Assessment of myocardial viability using F-18 fluorodeoxyglucose/Tc-99m sestamibi dual-isotope simultaneous acquisition SPECT: Comparison with Tl-201 stress-reinjection SPECT

Yen-Wen Wu, MD,^a Por-Jau Huang, MD,^b Chii-Ming Lee, MD, PhD,^b
Yi-Lwun Ho, MD, PhD,^b Lung-Chun Lin, MD,^b Tzung-Dau Wang, MD, PhD,^b
Shoei-Shen Wang, MD, PhD,^c Tony Hsiu-Hsi Chen, PhD,^d and Ruoh-Fang Yen, MD^{a,d}

Background. This study compared technetium 99m sestamibi/fluorine 18 fluorodeoxyglucose dual-isotope simultaneous acquisition (DISA) with stress-reinjection thallium 201 single photon emission computed tomography (SPECT) with regard to their ability to detect myocardial viability.

Methods and Results. The study cohort consisted of 42 angiographically significant coronary artery disease patients with symptomatic congestive heart failure or regional wall motion abnormalities. In total, 398 dysfunctional segments in 40 patients were analyzed (2 patients were excluded because of poor-quality F-18 fluorodeoxyglucose images). Of the segments, 217 were diagnosed as viable and 144 as nonviable by both DISA and Tl-201, 33 were viable by DISA but nonviable by Tl-201, and 4 were viable by Tl-201 but nonviable by DISA. Most discrepancies were in the inferior wall. Of the 40 patients, 16 underwent revascularization. From the follow-up results for the 105 dysfunctional segments in these 16 patients, DISA viability appears to be a significant predicting factor ($P = .014$) for functional recovery after revascularization statistically whereas Tl-201 viability does not ($P = .09$).

Conclusion. Our study suggests that DISA viability provides more accurate prediction of postrevascularization functional recovery than Tl-201 viability. Given the small number of patients who underwent revascularization, the superiority of DISA over Tl-201 in detecting myocardial viability may be firmly established by further study on a large scale for patients with profound left ventricular dysfunction. (J Nucl Cardiol 2005;12:451-9.)

Key Words: Myocardial viability • dual-isotope simultaneous acquisition • single photon emission computed tomography • fluorine 18 fluorodeoxyglucose • technetium 99m sestamibi

It has been well documented that the numbers of patients with chronic heart failure due to coronary artery disease have increased rapidly¹ and that patients with myocardial viability and impaired left ventricular (LV) function can benefit from coronary revascularization.^{2,3}

Currently, among the various techniques that have been introduced to assess myocardial viability,^{4,5} positron emission tomography (PET) by use of fluorine 18 fluorodeoxyglucose (FDG) as a metabolic tracer and nitrogen 13 ammonia as a perfusion tracer has emerged as the gold standard for such assessment.⁶⁻⁸ However, the high cost of the PET equipment and the requirement of an onsite cyclotron for production of short-life PET perfusion tracers have limited the scope of its clinical applications.⁹

Recently, F-18 FDG cardiac images obtained with a single photon emission computed tomography (SPECT) camera and 511-keV ultrahigh-energy collimators have been shown to provide clinically relevant data equivalent to those obtained with PET.¹⁰⁻¹³ Delbeke and colleagues^{14,15} have demonstrated the feasibility in analyzing myocardial perfusion/metabolism simultaneously by use of technetium 99m sestamibi (MIBI)/F-18 FDG with a dual-isotope simultaneous acquisition (DISA) protocol.

From Departments of Nuclear Medicine,^a Internal Medicine,^b and Surgery,^c National Taiwan University Hospital and National Taiwan University College of Medicine, and Institute of Preventive Medicine, National Taiwan University College of Public Health,^d Taipei, Taiwan.

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Reprint requests: Ruoh-Fang Yen, MD, Department of Nuclear Medicine, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei, Taiwan; rfyen@ha.mc.ntu.edu.tw.

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The objective of this study was to compare Tc-99m MIBI/F-18 FDG DISA with stress-reinjection thallium 201 SPECT with regard to their ability to effectively detect myocardial viability.

METHODS

Patient Population

We recruited 42 patients with angiographically significant coronary artery disease ($\geq 70\%$ diameter stenosis) (39 men with mean weight of 66.9 ± 6.0 kg and 3 women with mean weight of 50.7 ± 5.1 kg), aged 34 to 85 years, with chronic congestive heart failure (New York Heart Association [NYHA] functional class II or higher) or regional wall motion abnormalities on resting echocardiography. No patient had had recent (< 6 weeks) myocardial infarction, unstable angina pectoris, or concomitant valve disease. Eleven patients had diabetes mellitus. All patients received DISA and stress-reinjection Tl-201 SPECT within 1 week of each other. Written informed consent was obtained from all patients.

Tc-99m MIBI/F-18 FDG DISA SPECT

Nondiabetic patients received 50 g of glucose orally after fasting for at least 4 hours, whereas diabetic patients were administered soluble insulin intravenously according to their respective blood glucose levels.¹⁶ Sixty minutes later, each patient was injected with 6 to 8 mCi F-18 FDG and 20 mCi Tc-99m MIBI. After 60 minutes of uptake phase, each patient underwent DISA¹⁴ performed on a Hawkeye (GE Medical Systems, Milwaukee, Wis) equipped with 5/8-inch-thick sodium iodide (thallium) (NaI(Tl)) crystals and 511-keV ultrahigh-energy high-resolution collimators. The resolution of the system was 8.6 mm at 140 keV and 11.8 mm at 511 keV in full width at half maximum. Two energy windows were set at 140 keV ($\pm 10\%$) of Tc-99m and at 511 keV ($\pm 10\%$) of F-18. Thirty-two projections were acquired over a circular orbit of 180° (45° right anterior oblique to 45° left posterior oblique at 60 seconds per angle). The contribution to the Tc-99m window from downscatter caused by the presence of F-18 was insignificant.¹⁷ Transaxial slices, 2.8 mm in thickness (1 pixel), were reconstructed by ordered-subset expectation maximization from the raw data collected by use of a Butterworth filter. Simultaneous reconstruction of the 140- and 511-keV data sets allowed direct comparison of exactly aligned perfusion and metabolism images.

Stress-Reinjection Tl-201 SPECT

Nineteen patients were studied by use of the symptom-limited modified Bruce exercise protocol¹⁸ with 3 mCi Tl-201 injected at peak exercise. For those who were unable to exercise adequately, we used pharmacologic stress testing^{19,20}; dipyridamole was used in 16 patients, and dobutamine was used in the remaining 7 patients, who had a history of chronic obstructive pulmonary disease.

Stress imaging was started within 5 minutes of the completion of the stress test, and redistribution imaging was acquired 4 hours later. Tl-201 SPECT was performed by use of a dual-head gamma camera (DST-XL; SMV, Buc, France) equipped with 3/8-inch-thick NaI(Tl) crystals and low-energy high-resolution collimators. The resolution of the system was 7.5-mm full width at half maximum at 120 keV. Two energy windows were set at 72 keV ($\pm 10\%$) and at 167 keV ($\pm 10\%$) of Tl-201. Thirty-two projections were acquired from 45° right anterior oblique to 45° left posterior oblique at 30 seconds per angle. Images were reconstructed by use of filtered backprojection with a Butterworth filter (cutoff, 0.5; order, 4) and reoriented to obtain standard short-axis, horizontal long-axis, and vertical long-axis images of the heart.

If the resulting images showed irreversible defects, additional Tl-201 (1 mCi) was injected and a third set of images was obtained 15 minutes after reinjection.

Image Interpretation and Data Analysis

Attenuation correction for both DISA and Tl-201 SPECT was not used in this study. SPECT images were normalized such that peak myocardial activity was 100%. All images were interpreted qualitatively by 2 experienced nuclear medicine physicians who had no previous knowledge of any patient's clinical data. In the event that the 2 interpretations did not agree with one another, the image was reevaluated by the 2 physicians until a consensus was reached. The left ventricle was divided into 17 segments for analysis.²¹

For both DISA and Tl-201 SPECT, tracer activity in each segment was scored as follows: 3, normal (activity $> 70\%$ of peak activity); 2, mildly reduced (51%-70%); 1, moderately reduced (30%-50%); and 0, severely reduced ($< 30\%$). Segments with marked reduction of both F-18 FDG and Tc-99m MIBI (score of 0 or 1) were classified as DISA-nonviable. Segments with marked reduction of Tc-99m MIBI but normal or mildly reduced uptake of F-18 FDG (score of 2 or 3) were classified as DISA-viable.²²⁻²⁴

For Tl-201 SPECT, stress images were compared with redistribution and reinjection images to distinguish

Table 1. Patient profiles (N = 40)

Clinical characteristics	Finding
Age (y) (range)	61.3 ± 13.0 (34–85)
Male gender	37 (92.5%)
Hypertension	16 (40%)
Diabetes mellitus	11 (26.2%)
Hyperlipidemia	10 (25%)
LVEF (%) (range)	37.8 ± 15.5 (14–60)
Prior cardiac events	
Previous revascularization	21 (52.5%)
Previous MI	26 (67.5%)
Q-wave MI	11 (27.5%)

MI, Myocardial infarction.

reversible defects from irreversible defects. A myocardial segment with a severe perfusion defect (score of 0 or 1) was considered nonviable if the defect was irreversible or minimally reversible (TI-201 uptake in the reinjection images still <50%). A defected segment was considered to be viable if it was reversible (TI-201 uptake in the redistribution or reinjection images ≥50%).^{20,25-27}

Echocardiography

All patients had undergone resting 2-dimensional echocardiography to assess myocardial contractile function by use of a Sonos-4500/5500 imaging system (Hewlett-Packard, Palo Alto, Calif) with harmonic imaging. Standard parasternal long- and short-axis slices were obtained, as well as apical long-axis 2- and 4-chamber views, as recommended by the American Society of Echocardiography.^{21,28} In each analysis the left ventricle was divided into 17 segments and each segment was visually scored by 2 experienced observers who were unaware of the patients' angiographic and scintigraphic results. A 5-point scoring system (1, normokinesia; 2, mild hypokinesia; 3, moderate or severe hypokinesia; 4, akinesia; and 5, dyskinesia) was used. LV ejection fraction (EF) was measured by the area-length method. The consensus rate for interobserver agreement with regard to the echocardiographic findings in this study was 94.2%, which is consistent with previously reported results from our center.²⁹

Follow-up Assessment

Of the 42 patients in this study, 16 underwent revascularization after the TI-201 and DISA tests. To assess the functional recovery of dyssynergic segments,

Table 2. Numbers of concordant and discordant segments detected by TI-201 and DISA (n = 398)

	DISA SPECT	
	Viable	Nonviable
TI-201 SPECT		
Viable	217*	4
Nonviable	33	144*

*Concordant segments.

follow-up echocardiographic studies were performed 1 to 2 months after percutaneous transluminal coronary angioplasty (PTCA) or 3 months after coronary artery bypass grafting (CABG).^{3,30} The criteria for functional recovery were met if there was an improvement in resting wall motion score by 1 grade or more or an increase in global LVEF of 5% or greater. Echocardiography was reassessed at least 6 months after revascularization if functional recovery had not been evident from the initial echocardiographic follow-up.

Statistical Analysis

All results are expressed as mean ± SD, with categorical data presented as percentages. Comparison of continuous data between groups was performed by use of the Student *t* test. A χ^2 test was used for categorical variables (with the Fisher exact test in smaller sizes). Logistic regression was used to evaluate the statistical significance of DISA and TI-201 in predicting LV functional recovery. *P* < .05 was considered statistically significant. Statistic data analysis was done with Stata for Windows software (version 8; Stata Press, College Station, Tex).

RESULTS

Clinical Profiles

The study cohort consisted of 42 patients. The mean basal plasma glucose level was 101.0 ± 19.0 mg/dL (range, 72-120 mg/dL) in 31 nondiabetic patients and 222.3 ± 40.4 mg/dL (range, 167-303 mg/dL) in 11 diabetic patients. For diabetic patients, the mean amount of insulin injected was 7.3 ± 3.0 IU and the mean plasma glucose level at the time of F-18 FDG injection was 138.2 ± 28.4 mg/dL (range, 64-168 mg/dL).

All 42 Tc-99m MIBI images obtained in this study were developed with good resolution, but 2 of the 42 F-18 FDG images were not interpretable. These two patients, one of whom had diabetes, had normal glucose

Figure 1. Selected images illustrating discordance between TI-201 and DISA: DISA-viable but TI-201-nonviable images in a 70-year-old man with 3-vessel disease. Mismatched perfusion/metabolism was noted in the inferior and lateral walls on DISA, but fixed perfusion defects were shown in the same areas on stress-reinjection TI-201 SPECT.

levels at the time of F-18 FDG injection (110 and 122 mg/dL). Their subsequent F-18 FDG PET images turned out to have good resolution nevertheless. The clinical profiles of the remaining 40 patients (37 men and 3 women with a mean LVEF of $37.8\% \pm 15.5\%$) are listed in Table 1.

Comparison of TI-201 and DISA SPECT

The results of DISA and TI-201 SPECT analyzed for all 398 dysfunctional segments (wall motion score ≥ 2 on resting echocardiography) in 40 patients are listed in Table 2. DISA defined 62.8% (250/398) as viable, whereas TI-201 defined 55.5% (221/398) as viable. We found that 217 segments were viable by both TI-201 and DISA and 144 were nonviable by either TI-201 or DISA. The resulting concordance rate was 90.7%. The viability information obtained from Tc-99m MIBI and TI-201 was identical. When TI-201 and DISA results were compared on a per-patient basis, 17 patients (42.5%) had completely concordant results, 15 (32.5%) had 1 or 2 discrepant segments, and 8 (20%) had more than 2 discordant segments.

Among the 37 discordant pairs, 33 pairs (89.2%) were detected as viable by DISA but nonviable by TI-201 whereas only 4 pairs (10.8%) were detected as viable by TI-201 but nonviable by DISA. Such discrepancy was found to be statistically significant ($P < .0001$). Representative discordant and concordant images

are illustrated in Figures 1 and 2. The distribution of discordant segments is shown in Table 3.

Postrevascularization Follow-up

Revascularization was performed in 16 patients after TI-201 and DISA testing either by PTCA (11) or by CABG (5). Of these, 13 (76.5%) had previous myocardial infarction. The mean follow-up period after revascularization was 9.5 ± 3.3 months. Among the 105 dysfunctional segments, 62 segments are considered viable because wall motion improvements were detected during follow-up. The viability results for DISA and TI-201 are summarized in Table 4. DISA detected 52 of 62 viable segments accurately, whereas TI-201 detected only 47. The sensitivity and specificity for viability detection by DISA were 83.9% (52/62) and 37.2% (16/43), respectively, whereas those for viability detection by TI-201 were 75.8% (47/62) and 39.5% (17/43), respectively. Statistically, DISA viability appears to be a significant predicting factor for functional recovery after revascularization (odds ratio, 3.08; 95% confidence interval, 1.23-7.70; $P = .014$), whereas TI-201 viability does not (odds ratio, 2.05; 95% confidence interval, 0.88-4.76; $P = .09$).

In 14 patients who had 2 or more viable segments according to either DISA or TI-201, the mean LVEF increased from $38.4\% \pm 14.7\%$ (before revascularization) to $47.0\% \pm 13.0\%$ (after revascularization) ($P <$

Figure 2. Concordant images of TI-201 and DISA.

Table 3. Distribution of discordant segments of TI-201 and DISA SPECT

	TI-201-viable/ DISA- nonviable (n = 4)	DISA-viable/ TI-201- nonviable (n = 33)
Apex	0	3 (9.1%)
Anterior	0	3 (9.1%)
Septum	1 (25%)	11 (33.3%)
Anteroseptal	1	4
Inferoseptal	0	7
Inferior	1 (25%)	14 (42.4%)
Lateral	2 (50%)	2 (6.1%)

.001). The NYHA functional class improved in 10 of 14 patients (71.4%). There were 6 patients with DISA-viable but TI-201-nonviable segments, and their mean EF increased from $37.7\% \pm 18.1\%$ to $45.0\% \pm 18.7\%$ ($P < .001$). On the other hand, the remaining 2 patients with nonviable segments identified by both DISA and TI-201 testing showed no significant improvement in EF, regional wall motion, and NYHA functional class for 1 year after the intervention (Table 5).

DISCUSSION

In this study we have assessed myocardial viability in 40 patients using both DISA and TI-201 stress-reinjection SPECT. We have also followed up 16 of these 40 patients by echocardiography to compare the

Table 4. Viability results of DISA and TI-201 in follow-up of 16 patients who underwent revascularization

Imaging method	Follow-up results	
	Viable	Nonviable
DISA-viable	52	27
DISA-nonviable	10	16
TI-201-viable	47	26
TI-201-nonviable	15	17

ability of DISA versus TI-201 to effectively predict postrevascularization functional recovery.

Limited studies have been published on the comparison between F-18 FDG SPECT and TI-201 SPECT in the evaluation of myocardial viability.^{5,10,13,31} Although both F-18 FDG SPECT and TI-201 SPECT exhibit a high sensitivity for predicting postrevascularization improvement of functional recovery, the specificity of TI-201 is significantly lower compared with that of F-18 FDG SPECT.³² Our results also demonstrate that TI-201 SPECT can underestimate the extent of myocardial viability, particularly in the inferior region. This discrepancy may partly result from the difference in tracer uptake mechanisms. TI-201 myocardial uptake reflects cell membrane integrity,³³ whereas F-18 FDG uptake indicates the overall rates of transmembrane exchange and phosphorylation of glucose.^{34,35} In addition, the inferior

Table 5. Postrevascularization functional changes in 16 patients who underwent revascularization

Patient No.	Angiography	Target vessel	Vascular territory viability	
			Tl-201 SPECT	DISA SPECT
1	LM + 3VD	RCA	+	+
2	LAD, RCA	LAD	+	+
3	LAD, LCX	LAD	–	–
4	3VD	CABG (LAD, OM1, PDA)	+	+
5	3VD s/p CABG SVG→PDA failure	PTCA on SVG→PDA anastomosis	–	+
6	3VD	CABG (LAD, OM1, PDA)	+	+
7	3VD	LAD, LCX	LAD+ LCX–	+ –
8	LCX, RCA	RCA	–	+
9	LM, LAD, RCA	CABG (LAD, D1, PDA)	LAD+ RCA–	+ +
10	LAD	LAD	–	–
11	3VD s/p CABG SVG→LAD 60%, OM, RCA 100%	Re-CABG (LAD, OM, RCA)	LAD+ LCX– RCA–	+ + +
12	3VD	RCA	–	+
13	LAD, RCA	LAD	+	+
14	3VD	CABG (LAD, OM1, PDA)	+	+
15	LCX, OM2, RCA	LCX, OM1	+	+
16	3VD s/p CABG, retrograde flow of SVG, D1, OM1, PLA	LAD	–	+

LM, Left main; VD, vessel disease; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery; D1, first diagonal branch; OM, obtuse marginal branch; PDA, posterior descending artery; PLA, posterior lateral artery; SVG, saphenous venous graft; +, viable; –, nonviable; s/p, status post.

wall is one of the most severely attenuated regions, and greater attenuation of Tl-201 relative to F-18 FDG in the inferior segments may result.

Four segments in four patients were diagnosed as Tl-201–viable but DISA-nonviable. In addition to the aforementioned difference in tracer uptake mechanisms, this result may be attributed to the fact that Tl-201 is more sensitive than F-18 FDG PET in detecting segments containing less than 75% viable myocytes, as suggested by Baumgartner et al³⁶ in a histopathologic correlation study. Because none of these 4 patients had undergone revascularization, the clinical implication and relevance of the test results to these 4 segments remain to be determined.

There is a known pitfall when using DISA in patients with diabetes. Significant numbers of diabetic patients exhibit poor myocardium F-18 FDG uptake after the administration of soluble insulin. The use of the euglycemic hyperinsulinemic clamp has been reported to yield excellent metabolic images, but it can also increase the cost and complexity of DISA signif-

icantly.^{14,15} Recently, F-18 FDG SPECT after oral administration of the nicotinic acid derivative acipimox was shown to be a safe approach and to result in good image quality for patients with diabetes.^{37,38} If such a procedure is applicable to our studies, the preparation of DISA for diabetic patients can be further simplified accordingly.

Although Sandler and colleagues^{14,15} have proposed that good image quality can be obtained from DISA, the F-18 FDG SPECT images obtained for 2 of 42 sample patients in this study were too poor to be interpretable. The subsequent F-18 FDG PET images taken for these 2 patients did exhibit good resolution. Indeed, it has previously been reported by Hasegawa et al³⁹ that images obtained by use of ultrahigh-energy SPECT can exhibit poor resolution compared with those obtained by PET.

In general, the preparation procedures for DISA are more complicated than those for Tl-201 SPECT. Furthermore, F-18 FDG is an expensive reagent and must be provided by a nearby cyclotron because of its

LVEF (%) change	Wall motion	Functional class (NYHA)
No change (41%)	No change	III→II
↑ 6% (49%→55%)	Anterior anteroseptum: improved	II→II
No change (50%)	No change	II→II
↑ 7% (31%→37%)	No change	III→II
↑ 6% (42%→48%)	Inferior: improved	III→II
↑ 5% (47%→52%)	Anterior: improved	II→II
↑ 6% (52%→59%)	No change	II→I
↑ 11% (58%→69%)	Inferior: improved	II→I
No change (35%)	No change	III→III
No change (45%)	No change	II→II
↑ 12% (10%→22%)	Improved in 3-vessel territories	IV→III
↑ 9% (55%→64%)	Inferior: improved	II→II
↑ 6% (49%→55%)	Septum: improved	II→I
↑ 25% (20%→45%)	Improved in 3-vessel territories	IV→II
↑ 20% (22%→42%)	Anterior, lateral: improved	IV→II
↑ 12% (22%→34%)	Septum: improved	III→II

short half-life. Although the equipment for DISA is more costly than that of Tl-201 SPECT, the actual cost incurred from using Tl-201 SPECT may increase because a third acquisition of reinjection images is often needed. On the other hand, DISA requires only a single SPECT acquisition with shorter image acquisition time. We suggest that the cost-effectiveness of DISA in comparison with Tl-201 SPECT needs to be further studied and fully evaluated.^{40,41}

Study Limitations

No attenuation corrections were used for either DISA or Tl-201 SPECT in this study. The difference in attenuation by diaphragm between Tc-99m MIBI and F-18 FDG has been reported to be a potential source of false-positive results in the inferior myocardium in DISA.^{14,15,17} Furthermore, the inferior wall is one of the most severely attenuated regions of Tl-201 and may erroneously yield a false-negative Tl-201 result without attenuation correction. In this study most discrepancies of DISA and Tl-201 were observed in the inferior wall.

No follow-up angiography was performed after

revascularization to access coronary/graft patency for the 16 patients who received PTCA or CABG. Coronary/graft occlusion might have prohibited functional recovery of segments diagnosed as viable by DISA or Tl-201.

Patients with severe LV dysfunction are the most relevant group of patients whose diagnosed viability results may play a crucial role in management decisions. Unfortunately, only a relatively small number of these patients were included in this study. Nevertheless, we believe that our results will be reinforced by future study with a large sample of patients who have severe LV dysfunction.

Conclusion

Our study suggests that DISA viability provides a more accurate prediction of postrevascularization functional recovery than Tl-201 viability. Given the small number of patients who underwent revascularization in this study (16), the superiority of DISA over Tl-201 in detecting myocardial viability may be firmly established by further study on a large scale of patients with profound LV dysfunction.

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