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Original Citation:

Influence of the postexercise acquisition delay on the detection of functional abnormalities in sestamibi-gated SPECT / R. SCIAGRA'; B. SOTGIA; M. DONA; A. PUPI. - In: JOURNAL OF NUCLEAR CARDIOLOGY. - ISSN 1071-3581. - STAMPA. - 14:(2007), pp. 334-340. [10.1016/j.nuclcard.2007.02.015]

Availability:

The webpage <https://hdl.handle.net/2158/255998> of the repository was last updated on 2019-10-09T14:04:17Z

Publisher:

Mosby Year Book Incorporated:6277 Sea Harbor Drive:Orlando, FL 32887:(800)654-2452, (407)345-4000,

Published version:

DOI: 10.1016/j.nuclcard.2007.02.015

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Influence of the postexercise acquisition delay on the detection of functional abnormalities in sestamibi-gated SPECT

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Background. Gated single photon emission computed tomography (SPECT) identifies functional changes produced by ischemia, but the influence of acquisition delay on their detection is not established.

Methods and Results. In 80 patients with known or suspected coronary artery disease, gated SPECT was acquired twice: first, less than 30 minutes after peak exercise (stress 1), and second, more than 45 minutes after peak exercise (stress 2). End-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF) were compared with perfusion. The relationship between the Δ EF (stress EF – resting EF) and the summed difference score (SDS) was -0.443 ($P < .0001$) for stress 1 and -0.416 ($P < .0001$) for stress 2. In stress 1, EF increased in patients without inducible ischemia (SDS = 0) ($57\% \pm 10\%$ vs $54\% \pm 9\%$ at rest, $P < .02$) and decreased in those with an SDS of 1 or greater ($53\% \pm 10.8\%$ vs $55\% \pm 9.6\%$ at rest, $P < .05$). In stress 2, EF was unchanged in patients without ischemia ($55.8\% \pm 9.7\%$, $P = .06$) and decreased in the other patients ($52.8\% \pm 10.2\%$, $P < .01$). In patients without ischemia, both the EDV and ESV decreased significantly in stress 1 and were unchanged in stress 2. In patients with an SDS of 1 or greater, the EDV remained unchanged and the ESV minimally decreased in stress 1, whereas both volumes clearly and significantly increased in stress 2.

Conclusions. The early acquisition of postexercise gated SPECT is slightly more effective in detecting ischemia-related functional changes; however, a delayed acquisition within 60 minutes still permits the detection of functional abnormalities in most patients. (J Nucl Cardiol 2007;14:334-40.)

Key Words: Left ventricular function • coronary artery disease • exercise stress testing • gated single photon emission computed tomography

Several studies have demonstrated that stress-induced ischemia may cause wall motion abnormalities or a decrease in the left ventricular (LV) ejection fraction (EF) on poststress gated single photon emission computed tomography (SPECT), as well as that there is a relationship between the severity of stress-inducible perfusion defects and the functional changes detected by gated SPECT.¹⁻³ According to the model of myocardial stunning, it would be desirable to perform the poststress gated SPECT acquisition early after exercise, because this could increase the likelihood of identifying transient functional abnormali-

ties.³ On the other hand, by use of the technetium-labeled perfusion agents, early imaging might be disadvantageous in terms of image quality, mainly because of high subdiaphragmatic activity.⁴ Furthermore, an important advantage of these tracers over thallium 201 is the possibility of repeating the scan acquisition in case of major patient motion or other causes of inadequate image quality, without the risk of changes in perfusion. The duration of stress-induced functional impairment is controversial,⁵⁻¹⁰ and scanty data are available about the time course of functional changes after exercise in gated SPECT poststress images.³ It is therefore unclear what the rate of missed functional ischemic changes would be if the poststress acquisition had to be delayed (eg, because of persistent high subdiaphragmatic activity) or repeated (eg, because of excessive patient motion). To clarify this issue, we compared the functional parameters obtained in 2 consecutive gated SPECT poststress acquisitions and examined their relationship with the extent and severity of perfusion abnormalities, using the perfusion pattern for reference.

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Received for publication June 27, 2006; final revision accepted Feb 22, 2007.

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1071-3581/\$32.00

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doi:10.1016/j.nuclcard.2007.02.015

MATERIALS AND METHODS

Patient Population and Study Protocol

Among the patients who underwent exercise-resting myocardial perfusion gated SPECT in our laboratory, those who were scheduled for the first scan on the daily timetable, so that the scan could be easily repeated at 2 time intervals, were considered to be eligible for the study. Of these, 80 consecutive patients (66 men and 14 women; mean age, 63.4 ± 8.8 years [range, 41-80 years]) with known or suspected coronary artery disease (CAD) were selected. The diagnosis of CAD was based on 1 or more of the following criteria: history of prior myocardial infarction, history of prior coronary revascularization (either coronary artery bypass grafting or percutaneous coronary intervention), and detection of at least 1 luminal obstruction exceeding 70% in at least 1 major epicardial branch on coronary angiography performed less than 6 months before index scintigraphy. The suspicion of CAD was based on a history of typical anginal symptoms or the detection of ischemic changes on exercise electrocardiography (or both) in patients with at least 1 coronary risk factor (hypertension, dyslipidemia, diabetes, or smoking habit). The exclusion criteria were as follows: severe LV dysfunction (LV EF <30%), heart disease other than CAD, achievement of less than 85% of maximal predicted heart rate during exercise stress testing performed for perfusion scintigraphy, major arrhythmias preventing reliable gating (>1 ectopic beat every 6 heart cycles) or paced rhythm, and unwillingness to participate in the study.

According to our current policy, patients had been instructed to abstain from their antianginal medications if not otherwise decided by the referring cardiologist. β -Blockers and calcium antagonists were discontinued at least 48 hours before the study, and nitrates were discontinued 24 hours before the study. Patients underwent symptom-limited exercise with a bicycle ergometer. Arterial blood pressure, heart rate, and 12-lead electrocardiogram were monitored during exercise and for at least the first 5 minutes of recovery. Exercise was terminated when any of the following endpoints was reached: typical anginal pain, horizontal ST-segment depression exceeding 1.0 mm in the presence of chest pain or 3.0 mm in the absence of pain, life-threatening arrhythmias, or leg fatigue.

The protocol included the acquisition of 2 poststress scans: the standard scan (stress 1), beginning as usual approximately 30 minutes after the injection of sestamibi at peak exercise, and the second scan (stress 2), obtained 5 minutes after the completion of the first and therefore at least 45 minutes after tracer injection. The rest gated SPECT study was acquired 1 hour after tracer injection via a separate-day protocol.

Gated SPECT

Gated SPECT was acquired after technetium 99m sestamibi injection (740 MBq), by use of a double-head camera (SKYlight; Philips Medical Systems, Milpitas, Calif) equipped with high-resolution collimators, with the following parameters: 180° rotation arc, 32 projections, 60 seconds per projec-

tion, 8 frames per heart cycle, and 64×64 matrices. The studies were reconstructed via filtered backprojection without attenuation or scatter correction and realigned along the heart axis. Perfusion defects were evaluated semiquantitatively by use of the scoring system proposed by the group from Cedars-Sinai Medical Center (Los Angeles, Calif) on a 20-segment model.¹¹⁻¹³ Image evaluation was performed blindly by an experienced observer (B.S. or M.D.), who was unaware of the patient's data and the timing of the scan. The measurement of LV end-diastolic volume (EDV), end-systolic volume (ESV), and EF was performed by use of the QGS program (Cedars-Sinai Medical Center).¹⁴ The same program automatically calculated transient ischemic dilation (TID) as well.

Statistical Analysis

Results are expressed as mean \pm SD. Comparisons of continuous variables were performed with the Student *t* test for paired or unpaired samples as appropriate. The correlation between values was analyzed by use of the Pearson correlation coefficient. $P < .05$ was considered statistically significant.

RESULTS

General Findings

The indications for the gated SPECT study were (1) evaluation of anginal symptoms in patients with prior myocardial infarction ($n = 15$), (2) evaluation of chest pain in patients with previous revascularization ($n = 20$), (3) worsening of anginal symptoms in chronic CAD patients ($n = 32$), and (4) diagnosis of CAD in patients with positive exercise stress testing results ($n = 13$). Table 1 summarizes the baseline characteristics of the patient population.

Myocardial Perfusion

The resting gated SPECT study was normal in 50 patients; the mean summed rest score (SRS) was 3.7 ± 6.7 . In stress 1 (mean acquisition delay after tracer injection, 27 ± 4.5 minutes), the summed stress score (SSS) was 7.2 ± 8.6 and the summed difference score (SDS) was 3.4 ± 4.4 ; 45 patients showed exercise-induced ischemia ($\text{SDS} \geq 1$). In stress 2 (mean acquisition delay after tracer injection, 50.5 ± 5.1 minutes), the SSS was 7.4 ± 8.8 and the SDS was 3.5 ± 4.6 ; 48 patients had an SDS of 1 or greater. Therefore no significant difference was observed in the perfusion pattern between the 2 stress studies ($P = \text{not significant}$ [NS] for both comparisons, Pearson correlation coefficient of 0.98 and $P < .000001$ for SSS and Pearson correlation coefficient of 0.94 and $P < .000001$ for SDS).

Table 1. Clinical characteristics of patient population

Characteristic	n (%)
Previous myocardial infarction	30 (38)
Risk factors	
Family history of CAD	42 (53)
Systemic hypertension	55 (69)
Hypercholesterolemia (total cholesterol >200 mg/dL)	55 (69)
History of smoking	58 (73)
Diabetes mellitus	11 (14)
Prior coronary artery bypass grafting	9 (11)
Prior percutaneous coronary intervention	38 (48)
Recent coronary angiography	41 (53)
No significant stenoses	2 (3)
One-vessel disease	8 (15)
Two-vessel disease	19 (24)
Three-vessel disease	12 (15)
Antianginal therapy (at moment of exercise stress testing)	
Nitrates	11 (14)
β -Blockers	8 (10)
Calcium channel antagonists	6 (8)

LV Functional Data

The resting LV volumes were 97 ± 35 mL for EDV and 47 ± 28 mL for ESV. The resting LV EF was $54.7\% \pm 9.4\%$. In stress 1 the LV volumes were 96 ± 37 mL for EDV ($P = \text{NS}$ vs rest) and 47 ± 31 mL for ESV ($P = \text{NS}$ vs rest) and the EF was $54.7\% \pm 11\%$ ($P = \text{NS}$ vs rest). In stress 2 the LV volumes were 101 ± 38 mL for EDV ($P < .005$ vs rest and $P < .0001$ vs stress 1) and 49 ± 32 mL for ESV ($P < .05$ vs rest and $P < .0001$ vs stress 1). The EF was $54.1\% \pm 10\%$ ($P = \text{NS}$ vs rest and $P = \text{NS}$ vs stress 1). The TID was 0.97 ± 0.18 in stress 1 and 1.03 ± 0.13 in stress 2 ($P < .0001$).

Relationship Between Perfusion and Functional Data

We tested whether a relationship was present between functional changes in the poststress studies and the amount of inducible ischemia. Taking into account the very high agreement between the perfusion scores in the 2 stress studies, we used only the scores determined on stress 1 images. As shown in Table 2, there was a significant direct correlation between the SDS and the increase in EDV and the TID on the poststress images, both in stress 1 and in stress 2. Similarly, there was a significant inverse correlation between the amount of inducible ischemia and the change in EF in the 2 poststress studies (Figure 1).

Table 2. Relationship between stress perfusion abnormalities and exercise-induced functional changes

	ΔEDV		ΔEF	
	Stress 1	Stress 2	Stress 1	Stress 2
SSS				
Pearson r	0.404	0.386	-0.384	-0.335
P value	<.0001	<.0001	<.0001	<.005
SDS				
Pearson r	0.353	0.463	-0.443	-0.416
P value	<.002	<.0001	<.0001	<.0001

In the patients without inducible ischemia ($\text{SDS} = 0$), the EF significantly increased in stress 1 as compared with the resting value ($57\% \pm 10\%$ vs $54\% \pm 9\%$, $P < .02$), whereas in stress 2 it was not significantly higher than at rest ($55.8\% \pm 9.7\%$, $P = .06$). In these patients both the EDV and the ESV decreased significantly in stress 1 as compared with resting gated SPECT, whereas they were unchanged in stress 2. In the patients with an SDS of 1 or greater, the EF significantly decreased both in stress 1 ($53\% \pm 10.8\%$ vs $55\% \pm 9.6\%$ at rest, $P < .05$) and in stress 2 ($52.8\% \pm 10.2\%$, $P < .01$ vs rest). In these patients the EDV remained unchanged and the ESV minimally decreased in stress 1 whereas both volumes clearly and significantly increased in stress 2. No significant differences were found in EF or volumes in any gated SPECT study between patients with ischemia versus those without ischemia (Figures 2-4).

The ΔEF (stress EF – resting EF) between rest and stress 1 and between rest and stress 2 was almost the same in the patients with an SDS of 1 or greater (-2.3 ± 6.3 EF units vs -2.4 ± 5.8 EF units), whereas in the patients without ischemia there was a significantly higher EF increase in stress 1 versus that observed in stress 2 (3 ± 6.5 EF units vs 1.8 ± 5.4 EF units, $P < .05$). In both poststress gated SPECT studies, the ΔEF was significantly different in the patients with inducible ischemia versus those without inducible ischemia ($P < .0001$ and $P < .005$, respectively, for stress 1 and stress 2). Similarly, the TID was significantly higher in the patients with inducible ischemia than that in those without inducible ischemia in both poststress acquisitions (Figure 5). Stress 1 demonstrated a clearly abnormal TID (>1.22) in 5 patients,¹⁵ which was still detectable in 3 of them in stress 2.

A decrease of 5 EF units or greater in poststress images as compared with resting gated SPECT was registered in 20 patients in stress 1 and in 20 patients

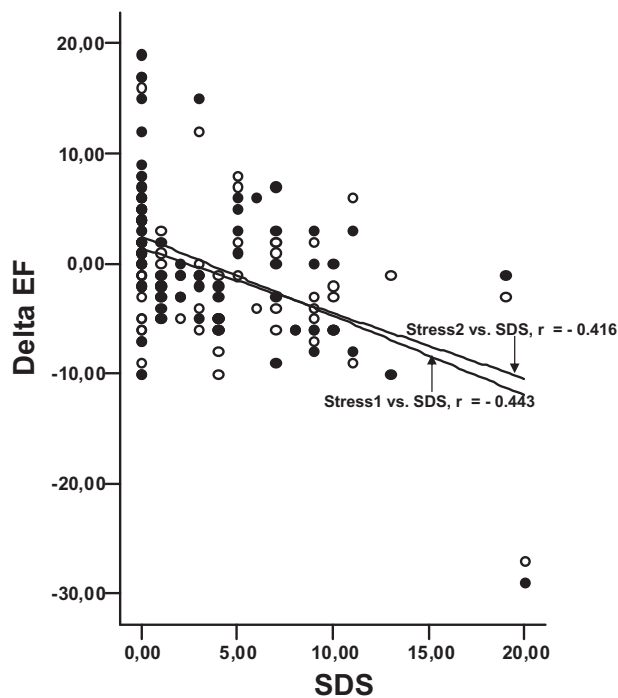


Figure 1. Scatterplot showing relationship of Δ EF versus SDS in early (stress 1, solid circles) or late (stress 2, open circles) gated SPECT study.

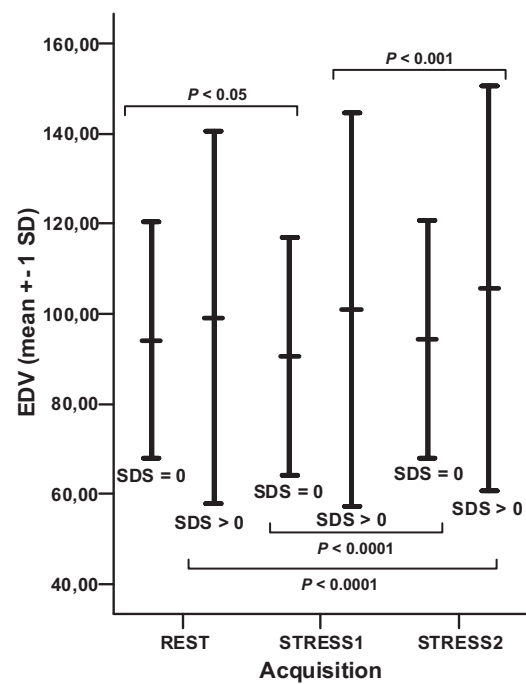


Figure 3. Graph showing LV EDV in resting, early (stress 1), and late (stress 2) gated SPECT studies in patient population divided according to absence (SDS = 0) or presence (SDS > 0) of exercise-induced ischemia.

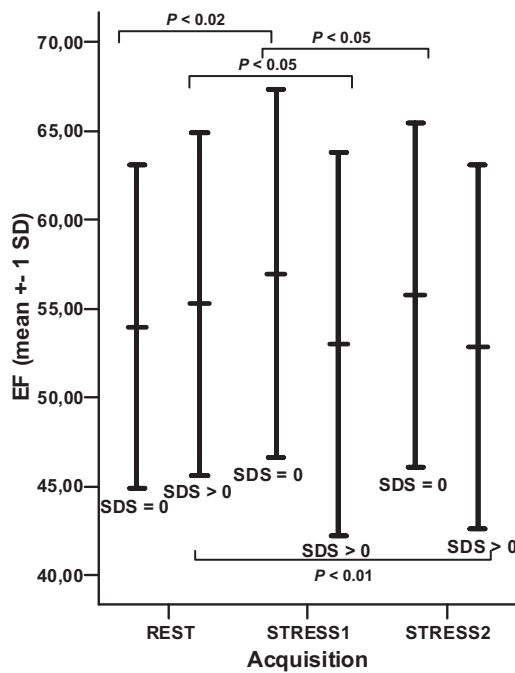


Figure 2. Graph showing LV EF in resting, early (stress 1), and late (stress 2) gated SPECT studies in patient population divided according to absence (SDS = 0) or presence (SDS > 0) of exercise-induced ischemia.

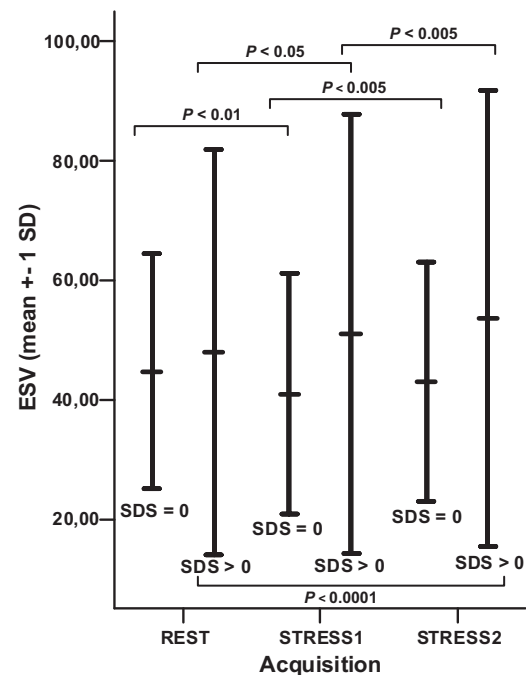


Figure 4. Graph showing LV ESV in resting, early (stress 1), and late (stress 2) gated SPECT studies in patient population divided according to absence (SDS = 0) or presence (SDS > 0) of exercise-induced ischemia.

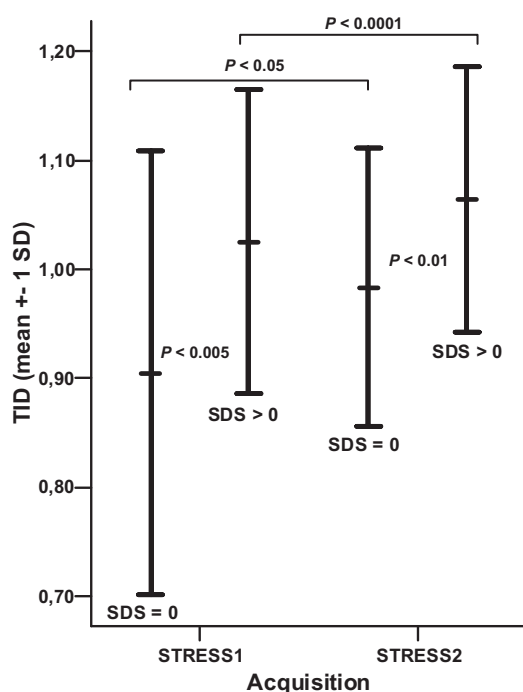


Figure 5. Graph showing TID in early (stress 1) versus late (stress 2) gated SPECT study in patient population divided according to absence (SDS = 0) or presence (SDS >0) of exercise-induced ischemia.

in stress 2. There were 15 patients who showed a decrease of 5 EF units or greater in both stress gated SPECT studies. Of the 10 patients with conflicting findings, 3 had severe inducible ischemia, all of whom had a decrease of 5 EF units or greater in stress 1 but not in stress 2; 4 had mild to moderate inducible ischemia, 1 of whom had a decrease of 5 EF units or greater in stress 1 versus 3 in stress 2; and 3 had no ischemia (1 with a decrease of ≥ 5 EF units in stress 1 and 2 in stress 2). Thus the finding of a significant poststress EF decrease without concomitant ischemia was registered in 1 of 80 patients with stress 1 and 2 of 80 with stress 2.

DISCUSSION

Acquisition Delay and Ischemia-related Functional Changes

With the use of the technetium-labeled perfusion agents (sestamibi and tetrofosmin), the indirect signs of functional impairment as a result of ischemia are valuable, but the poststress image acquisition delay might influence their reliability.¹⁵⁻¹⁸ Nowadays, gated SPECT allows the measurement of LV volumes and EF, and therefore the functional consequences of ischemia can be directly appreciated.¹⁻³ In the studies

about poststress gated SPECT functional changes, the time interval between tracer injection and poststress imaging ranged from 15 minutes to more than 60 minutes, and there was no direct comparison between different delays.^{1,2,19-28} Recently, Toba et al³ reported that in patients with single-vessel CAD, a very early (10 minutes) poststress gated SPECT study was superior to the usual 30- and 50-minute intervals to identify transient decreases in EF in the subjects with stress-induced ischemia, and they confirmed the relationship between severity of ischemia and degree of functional impairment. To our knowledge, their study is the only one addressing the issue of ischemia-related functional changes by comparing different acquisition delays.

Results of Our Study

If the patient population was considered in its entirety, the only significant difference between the 2 poststress gated SPECT studies was that both the EDV and ESV appeared slightly but significantly larger on the delayed poststress acquisition than on the resting scan and on the early gated SPECT scan. If the presence of exercise-induced ischemia was considered, however, the early poststress gated SPECT scan showed an EF increase (together with a volumetric reduction) in the subset of patients without ischemia, as well as a significant EF decrease (together with a substantial stability of LV volumes) in the patients with an SDS of 1 or greater. On the contrary, in stress 2 the patients without ischemia showed stable EFs (and volumes) as compared with rest gated SPECT, whereas the patients with inducible ischemia had both a significant EF reduction and a volumetric increase.

The capability to detect the presence of a significant poststress EF decrease did not appear to be influenced by the acquisition delay. The relationship of EF decrease versus SDS was almost equally close and significant in the 2 poststress studies. The Δ EF was not significantly different in the 2 poststress studies in the subset of patients with inducible ischemia. In both poststress gated SPECT studies, the Δ EF and the TID were significantly different between the patients with inducible ischemia versus those without inducible ischemia. The large majority of patients with significant (≥ 5 EF units) functional worsening early after exercise showed this finding on the delayed acquisition as well.

Clinical Implications

These results do not contradict the concept that an early acquisition optimizes the detection of exercise-induced functional changes. In particular, the difference

in EF changes between patients with ischemia and those without ischemia was slightly more significant when the gated SPECT study was started with 30 minutes of tracer injection at peak exercise. However, the exercise-induced functional changes were usually prolonged enough to be detected even with an acquisition starting more than 45 minutes after tracer injection. The clinical implication of our results for the routine practice of a busy nuclear medicine laboratory is that a prolonged delay in the postexercise acquisition or its repetition—for instance, because of major patient movement—does not preclude the detection of exercise-induced functional abnormalities in most cases.

This conclusion somewhat challenges the study by Toba et al,³ who proposed a very early acquisition (10 minutes after tracer injection) of gated SPECT to obtain reliable detection of ischemic functional changes. The differences between the two studies could partly explain this disagreement. Toba et al examined only patients with single-vessel disease, who reached a target heart rate greater than 85% of expected maximum in a minority of cases. Therefore the possibility that functional changes were less severe and hence more short-lived should be considered. Moreover, Toba et al did not evaluate myocardial perfusion on the early gated SPECT images, and thus the practicability of their very early acquisition protocol in the clinical routine is not yet demonstrated.

Study Limitations

Several limitations of our study must be considered. The patient population was unselected. This, however, offers the advantage that our study cohort is close to that in common practice. Naturally, the prevalence of male patients with preserved LV function, though corresponding to the population seen in daily practice, does not allow our findings to be transferred automatically to other populations, such as women with small hearts or, conversely, patients with LV dysfunction. Without the performance of coronary angiography in all patients, it is difficult to identify those in whom diffuse CAD could be revealed by a significant EF decrease in the absence of severe inducible perfusion defects. Our data merely allow us to conclude that no major differences exist with regard to this issue between the 2 poststress acquisitions but do not exclude that some such patients were missed by both studies. The differences in LV volumes must be interpreted with caution, because we did not assess the intrinsic variability of volumetric measurements. The time points chosen for the 2 gated SPECT acquisitions were not very far apart, and therefore it could be expected that very early (10-15 minutes) or very delayed (>60 minutes) studies would have given results that are

more dissimilar. However, we made our choice keeping in mind the acquisition timing in routine clinical practice and the possible need to repeat the acquisition because of technical problems. We did not consider the possible value of the analysis of regional wall motion or thickening abnormalities (or both).²⁴ Finally, we limited our analysis to patients submitted to exercise stress testing. Although several data indicate that stress-induced functional changes are most valuable even with the use of pharmacologic tests, dedicated studies are necessary to establish their time dependency.²⁵⁻²⁷

Conclusion

Our results indicate that the repetition or delaying of postexercise gated SPECT acquisition until within 60 minutes of tracer injection still provides the possibility of detecting, with reasonable reliability, the presence and extent of ischemia-related functional changes. Although an early acquisition remains preferable, our study supports the concept that it is possible to maintain operational flexibility in the clinical routine without the risk of missing ischemic functional abnormalities in the majority of patients if the acquisition delay does not exceed 1 hour.

Acknowledgment

The authors have indicated they have no financial conflicts of interest.

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