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99mTc–MIBI Stress Gated-SPECT Can Obviate the Need for Conventional Stress-Rest SPECT Imaging for the Diagnosis of Coronary Artery Disease

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ABSTRACT

Myocardial perfusion imaging is a commonly used procedure to diagnose coronary artery disease (CAD). Based on the assumption that preserved wall thickening on the stress perfusion defect is most likely predictive of stress defect reversibility. Conversely absent wall thickening is associated with fixed regional perfusion defect (scar or hibernating myocardium).

Purpose: The purpose of this work is to test the predictive value of stress Gated SPECT with Tc-99m MIBI in diagnosing stress induced perfusion defect. Further, we also aim at evaluating the clinical feasibility and limitation of Tc-99m MIBI stress Gated SPECT compared with the conventional protocol of stress rest SPECT imaging.

Patients and methods: This study included 109 patients referred for myocardial perfusion imaging for possible CAD or follow up of CAD. Gated SPECT using Tc-99m MIBI or Myoview was used in all patients. 78 males and 31 females with mean age of 61+-11. 63% of patients were exposed to one day protocol and 37% underwent two days protocol.

Results: A total of 2180 (109x20 segments each) were evaluated. 415 segments (19%) showed stress perfusion defects, 305 out of them showed apparent wall thickening motion in G-SPECT study and the reminder 110 showed defects with no evidence of wall motion or wall thickening. Among those 305 segments 284 showed reversible perfusion defects in the rest images with a predictive value of 95.5%. Out of the 110 stress induced perfusion defect segments with no wall thickening or wall motion, 71 segments demonstrated no reversibility in the rest image with negative predictive value of 64.5%.

Conclusion: We concluded that stress Tc-99m MIBI G-SPECT may obviate the need to perform rest image with cost and time reduction to patients, physician and gamma camera time as well. However, in absence of wall thickening and wall motion rest imaging must be performed to differentiate reversible ischaemia from infarctions in a stress induced perfusion defect.

Key Words: *MIBI- Gated - SPECT- Diagnosis - Coronary artery disease.*

INTRODUCTION

Myocardial perfusion scintigraphy is commonly used for the diagnosis of patients with suspected coronary artery disease (CAD). Traditionally 201Tl was used for myocardial perfusion imaging, however, the high count flux and stable distribution achieved with myocardial 99mTc labeled agents (99mTc-MIBI and 99mTc-Tetrofosmin) allows acquisition of the scintigraphic data in an electrocardiographic (ECG) - Gated Mode [1,2]. Gated Single emission computerized tomography (G-SPECT) imaging provides additional information about wall motions, wall thickening, left ventricular cavity volumes and ejection fraction. Germano et al., [3-6] developed a completely automated algorithm to visualize left ventricular wall motion and thickening and to quantify left ventricular ejection fraction. Dobutamine stress echocardiography can be done to assess wall motion and wall thickening to diagnose coronary artery disease (CAD). In patients with CAD, this technique reveals transient wall motion abnormalities that are absent during rest [7,8]. Similarly, we presumed that knowledge of preserved wall motion or thickening by G-SPECT in the region of a stress-induced perfusion defect may facilitate the assessment of ischaemia to the extent that the presence of normal wall thickening in the territory of a stress perfusion defect can predict the reversibility of that defect on resting images. Therefore, the purpose of the current study was to determine whether visual analysis of wall thickening and motion by means of single injection stress G-SPECT 99mTc-MIBI imaging, accurately predicts the reversibility of stress induced perfusion defects. Secondly, to evaluate the clinical feasibility and limitations of stress 99mTc-MIBI G-SPECT compared with the conventional protocol of stress-rest SPECT imaging.

PATIENTS AND METHODS

Participants

The patient population consisted of 109 patients referred for myocardial perfusion imaging for possible CAD or for follow-up of CAD. G-SPECT using 99mTc-MIBI or 99mTc-Myoview was used in all the patients. They were 78 men and 31 women, with a mean (+SD) age of 61+11 years (range 31 to 71 years). The baseline characteristics of the 109 patients are listed in table (1). The indications for myocardial perfusion imaging included assessment of suspected CAD in 71% of patient, pre-operative risk stratification testing in 18% and post-myocardial ischaemic attacks follow-up in 11%. Twenty-nine percent of these patients had a known history of previous myocardial infarction (MI), which in addition was confirmed by the presence of Q-waves on the electrocardiogram or by previous elevation of myocardial enzymes (CPK-MB fraction). Symptoms before stress testing included history of typical pain in 73 patients, dyspnea in 13 patients, heart failure in 3 patients and 20 patients were asymptomatic or have no chest pain post-MI. Patients with history of unstable angina or arrthymia were not included in this study.

Study Protocol

Sixty-nine patients (63%) underwent a 1-day stress-rest protocol while forty patients (37%) underwent a 2-day stress/rest protocol. These patients underwent either an exercise (n=35) or a pharmacological (n=74) stress protocol based on their clinical situation. Beta-blockers, Calcium channel antagonists and Nitrates were discontinued for 24 to 48 hours before the stress test.

The G-SPECT acquisition was performed 45 to 60 minutes post-stress in all the patients while the resting G-SPECT study was done in all 40 patients with the 2-day protocol and in only 39 out of 69 patients from the group who underwent a 1-day stress/rest protocol. Pharmacological stress testing was performed with an intravenous infusion of Dipyridamole at a total dose of 0.56 mg/kg. infused over a 4-minute period. Four minutes after completion of the Dipyridamole infusion, 370 MBq or 750 MBq 99mTc-MIBI dose was injected according to whether the 1-day or 2-day stress/rest protocols were used respectively. The exercise stress protocol included a step-wise increase in workload according to Bruce protocol to reach the age-dependant target heart rate. Exercise was considered inadequate if the patient achieved less than 85% of the predicted heart rate depending on the age in the absence of angina or an ischaemic ST-segment depression. 99mTc-MIBI was injected at peak exercise and the exercise was continued at the same level for an additional 60-90 sec. after injection.

Patients were given 250 ml. of whole milk 15 minutes after injection to increase hepatic clearance of the isotope. 99mTc-MIBI G-SPECT acquisitions began 45-60 minutes after the stress injection. G-SPECT imaging was acquired using a dual-head variable angle 90Ú? configuration ADAC vertex gamma camera in an electrocardiographic-gated mode at a frame rate of 8-frames per cardiac cycle. Sixty-four projections (32 per detector, matrix size 64 X 64) were acquired over a 180 degree anterior arc. The acquisition lasted for 30 seconds per projection with a total imaging time of 16 minutes. Examining sinogram and viewing cine images evaluated the patient motion, and in case of apparent motion, the motion correction software corrected this. The same acquisition protocol was also used for the G-SPECT imaging during rest studies.

Image Processing

The raw 99mTc-MIBI data were reconstructed using filtered back-projection technique. Transaxial slices were reconstructed with a Butterworth filter 5 and a cut-off frequency of 0.42 Cycles/Pixel for the stress-gated study and 0.55 for the rest-gated study. Left ventricular wall motion and wall thickening were calculated using a commercially available software package yielding a dynamic three-dimensional image of the left ventricle, Bull's eye analysis as well as numerical values of left ventricular volumes and ejection fraction 5.

Image Interpretation:

Stress 99mTc-MIBI G-SPECT

On static perfusion images, semi-quantitative analysis of the left ventricle perfusion was performed for 20 segments. Six segments on each of a pre-apical, mid and basal short axis slice and two apical segments on the vertical long axis slice as seen in Fig. (1).

This segment scheme is the same as the one used by Germano et al. [4,5]. The analysis was done initially for the stress perfusion images. All segments were scored using a 4-point scale: 0 = no uptake, 1 = severely diminished uptake, 2 = slightly diminished uptake and 3 = normal uptake (maximum counts in the heart). No uptake corresponded with < 25% of normal perfusion, severely diminished uptake with 25-50%, and slightly diminished uptake with 50-75% of normal perfusion and normal uptake with 75-100% of normal perfusion. These percentages were judged using the color scale system of the cardiac SPECT software. Wall motion was scored using a four-point grade (0 = dyskinetic, 1 = no wall motion, 2 = mildly reduced and 3 = normal wall motion) for all the 20 segments. Wall thickening was scored as good (1) or poor (0) on the basis of the visual assessment of brightening of the myocardial wall during systole.

On stress G-SPECT study only, "reversibility" was defined as the presence of a definite perfusion defect (perfusion score > 2) and either a wall motion score > 2 (mildly reduced to normal wall motion) or a wall thickening score = 1 (good wall thickening). In addition, the left ventricular end-diastolic and end-systolic volumes as well as the left ventricular ejection fraction were determined. The presence (or absence) of regional myocardial thickening on the post-stress G-SPECT images was compared subsequently to the reversibility of stress-induced perfusion defects on the combined stress and rest myocardial perfusion images.

Resting 99mTc-MIBI G-SPECT

As was used for assessment of perfusion in stress images, a four-point scale system (0-3 for absent tracer uptake to normal perfusion) was used to grade the rest perfusion for the 20 segments of the left ventricular myocardium mentioned in Fig. (1). Reversibility of stress perfusion defects was defined as an improvement in the perfusion score by more than 1 grade at rest when compared with the stress perfusion score. As a result all the myocardial perfusion segments were graded into three categories, normal uptake at stress and rest; reversible stress defect and irreversible stress defect.

Statistical Analysis

Data are reported as mean + SD or frequency when appropriate. Agreement among the stress G-SPECT and the stress / rest SPECT studies was evaluated by analysis of variance (ANOVA) and the use of regression analysis (Pearson's). Two-tail *t*-test was used when appropriate. Positive and negative predictive values were calculated from standard frequency equations. A p value less than 0.05 were considered statistically significant.

RESULTS

A total of 2180 segments (109 pts. X 20 segments) were evaluated in the current study. Of the 109 patients evaluated, 81 patients (74%) had one or more significant segmental perfusion defects at stress images. Among the total number of segments analyzed 415 segments (19%) showed a perfusion defect on the stress scan. Of these defects, 305 segments showed apparent wall motion and wall thickening while the rest (n=110) of these perfusion defects showed severely diminished or no evident wall motion and wall thickening.

Among the 305 segments with stress-induced perfusion defects and visually apparent wall thickening on G-SPECT images, 284 were reversible or partially reversible on rest imaging. The rest of segments (n=21) were irreversible as illustrated in figure 2. This gives a positive predictive value of 95.5% for wall thickening to predict stress defect reversibility.

Fig. (3) shows stress-induced defects associated with preserved wall motion that predict the reversibility seen in Fig. (3c) in the resting study.

However, of the 110 segments with stress-induced defects and no apparent wall thickening on G-SPECT images, 71 segments demonstrated no stress defect reversibility on rest imaging. This represents a negative predictive value of 64.5 % for the lack of apparent wall thickening to predict correctly an irreversible stress defect (Fig. 2).

A significant percentage (35%) of segments with stress induced perfusion defects and no wall thickening proved to have stress defect reversibility in the resting SPECT study. To evaluate this finding, the effect of stress defect severity and previous myocardial infarction in relation to wall thickening and stress defect reversibility were assessed. Effect of stress-defect severity and previous myocardial infarction.

Stress defect severity was analyzed by the color scale profile present in the Bull's eye mapping compared to the area of maximum uptake and the defect severity was scored as mild, moderate or sever.

In the 284 segments with concordant data (i.e. reversible stress defects with evident wall thickening), relative 99MTc-MIBI activity was > 50% (percentage of peak uptake), while in 39 segments with discordant data (i.e. reversible defects with no wall thickening). The relative 99MTc-MIBI activity was significantly lower < 35% of peak activity. This finding suggests that wall thickening may be influenced significantly by the severity of the defect; that is, wall thickening may not be apparent if regional counts are low.

In the current study 32 patients had a history of MI or ECG Q-waves. In this group of patients, 142 segments showed perfusion defects on stress imaging (Fig. 4), 80 demonstrated evidence of wall thickening on G-SPECT images and 58 of these segments were reversible on resting images (positive predictive value of 73%).

In contrast, the negative predictive value was only 53% for the absence of wall thickening to correctly identify the fixed perfusion defects as among the 62 segments with no wall thickening only 33 proved to have no reversibility in the subsequent resting SPECT study.

Table (1): Patient characteristics and the protocols used in the study.

	No of patients	Percentage
Number of Patients	109	
Men	78	72
Women	31	28
Reasons for referral		
Assessment of chest pain	77	71
Risk stratification	20	18
Follow up of CAD	12	11
History of Myocardial infarction	32	29
Cardiac risk factors		
Age > 50 years	71	65
Hypertension	81	75
Diabetes	43	39
Hypercholesterolaemia	63	58
Smoking	52	48
Baseline ECG		
Normal	68	62
Abnrmal	41	38
GSPECT protocol		
1-day stress/ rest protocol	69	63
2-day stress / rest protocol	40	37
Type of stress		
Exercise treadmil	35	32
Dipyridamole	74	68

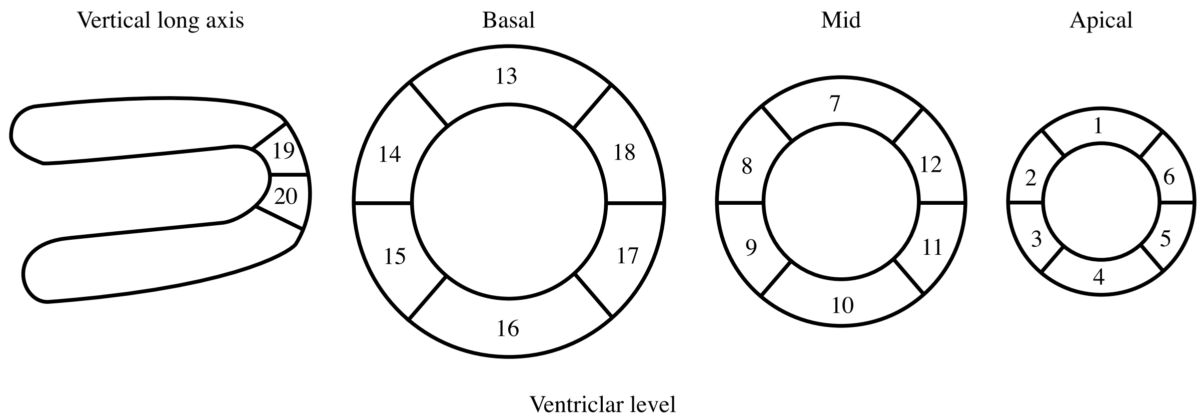

Fig. (1): Schematic representation of the 20-segment model of left ventricle used for interpretation of the myocardial perfusion images.

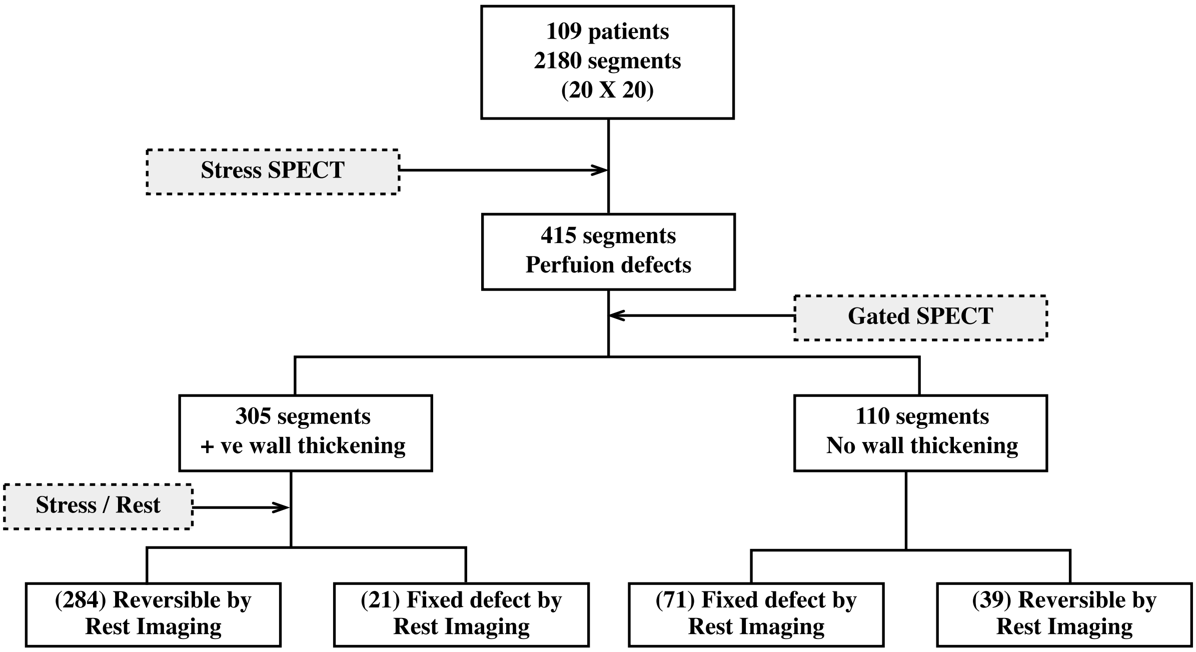

Fig. (2): A flow diagram presenting summary of the findings in the whole group of ptients, illustrating the prevalence of wall thickening judged by G-SPECT and its relation to the reversibility of the stress-induced perfusion defects.

Fig. (3-A): The stress Perfusion images showing perfusion defects affecting the anterolateral and inferior walls.

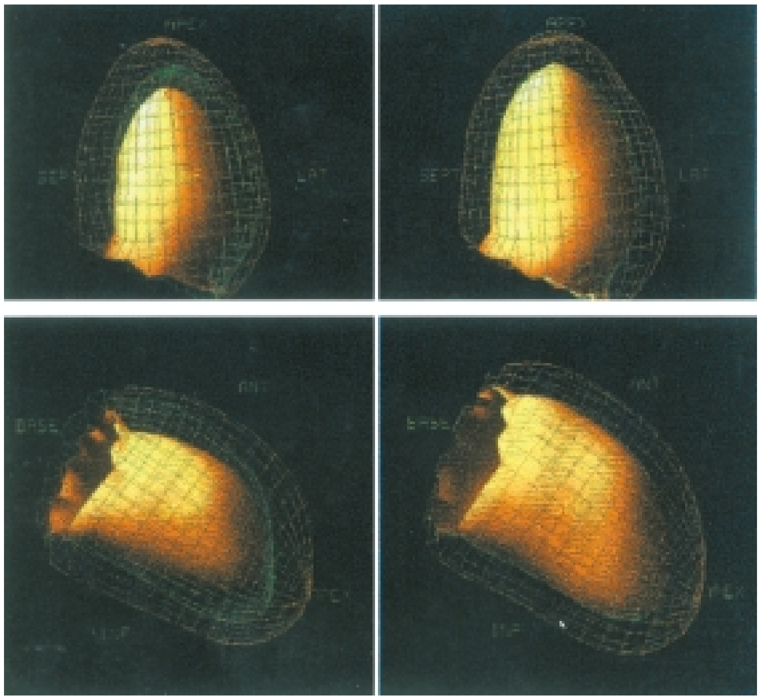

Fig. (3-B): The 3D-Gated SPECT picture showed obvious wall motion in both affected walls predicting viability and reversibility.

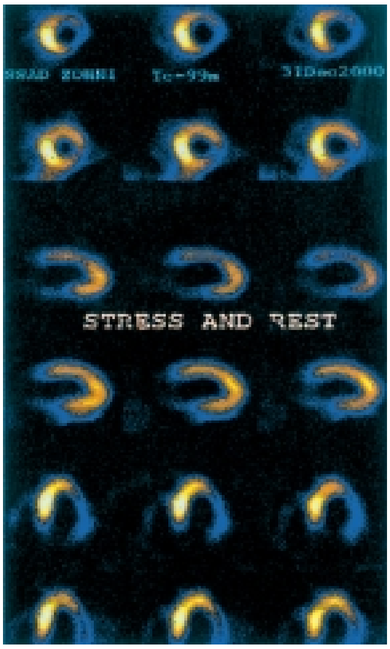

Fig. (3-C): The complete stress/rest study showing the reversibility in the antero-lateral and the inferior walls.

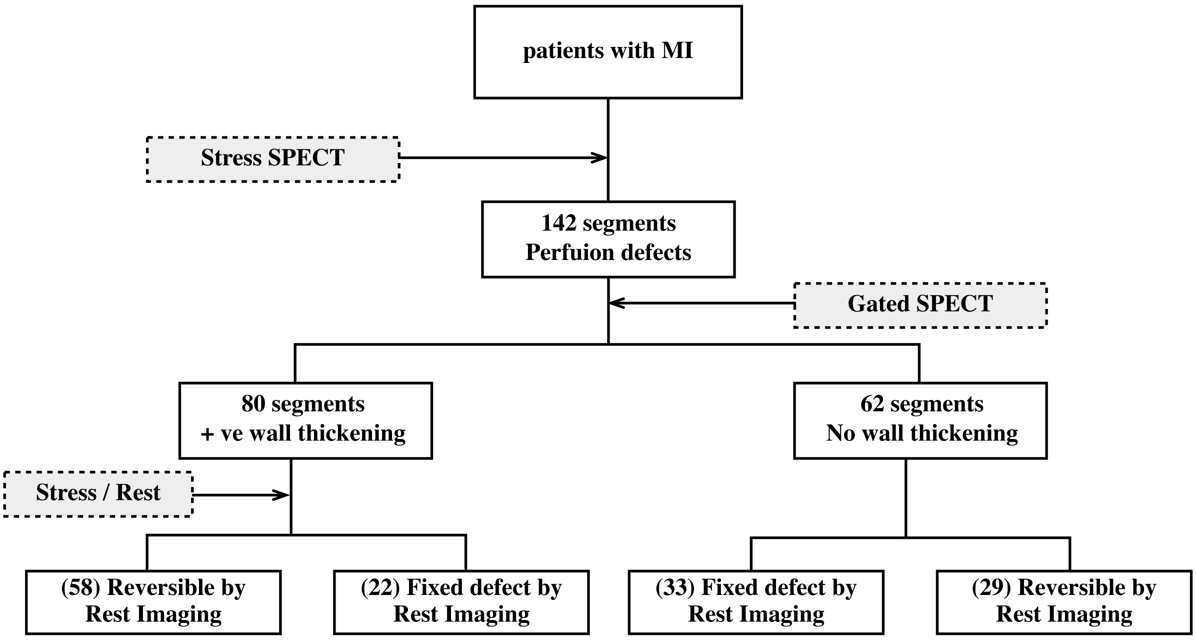

Fig. (4): A flow diagram showing the prevalence of wall thickening by G-SPECT and portrays the presence or absence of reversibility of a stressinduced perfusion defect in patients with previous myocardial infarction (MI).

DISCUSSION

The background of our study was based on the assumption that preserved wall thickening in a stress induced perfusion defect is most likely predictive of stress defect reversibility and conversely, absent wall thickening is associated with fixed regional perfusion defect (infarction / hibernation). To achieve the objectives of this work we used the G-SPECT stress imaging which has been shown to be an accurate and reliable measure of both left ventricular perfusion and functions **[3-5,9-11]**.

The current results indicate excellent predictive value for wall thickening, as the detection of wall thickening in a stress-induced perfusion defect correlates with reversibility of that defect in 93 % of such segments. The overall agreement between G-SPECT functional data (wall thickening) and the results of the stress-rest 99mTc-MIBI SPECT was 85% in all the segments in-patients with and without myocardial infarction. These findings are similar to other published data [12-16]. It has been postulated that if wall thickening is well preserved, that region of the myocardium should be viable. However, if a region does not show wall thickening, viability cannot be excluded [17,18].

Chau et al. [14] found that wall thickening on G-SPECT 99mTc-MIBI images correlated with stress defect reversibility, with a segmental agreement of 98% in patients without clinical evidence of myocardial infraction. Analogous data were reported by Guerra et al. [15], for patients without myocardial infarction, where the detection of wall thickening in a stress-induced perfusion defect correlates with reversibility on resting images in 95% of the segments. Close agreement of 86% was reported by Yoon et al., [19] between reversible perfusion defects on stress-rest 99mTc-MIBI SPECT and wall thickening on stress G-SPECT images in patients without myocardial infarction.

On the other hand, for the group of patients with history of myocardial infraction (n = 32), the current results revealed a modest overall agreement of only 65% with PPV and NPV of only 73% and 53% respectively. Similarly, other authors [16,18,20] have shown that in the presence of previous myocardial infarction a significant percentage of segments with stress induced defects may show no apparent wall thickening on G-SPECT imaging in spite of evident stress defect reversibility in the resting images. Snapper et al., [18] found that among his study 17 patients with a history of myocardial infarction presented with 40 segments of perfusion defects on G-SPECT stress imaging, 20 demonstrated evidence of wall thickening, and 17 of these segments (85%) were reversible on resting images. This was far less than their findings in patients without previous infarction, in whom they reported a PPV of 100%. They mentioned an overall NPV of only 60 %, however, without reporting on the NPV for either group of patients separately.

Amongst a group of patients with previous myocardial infarction studied for the evaluation of viability after bypass surgery, Yoon et al., [19] presented an overall agreement of 73% between stress 99mTc-MIBI G-SPECT and stress-rest perfusion SPECT, in comparison with 86% agreement in patients without previous myocardial infraction. Furthermore, considerable discordance was found between the two protocols in patients with previous myocardial infarction with respect to reversibility with PPV and NPV of 73% and 50% respectively. These data suggest, as do those of the current study, that the correlation of wall thickening data with stress defect reversibility is less optimal in patients with previous history of myocardial infarction.

In the current work, the negative predictive values of wall thickening was lower than expected, as for the whole cohort the negative predictive value was 64.5% due to the lack of apparent wall thickening to predict correctly a fixed perfusion defect. Moreover, in patients with a history of previous myocardial infarction, the NPV of single-injection stress 99mTc-MIBI G-SPECT was 53% witch is considered less than satisfactory compared to the conventional stress-rest perfusion reversibility approach. Previous investigations were in keeping with the current findings on the relatively less optimal correlation between absence of wall thickening and the absence of stress defect reversibility on rest imaging [13,14,19,21]. This finding was similar to that of a recent report by Snapper et al., [18] who found that 40% of segments with no apparent wall thickening in the territory of a stress perfusion defect had significant reversibility of those defects on rest imaging.

In our opinion, the explanation for the disagreement between wall thickening and defect reversibility, may be related to various causes. 1) The stress defect severity may influence the apparent wall thickening on G-SPECT imaging as a certain threshold of regional counts may be necessary to show evident wall thickening on G-SPECT 99mTc–MIBI imaging. This was statistically true in our investigation as the segments with absent wall thickening that appeared reversible in resting images show a defect severity more pronounced than in segments with concordant findings on wall thickening and stress defect reversibility. 2) It is also possible that the lack of apparent wall thickening by G-SPECT, 45-60 min. after exercise, in a region with a reversible stress defect represents myocardial stunning. The myocardial stunning indicates a more extended area of affected left ventricular myocardium than the severity of the perfusion defects alone would suggest.

Furthermore, even if uncommon, in-patients with chronic history of severe coronary artery disease, the presence of chronic regional dysfunction (hibernation) in a setting of preserved viability may explain the discordance between lack of apparent wall thickening by G-SPECT in some stress-induced defects and their reversibility in the resting images. These phenomenae of stunning and hibernation with their scintigraphic representations are known in-patients with coronary artery disease **[18,22-26]**.

Study Considerations

We acknowledge both strengths and limitations of the current study. In this study, we included patients with different stress modalities as pharmacological and exercise testing, besides the absence of standard protocol for imaging as some patients were imaged using 1-day versus others with a 2-day protocol. However, the current results are analogous to those of other investigators that have used various imaging protocols **[9,15,17,27]**. This would suggest that the current use of different imaging protocols would not be expected to significantly influence the results of the present analysis of wall thickening in G-SPECT. Another limitation might be attenuation artifacts; as attenuation artifacts may affect the segmental counts in the apparent perfusion defects to the extent that it may influence the ability to visualize significant wall thickening and falsely interpret the lesion as irreversible defect. However, it would be expected that this finding could occur in special cases of obese and large breasted patients. In our practice, if an artifact is believed to be present, based on patient body habitués and there is significant wall thickening in such apparent perfusion defects, we consider it an attenuation artifact. However, when segments with apparent perfusion defects do not contract on G-SPECT, patient should return for a resting perfusion SPECT.

Other investigators **[15,19]** reported that among the limitations of G-SPECT are the increase acquisition, processing and interpretation time requirements. However, we do believe that these are not anymore considered as limitations in view of the new multi-head (dual-head 90 cardiac-configuration) gamma cameras, the faster and more sophisticated user-friendly G-SPECT software.

The strength of the current study comes from its potential implication on the imaging protocol with 99mTc–MIBI or 99mTc-Myoview. The data suggest, as do other authors **[10,13,14,18]**, that rest perfusion study may be unnecessary if the post-stress G-SPECT myocardial perfusion image shows normal wall thickening in the area of a perfusion defect. Nevertheless, when segments with apparent perfusion defects do not contract on G-SPECT, the patient should return for a resting perfusion SPECT. In addition, G-SPECT can help to eliminate possible misalignment errors, which can occur in stress-rest studies. Finally, G-SPECT provides more functional data (ventricular volumes, ejection fraction and segmental wall motions) that have their significant implications on the clinical management for patients with CAD.

In conclusion, preserved wall thickening and motion in a stress-induced perfusion defect, highly correlates with the defect reversibility on resting images. This protocol (Stress 99mTc-MIBI G-SPECT) obviates the need to perform rest imaging, Thereby potentially has an important implication for cost and time reduction for patients, physicians and gamma camera use. In absence of wall thickening, however, rest imaging must be performed to differentiate ischaemia from infarction in a stress-induced perfusion defect.

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