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Functional evaluation of myocardial viability by ^{99m}Tc tetrofosmin gated SPECT —A quantitative comparison with ^{18}F fluorodeoxyglucose positron emission CT (^{18}F FDG PET)—

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To validate functional analysis of gated SPECT in detecting myocardial viability, seventeen patients (male 15, female 2, mean age 58) with angiographically proven chronic ischemic heart disease (RCA 6, LAD 10, LCX 1) and eight normal volunteers (all male) were studied. All patients underwent ^{18}F FDG PET and ^{99m}Tc tetrofosmin (TF) gated SPECT within a week. After being displayed in a polar map, myocardial perfusion was regionally determined by the mean count in 9 segments at end diastole (ED) and end systole (ES) in gated SPECT. Systolic function was determined by the count increase ratio from ED to ES (WTI: ES − ED/ED). Glucose metabolism was assessed by ^{18}F FDG PET in the segments correspondent to those defined for SPECT. TF %uptake of < 60% was defined as hypoperfusion, and FDG %uptake of < 50% was defined as reduced glucose metabolism. Results: The myocardial segments were classified into 3 categories: "normal" perfusion (n = 85), "mismatch" (reduced perfusion with reserved FDG uptake, n = 25) and "matched" reduced perfusion and metabolic reduction (n = 26). Mean WTI in "mismatch" segment was 0.38 ± 0.21, and was significantly greater than that in "matched reduced" segments, 0.15 ± 0.20 ($p < 0.001$). It was also greater than that in "normal" segments, 0.27 ± 0.16. Regression analysis showed that association between WTI and FDG %uptake was significant ($r = 0.57$, $p < 0.0005$) for the ischemic segments ("mismatch" + "matched", n = 51), but the association was weak for the entire segments although it was statistically significant ($r = 0.26$, $p = 0.02$, n = 136). Conclusion: For the segments determined as infarct by perfusion image, systolic functional analysis by gated SPECT is helpful in differentiation of a viable myocardial region or artifact from a scar. Nevertheless, further clinical and technical assessment is required for ECG gating to eliminate overestimation of viability and to warrant clinical use.

Key words: myocardial viability, gated SPECT, positron emission tomography (PET), ^{99m}Tc tetrofosmin, ^{18}F FDG (fluorodeoxyglucose)

INTRODUCTION

ALTHOUGH many clinical data indicate that imaging of myocardial perfusion provides clinically relevant information about the status of myocardial viability, underestimation of myocardial viability by ^{99m}Tc SPECT imaging was observed.[1,2] Systolic functional analysis is another important marker of myocardial viability. Myocardial segments with relatively well preserved wall thickening are expected to have viable tissue even if myocardial imaging indicates hypoperfusion, and myocardial segments with irreversible perfusion defect and with no wall thickening would be regarded as non-reversible.

Electrocardiography (ECG)-gated acquisition of single photon emission computed tomography (gated SPECT) offers the potential for systolic function in addition to

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perfusion, since thickening parallels change in the intensity of counts throughout the cardiac cycle. This study is designed to compare wall thickening seen in gated SPECT in "mismatch" and "matched reduced" ischemic segments in terms of perfusion and metabolism, and to validate the usefulness of gated SPECT in detecting myocardial viability.

MATERIALS AND METHODS

Study design and study patients

The study population consisted of 8 normal volunteers (all male, mean age 42 ± 10 years old) and 17 consecutive patients (male 15, female 2, mean age 58 ± 8 years old) admitted to our institute because of chronic ischemic heart disease. All patients had a previous angiographically proven myocardial infarction prior to acquisition of the nuclear studies (Median interval between the onset of myocardial infarction and acquisition of nuclear studies was 3 months, Table 1). The subjects who had myocardial infarction within a month or those who had diabetes mellitus were excluded from this study. All patients underwent ^{18}F FDG PET with 75 g glucose loading and ^{99m}Tc tetrofosmin gated SPECT within 10 days.

Table 1 Summary of patient data

Patient No.	Sex	Age	Coronary lesion	Segments of infarction	Months after infarction
1	M	62	LAD	AS	32
2	M	65	RCA	IP	2
3	M	60	LAD	AS	2
4	M	60	LAD	AS	103
5	M	61	RCA	IP	4
6	M	49	RCA	IP	2
7	M	42	LAD, RCA	AS	2
8	M	65	LAD	AS	2
9	F	82	LAD	AS	2
10	M	62	LCX	PL	1
11	M	71	LAD	AS	27
12	M	56	RCA	IP	21
13	F	68	LAD	AS	3
14	M	45	LAD	AS	4
15	M	86	RCA	IP	1
16	M	78	LAD	AS	78
17	M	64	RCA, LCX	PL	76

Median: 3

AS: Antero-septal, IP: Infero-posterior, PL: Postero-lateral
LAD: Left anterior descending artery, LCX: Left circumflex artery, RCA: Right coronary artery

Gated SPECT

Twenty mCi (740 MBq) of ^{99m}Tc tetrofosmin was intravenously administered at rest in a fasting period, and subjects were encouraged to drink 250 m*l* of milk shortly thereafter in order to accelerate the hepatobiliary clearance. Forty minutes after the injection, 16 frames per cardiac cycle were acquired on a three headed gamma camera and a computer system (Prism 3000XP, Odyssey super computer, Picker co., UTA, USA). Using a 120° × 3 imaging arc, high resolution parallel-hole collimator, SPECT imaging was acquired in a 64 × 64 matrix size on 72 steps with 70 cardiac cycles per step, for a total imaging time of about 30 minutes. Gated frames were processed as 5.3 mm tomographic slices using a Butterworth filter with a 0.2 cut-off frequency and power of 8.0. The first frame was defined as the end diastolic phase. The end systolic phase was determined for each subject as a frame with the peak count on the count/time curve of mid slice of short axis imaging (Figure 1). For all patients, a polar map display was figured for the end diastolic phase and for the end systolic phase by using short axis slices after correcting cardiac rotation. Thereafter, wall thickening was quantitatively evaluated by the percent increase in counts from diastole to systole; a ratio defined as the wall thickening index (WTI; ES – ED/ED) on all pixels, and a polar map was also figured for WTI (Figure 2). Each polar map was divided into 9 segments: anterior, septal, inferior, lateral portions (they were further divided into basal and middle portions), and the apex. Regional myocardial perfusion was quantitatively assessed by %uptake of these segments on the polar map of the end diastolic phase. Regional wall thickening was assessed by the mean WTI of each segment on the polar map.

^{18}F FDG PET

Transmission scans were obtained in all patients with ^{68}Ge ring source of to correct for photon attenuation followed by administration of 370 MBq (10 mCi) ^{18}F fluorodeoxyglucose (^{18}F FDG). After a 60 minute distribution phase, ^{18}F FDG PET imaging was performed with a HEADTOME II (Shimadzu, Kyoto, Japan) under 75 g oral glucose loading, producing 6 transaxial slices, each 8 mm thick.[3] Nine myocardial segments were also defined on the six transaxial slices of PET images corresponding to the SPECT images. Since HEADTOME II could produce only transaxial slices, the middle portion of inferior segment was excluded from the analysis.

Statistical analysis

Analysis of variance (ANOVA) was used for comparing mean values, and Schéffe criteria was applied for multiple comparison. A linear regression analysis was used for evaluating the association between continuous variables. A two tailed p-value of less than 0.05 was defined as statistically significant.

RESULTS

Perfusion and systolic function normal subjects

Demographic statistics of regional ^{99m}Tc tetrofosmin %uptake at end diastole and WTI values in normal volunteers are shown in Table 2. Among the normal subjects,

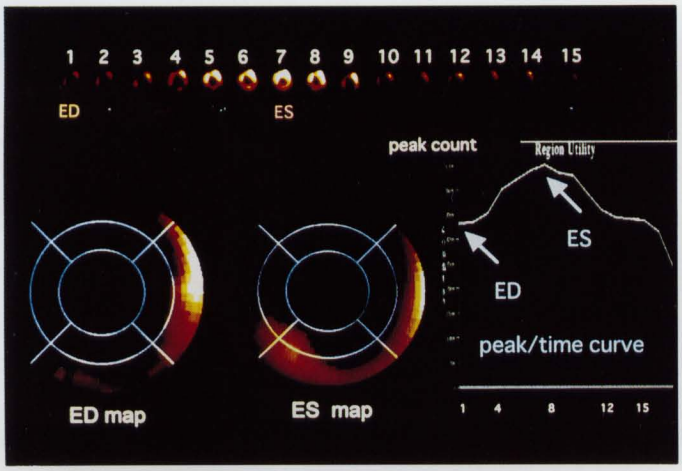


Fig. 1 Maximum count curve for cardiac cycle intervals of mid-slice of short axis imaging. End systole phase was determined by the point with the peak counts (arrow).

Fig. 2 Polar map display of end diastolic phase (ED map), end systolic phase (ES map) and WTI ((ES – ED)/ ED). Each polar map was divided into 9 segments; middle and basal of anterior, septal, inferior, lateral and apex. Regional mean count and WTI were displayed in the table.

Fig. 3 Transverse slices of ^{18}F FDG PET imaging. Nine myocardial segments were also defined in correspondent to SPECT imaging. Regional mean count density in ^{18}F FDG PET imaging was obtained to calculate FDG regional %uptake for each segment.

▲
Fig. 1

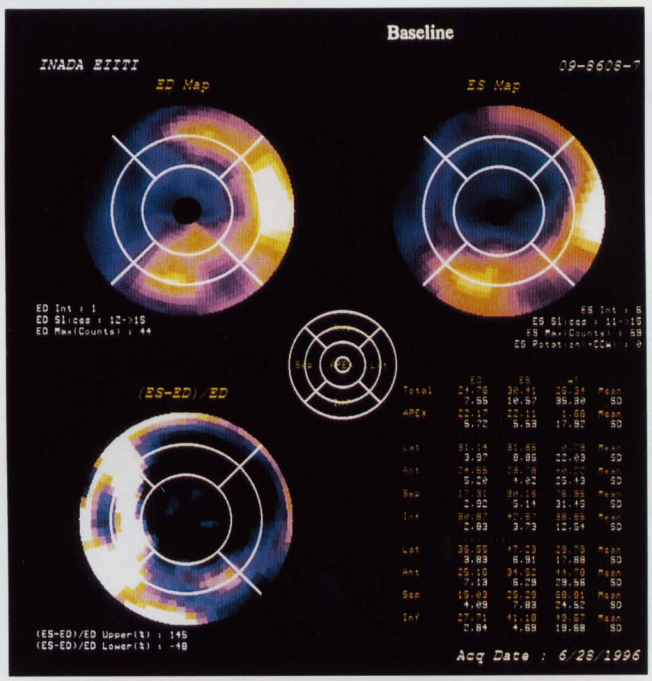


Fig. 2

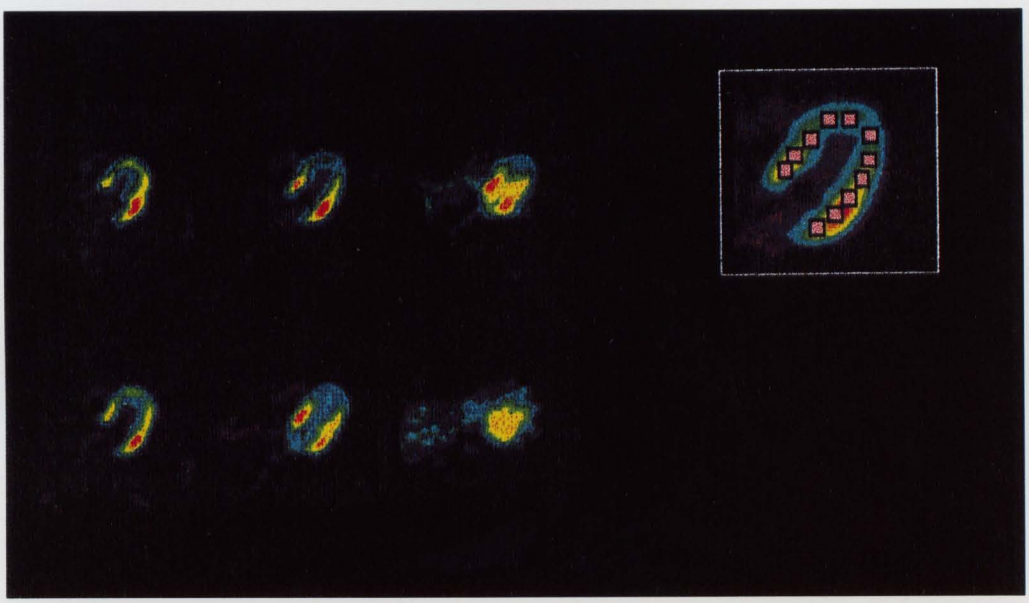


Fig. 3

Table 2 Regional mean and total mean of WTI values in normal volunteers

Myocardial segment		%uptake		WTI	
		Mean value	Minimal value	Mean value	Minimal value
Anterior	Middle	0.8	0.73	0.49	0.33
	Basal	0.75	0.71	0.48	0.33
Septal	Middle	0.74	0.68	0.45	0.30
	Basal	0.62	0.55	0.47	0.32
Inferior	Middle	0.65	0.54	0.56	0.39
	Basal	0.65	0.58	0.48	0.33
Lateral	Middle	0.83	0.76	0.49	0.37
	Basal	0.80	0.72	0.47	0.37
Apex		0.74	0.63	0.55	0.45

WTI: Wall thickening index

mean regional %uptake ranged from 0.62 to 0.83. Regional mean WTI values ranged from 0.47 to 0.56, and no single WTI value among them was no less than 0.30 in all segments.

Regional classification of myocardial viability

Myocardial segments were regionally classified by perfusion and glucose metabolism. Myocardial perfusion was evaluated by mean %uptake of ^{99m}Tc tetrofosmin on the polar map in the end diastolic phase for each segment. The segment with mean %uptake of < 60% was defined as hypoperfusion based on the results for normal subjects. Glucose metabolism was evaluated by mean %uptake of FDG PET for each correspondent segment. A segment with a mean FDG uptake of < 50% was defined as reduced glucose metabolism. Of the 136 segments, 85 (63%) segments were determined as normal perfusion. The remaining 51 (37%) segments demonstrated hypoperfusion. Of these, 25 (18%) segments demonstrated preserved (≥ 50%) ^{18}F FDG PET uptake and were classified as "mismatch." Twenty six (19%) segments demonstrated abnormal perfusion and abnormal metabolism, and were classified as "matched reduced" (Figure 4).

Wall thickening index (WTI)

Figure 5 shows the regional mean WTI value in the segments with "mismatch" and "matched reduced." The mean WTI was 0.38 ± 0.21 in the segment with "mismatch" (i.e., preserved FDG uptake and reduced tetrofosmin uptake), and was significantly greater than mean WTI in the "matched reduced" segment, 0.15 ± 0.20 ($p < 0.001$). If the regional WTI was dichotomously defined as reduced (< 0.30) and normal (≥ 0.30) according to the data for normal subjects. Seventy percent of the "mismatch" segments had WTI above the threshold value. In contrast, only 30% had normal WTI value in "matched reduced" segments ($p < 0.01$).

Figure 6-b shows the association between WTI and FDG %uptake in the segments with hypoperfusion. WTI

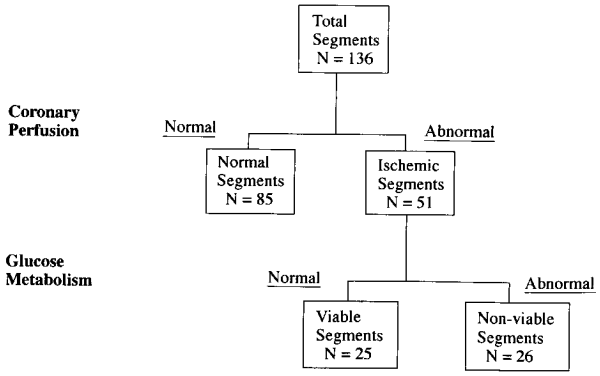


Fig. 4 Normograms of classification of regional viability of myocardium by perfusion (^{99m}Tc tetrofosmin) and metabolism (^{18}F FDG PET).

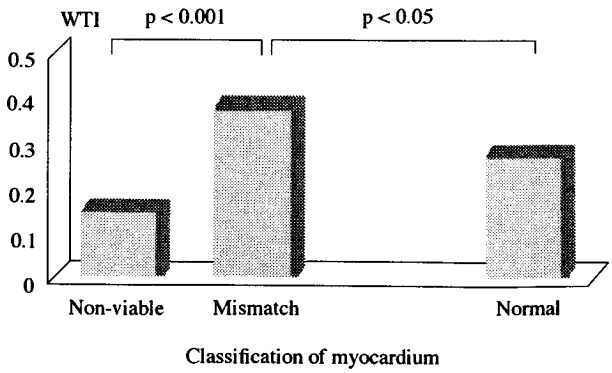
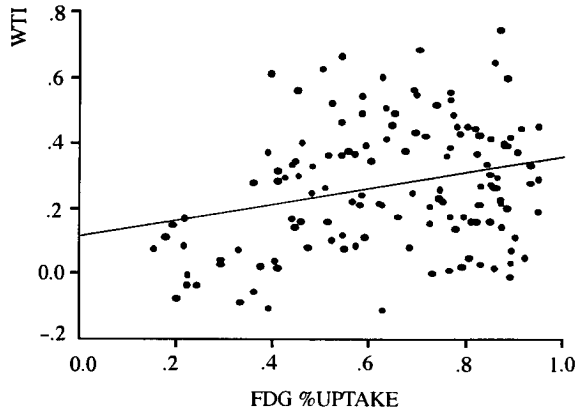


Fig. 5 WTI value in non-viable, mismatch (by FDG and Tetrofosmin) and normal segments. The mean WTI was 0.38 ± 0.21 in the mismatch segment, and was significantly greater than mean WTI in the non-viable segment, 0.15 ± 0.20 ($p < 0.001$). Mean WTI in the normal segment was 0.27 ± 0.16 and was also smaller than that in ischemic segment.

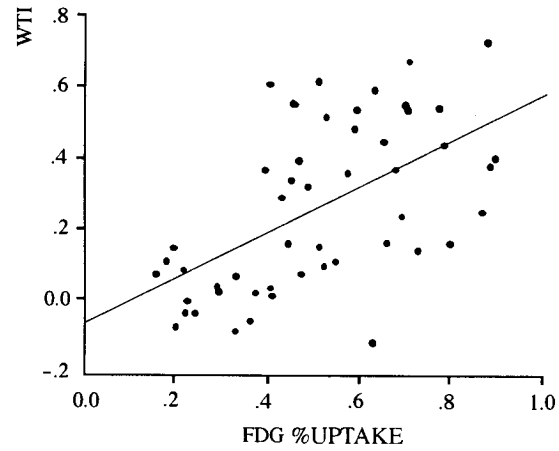
had a strong positive linear correlation with %uptake of FDG (correlation coefficient (r) = 0.57, $p < 0.0005$). Their association is also evaluated for entire myocardial segments in Figure 6-a. Although their correlation was statistically significant ($r = 0.26$, $p = 0.02$), they did not seem to have a simple linear correlation.

Sub-analysis was performed regarding the duration after the onset of myocardial infarction and the location of infarction. Percent uptake of ^{99m}Tc tetrofosmin in the segments with resent MI (1 month after to 3 months) was 0.49 ± 0.1, and was similar to those in the segments with old MI (4 months and later), 0.45 ± 0.1, but, FDG uptake was significantly greater for the segment with resent MI (0.61 ± 0.1 vs. 0.43 ± 0.2, $p < 0.005$). WTI was also greater in the segment with resent MI (0.32 ± 0.1 vs. 0.22 ± 0.2), although short of statistically significant ($p = 0.1$). As for segments with perfusion and glucose metabolism mismatch, 2 were located in the apex, 6 in the inferior, and 17 in the septal segment.



r = 0.26, p = 0.02

a) For entire segments (n = 136)



r = 0.57, p < 0.0005

b) For segments with hypoperfusion (n = 51)

Fig. 6 Association betwenn WTI and FDG uptake. a) For entire segments: b) Only for segments with hypoperfusion (^{99m}Tc-TF %uptake < 60%). WTI had strong positive linear correlation with %uptake of FDG for the segments with hypoperfusion. However, their association was weak and did not seem to have simple linear correlation for entire segments.

DISCUSSION

Accurate detection of myocardial viability is important for clinical decision making, since these segments are expected to be functionally reversible after revasuculari-zation, and patients with such segments have a high risk of cardiac events.

The radionuclide technique is frequently applied for the detection of myocardial viability and perfusion SPECT imaging using ^{201}Tl or ^{99m}Tc agents. If the segment with asynergy detected by echocardiography or contrast left ventriculography has relatively preserved perfusion, it can be regarded as viable, but, underestimation is not rare in the viability assessment by perfusion imaging, especially when artifacts of the SPECT agents such as attenuation in the inferior or septal segments are involved. Currently, metabolic activity by ^{18}F FDG PET has been regarded as a noninvasive gold standard for this assessment. A pattern of enhanced FDG uptake in the segments with reduced perfusion (termed the FDG blood flow "mismatch") indicates ischemic or hibernating myocardium that has shifted its metabolic substrate toward glucose utilization. Several studies have shown that these mismatch segments will manifest improved function after revascularization,[4–7] and have a high mortality rate during medical therapy.[7]

Myocardial wall thickening is also one of the important marker of the existence of vital tissue. This phenomenon may conceivably exist even if apparent inward movement of the myocardial wall is absent. In gated ^{99m}Tc tetrofosmin SPECT, regional wall thickening is sensitively measured by the increase in the count from diastole to systole due to a partial volume effect of the accumulated radioisotope. Regional myocardial perfusion with a less functional effect is also evaluated in gated SPECT at diastole. In this study, myocardial segments with hypoperfusion (TF %uptake < 60%) was classified in terms of viability by incorporating FDG uptake, then wall thickening in them was quantitatively compared by WTI, i.e., percent increase in counts from diastole to systole. The result demonstrated that WTI in the segment which was ischemic but viable was significantly greater than that in the non-viable segment, and good linear correlation was observed between WTI and FDG %uptake among hypoperfused segments. These results suggested that WTI could distinguish the viable segment from the scar.

Nevertheless, WTI demonstrated only weak correlation with FDG %uptake when the segments with normal perfusion were added to the regression analysis, and the expected slope began to lean as FDG uptake increasing. This phenomenon may partly be explained by the influence of limited spatial resolutions of ^{99m}Tc, in which the relationship between the measured maximum count in a region and the characteristic dimension of the object has a relatively steep slope of the curve over the range of dimensions.[8–10] Figure 5 also showed that WTI in the segment which was ischemic but viable was even greater than that in the normal segments. Possible reasons for lower WTI values in the normal segments are; (1) The WTI values in the segments with infarction might be exaggerated because of the small denominator, i.e., low uptake of ^{99m}Tc tetrofosmin at end diastole. (2) Significant movement in normal segment can lead to image degradation. Although they are serious limitation in precise evaluation of wall thickening, they may facilitate the distinction of the viable region from the scar.

In the sub-analysis, perfusion metabolism mismatch and greater WTI was more frequently observed in the segments with recent myocardial infarction, in which stunned myocardium is more likely to be expected. Many

segments with perfusion metabolism mismatch was located in the inferior and septal segments. This phenomenon may partly be explained by the attenuation artifacts of SPECT agents in these segments. It was previously reported that the count density change from diastole to systole can supplement the attenuation artifacts in the diagnosis of SPECT studies.[11]

Besides the wall thickening analysis, wall motion can also be evaluated by gated SPECT. Global functional analyses such as ejection fraction and regional motion has been assessed by edge detection of SPECT imaging through diastole to systole, and they have reportedly a good correlation with contrast ventriculography[12] and blood pool studies.[13,14] Nevertheless, quantitative wall motional studies have currently been limited to global function, and only visual analysis was performed for regional evaluation.[15] Considering that motional analysis is readily available by means of contrast ventriculography, echocardiography or gated pool study for candidates for revascularization, assessment of wall thickening by gated SPECT can be another sensitive option for viability assessment in a region with severe functional damage.

Study limitation

Myocardial viability is determined only by nuclear study, and it does not promise improvement of ventricular function after coronary revascularization. Among the subjects studied, 4 patients have undergone coronary bypass operation. Of those, all asynergic segments with WTI value of > 30% showed signs of wall motion recovery in contrast ventriculography after angioplasty.

For simplicity of analysis and contrast with visual assessment in a clinical situation, definition of hypoperfusion with %uptake of < 60% was applied for all segments. Although middle of inferior segment was excluded from analysis, this may compromise the results.

Since nonviable myocardium is encompassed by the minimum resolvable volume, normally contracting myocardium will contribute to an increase in the intensity of the scarred segment during systole, and this will overestimate the viability of the scar by the rotation and translation of the heart during the cardiac cycle. Further study involving gated SPECT reconstruction algorithms which compensate for cardiac motion is needed.

In conclusion, for those segments determined as infarct by perfusion images, systolic functional analysis with gated SPECT is helpful in the differentiation of a viable myocardial region or artifact from scar, but, further clinical and technical assessment is required to eliminate overestimation of viability and to deserve clinical use.

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