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Classification of ischemic dysfunctional myocardium combining perfusion quantification and contractile reserve evaluation using nitrate-enhanced gated single photon emission computed tomography with dobutamine test

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Aim. **In patients with ischemic cardiomyopathy, the differentiation of dysfunctional myocardium in scarred *versus* hibernating is oversimplified. We evaluated a more complex classification using an imaging technique currently employed for viability detection, having as reference the postrevascularization outcome of dysfunctional segments.**

Methods. **In 35 patients, we performed gated single-photon emission computed tomography (SPECT) (resting and nitrate-enhanced study, the latter with baseline and dobutamine acquisition) before revascularization. The outcome after revascularization was assessed by repeating resting gated SPECT. Dysfunctional segments without functional recovery in postrevascularization gated SPECT were defined scar (either nontransmural or transmural according to tracer activity); those with recovery were divided in stunned (unchanged uptake) or hibernating (improved postrevascularization activity). This reference classification was compared with the categorization based on prerevascularization gated SPECT.**

Results. **Contractile reserve in dobutamine gated SPECT differentiated scarred from viable segments with 78% accuracy. Tracer activity in nitrate imaging distinguished the degree of transmurality. Nitrate-induced activity increase was significantly higher ($p<0.0001$) in the hibernating segments (14.9±20.4%) than in transmural (4.8±13.4%) nontransmural scars (3.3±13%), or stunned segments (2.2±8%). The presence or absence of nitrate-induced activity increase predicted the postrevascularization perfusion changes in viable myocardium and differentiated hibernating from stunned segments. The prerevascularization classification showed a good agreement with the reference categorization ($\kappa=0.50$).**

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Conclusion. **Combining contractile reserve evaluation and perfusion quantification within a single study with baseline-nitrate gated SPECT and dobutamine test it is possible to achieve a comprehensive classification of dysfunctional segments.**

KEY VORDS: Tomography, emission computed, single photon - Myocardial stunning.

The importance of detecting viable tissue within dysfunctional myocardium in patients with left ventricular (LV) functional impairment due to chronic coronary artery disease is well known.[1, 2] After revascularization, viable myocardium is expected to have functional recovery, with consequent increase in global LV function, reduction of heart failure symptoms and improvement in prognosis.[1-6] For years, the physiopathologic substrate of reversible dysfunction in these patients has been considered to be an adaptive reduction in function related to a decrease in coronary blood flow, a situation described with the term of hibernation.[1] According to this paradigm, the demonstration of preserved glucose metabolism in hypoperfused segments (perfusion/metabolism mismatch)

has been considered to be the most reliable viability marker.[2, 3, 7] However, the hypothesis of a baseline reduction in blood flow in hibernating segments has been challenged, and the alternative concept of a very severe decrease in the coronary flow reserve leading to a status of repeated ischemic insults and consequently to a sort of chronic stunning has been proposed.[8] The possibility that both hibernation and repetitive stunning coexist is now regarded as the most reasonable.[9-11] Moreover, the presence of segments with signs of relatively preserved viability but without functional recovery after revascularization has been recognized, and the definitions of remodeled segments or nontrasmural scars have been proposed.[10, 12, 13] Attempts have been made to use different viability markers to obtain a more precise definition of the various kinds of myocardial abnormality related to the presence of dysfunctional tissue in ischemic cardiomyopathy.[10, 14] The postrevascularization outcome of those segments appears a most straightforward way to characterize their status. The aim of the present study was 2-fold: first, to evaluate the possibility to differentiate the various myocardial conditions on the basis of the evolution of both function and perfusion after revascularization; second, to examine the relationship between the various kinds of myocardial abnormality and 2 markers of viability, such as preserved contractile reserve under dobutamine infusion and perfusion assessment using baseline-nitrate Sestamibi imaging, taking advantage from the possibility to evaluate both parameters with a single imaging modality by means of gated single-photon emission computed tomography (SPECT).

Materials and methods

Patient population

We studied 35 consecutive patients (32 male and 3 female, mean age 64±9 years, range 39-80) with coronary artery disease, who were scheduled for a revascularization procedure. The other selection criteria were impaired LV function (LV ejection fraction <50%), and presence of a clear regional asynergia in at least one coronary artery territory. The data of the present study were not a prerequisite for the revascularization. The exclusion criteria were: recent (<1 month) myocardial infarction or unstable angina, heart disease other than coronary artery disease, atrial fibrillation or history of sustained ventricular tachycardia, unwillingness to participate in the study.

Study protocol

After enrolment, all patients underwent on separate days with a 24-hour interval baseline resting and nitrate ^{99m}Tc Sestamibi (Sestamibi) gated SPECT. The nitrate-enhanced study was performed with a 1st acquisition at rest and a 2nd during low-dose dobutamine infusion. Resting Sestamibi gated SPECT was repeated after revascularization. All scintigraphic studies were performed after overnight fasting. Nitrates and β-blocking agents were withdrawn 48 hours before the tests. All patients gave informed consent to participate in the study, which was approved by the Ethics Committees of our institutions.

Sestamibi SPECT

The prerevascularization baseline gated SPECT study was acquired 1 hour after the injection of Sestamibi (925 MBq, 25 mCi) to the patients lying supine. For the nitrate study, patients received 10 mg of isosorbide dinitrate in 100 ml of isotonic saline solution administered over 20 minutes, according to a previously described procedure.[15] Sestamibi at the same dosage as for the baseline study was injected after 15 minutes of infusion or earlier if it was registered either a decrease >20 mmHg in systolic blood pressure or a systolic blood pressure <90 mmHg.[15] At least 1 hour later, resting gated SPECT was acquired. Immediately thereafter, dobutamine infusion (5 μg/kg body weight/min) was started, and increased after 5 min to 10 μg/kg/min. Early interruption criteria were hypotension, angina, or significant ventricular arrhythmia. Gated SPECT acquisition was started after 3 min of the 10 μg dose that was maintained until the acquisition was completed.[16] For the postrevascularization study, the same dose of Sestamibi was injected at rest to the patient lying supine and gated SPECT collected 1 hour later. Images were acquired using a dual-head γ camera (ADAC Vertex) equipped with high-resolution collimators, using a 15% window centered on the 140 keV photopeak of technetium-99m. Acquisition was performed in step-and-shoot mode, using 32 projections over a 180° elliptical orbit, matrix size 64×64, 45 s/projection, 8-frames/cardiac cycle. SPECT images were reconstructed using filtered back-projection without attenuation or scatter correction. To

quantify tracer uptake, gated SPECT images were summed to generate a standard perfusion study.

Data analysis

For perfusion and function analysis, the LV was divided in 16 segments.[16] Circumferential profiles from the short axis slices were generated and displayed in polar map format. Tracer uptake was quantified using an automatic program that calculated the mean uptake of each segment, identified the segment with peak uptake, set it to 100% activity, and scaled the other segments in percent of peak activity.[17] Regional function (wall motion and thickening) was assessed visually by consensus of 2 experienced observers unaware of patient's data and image sequence, and was scored using a 4-point scoring scheme (1=normal, 2=hypokinesis; 3=akinesis; 4=dyskinesis).[18] Previous data indicate a good interobserver and intraobserver reproducibility of visual scoring in our laboratory.[19] Baseline dysfunctional segments (score >1) that exhibited a decrease ≥1 grade in regional score at follow-up were considered to have functional recovery.[20] Similarly, contractile reserve was defined on the basis of a decrease ≥1 grade in regional score during dobutamine administration.[16, 20] However, a change form dyskinesis to akinesis was not considered to be significant.[21]

Characterization of dysfunctional myocardium

The segments with abnormal function in prerevascularization baseline resting Sestamibi gated SPECT were differentiated in 4 groups according to the following definitions: segments that in the postrevascularization gated SPECT study showed no functional recovery and Sestamibi activity under the threshold of viability (<50%) [16] were defined as transmural scars;[10] segments that in the postrevascularization gated SPECT study showed no functional recovery but had a Sestamibi activity in the viability range (≥50%) were defined as nontransmural scars;[12, 13] segments that in the postrevascularization study showed a significant functional recovery as above defined but no significant increase (at least >20% of the baseline prerevascularization value) in Sestamibi activity were defined as stunned myocardium;[8-10, 13] segments that in the postrevascularization study showed both a significant functional recovery and a significant increase in Sestamibi activity were defined as hibernating myocardium.[1, 20]

Statistical analysis

Results are expressed as mean value±standard deviation. The comparison of continuous variables within and between groups was made with the one-way analysis of variance (ANOVA) with the Tukey's post-hoc test for repeated measurements as appropriate. Nonparametric variables were compared with the Wilcoxon matched pair test or the Mann-Whitney U test, as appropriate. The comparison of proportions was made using the χ^2 test with Yates correction, as appropriate. The agreement in segment classification was assessed with kappa statistics. A p value <0.05 was considered statistically significant.

Results

Baseline prerevascularization findings

In the 35 patients a total of 49 infarcts were reported: 19 patients had prior anterior, 9 prior inferior, 5 both a prior anterior and an inferior and 2 both a prior anterior and a lateral infarction. The mean LVEF was 33.7±9.8%, range 16-49%. According to the most recent coronary angiography available, which was the basis for the revascularization intervention, 14 patients had 1-vessel coronary artery disease, 13 2-vessel and 8 3-vessel disease. In the 64 territories with significant coronary stenosis, a total of 304 segments showed baseline dysfunction (119 hypokinesis, 161 akinesis, and 24 dyskinesis).

Postrevascularization findings

Complete revascularization of all stenotic territories was performed in 13 patients by means of bypass grafting and in 22 by means of coronary angioplasty. The time interval between prerevascularization gated SPECT and the revascularization procedure was 27.7±17.5 and 25.1±18.3 days, respectively for bypass grafting and coronary angioplasty. Perioperative infarction was excluded on the basis of the usual clinical, electrocardiographic and enzymatic criteria. The time interval between revascularization and follow-up was 118.4±33 days for bypass grafting and 69.6±30.7 days for coronary angioplasty. At the moment of the follow-up control, all patients were asymptomatic at rest and did not report effort angina. The postrevascularization LVEF was 37.6±12.8%, range 16-64%. Of the 304

TABLE I.—*Features of the groups of dysfunctional segments identified on the basis of postrevascularization functional and perfusion changes.*

	Scar		Viable	
	Transmural	Nontransmural	Stunned	Hibernating
Hypokinetic segments (%)	9 (12%)	61 (58%)	33 (46%)	16 (30%)
Akinetic segments (%)	47 (65%)	40 (38%)	37 (51%)	37 (68%)
Dyskinetic segments (%)	17 (23%)	4 (4%)	2 (3%)	1 (2%)
Baseline wall motion score	3.1±0.6 [a]	2.5±0.6 [b]	2.6±0.6	2.7±0.5
Dobutamine wall motion score	3±0.8 [c]	2.3±0.6 [d]	1.9±0.8	2±0.8
Nitrate-induced activity increase (% of baseline value)	4.8±13.4%	3.3±13%	2.2±8%	14.9±20.4% [e]

[a]) $p<0.003$ *vs* all other groups; [b]) $p<0.01$ *vs* hibernating; [c]) $p<0.00001$ *vs* all other groups; [d]) $p<0.03$ *vs* stunned and hibernating; [e]) $p<0.0001$ *vs* all other groups.

asynergic segments, 126 (49 hypokinetic, 74 akinetic, and 3 dyskinetic before revascularization) showed significant functional recovery in the follow-up control, whereas 178 (70 hypokinetic, 87 akinetic, and 21 dyskinetic) showed unchanged regional dysfunction.

Classification of the dysfunctional myocardium

Taking into account the previously stated definitions of the different types of dysfunctional myocardium, 73 segments (9 hypokinetic, 47 akinetic, and 17 dyskinetic) had unchanged dysfunction and postrevascularization Sestamibi activity under the appropriate viability threshold and were then classified as transmural scars. There were 105 segments (61 hypokinetic, 40 akinetic, and 4 dyskinetic) with persistent dysfunction, but with postrevascularization Sestamibi activity over the viability threshold, which were classified as nontransmural scars. Of the segments with functional recovery after revascularization, there were 72 (33 baseline hypokinetic, 37 akinetic, and 2 dyskinetic) that did not show a significant increase in Sestamibi activity, and were accordingly classified as stunned myocardium. Finally, 54 segments (16 baseline hypokinetic, 37 akinetic, and 1 dyskinetic) showed both functional recovery and significant Sestamibi activity increase after revascularization and were defined hibernating myocardium.

Relationship between prerevascularization findings and segment classification

Table I depicts the prerevascularization characteristics of the 4 segment groups. The mean baseline wall motion score before revascularization was significantly higher in transmural scars than in the other groups. Nontransmural scars showed a significantly lower mean wall motion score than hibernating segments. When the proportion of segments pertaining to each of the 3 different classes of baseline dysfunction (hypokinesis, akinesis and dyskinesis) was examined, a significant difference was registered between transmural scars and the other groups because of a clearly higher proportion of dyskinetic segments in the former group. On the other hand, hibernating myocardium was significantly different from nontransmural scars and stunned myocardium due to a larger incidence of akinetic segments. Finally, the difference between nontransmural scars and stunned segments was just borderline (Figure 1).

In dobutamine gated SPECT, a very significant decrease in the mean wall motion score was registered both in the stunned (from 2.6±0.6 to 1.9±0.8, $p<0.00001$) and in the hibernating segments (from 2.7±0.5 to 2±0.8, $p<0.00001$). The difference in the nontransmural scars was less marked (from 2.5±0.6 to 2.3±0.6, $p<0.002$), and the transmural scars showed no improvement in the mean wall motion score compared with baseline. The mean dobutamine wall motion score in the 2 groups of scars was significantly higher than in the other 2 (Table I). The percentage of segments with contractile reserve was significantly higher ($p<0.00001$) in the stunned (67%) and in the hibernating (65%) segments compared with the transmural (15%) and nontransmural (10%) scars. Using as reference the postrevascularization outcome, contractile reserve detection during low dose dobutamine gated SPECT was 78% accurate in predicting functional recovery in asynergic segments.

As regards baseline and nitrate Sestamibi activity before revascularization, Figure 2 shows that a signif-

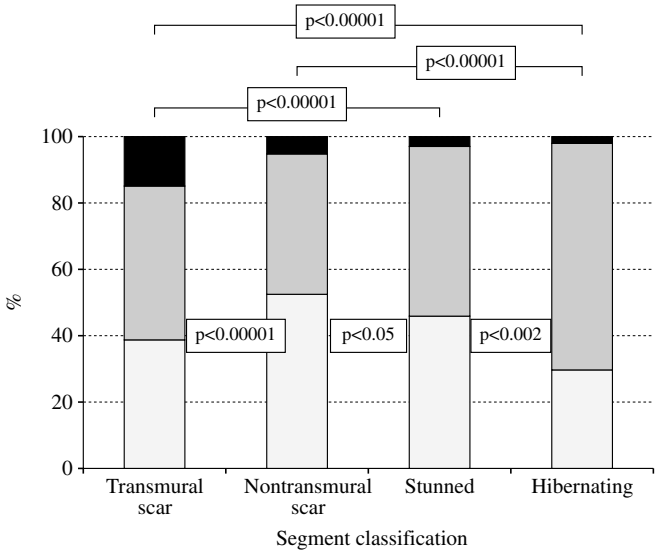

Figure 1.—Bar graph showing the distribution of baseline dysfunction within the 4 groups of segments identified on the basis of postrevascularization functional and perfusion changes (see text).

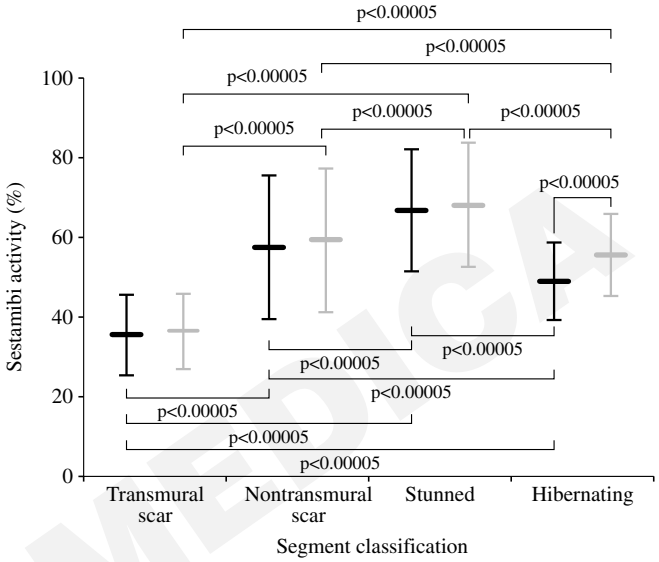

Figure 2.—Baseline resting (solid lines) and nitrate (dotted lines) Sestamibi activity in the groups of dysfunctional segments identified on the basis of postrevascularization functional and perfusion changes.

TABLE II.—*Agreement between the reference classification based on postrevascularization functional and perfusion changes and the classification based on baseline-nitrate gated SPECT with dobutamine test.*

		Scar		Viable	
		Transmural	Nontransmural	Stunned	Hibernating
No inotropic reserve	Sestamibi activity <50%	92	24	5	12
	Sestamibi activity ≥50%	7	32	19	7
Inotropic reserve	Nitrate-induced increase ≤10%	12	1	37	0
	Nitrate-induced increase >10%	5	5	11	35

icant difference was observed for both values among the 4 groups of dysfunctional segments. However, a significant difference between baseline and nitrate Sestamibi activity was registered only within the group of hibernating segments: in this particular group, the administration of nitrates caused an increase in Sestamibi activity from 48±9% to 55±10% (p<0.00005). Accordingly, the nitrate-induced activity change within this group was significantly larger than in the remaining 3 groups (Table I). Furthermore, there was a significantly higher percentage (52%) of segments in the hibernating group with clear (>10% of baseline value) nitrate-induced increase in activity, (*vs* 19%, 19%, and 10%, respectively in transmural scars, nontransmural scars and stunned segments, p<0.0001).

Therefore, according to the results of baseline-nitrate Sestamibi gated SPECT with dobutamine test, the dysfunctional segments could be classified in segments with (=viable) and without (=nonviable) contractile reserve. The latter group could be further divided in transmural *versus* nontransmural scars on the basis of nitrate Sestamibi activity using the 50% threshold.[16] The viable segments could be divided in stunned or hibernating according to nitrate-induced activity increase ≤10% or >10% of baseline.[17] When this segment classification was compared with the reference classification based on postrevascularization outcome a fair-to-good agreement was found with a 0.50 κ value (Table II).

Discussion

This study represents the attempt to differentiate the various kinds of myocardium that can be found

within dysfunctional segments taking into account their response to revascularization. By definition, viable and nonviable dysfunctional myocardium can be distinguished on the basis of the presence or absence of functional recovery after revascularization.[1] According to the detection of myocardial blood flow within or below the normal range, dysfunctional segments in ischemic cardiomyopathy have been deemed to be chronically stunned or hypoperfused hibernating myocardium.[8, 9, 11] Finally, the recognition of dysfunctional segments with preserved cellular integrity but without contractile reserve has been related to the presence of nontransmural scarring.[10] The comprehensive characterization of all these different sorts of dysfunctional tissue would require the concomitant use of various imaging modalities or the execution of repeated examinations in time.[10, 13] In the present study it was possible to differentiate the viable asynergic segments from the scarred ones by demonstrating functional recovery in the gated SPECT repeated after revascularization. The level of tracer uptake then estimated the degree of transmurality in scarred segments. Similarly, it was possible to differentiate chronically stunned from hibernating tissue by considering the level of tracer uptake before and after revascularization. By combining all those pieces of information it was possible to approximate the results of other studies.[10, 12, 13]

Every characterization based on postrevascularization studies, however, has a limited relevance for the clinical management of patients with ischemic cardiomyopathy. Thus, a further step of this study was to evaluate the possibility of an approximate assessment based on the use of a single and widely used technique that can be easily applied in the working up of these patients before revascularization. On the basis of previous experiences of our and other groups,[10, 16] we tried to combine contractile reserve data with perfusion quantification and, in the latter instance, to take advantage of the contribution of nitrate-enhanced imaging. According to our results, a relationship can be found between the different groups of dysfunctional segments defined on the basis of postrevascularization outcome and the prerevascularization pattern of baseline-nitrate and of resting and low dose dobutamine gated SPECT. First of all, the presence or absence of contractile reserve during dobutamine gated SPECT quite accurately foresees the presence or absence of functional recovery after revascularization. Then, the level of tracer uptake in the prerevascularization study seems able to differentiate within the segments without contractile reserve those with transmural from those with nontransmural scar. The importance of this difference is substantiated by the distribution of baseline asynergy between the two groups of segments. The higher proportion of baseline hypokinetic segments within the group classified as nontransmural scar is consistent with the well known observation that even a limited damage of the myocardial wall produces a decrease in regional function.[22] Furthermore, in agreement with our results, Bax *et al.* demonstrated that segments with mild reduction in Tl-201 activity with a matching decrease in FDG uptake do not show postrevascularization functional recovery, although their Tl-201 uptake could be considered over the viability threshold.[23] The authors argued that perfusion-FDG matches indicate some degree of scarring, the more transmural the more severe the decrease in Tl-201 and FDG uptake is.[23] The clinical importance of this classification before intervention is that LV function will not improve in the presence of scar, but if this is nontrasmural, remodeling should not be expected.

The issue of myocardial blood flow in the segments with reversible dysfunction has been extensively debated.[8, 9, 11] The characterization of those with chronic stunning versus those with chronic hypoperfusion (hibernating) is of limited interest from a practical point of view, since in both cases revascularization is needed to obtain functional recovery. Nevertheless, it is certainly attractive the possibility to identify these 2 kinds of dysfunctional segments without the need of complex measurements of blood flows. According to our data, it seems that the response of dysfunctional segments with reduced perfusion tracer uptake to the acute administration of nitrate predicts the segments with postrevascularization increase in tracer uptake. These are the segments that, albeit approximately, fulfill the definition of hibernating myocardium (impaired function together with reduced blood flow). The favorable effects of nitrates on coronary circulation are well known, and include the direct dilatation of stenosis in pericardial vessels and the improvement in collateral flow.[24, 25] Moreover, a preferential increase in $^{13}NH_3$ retention in ischemic *versus* non-ischemic segments after nitroglycerin administration has been demonstrated using positron emission tomography.[26] Thus, it is reasonable that using nitrates perfusion tracer uptake could selectively increase as well in chronically hypoperfused regions. Conversely, the asynergic segments

with already normal or near normal tracer uptake before revascularization and without significant increase in tracer uptake thereafter (and during nitrate infusion) are consistent with the definition of chronic stunning. In patients with acute myocardial infarction submitted to thrombolysis or primary coronary angioplasty, various studies had already demonstrated that dysfunctional segments with preserved or only mildly reduced Sestamibi uptake showed spontaneous functional recovery and could therefore be classified as stunned.[27, 28] Accordingly, the finding of fairly preserved tracer activity in a proportion of dysfunctional segments in patients with ischemic cardiomyopathy was not unexpected.

Several studies have already examined the possible advantage for the issue of myocardial viability of performing perfusion imaging with the gated SPECT technique. It has been demonstrated that baseline wall motion assessment just marginally improves the diagnostic accuracy of perfusion scintigraphy in terms of viability detection.[29-31] Probably the most important contribution of baseline wall motion assessment is to allow the choice of the most appropriate viability threshold for perfusion tracer quantification, with good results in combination with nitrate-enhanced imaging.[32] On the other hand, the evaluation of the inotropic response during dobutamine infusion, most frequently performed with 2-D echocardiography, is a very effective approach to viability detection.[33] The combination of dobutamine test with gated SPECT was already demonstrated to be a very reliable approach to the issue of viability detection.[16, 34] The more complex protocol examined in the present study, with the inclusion of baseline resting gated SPECT and the additional evaluation of the nitrate-induced changes in Sestamibi activity, does not significantly modify the already good accuracy of dobutamine gated SPECT, but allows the further classification of viable segments in probably stunned and probably hibernating. The clinical implications of this classification of dysfunctional segments are not yet defined. The time course of functional recovery is shorter in chronic stunning than in hibernating myocardium.[13] This could be relevant for postoperative clinical improvement and for planning follow-up controls after revascularization procedures. Theoretically, prognostic stratification could be improved if the various sorts of myocardial abnormality were differentiated instead of simply distinguishing viable from nonviable tissue.

Conclusions

The results of the present study suggest that the various kinds of dysfunctional myocardium that can be differentiated according to of their evolution after revascularization can be identified as well on the basis of contractile response to dobutamine and nitrate-induced activity changes. The feasibility of this classification using a single imaging modality could expand its usage. From the point of view of methodology, the results of the present study support the value of perfusion gated SPECT as a potential 1-stop-shop for the issue of myocardial viability detection and characterization in patients with ischemic cardiomyopathy.

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