–90 s after radiotracer injection. For the pharmacological stress, 0.56 mg/kg dipyridamole was infused intravenously over a 4 min period. Radiotracer was injected intravenously, 3–5 min after the completion of dipyridamole infusion. In pharmacological stress protocol, 30 min after injection of  $^{99m}\text{Tc}$ -sestamibi, the patients were encouraged to eat a fat-rich snack to accelerate hepatobiliary excretion of the radiotracer. Patients were not allowed to take soft drinks. After fifteen minutes of radiotracer injection for patients with exercise stress or 60 minutes for those with pharmacologic stress, image acquisition was done 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 140 keV energy peak of  $^{99m}\text{Tc}$ -sestamibi was used. Patients were in a supine position during the image acquisition. Thirty-two azimuth images, 60 s/projection, were obtained in a 180° circular orbit, beginning from 45° right anterior oblique to 135° left posterior oblique with step and shoot acquisition on a 64 × 64 × 16 matrix and 38.5 cm detector mask (1.22 zoom) using a gated mode with prefixed R–R interval at a rate of eight frames per cardiac cycle and beat acceptance window of 40%. An expert nuclear physician used the cine-display of the rotating planar projections to assess sub-diaphragmatic activities, attenuations and patient motion to optimize the technical quality of the images. The raw data from stress acquisition were prefiltered by ramp and subsequently by Butterworth filters with frequency cut-off of 0.45 and order of 9 for each of the eight gated frames and then frequency cut-off of 0.40 and order of 9 for summed gated frames (composite images) without attenuation correction. Filtered back-projected data was reconstructed into short-axis, vertical long-axis and horizontal long-axis slices.

**Step 2. Image acquisition during infusion of low dose dobutamine:** Immediately after the end of the first acquisition and image processing, dobutamine was intravenously infused via a serum micro-set at a constant rate of about 7.5  $\mu\text{g}/\text{kg}/\text{min}$ . Adjusting the rate of infusion, none of the patients were allowed to become tachycardic (heart rate more than 100 beats/s) during the LDD infusion. Approximately ten minutes later, when the heart rate became stable, showing less than 15% variation compared with the baseline heart rate, the second imaging and processing were started in the same manner—as described above—without any additional radiotracer injection. LDD infusion was continued throughout the second acquisition. The intravenous infusion of dobutamine was performed with the patient under continuous electrocardiographic and blood pressure monitoring. Criteria for early interruption included hypotension, angina, and significant ventricular arrhythmias.

**Step 3. Standard rest phase image acquisition:** The standard rest phase imaging was carried out on the following day, 60 min after intravenous injection of 740–925 MBq  $^{99m}\text{Tc}$ -sestamibi following administration of three pearls of sublingual trinitroglycerin with 3 min intervals [12]. The blood pressure was checked before and between administrations of TNG, in order to prevent remarkable drop in blood pressure.

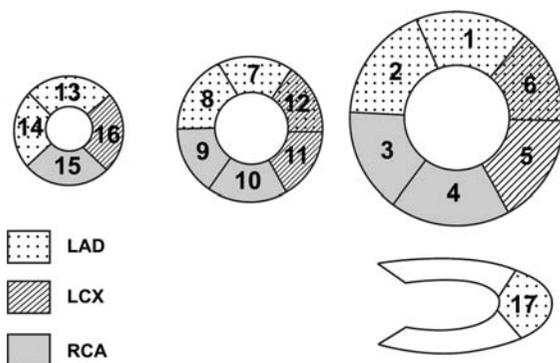
#### Image analysis

The obtained images were interpreted in three sets of slices: as the first set, the dynamic and static images of the post-stress gated acquisition (first step slices) and the second stress acquisition during LDD infusion (second step slices) were simultaneously displayed and compared for motion, thickening and the presence of any reversible or non-reversible myocardial perfusion abnormality (*SIDAGS-LDD protocol*: single-injection double-acquisition gated SPECT before and during LDD infusion). As the second set, stress phase images (first step slices) and standard rest phase images (third step slices) were compared (*standard stress/rest protocol*: a double-injection double-acquisition method). Finally as the third set, only the first step slices were displayed for the readers to assess myocardial perfusion, motion

and thickening (*gated stress-only SPECT protocol*: a single-injection single-acquisition method).

### Visual interpretation

Two blinded expert nuclear physicians visually reviewed the images based on the standard 17-segment model. Each major vascular territory was attributed to a number of segments, as illustrated in the Fig. 1. As all three sets of images had the stress phase in common, the conjugated and gated stress images were used for assessment of the presence, location and extent of perfusion defects in different protocols. In *standard stress/rest protocol*, the assessment of “*perfusion reversibility*” was performed with simple visual comparison of myocardial uptake on stress and rest images. Since radiotracer was not re-injected for the two other protocols, the term reversibility was not applicable and therefore, a new term “*reversibility equivalent*” was employed as the marker of reversibility in these two protocols. In order to have a similar scoring system for grading the perfusion state (concerning perfusion abnormality and corresponding reversibility) in all three different protocols, a 5-point scale named “*visual segmental score*” was adopted (Table 1). Summating the visual segmental scores, a “*visual perfusion index*” (VPI) for each protocol was obtained (ranging from 17 to 85 for all 17 segments of myocardium, 9 to 45 for 9 segments of LAD territory and 5 to 25 for 5 segments of LCx or RCA territories; for which the higher the index, the better the perfusion state). Final interpretations were obtained by consensus. To achieve unbiased interpretation, the sessions for interpreting each set of slices (protocols) were held at least one week apart.



**Fig. 1** Standard 17-segment model. Each major vascular territory was attributed to a number of segments

### Automated semiquantitative analysis

For automated semiquantitative display of different parameters [cardiac motion, systolic thickening, left ventricular ejection fraction (LVEF) and end-systolic and end-diastolic volumes], the reconstructed images were analyzed by an automatic quantifying software package (AutoQUANT; ADAC Laboratories). Myocardial thickening for the 1st and 2nd step gated imaging were scored (based on systolic brightening) using a 10-step color scale: normal (9–10), mildly decreased (7–8), moderately decreased (4–6), severely decreased (2–3) and absence of thickening (0–1).

### Coronary angiography

Coronary angiography was performed for all patients within three months after myocardial perfusion imaging and the findings were reported by consensus of two expert cardiologists who were blinded to the results of MPI. Significant CAD was defined as at least 50% stenosis in one or more main coronary arteries or their major branches.

### Statistical analysis

Receiver operating characteristic (ROC) curve analysis was used for comparing *SIDAGS-LDD*, *gated stress-only SPECT* and *standard stress/rest protocol* in the diagnosis of coronary artery disease. The area under the curve represents the probability that the VPI values of each protocol for a randomly chosen case of CAD will be less than the value of a randomly chosen normal case (without CAD) and the significance (*P*-value) indicates the difference from guessing by chance. The degree of agreement between *SIDAGS-LDD*, *gated stress-only SPECT* and *standard stress/rest protocols* for the presence and extent of perfusion defects and corresponding reversibility were evaluated by *Cohen kappa* coefficient using SPSS 11.5 for Windows (SPSS Inc., Chicago, Illinois). Also the correlation coefficient analysis with *Spearman Rho* test was used to analyze the correlation between protocols for calculated VPI. A *P*-value of <0.05 was considered to indicate a statistically significant difference for all compared variables.

**Table 1** 5-point perfusion scale in each segment (visual segmental score) for three studied protocols

Visual segmental score	Standard stress-rest		Gated stress-only		SIDAGS-LDD	
	1st step	3rd step	Only 1st step	1st step	2nd step	
1. Transmural fixed perfusion defect	Absent uptake	No change	Absent uptake with no systolic thickening	Absent uptake with no systolic thickening	No change in both uptake and systolic thickening	
2. Nontransmural fixed perfusion defect <sup>a</sup>	Decreased uptake	No change	Decreased uptake with no systolic thickening	Decreased uptake with no systolic thickening	No change in both uptake and systolic thickening	
3. Partially reversible perfusion defect	Absent or decreased uptake	Partial improvement of uptake	Absent or decreased uptake to severe decreased thickening	Absent or decreased uptake and/or thickening	Partial improvement of either uptake or systolic thickening	
4. Completely reversible perfusion defect <sup>b</sup>	Absent or decreased uptake	Complete improvement of uptake	Absent or decreased uptake with normal thickening	Absent or decreased uptake and/or thickening	Complete improvement of either uptake or systolic thickening	
5. Normal perfusion	Normal uptake	Normal uptake	Normal uptake and systolic thickening	Normal uptake and systolic thickening	Normal uptake and systolic thickening	

<sup>a</sup> For better interpretation of fixed decreased uptake in the anterior or inferior walls in *standard stress/rest* protocol, the raw images were reviewed to exclude attenuation artifacts by consensus of two blinded readers

<sup>b</sup> In the rare case of normal uptake and decreased systolic thickening that is suggestive of stunned myocardium, the segment was scored as grade 4 for *gated stress only* and SIDAGS-LDD protocols and grade 5 for *standard stress/rest* protocol

## Results

Among 51 patients entered into the study, seven had normal coronary arteries or nonsignificant lesions. A total of 44 patients revealed abnormal angiography, showing significant stenosis in one or more coronary vessel(s). Significant stenoses were found in 35 cases (68.6%) in the territory of left anterior descending (LAD) artery, in 24 cases (47.1%) in right coronary artery (RCA) and in 26 cases (51.0%) in the territory of left circumflex artery (LCx). Ten patients (19.6%) suffered from three-vessel disease, while 21 patients (41.2%) had two-vessel involvement.

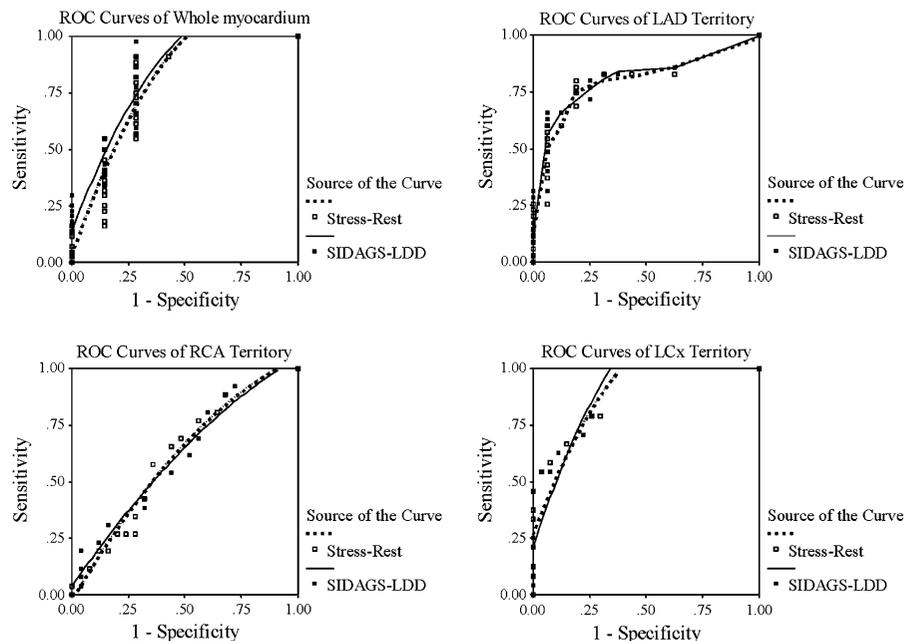
Presence, extension and localization of perfusion defect(s)

ROC analysis comparing the perfusion state obtained *SIDAGS-LDD* versus *standard stress/rest protocol* and *gated stress-only SPECT* in the diagnosis of CAD with all vessels combined, revealed superiority of *SIDAGS-LDD* (Fig. 2). The area under the *SIDAGS-LDD* protocol ROC curve was  $0.83 \pm 0.10$  ( $P = 0.006$ ), compared to  $0.78 \pm 0.11$  ( $P = 0.017$ ) and  $0.81 \pm 0.10$  ( $P = 0.009$ ) for the area under the *standard stress/rest* and *gated stress-only SPECT* protocol ROC curves, respectively. ROC curve analysis was also used to determine the accuracy of each

protocol to localize the CAD, based on perfusion state in each major vascular territory (Fig. 2). The area under the ROC curve for predicting the LAD stenosis was  $0.81 \pm 0.06$  ( $P < 0.0001$ ) for *SIDAGS-LDD*, versus  $0.80 \pm 0.07$  ( $P = 0.001$ ) for the *standard stress/rest* protocol resulting in no difference. In the LCx territory, these values for both protocols were exactly identical;  $0.83 \pm 0.06$  ( $P < 0.0001$ ). The above values for RCA territory were  $0.62 \pm 0.08$  ( $P = 0.152$ ) and  $0.62 \pm 0.08$  ( $P = 0.144$ ) with *SIDAGS-LDD* and *standard stress/rest* protocols, respectively. Considering 83 as the best cut off point for *visual perfusion index* value (positive for CAD if less than 83), a sensitivity of 90.9% (40/44), specificity of 71.4% (5/7), positive predictive value (PPV) of 95.2% (40/42), negative predictive value (NPV) of 55.6% (5/9) and accuracy of 88.2% (45/51) was obtained for the presence of CAD in both *SIDAGS-LDD* and *standard stress-rest* protocols. Table 2 compares the results of *SIDAGS-LDD* versus *standard stress-rest* protocols, concerning the number of vascular territories with perfusion abnormality.

The agreement between *SIDAGS-LDD* and *gated stress-only SPECT* for the presence of perfusion abnormality and the number of territories involved with abnormal perfusion was perfect (Kappa = 1,  $P < 0.0001$ ). The overall agreement between *SIDAGS-LDD* and *standard stress-rest* protocols for the detection of any

**Fig. 2** ROC curves of standard stress–rest and *SIDAGS-LDD* protocols for “visual perfusion index” in all vessels combined and for each separate vascular territory



**Table 2** *SIDAGS-LDD* versus *Standard stress–rest* protocols, concerning the number of vascular territories with perfusion abnormality

<i>SIDAGS-LDD</i> protocol	<i>Standard stress–rest</i> protocol				Total
	Normal	Abnormal in one vascular territory	Abnormal in two vascular territory	Abnormal in three vascular territory	
Normal	8	1	0	0	9
	88.9% <sup>a</sup>	11.1%	.0%	.0%	100.0%
	88.9% <sup>b</sup>	33.3%	.0%	.0%	17.6%
Abnormal in one vascular territory	1	2	1	0	4
	25.0%	50.0%	25.0%	.0%	100.0%
	11.1%	66.7%	5.6%	.0%	7.8%
Abnormal in two vascular territory	0	0	16	4	20
	.0%	.0%	80.0%	20.0%	100.0%
	.0%	.0%	88.9%	19.0%	39.2%
Abnormal in three vascular territory	0	0	1	17	18
	.0%	.0%	5.6%	94.4%	100.0%
	.0%	.0%	5.6%	81.0%	35.3%
Total	9	3	18	21	51
	17.6%	5.9%	35.3%	41.2%	100.0%
	100.0%	100.0%	100.0%	100.0%	100.0%

<sup>a</sup> Row percent<sup>b</sup> Column percent

visual perfusion abnormality throughout the myocardium was seen in 49 of 51 (96.1%) patients ( $\kappa = 0.87 \pm 0.09$ ,  $P < 0.0001$ ) and for the number of major vascular territories affected by abnormal perfusion was 84.3.0% ( $\kappa = 0.77 \pm 0.07$ ,  $P < 0.0001$ ). One patient with angiographically documented two-vessel CAD showed normal perfusion on *standard stress–rest* images but revealed segmental abnormality in wall motion and thickening on *SIDAGS-LDD* and *gated stress-only SPECT (stunned myocardium)*. On the other hand, one other patient affected by one-vessel CAD revealed normal findings on the latter two protocols and abnormal perfusion on *standard stress–rest* images, pointing to equal sensitivity for all three protocols.

The correlations between the *SIDAGS-LDD* and *standard stress–rest* protocols for assessment of perfusion state derived from “VPI” in the entire myocardium and the three different vascular territories are shown in Fig. 3.

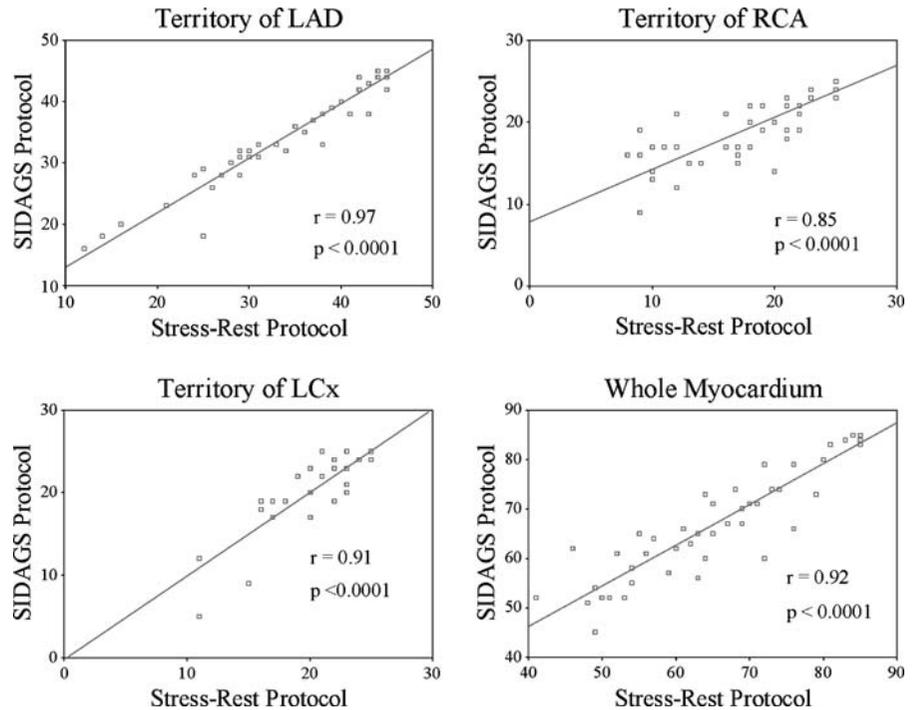
### Reversibility

The agreement for the presence of perfusion reversibility or reversibility equivalent in entire myocardium, and for

the number of major vascular territories with visual reversible defect(s) for *SIDAGS-LDD* and *standard stress–rest* protocols were 74.5% ( $\kappa = 0.45 \pm 0.12$ ,  $P < 0.0001$ ) and 59.0% ( $\kappa = 0.46 \pm 0.09$ ,  $P < 0.0001$ ), respectively. To simplify, henceforward the term reversibility will represent both “*perfusion reversibility*” in the *standard stress/rest* protocol and “*reversibility equivalent*” in the two other protocols.

In 34 of 44 patients (77.2%) with confirmed CAD, the findings of *SIDAGS-LDD* and *standard stress–rest* images were concordant for the presence or absence of significant reversibility. Of 13 patients who showed no evidence of perfusion reversibility in *standard stress–rest* protocol, 9 (69.2%) revealed significant reversibility on *SIDAGS-LDD* images, while only one out of 5 patients with no reversibility on this protocol had *standard stress–rest* studies indicating significant perfusion reversibility ( $P = 0.022$ ). On the other hand, 4 out of 9 cases (44.4%) with no evidence of significant reversibility on *gated stress-only SPECT*, revealed significant reversibility on *standard stress–rest* and *SIDAGS-LDD* images. The number of segments with reversible perfusion defect (extent of reversibility) on *SIDAGS-LDD* when

**Fig. 3** Correlation between two protocols for “visual perfusion index” in all vessels combined and for each separate vascular territory



compared with *standard stress/rest* imaging was the same in 17 cases, more in 21 cases, and less in 6 other cases. Comparing with *gated stress-only SPECT* images, the number of segments with reversible perfusion defect on *standard stress–rest* images was greater in 12, lesser in 16 and equal in 16 other cases, meaning that in 12 cases the size of reversible defects are underestimated by *gated stress-only SPECT* as compared with *standard stress–rest protocol*. Adding 2nd step imaging during LDD infusion to *gated stress-only SPECT* (*SIDAGS-LDD* protocol), reduced this number from 12 to 3, indicating improvement in estimation of reversibility.

In 24 of 34 patients in group A with history of recent hospitalization, evidences of myocardial reversibility were detected in the areas of stress perfusion defects on the *standard stress–rest* images. Twenty one out of these 24 cases showed some degree of reversibility on *gated stress-only SPECT*, while 3 cases were completely failed to show reversibility. However, no case with reversible myocardium identified by *standard stress–rest* protocol was missed by *SIDAGS-LDD*. Moreover, of those 10 cases with nonreversible defect(s) on standard stress and nitrate-enhanced rest images, myocardial reversibility was detected by *SIDAGS-LDD* protocol in 9 [based on the

presence of myocardial thickening either before (7/9) or during LDD infusion (9/9)]. One of these nine patients died after 2 months from a new episode of documented MI in the corresponding reversibility territory. Also viability was confirmed by LDD stress-echocardiography in 4 of 8 other patients.

## Discussion

One of the main challenges in the field of cardiac imaging is to modify the current diagnostic procedures to be less expensive, less time consuming and with less radiation burden along with achieving more diagnostic information and accuracy. As an initial step to achieve this goal, we designed a novel protocol, in which the rest phase of the routine protocol of  $^{99m}\text{Tc}$ -MIBI myocardial perfusion SPECT was substituted by another phase of image acquisition under continuous LDD infusion, immediately after the initial phase of stress imaging.

When the clinical question is the diagnosis of CAD based on perfusion state, the diagnostic accuracy of this protocol is equal to that of the *standard stress/rest* (double-injection double-acquisition) method, introducing it as a reliable substitute. Moreover, as it was

confirmed in one of our patients, the *SIDAGS-LDD* protocol may provide additive information concerning stunned myocardium, emphasizing on its probable additive value for the diagnosis of CAD in patients with transient ischemia. Assigning 83 as the cut-off point of VPI for positive test result, the overall sensitivity, specificity, PPV, NPV and accuracy of both protocols are the same for diagnosis of CAD; however, the surface area under the ROC curve confirms the minor superiority of the *SIDAGS-LDD* protocol over the *standard stress/rest* protocol. This can be explained by the fact that for other cut-off points of VPI, the *SIDAGS-LDD* protocol gives better sensitivity and/or specificity than the *standard stress/rest* method.

Most of the previous studies found a satisfactory agreement between the results of *gated stress-only SPECT* and that of the standard protocol [2], however, the limitation of the *gated stress-only SPECT* is that, without attenuation correction, it can confuse the diagnostician, who may misinterpret an attenuation artifact in a stress study of a normal patient as an ischemic event of a patient with CAD [2, 13, 14].

In addition to the diagnosis of CAD, estimating the size of the perfusion abnormality and reversibility and also its localization are of paramount importance. Based on our study findings, *SIDAGS-LDD* accurately predicts the number of involved territories. Moreover, the accuracy of *SIDAGS-LDD* in localizing CAD in the territory of LAD or LCx was equal to that of the *standard* protocol. However, the main drawback was unreliability of *SIDAGS-LDD* in localizing CAD in the territory of RCA, a pitfall which was also existent in the *standard stress/rest* protocol.

On the other hand, our study confirmed that the value of the *SIDAGS-LDD* protocol in unveiling the presence and extent of reversibility of the perfusion defects is at least equal or possibly higher than *standard* method. In our study, 34 of 44 patients with documented CAD showed the same findings as to the reversibility on the *SIDAGS-LDD* and *standard* protocol. Of the remaining 10 cases with discordant results, 9 showed reversibility only on *SIDAGS-LDD* (but not on *standard stress/rest*) and only one showed reversibility on *standard stress/rest* (but not on the *SIDAGS-LDD*). This may propose the superiority of the *SIDAGS-LDD* protocol in detecting reversibility over the *standard* method. To support this assumption especially for the patients with history of

hospitalization for assessment of a suspicious unstable angina or MI; four of nine patients with reversible defects on *SIDAGS-LDD* protocol and fixed defects on *standard* protocol showed considerable viability on stress echocardiography. Also another patient who revealed reversibility on *SIDAGS-LDD* protocol (but not on *standard stress/rest* protocol) died from another episode of extensive MI revealing a true reversibility. Hence in these 5 cases, the results for detection of reversibility were truly positive by our proposed method but falsely negative by stress/rest study. Although, we found no identical study which has compared stress-phase gated images before and after LDD infusion for CAD diagnosis and viability assessment, some studies have used LDD infusion only during the rest phase imaging to improve test value in detection of the viable tissue. Leoncini et al. [15] showed higher predictive accuracy for reversible dysfunction using LDD infusion at rest phase gated SPECT than with LDD echocardiography. Also the value of rest phase gated SPECT during LDD infusion plus nitrate for detection of more viability in hibernated myocardium has been reported by Entok et al. [16]. The findings of these two studies in concordance with our research, may confirm the role of LDD for further improvement of viability assessment. However, the potential clinical impact and the prognostic importance of such reversible perfusion defects (detectable by *SIDAGS-LDD* and missed by *standard* protocol) need to be confirmed by further studies using FDG-PET and/or post-intervention evaluations as the gold standard.

Regarding the confirmed advantages of gated stress-only protocol in reducing the time, cost and radiation exposure, what is the justification to design the *SIDAGS-LDD* protocol?

Marzullo et al. [17] and few other groups [2, 6, 7, 18–20] used ECG-gated post-stress  $^{99m}\text{Tc}$ -MIBI images for the detection of wall motion abnormalities and reversibility of stress induced perfusion defects. The common advantage in all these studies was the use of single injection as well as single image acquisition for the detection of CAD. Although most of these studies have reported a good accuracy for the diagnosis of CAD by single-phase stress gated SPECT [17, 20], a few others have revealed some conflicting results, particularly in patients with past-

history of myocardial infarction [6, 7]. One of the main reasons for such conflicts is the presence of myocardial stunning or hibernation, which results in abnormal myocardial motion/thickening with normal or abnormal perfusion [2, 13, 19, 21]. In fact, previously some investigators stated that the most important limitation of the *gated stress-only SPECT* is related to the difficulty in interpreting whether a stress induced perfusion defect is reversible or fixed [2]. Although attenuation correction should help reach the correct interpretation in a number of these confounding cases [2], there are still other situations such as functional stunning and subendocardial myocardial infarctions where the rest images will be needed to assess the presence and degree of myocardial ischemia. Considering that viable myocardium may functionally improve in response to inotropic stimulation and contractile reserve elicited by LDD is a predictor of functional recovery in patients with chronic CAD [22], the above-mentioned dilemma is expected to be overcome using constant infusion of LDD during another session of image acquisition. With the same logical basis, LDD infusion was added to the routine procedures of echocardiography and rest gated SPECT, and it has been shown to result in higher diagnostic and prognostic value in patients with CAD [15, 23]. In fact, our study confirmed that *SIDAGS-LDD* is superior to the *gated stress-only* protocol in detecting more reversibility in patients with previous MI.

Also, there are other valuable advantages with this technique. In our designed protocol only one injection of radiotracer is needed, which in fact causes a remarkable reduction in the patient's radiation exposure. On the other hand using *SIDAGS-LDD* protocol, it is possible to perform the second phase of the study only a few minutes after the first one. This presents the potential advantage of remarkable time saving. Moreover the conventional method is more expensive as it needs two injections of radiotracer in two separate sessions.

#### Study limitations

The relatively lower negative predictive value of the test is partly due to a limitation in the studied population. In our study, most of cases had a history of hospitalization due to a suspected MI or unstable angina that may lead to a bias for CAD diagnosis;

however the main goal of this study was to compare the value of different protocols in assessment of perfusion reversibility rather than the diagnosis of CAD. As assessment of reversibility is not affected by this limitation, it seems that this bias is not a major drawback in our study.

As in this study, the rest images was not obtained in gated mode, there is a possibility that stress-induced myocardial stunning (that may take minutes, or hours) can affect later gated findings acquired during LDD infusion. In fact, there may some patients in this research that had abnormal wall motion/thickening in both first-step post-stress and during LDD infusion images but not in rest standard images. In addition, since no gold standard for confirming reversibility/viability was used in our study, this can be a subject for further evaluation.

#### Conclusion

The *SIDAGS-LDD* protocol reveals good correlation and agreement with *standard stress/rest* method and even in some cases is superior for both diagnosis of CAD and defining the corresponding reversibility. In spite of the above limitations, our study may give an impression as an initial step to replace the conventional stress/rest protocol by this single-injection-double-acquisition method for preventing administration of additional radiotracer, shortening the time-length of the study and reducing cost and radiation to the patients and personnel. Multi-centric studies with a larger series of patients are needed to confirm this impression.

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#### References

1. Poon M, Fuster V, Fayad Z et al (2002) Cardiac magnetic resonance imaging: a "one-stop-shop" evaluation of myocardial dysfunction. *Curr Opin Cardiol* 17(6):663–670. doi:10.1097/00001573-200211000-00013
2. Santana CA, Garcia EV, Vansant JP et al (2003) Gated stress-only  $^{99m}\text{Tc}$  myocardial perfusion SPECT imaging accurately assesses coronary artery disease. *Nucl Med Commun* 24(3):241–249. doi:10.1097/00006231-200303000-00003

3. Marzullo P, Marcassa C, Sambuceti G et al (1992) The clinical usefulness of electrocardiogram-gated Tc-99m methoxy-isobutyl-isonitrile images in the detection of basal wall motion abnormalities and reversibility of stress induced perfusion defects. *Int J Card Imaging* 2:131–141. doi:[10.1007/BF01137534](https://doi.org/10.1007/BF01137534)
4. Guerra UP, Giacomuzzi F, Di Gregorio F et al (1999) Gated Tc-99m sestamibi SPECT versus stress–rest SPECT in detecting coronary artery disease: correlation with coronary angiography in patients without myocardial infarction. *Clin Nucl Med* 24:921–926. doi:[10.1097/00003072-199912000-00002](https://doi.org/10.1097/00003072-199912000-00002)
5. Williams KA, Taillon LA (1995) Reversible ischemia in severe stress technetium 99m-labeled sestamibi perfusion defects assessed from gated single-photon emission computed tomographic polar map Fourier analysis. *J Nucl Cardiol* 3:199–206. doi:[10.1016/S1071-3581\(05\)80056-X](https://doi.org/10.1016/S1071-3581(05)80056-X)
6. Snapper HJ, Shea NL, Konstam MA et al (1997) Combined analysis of resting regional wall thickening and stress perfusion with electrocardiographic-gated technetium 99m-labeled sestamibi single-photon emission computed tomography: prediction of stress defect. *J Nucl Cardiol* 4:3–10. doi:[10.1016/S1071-3581\(97\)90043-X](https://doi.org/10.1016/S1071-3581(97)90043-X)
7. Chua T, Kiat H, Germano G et al (1994) Gated technetium-99m sestamibi for simultaneous assessment of stress myocardial perfusion, postexercise regional ventricular function and myocardial viability. Correlation with echocardiography and rest thallium-201 scintigraphy. *J Am Coll Cardiol* 23(5):1107–1114
8. Ruiz-Salmerón RJ, Ponce De León E et al (2000) The capacity of the rest-dobutamine gated SPECT protocol to predict contractile recovery after revascularization of myocardial dysinergic areas. *Rev Esp Cardiol* 53(8):1052–1062
9. Leoncini M, Marcucci G, Sciagrà R et al (2000) Comparison of baseline and low-dose dobutamine technetium-99m sestamibi scintigraphy with low-dose dobutamine echocardiography for predicting functional recovery after revascularization. *Am J Cardiol* 86(2):153–157. doi:[10.1016/S0002-9149\(00\)00852-3](https://doi.org/10.1016/S0002-9149(00)00852-3)
10. Zafrir N, Arditi A, Ben-Gal T et al (2003) Additive value of low-dose dobutamine to technetium-99m sestamibi-gated single-photon emission computed tomography for prediction of wall motion improvement in patients undergoing coronary artery bypass graft. *Clin Cardiol* 26(11):530–535. doi:[10.1002/clc.4960261111](https://doi.org/10.1002/clc.4960261111)
11. Gibbons RJ, Balady GJ, Bricker JT et al (2002) ACC/AHA 2002 guideline update for exercise testing summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1997 Exercise Testing Guidelines). *Circulation* 106:1883–1892. doi:[10.1161/01.CIR.0000034670.06526.15](https://doi.org/10.1161/01.CIR.0000034670.06526.15)
12. Saeed MA, Saeed S, Hyder SW et al (2001) Enhanced <sup>99m</sup>Tc(m)-MIBI SPECT detection of hibernating myocardium following the use of sub-lingual nitroglycerine. *Nucl Med Commun* 22:65–72. doi:[10.1097/00006231-200101000-00009](https://doi.org/10.1097/00006231-200101000-00009)
13. Hendel RC, Corbett JR, Cullom SJ et al (2002) The value and practice of attenuation correction for myocardial perfusion SPECT imaging: a joint position statement from the American Society of Nuclear Cardiology and the Society of Nuclear Medicine. *J Nucl Cardiol* 9:135–143. doi:[10.1067/mnc.2002.120680](https://doi.org/10.1067/mnc.2002.120680)
14. Gibson PB, Demus D, Noto R et al (2002) Low event rate for stress-only perfusion imaging in patients evaluated for chest pain. *J Am Coll Cardiol* 20:999–1004. doi:[10.1016/S0735-1097\(02\)01720-5](https://doi.org/10.1016/S0735-1097(02)01720-5)
15. Leoncini M, Sciagra R, Bellandi F et al (2002) Low-dose dobutamine nitrate-enhanced technetium 99m sestamibi gated SPECT versus low-dose dobutamine echocardiography for detecting reversible dysfunction in ischemic cardiomyopathy. *J Nucl Cardiol* 9:402–406. doi:[10.1067/mnc.2002.123856](https://doi.org/10.1067/mnc.2002.123856)
16. Entok E, Cavusoglu Y, Kaya E et al (2005) Detection of hibernate myocardium by <sup>99m</sup>Tc sestamibi gated SPECT during low-dose dobutamine infusion plus nitrate in patients with first acute myocardial infarction. *Nucl Med Commun* 26:765–772. doi:[10.1097/01.mnm.0000172739.90746.f3](https://doi.org/10.1097/01.mnm.0000172739.90746.f3)
17. Marzullo P, Marcassa C, Sambuceti G et al (1992) The clinical usefulness of electrocardiogram-gated Tc-99m methoxy-isobutyl-isonitrile images in the detection of basal wall motion abnormalities and reversibility of stress induced perfusion defects. *Int J Card Imaging* 2:131–141. doi:[10.1007/BF01137534](https://doi.org/10.1007/BF01137534)
18. Guerra UP, Giacomuzzi F, Di Gregorio F et al (1999) Gated Tc-99m sestamibi SPECT versus stress–rest SPECT in detecting coronary artery disease: correlation with coronary angiography in patients without myocardial infarction. *Clin Nucl Med* 24:921–926. doi:[10.1097/00003072-199912000-00002](https://doi.org/10.1097/00003072-199912000-00002)
19. Ziffer JA, Cooke CD, Folks RD et al (1992) Quantitative myocardial thickening assessed with sestamibi: clinical evaluation of a count-based method. *J Nucl Med* 32:1006
20. Williams KA, Taillon LA (1995) Reversible ischemia in severe stress technetium 99m-labeled sestamibi perfusion defects assessed from gated single-photon emission computed tomographic polar map Fourier analysis. *J Nucl Cardiol* 3:199–206. doi:[10.1016/S1071-3581\(05\)80056-X](https://doi.org/10.1016/S1071-3581(05)80056-X)
21. Heller GV (1998) Gated SPECT imaging: increasing the armamentarium of nuclear cardiology. *J Nucl Cardiol* 4:442–444. doi:[10.1016/S1071-3581\(98\)90151-9](https://doi.org/10.1016/S1071-3581(98)90151-9)
22. Geskin G, Kramer CM, Rogers WJ et al (1998) Quantitative assessment of myocardial viability after infarction by dobutamine magnetic resonance tagging. *Circulation* 98(3):217–223
23. Bolognese L, Antoniucci D, Rovai D et al (1996) Myocardial contrast echocardiography versus dobutamine echocardiography for predicting functional recovery after acute myocardial infarction treated with primary coronary angioplasty. *J Am Coll Cardiol* 28(7):1677–1683. doi:[10.1016/S0735-1097\(96\)00400-7](https://doi.org/10.1016/S0735-1097(96)00400-7)