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Noninvasive Characterization of Stunned, Hibernating, Remodeled and Nonviable Myocardium in Ischemic Cardiomyopathy

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OBJECTIVES We evaluated a novel protocol of dual-isotope, gated single-photon emission computed tomographic (SPECT) imaging combined with low and high dose dobutamine as a single test for the characterization of various types of altered myocardial dysfunction.

BACKGROUND Myocardial perfusion tomography and echocardiography have been used separately for the assessment of myocardial viability. However, it is possible to assess perfusion, function and contractile reserve using gated SPECT imaging.

METHODS We studied 54 patients with ischemic cardiomyopathy using rest and 4 h redistribution thallium-201 imaging and dobutamine technetium-99m sestamibi SPECT imaging. The sestamibi images were acquired 1 h after infusion of the maximal tolerated dose of dobutamine and again during infusion of dobutamine at a low dose to estimate contractile reserve. Myocardial segments were defined as hibernating, stunned, remodeled or scarred.

RESULTS Severe regional dysfunction was present in 584 (54%) of 1,080 segments. Based on the combination of function and perfusion characteristics in these 584 segments, 24% (n = 140) were labeled as hibernating; 23% (n = 136) as stunned; 30% (n = 177) as remodeled; and 22% (n = 131) as scarred. Contractile reserve, represented by improvement in wall motion/thickening by low dose dobutamine, was observed in 83% of stunned, 59% of hibernating, 35% of remodeled and 13% of scarred myocardial segments ($p < 0.05$).

CONCLUSIONS It is possible with this new imaging technique to characterize dysfunctional myocardium as stunned, hibernating, remodeled and nonviable. These subtypes often coexist in the same patient. (J Am Coll Cardiol 2000;36:1913–9) © 2000 by the American College of Cardiology

Diagnostic evaluation for the assessment of the magnitude of dysfunctional but viable myocardium has become an integral component of the management of patients with coronary artery disease (CAD) and impaired left ventricular (LV) ejection fraction (EF) (1,2). The functional impairment in these patients is not always irreversible (3–7), and up to 40% of patients may demonstrate improvement on restoration of blood flow to the myocardium (2,5). However, the high operative risk associated with revascularization procedures in such patients necessitates accurate differentiation of viable from nonviable myocardium (1,2). Various noninvasive imaging procedures have been used for the detection of reversible systolic dysfunction. Demonstration of preservation of myocardial metabolism by positron emission tomography (PET) (8–16), determination of the sarcolemmal membrane integrity by myocardial uptake and retention of radioactive perfusion tracers (17–22) and echocardiographic observation of contractile reserve on inotropic stimulation (21,23–25) form the basis of assessment of myocardial viability. Several studies have employed both thallium scintigraphy and echocardiography for the assessment of myocardial perfusion and contractile reserve in the same patient (26,27). Although they are attractive, comparative studies have the potential for anatomic malalignment, because orientation of the heart is inherently different between two techniques. The assessment of LV function simultaneously with myocardial perfusion has now become possible with gated single-photon emission computed tomographic (SPECT) imaging (28–30). The present study was undertaken to evaluate the clinical feasibility of using radionuclide imaging for the assessment of perfusion and function in the same myocardial segments in patients with CAD and LV dysfunction. We reasoned that knowledge of perfusion at rest and during stress, wall motion at rest and contractile reserve in same myocardial segment would allow better characterization of altered myocardial states.

METHODS

Patients. We studied 54 patients of CAD and impaired LV systolic function (EF, 25 ± 10%). There were 45 men

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Abbreviations and Acronyms

CAD	=	coronary artery disease
EF	=	ejection fraction
LV	=	left ventricular
PET	=	positron emission tomography
SPECT	=	single-photon emission computed tomography
Tl-201	=	thallium-201
Tc-99m	=	technetium-99m

(83%) and 9 women (17%) (age 65 ± 9 years). All patients were studied because of angina or heart failure, or both, but none had a recent acute myocardial infarction (<3 months), unstable angina or primary valvular heart disease. Of those, 44 (82%) had a history of myocardial infarction and 23 (43%) had previous coronary revascularization procedures. The risk factor profile was as follows: diabetes, 43%; hypertension, 31%; hypercholesterolemia, 46%; smoking, 28%; and family history, 40%. Most patients were receiving beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, digoxin or nitrates. There were 34 patients (63%) with severe triple-vessel disease; 13 patients (24%) with two-vessel disease; and 7 patients (13%) with single-vessel disease. All patients signed a consent form approved by the Institutional Review Board, and there were no complications related to the study.

Study protocol. The protocol consisted of a four-step imaging procedure: first, two SPECT images (SPECT–1 and 2) were obtained with thallium-201 (Tl-201), and next, two gated SPECT images (SPECT–3 and 4) were obtained with technetium-99m (Tc-99m) sestamibi. The study protocol has been previously described (1), and is described briefly as follows. After an overnight fast, 3.5 mCi of Tl-201 was injected intravenously at rest, and SPECT images were obtained 20 min later (SPECT-1). The thallium SPECT images were repeated 4 h later (redistribution images, SPECT-2). Shortly after SPECT-2 was completed, dobutamine was infused to a maximal tolerated dose (up to 40 μg/kg body weight per minute). At the peak dobutamine dose, Tc-99m sestamibi (30 mCi) was injected intravenously. The dobutamine infusion was continued ≈1 to 2 min after intravenous injection and stopped. Gated SPECT sestamibi images were performed 1 h after radiotracer administration (SPECT-3). After acquisition of SPECT-3 images, dobutamine was reinfused at a low dose of 5 μg/kg per min, and gated SPECT images (SPECT-4) were acquired during infusion. Thus, a total of four SPECT images were acquired—two with thallium and two with sestamibi. The total imaging protocol is ≈6 h. The radiation burden is comparable to a standard dual-isotope protocol or to the stress–rest sestamibi protocol.

Interpretation of SPECTimages. Data analysis was performed using a 20-segment model to assess regional perfusion and regional function (wall motion/thickening) using a semiquantitative scoring system, as previously described (1). Perfusion and function were scored on a semiquantitative scale of 0 to 4, where 0 = no perfusion or no wall thickening or akinesia/dyskinesia, and 4 = normal perfusion and function.

Comparison of SPECT–1 and 2 images provided the status of rest perfusion and was defined as normal; mild to moderate fixed defect; severe fixed defect; or reversible defect. Reversible defects provided evidence of rest ischemia, or hypoperfusion at rest (1,30,31).

Comparison of SPECT–1 and 3 allowed the assessment of stress-induced ischemia. For instance, a normal segment by SPECT–1 and 2 may become ischemic on stress by SPECT-3, or a reversible defect by SPECT–1 and 2 may show more severe ischemia with stress by SPECT-3 (Fig. 1).

The SPECT-3 image also provided information on regional function in each segment (wall motion/thickening) and LVEF. The functional data reflect baseline or rest variables, because the images were obtained 1 h after completion of dobutamine infusion. The 1-h interval also avoided the potential problem of post-stress stunning (30).

The SPECT-4 image provided information on contractile reserve. An improvement in wall motion/thickening in previously abnormal segments represented the presence of contractile reserve. In contrast, the lack of improvement was considered a lack of contractile reserve.

Definitions of altered myocardial states and rationale. Based on segmental perfusion and function, the following definitions of altered myocardial states were developed.

MYOCARDIAL HIBERNATION: Segments with severe systolic dysfunction were called hibernating if they demonstrated evidence of hypoperfusion at rest (rest ischemia) (3,32,33). Therefore, the segments with regional dysfunction (SPECT-3 wall motion score = 0 or 1) and evidence of reversible thallium defects (SPECT-2 perfusion score > SPECT-1 perfusion score) were considered to represent hibernating myocardium.

MYOCARDIAL STUNNING: The presence of function–flow mismatch (contractile abnormality with normal perfusion) has traditionally been considered as stunned myocardium (34,35). Therefore, segments with regional dysfunction (SPECT-3 wall motion score = 0 or 1) and normal thallium at rest or mild to moderate fixed thallium defects (SPECT–1 and 2 perfusion score = 2 to 4) were considered stunned if they developed ischemia with dobutamine stress (SPECT-3 perfusion score < SPECT-1 perfusion score).

MYOCARDIAL REMODELING: Segments with regional dysfunction (SPECT-3 wall motion score = 0 or 1) and normal thallium at rest or redistribution or only mild to moderate perfusion defects (SPECT–1 and 2 perfusion score = 2 to 4) and no dobutamine-inducible ischemia (SPECT-3 perfusion score = SPECT-1 perfusion score) were referred as "remodeled segments" (1,31,36).

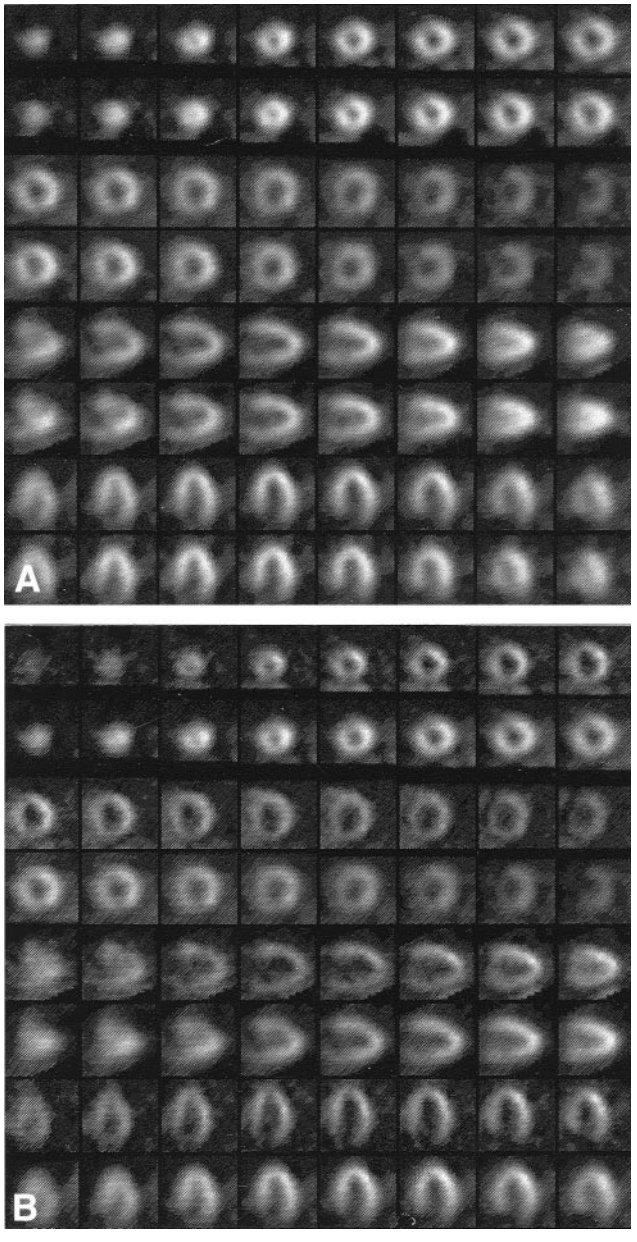

Figure 1. A, Rest and 4-h SPECT thallium images in a woman with severe two-vessel disease and severe LV dysfunction (EF 21%). There are severe diffuse wall motion abnormalities. The SPECT images are shown in the short-axis (apex to base, rows 1 and 3), vertical long-axis (septum to lateral wall, row 5) and horizontal long-axis projections (inferior wall to septum, row 7). The corresponding 4-h redistribution images are shown in rows 2, 4, 6 and 8 in the same orientations. There is only a mild perfusion defect involving the septum. **B,** Dobutamine sestamibi and rest thallium SPECT images from the same patient using the same format as in A. Here the sestamibi images are displayed in rows 1, 3, 5 and 7, and the rest thallium images in rows 2, 4, 6 and 8. There are now multiple reversible perfusion defects with transient LV dilation. This patient has a substantial amount of viable myocardium, and the LV dysfunction is secondary to myocardial stunning, hibernation and remodeling.

MYOCARDIAL SCARRING: Segments with regional dysfunction (SPECT-3 wall motion score = 0 or 1) with severe fixed perfusion defects at rest, redistribution and stress (SPECT–1, 2 and 3 perfusion score = 0 or 1) were considered as scar or irreversibly damaged myocardium.

Choice of stress imaging and dosage of pharmaceutical stress. Dobutamine rather than exercise or vasodilator therapy was used as a stress modality, because dobutamine enables assessment of both stress-induced changes as well as contractile reserve. Other forms of stress may be used if contractile reserve assessment is not needed. All patients in the present study had echocardiographic assessment at baseline and during dobutamine infusion. The peak dose of dobutamine was based on the development of a new or worsening wall motion abnormality, conventional end points or a maximal dose of 40 μg/kg per min. The choice of low dose dobutamine of 5 μg/kg per min was based on the fact that none of the patients given this dose developed a new or worsening wall motion abnormality on two-dimensional echocardiography. This dose was therefore considered safe for continuous infusion while SPECT-4 was being acquired.

Follow-up. As this was a pilot study and not an outcome study, follow-up was available in only 27 patients at a mean interval of 25 months. The patient was considered to have significant viability if scarring was <40% of the myocardium.

Statistical analysis. The data are presented as the mean value ± SD or percentage. The data were analyzed using analysis of variance with a multiple-comparison procedure, the Wilcoxon rank-sum test, the Student t test and the chi-square test, as appropriate. It was clear that different segments behaved differently in the same patient, and therefore the analysis was based on segments. A p value <0.05 was considered statistically significant.

RESULTS

Myocardial perfusion. Of 1,080 segments analyzed, the thallium perfusion pattern at rest (SPECT-1) was normal in 557 segments (52%) and showed mild to moderate perfusion defects in 273 segments (25%) and severe defects in 250 segments (23%). Redistribution images acquired 4 h later (SPECT-2) demonstrated improvement in perfusion in 127 (47%) of the 273 segments with mild to moderate defects and in 93 (37%) of 250 segments with severe defects. The SPECT-3 images demonstrated ischemia in 223 (40%) of 557 segments with normal thallium perfusion and 159 (58%) of 273 segments with mild to moderate fixed thallium defects.

Assessment of segmental wall motion abnormality. Of 1,080 segments, 144 (13%) demonstrated normal regional wall motion/thickening; 352 (33%) had mild to moderate dysfunction and 584 (54%) had severe dysfunction. The thallium perfusion was normal in 72% of segments with normal function and 61% of segments with mild to moderate dysfunction.

Assessment of altered myocardial states. In the 584 myocardial segments with severe dysfunction, the thallium uptake was normal in 239 segments. Dobutamine stress demonstrated inducible ischemia in 88 (37%) of the 239

Table 1. Semiquantitative Perfusion and Wall Motion Scores

Myocardial State	Perfusion SPECT-1	Perfusion SPECT-2	Perfusion SPECT-3	Wall Motion SPECT-3	Wall Motion SPECT-4	Contractile Reserve
Normal	4.0 ± 0.0	4.0 ± 0.0	4.0 ± 0.0	4.0 ± 0.0	4.0 ± 0.0	NA
Stunned	4.0 ± 0.0	4.0 ± 0.0	1.1 ± 0.7*	1.0 ± 0.2	3.4 ± 1.2†	2.5 ± 1.2
Remodeled	4.0 ± 0.0	4.0 ± 0.0	4.0 ± 0.0	0.9 ± 0.2	1.4 ± 0.8†	0.5 ± 0.8‡
Hibernating	1.7 ± 0.8	3.0 ± 0.7*	0.8 ± 0.6*	0.6 ± 0.5	1.5 ± 1.0†	0.9 ± 1.0‡
Scar	0.5 ± 0.5	0.5 ± 0.5	0.5 ± 0.5	0.3 ± 0.4	0.4 ± 0.8	0.2 ± 0.8‡

*$p < 0.001$ as compared with rest perfusion. †$p < 0.001$ as compared with rest wall motion. ‡$p < 0.001$ as compared with stunned, true. Data are presented as mean ± SD. NA = not applicable; SPECT = single-photon emission computed tomography.

segments, and they were considered to represent stunned myocardium. The remaining 151 (63%) of the 239 segments did not have inducible ischemia and were considered to represent remodeled segments. The perfusion score decreased in the stunned but not the remodeled segments ($p = 0.001$) (Table 1).

The thallium uptake showed mild to moderate fixed defects in 74 of the 584 segments with a severe wall motion abnormality. Two-thirds of these segments showed ischemia on SPECT-3 and were considered to represent a combination of stunned myocardium and mild scarring.

The thallium uptake showed reversible defects in 140 of the 584 segments with severe systolic dysfunction. These segments were considered to represent hibernating myocardium (Fig. 1). The rest perfusion score improved from SPECT-1 to SPECT-2 and then worsened on SPECT-3 ($p = 0.001$) (Table 1). Dobutamine produced more severe defects in 91 (65%) of the 140 segments, possibly representing a combination of hibernation and stunning.

The remaining 131 of 584 myocardial segments with a severe contractile abnormality demonstrated severe, fixed thallium defects. Most of these segments ($n = 105$; 80%) demonstrated no further worsening of perfusion with dobutamine. These segments represented scarred or nonviable myocardium. The rest thallium, delayed thallium and dobutamine stress perfusion scores were unchanged.

Thus, 140 (24%) of 584 dysfunctional segments represented hibernating myocardium (with or without concomitant stunning), 136 (23%) were stunned (with and without scarring), 177 (30%) were remodeled (with or without scarring) and 131 (22%) were nonviable segments.

Contractile reserve in dysfunctional myocardial segments. Improvement in systolic wall motion/thickening with low dose dobutamine was seen in 73 (83%) of the 88 stunned segments (segments with no scar); 82 (59%) of 140 hibernating segments; 53 (35%) of 151 remodeled segments; and 17 (13%) of 131 scarred segments ($p < 0.05$). The contractile reserve (change in wall motion/thickening score from SPECT-3 to SPECT-4) was higher in stunned segments than in other segments ($p = 0.001$) (Table 1). The contractile reserve in hibernating segments was confined predominantly to those segments that had shown worsening of rest ischemia with high dose dobutamine. Of 91 hibernating segments with inducible ischemia, 68 (75%) demonstrated positive contractile reserve, as compared with 14 (29%) of 49 segments with no evidence of inducible ischemia ($p < 0.05$).

Follow-up. Of the 27 patients with follow-up data, 4 underwent coronary revascularization and 23 were treated medically. Twelve of 23 patients had predominantly viable and 11 had nonviable myocardium; 5 and 3 of these patients, respectively, either died or had heart transplantation. The number of patients in each group was too small to allow meaningful statistical comparison.

DISCUSSION

The results of the present study document different pathophysiologic mechanisms (stunning, hibernation, remodeling and scarring) for LV dysfunction in patients with ischemic cardiomyopathy. Within a given myocardial region, more than one feature may exist, and in a given patient, one or more of the aforementioned features may predominate. These results are based on a novel protocol used in the present study that allowed precise registration of regional myocardial perfusion (at rest and during stress) with regional function (at baseline and in response to low dose dobutamine) using dual-isotope, gated SPECT imaging.

Assessment of reversible LV dysfunction. Previous studies show that the coronary flow reserve is abnormal in regions with reversible LV dysfunction (37). The limited flow reserve may result in dysfunction secondary to repetitive stunning (flow–function mismatch). In contrast, a reduction in rest myocardial flow has also been reported in viable dysfunctional segments (flow–function match). Imaging with PET has shown flow–metabolism mismatch in both forms of reversible LV dysfunction (8,9). Such mismatch in the presence of normal rest flow suggests an alteration in the pattern of substrate utilization, probably related to changes in activity of glucose transporters (13,14).

Previous SPECT studies have shown that myocardial tracer activity is a marker of viable myocardium (17–22). Good correlation between tracer activity and the degree of fibrosis has been reported in biopsy specimens and extransplanted hearts. (38,39). Although in many studies a threshold was used to define viable myocardium, the probability of recovery of function correlates with uptake as a continuum, and no single threshold could accurately distinguish regions that recover from those that do not recover after coronary revascularization (40). These studies, how-

ever, relied on independent methods to assess perfusion and function, with inherent problems in segment registration.

Viability has traditionally been defined as an improvement in regional wall motion after coronary revascularization (41,42). It is clear, however, that 1) recovery of regional function could not be the only benefit of revascularization of viable myocardium; and 2) myocardial viability may exist, even though recovery of function could not be demonstrated. Lack of recovery may be due to subendocardial fibrosis, remodeling, incomplete revascularization or advanced ultrastructural, biochemical and metabolic alterations that may require a much longer period to recover, if at all (13,14).

Restoration of blood supply to the viable myocardium may provide clinical benefit by eliminating life-threatening ventricular arrhythmias, preventing LV dilation, improving exercise function, improving diastolic function and preventing repetitive stunning (16,43–48). These changes may result in improvement of quality of life and survival. It has been recently proposed that continued low grade ischemia, particularly in the subendocardial layers, might lead to apoptosis (49,50). The process of apoptosis, a genetically programmed cell death, occurs when the ischemic insult is delivered in doses milder than that required for necrosis. Apoptosis may also occur in terminally differentiated myocytes that are exposed to constant growth stimulus in the failing myocardium. The myocytes respond by hypertrophy initially, but undergo apoptosis because they fail to replicate (51,52). Prevention of apoptosis and an inexorable loss of myocytes may contribute to reverse remodeling and recovery of LV function gradually over many months.

The present study: identification of altered myocardial states. The present study showed that different pathophysiologic states might explain LV dysfunction, and these might coexist in the same patient, in the same vascular territory or even in the same segment. These altered states include hibernation, stunning, remodeling and scarring. These classifications were made possible by evaluating rest and stress-induced ischemia, as well as rest and contractile response with dual-isotope, gated SPECT imaging. Previous studies have shown that tracer uptake is normal in stunned myocardium, but is decreased in regions with low flow (53). Myocardial segments with systolic dysfunction but normal perfusion at rest and no stress-induced ischemia were considered to represent remodeled segments (36); such segments may represent compensatory changes in remote segments with no coronary stenosis, and their ultimate faith might depend on the associated changes elsewhere in the myocardium. It is important to note that dobutamine induced further ischemia in most segments that were classified as hibernating with reduced rest flow. This may explain why such segments may not improve function with inotropic stimulation. Detection of ischemia is important in predicting recovery of function after coronary revascularization. Kitsiou et al. (54) demonstrated that 79% of myocardial segments with reversible defects improved after coronary artery bypass graft surgery, as compared with 30% of segments with mild to moderate fixed defects.

In our study, stunned segments were more likely to show positive contractile reserve, as compared with hibernating segments, which is in agreement with other reports. In one study, 54% of hibernating segments did not demonstrate contractile reserve (55), and the myocardial blood flow during dobutamine stress was lower in hibernating segments with no contractile reserve, as compared to those segments with contractile reserve. Sambuceti et al. (56) also showed that contractile response was more common in stunned than in hibernating myocardium.

Study limitations. Several limitations of the present study need to be considered. First, the data on postoperative assessment of LV function are not available. However, as discussed earlier, recovery of function may not be the optimal gold standard. Second, we used a small dose of dobutamine for the assessment of contractile reserve. It has been suggested that contractile reserve in some patients may require a higher dose, although the relation of contractile reserve with recovery of LV function remains to be elicited (57). Third, it is also possible that some of the remodeled segments may have shown evidence of ischemia if the dose of dobutamine was higher. As indicated in the Methods section, dobutamine infusion was discontinued when a new or worsening wall motion abnormality was demonstrated by two-dimensional echocardiography. This may be a drawback of using an echocardiographic end point. Dobutamine, as used in nuclear imaging, follows a more standard protocol using clinical end points rather than wall motion abnormality. Fourth, our measurements of wall motion/thickening were based on subjective interpretation of the gated SPECT images, which may have their own limitations. Several studies, including our own, have shown good correlation between wall motion/thickening assessment by gated SPECT and other independent methods, such as two-dimensional echocardiography and magnetic resonance imaging (27,28). It is now possible, however, to use a completely automated method for the assessment of both wall motion and wall thickening using gated SPECT imaging.

Conclusions. Myocardial hibernation, stunning, remodeling and scarring often coexist in patients with ischemic cardiomyopathy. Approximately 50% of the myocardium in our patients was either stunned or hibernating, or both. Future studies need to examine the relation of the type of altered myocardial states with recovery of function and patient outcome, with or without surgical revascularization.

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