Effect of Diabetes Mellitus on Myocardial ^{18}F-FDG SPECT Using Acipimox for the Assessment of Myocardial Viability

Arend F.L. Schinkel, MD[1]; Jeroen J. Bax, MD[2]; Roelf Valkema, MD[3]; Abdou Elhendy, MD[1]; Ron T. van Domburg, PhD[1]; Eleni C. Vourvouri, MD[1]; Manolis A. Bountioukos, MD[1]; Eric P. Krenning, MD[3]; Jos R.T.C. Roelandt, MD[1]; and Don Poldermans, MD, PhD[1]

[1]Thoraxcenter, Department of Cardiology, Erasmus Medical Center, Rotterdam, The Netherlands; [2]Department of Cardiology, Leiden University Medical Center, Leiden, The Netherlands; and [3]Department of Nuclear Medicine, Erasmus Medical Center, Rotterdam, The Netherlands

During the noninvasive assessment of myocardial viability with ^{18}F-FDG metabolic imaging, adequate regulation of metabolic conditions is needed to ensure optimal image quality. The aim of this study was to compare the feasibility and image quality of cardiac ^{18}F-FDG SPECT imaging using acipimox in patients with diabetes and patients without diabetes. **Methods:** Seventy patients with ischemic cardiomyopathy underwent ^{18}F-FDG SPECT using acipimox for the assessment of myocardial viability, followed by resting 2-dimensional echocardiography to identify dysfunctional myocardial tissue. The image quality was scored visually and quantitatively; the myocardium-to-background ratio was determined by region-of-interest analysis. The plasma concentrations of glucose and free fatty acids were determined to evaluate the metabolic conditions before and during ^{18}F-FDG imaging. **Results:** Thirty-four patients had diabetes mellitus; of these, 12 had insulin-dependent diabetes mellitus and 22 had non–insulin-dependent diabetes mellitus. The remaining 36 patients had no diabetes. During ^{18}F-FDG SPECT, no severe side effects occurred. Acipimox significantly lowered plasma levels of free fatty acids in both groups. Fifteen of 34 patients with diabetes had a plasma glucose level $>$ 9 mmol/L, which was lowered successfully in all patients with additional insulin. Visual evaluation of the ^{18}F-FDG images showed good, moderate, and poor image quality in 27, 5, and 2 patients, respectively, with diabetes mellitus and in 32, 4, and 0 patients, respectively, without diabetes (P = not statistically significant). The myocardium-to-background ratio of ^{18}F-FDG SPECT images was comparable in patients with and without diabetes mellitus (3.1 $\pm$ 1.0 vs. 3.5 $\pm$ 0.9, P = not statistically significant). The type of diabetes had no influence on ^{18}F-FDG image quality. **Conclusion:** ^{18}F-FDG SPECT metabolic imaging after acipimox is safe and practical for routine assessment of viability in patients with ischemic cardiomyopathy. Image quality is good, even in patients with diabetes, although additional insulin is sometimes needed.

Key Words: metabolic imaging; diabetes mellitus; tomography; myocardial viability

J Nucl Med 2003; 44:877–883

Diabetes mellitus is an independent predictor of morbidity and mortality in patients with chronic left ventricular (LV) dysfunction (*1,2*). Patients with dysfunctional but viable myocardium may considerably benefit from coronary revascularization in terms of functional outcome and survival, but revascularization procedures are associated with a higher morbidity and mortality in patients with diabetes mellitus than in nondiabetic patients (*3*). Therefore, the assessment of myocardial viability is particularly relevant in these patients, for selection of the appropriate management strategy. Metabolic imaging with ^{18}F FDG is an accepted technique for the assessment of myocardial viability (*4–7*). However, adequate regulation of metabolic conditions is needed to ensure optimal image quality. Hyperinsulinemic–euglycemic clamping guarantees excellent image quality but is impractical. The use of nicotinic acid derivatives (acipimox; Byk) is a practical alternative that increases patient throughput in busy nuclear cardiology laboratories. Preliminary data suggest that ^{18}F-FDG imaging after acipimox administration is of good quality (*8–10*). However, the image quality of this protocol in patients with diabetes is unclear and remains to be evaluated. The aim of this study was to compare the feasibility and image quality of cardiac ^{18}F-FDG SPECT imaging using acipimox in patients with diabetes and patients without diabetes. In addition, subsets of patients with insulin-dependent diabetes mellitus (IDDM) and with non–insulin-dependent diabetes mellitus (NIDDM) were studied.

MATERIALS AND METHODS

Patient Population and Study Protocol

The study population consisted of 70 patients with chronic coronary artery disease and a moderately to severely impaired LV

Received Oct. 2, 2002; revision accepted Jan. 21, 2003.

For correspondence or reprints contact: Don Poldermans, MD, PhD, Thoraxcenter Room Ba 300, Department of Cardiology, Erasmus Medical Center, Dr. Molewaterplein 40, 3015 GD Rotterdam, The Netherlands.

E-mail: poldermans@hlkd.azr.nl

function. The patients were prospectively studied according to a structured protocol. This consecutive group of patients was referred for assessment of myocardial viability, and all patients were considered for myocardial revascularization. Thirty-four patients had diabetes mellitus; of these, 12 had IDDM and 22 had NIDDM. All patients with diabetes mellitus were controlling their disease with diet. The remaining 36 patients had no diabetes. Patients with primary cardiomyopathy or concomitant significant valvular disease were not included. All patients were in a clinically stable condition at the time of the study. All patients underwent dual-isotope SPECT with ^{99m}Tc tetrofosmin to evaluate perfusion and ^{18}F-FDG imaging to evaluate glucose use, followed by resting 2-dimensional echocardiography to identify dysfunctional myocardial tissue. The precise LV ejection fraction was assessed by radionuclide ventriculography. The local ethics committee approved the protocol, and all patients gave informed consent.

Assessment of Regional Contractile Dysfunction: 2-Dimensional Echocardiography

For echocardiography, a Sonos-5500 imaging system (Hewlett-Packard) was used, equipped with a 1.8-MHz transducer using second-harmonic imaging to optimize endocardial border visualization. Cine loops in 4 standard views were digitized (parasternal long and short axes, apical 2- and 4-chamber views), and 2 experienced reviewers scored the regional contractile function. The left ventricle was divided according to the standard 16-segment model suggested by the American Society of Echocardiography (*11*). Regional wall motion and systolic wall thickening were scored using a 5-point grading scale: 1 = normal, 2 = mildly hypokinetic, 3 = severely hypokinetic, 4 = akinetic, and 5 = dyskinetic. Segments with severe hypokinesia, akinesia, or dyskinesia were evaluated for myocardial viability.

The LV ejection fraction was assessed by radionuclide ventriculography. A small-field-of-view gamma camera (Orbiter; Siemens) was used, oriented in a 45° left anterior oblique position with a 5°–10° caudal tilt. After injection of ^{99m}Tc-pertechnate labeled autologous erythrocytes (550 MBq), radionuclide ventriculography was performed at rest with the patient supine. The LV ejection fraction was calculated by standard methods (Odyssey VP; Picker).

SPECT: Data Acquisition and Analysis

Patients received, after a light breakfast, an intravenous injection of ^{99m}Tc-tetrofosmin (600 MBq) to evaluate resting perfusion as described previously (*10*). Patients with diabetes mellitus were instructed to continue their antidiabetic medication. To determine the plasma concentration of glucose and free fatty acids, venous blood samples ware taken at baseline and once immediately before the ^{18}F-FDG injection. In patients with a plasma glucose level $>$ 9 mmol/L at baseline, 6 units of insulin were administered subcutaneously. When plasma glucose levels remained $>$9 mmol/L, additional insulin was administered. ^{18}F-FDG imaging, to evaluate myocardial glucose use, was performed after acipimox administration (500 mg, oral dose) in all patients. Acipimox enhances myocardial ^{18}F-FDG uptake by reducing the plasma level of free fatty acids (*12–14*). After the acipimox administration, the patients received a low-fat, carbohydrate-rich meal. This small meal further enhanced myocardial ^{18}F-FDG uptake by stimulating endogenous insulin release. Sixty minutes after the meal, ^{18}F-FDG (185 MBq) was injected, and after an additional 45 min to allow cardiac ^{18}F-FDG uptake, dual-isotope simultaneous acquisition SPECT was performed. Perfusion and metabolic imaging were performed at rest without stressors.

A triple-head gamma camera (Prism 3000XP; Philips Medical Systems) was used. The camera was equipped with commercially available high-energy 511-keV collimators (*15*). The energies were centered on the 140-keV photon peak of ^{99m}Tc-tetrofosmin with a 15% window and on the 511-keV photon peak of ^{18}F-FDG with a 15% window. Data were acquired over 360° (120 sectors of 3°) with the patients supine. Total imaging time was 32 min. Data were stored in a 64 $\times$ 64, 16-bit matrix.

From the raw scintigraphic data, 6-mm-thick (1 pixel) transaxial slices were reconstructed by filtered backprojection using a Butterworth filter (cutoff frequency, 0.17 cycle per pixel; order, 3.5). Attenuation correction was not applied. Further reconstruction yielded standard short- and long-axis projections perpendicular to the heart axis. The ^{99m}Tc-tetrofosmin and ^{18}F-FDG data were reconstructed simultaneously, to obtain an exact alignment of the perfusion and metabolic images.

The perfusion and ^{18}F-FDG short-axis slices were plotted in polar maps, which were normalized to maximum activity (set at 100%); the polar maps were divided into 16 segments matching the echocardiographic segments (*10,16*). The spatial resolution of our system is 1.8 cm in full width at half maximum, as determined with a line source in air. The final spatial resolution also depends on the absorption and scatter in the chest wall. The ^{18}F-FDG SPECT images were scored by 2 experienced observers. The segments were divided into 4 groups, based on the tracer activities: 0 = normal tracer uptake (activity $>$ 75%), 1 = mildly reduced tracer uptake (activity $\leq$ 75% and $>$ 50%), 2 = moderately reduced tracer uptake (activity $\leq$ 50% and $>$ 25%), and 3 = severely reduced or absent tracer uptake (activity $\leq$ 25%). Dysfunctional segments (identified by resting echocardiography) were subsequently evaluated for viability. Segments with normal perfusion (^{99m}Tc-tetrofosmin score $\leq$ 1) and segments with a perfusion defect (score $\geq$ 2) but relatively increased ^{18}F-FDG uptake (^{18}F-FDG score higher than perfusion score, mismatch pattern) were considered viable. Segments with a perfusion defect and concordantly reduced ^{18}F-FDG uptake (match pattern) were considered nonviable.

Assessment of Image Quality

The image quality was scored visually using a 3-point grading scale: 1 = good (high target-to-background ratio), 2 = moderate but interpretable (moderate target-to-background ratio), and 3 = uninterpretable (poor target-to-background ratio). To quantitatively assess the quality of the ^{18}F-FDG images, the myocardium-to-background (M/B) ratio was measured in the midventricular short-axis plane. A 2 $\times$ 2 pixel region of interest was drawn over the myocardium with the highest activity, and a similar region of interest was placed in the center of the LV cavity. From these activities, the M/B ratio was calculated. The measurements were repeated 3 times, and the results were averaged.

Plasma Samples and Analytic Techniques

Venous blood samples were obtained at baseline and immediately before ^{18}F-FDG injection to measure plasma levels of glucose and free fatty acids. Plasma glucose was determined with an analyzer using the glucose oxidase method (YSI). The free fatty acid levels were assessed by enzymatic colorimetric methods (NEFAC; Wako Chemicals).

Statistical Analysis

All continuous data are expressed as mean $\pm$ SD; percentages are rounded. Continuous variables were compared using the Stu-

TABLE 1
Clinical Characteristics of the 70 Study Patients

Characteristic	Patients with diabetes (n = 34)	P	Patients without diabetes (n = 36)
Men/women	30 (88%)/4 (12%)	NS	31 (86%)/5 (14%)
Age (y)	59 ± 8	NS	60 ± 11
Hypertension	5 (15%)	NS	7 (19%)
Hypercholesterolemia	17 (50%)	NS	13 (36%)
Smoking history			
Previous	12 (35%)	NS	10 (28%)
Current	10 (29%)	NS	19 (53%)
Family history of CAD	22 (65%)	NS	16 (44%)
Previous MI	31 (91%)	NS	35 (97%)
Multivessel disease	30 (88%)	NS	33 (92%)
LV ejection fraction (%)	32 ± 13	NS	34 ± 10

Data presented are mean value ± SD or number of patients.
NS = not statistically significant; CAD = coronary artery disease; MI = myocardial infarction.

dent t test. Differences between proportions were compared using the χ^2 test. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Patient Characteristics and Plasma Substrate Levels

Clinical characteristics were comparable between the group of patients with diabetes mellitus and the group without diabetes mellitus (Table 1). All patients presented with symptoms of heart failure and had severely impaired LV function due to chronic coronary artery disease.

Glucose. Figure 1 demonstrates the plasma glucose levels measured at baseline and immediately before ^{18}F-FDG injection. At baseline, the patients with diabetes had higher plasma glucose levels than did the patients without diabetes. After subcutaneous administration of insulin, glucose levels decreased significantly in patients with diabetes mellitus (Fig. 1). Fifteen of 34 patients with diabetes (7 IDDM, 8 NIDDM) had a plasma glucose level > 9 mmol/L, which was lowered successfully in all patients with additional insulin. Still, 4 patients had a plasma glucose level > 9 mmol/L.

Free Fatty Acids. At baseline, the patients with diabetes had plasma levels of free fatty acids similar to those of the nondiabetic patients; at the time of ^{18}F-FDG injection, plasma levels of free fatty acids had declined significantly in both groups (Fig. 2).

Safety and ^{18}F-FDG SPECT Image Quality Using Acipimox

No serious side effects (evaluated by direct questioning and physical examination) occurred during ^{18}F-FDG SPECT imaging. Nineteen patients had a mild and transient skin flush after acipimox administration. Mild skin flushing occurred in 5 of 34 (15%) patients with diabetes and in 14 of 36 (39%) patients without diabetes ($P < 0.05$).

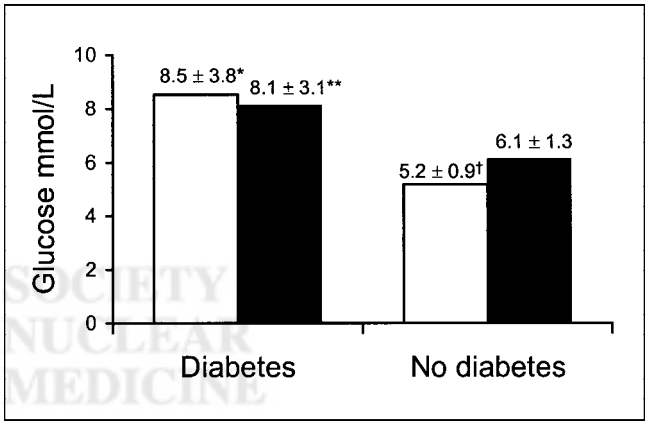

FIGURE 1. Bar graft demonstrates plasma glucose levels measured at baseline (white bars) and immediately before ^{18}F-FDG injection (black bars). *$P < 0.0001$ vs. no diabetes. **$P < 0.005$ vs. no diabetes. †$P < 0.001$ vs. immediately before ^{18}F-FDG injection. Values are expressed as mean ± SD.

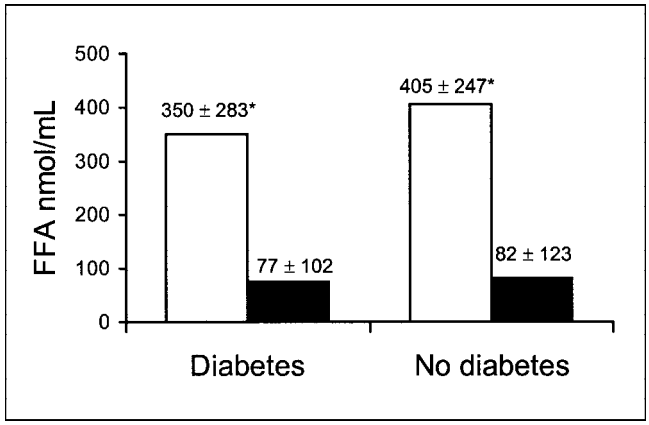

FIGURE 2. Plasma concentration of free fatty acids (FFA) in patients with diabetes mellitus and those without diabetes, at baseline (white bars) and after oral administration of acipimox (black bars). *$P < 0.0001$ vs. after acipimox.

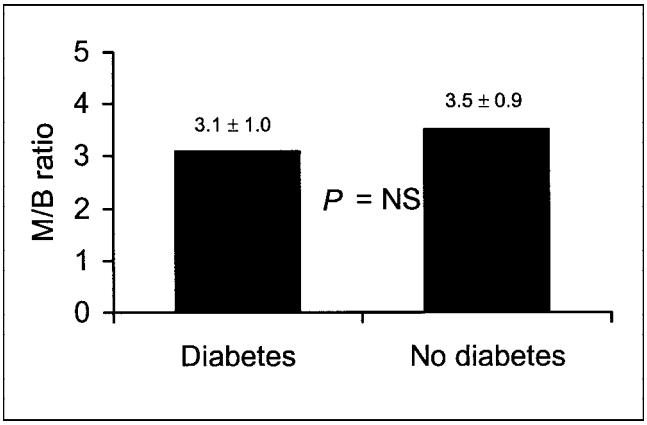

FIGURE 3. Quality of ^{18}F-FDG SPECT images (M/B ratio) was comparable in patients with and without diabetes mellitus.

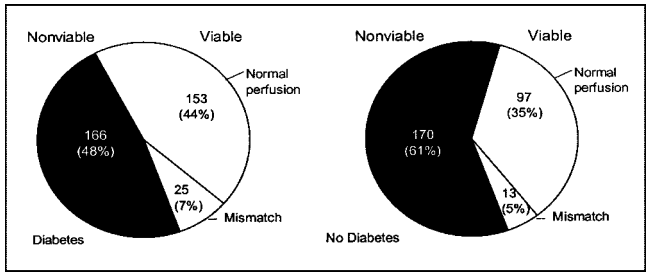

FIGURE 5. Number of viable (normal perfusion or blood-flow–metabolism mismatch) and nonviable dysfunctional myocardial segments as assessed by ^{18}F-FDG SPECT in patients with and without diabetes mellitus.

Visual evaluation of the ^{18}F-FDG images showed good, moderate, and poor image quality in 27, 5, and 2 patients with diabetes mellitus, respectively, and in 32, 4, and 0 patients without diabetes, respectively (not statistically significant). In the patients with ^{18}F-FDG SPECT images of moderate or poor quality, the fasting blood glucose was, on average, 9.1 ± 4.8 mmol/L, free fatty acid levels were 404 ± 277 nmol/mL at baseline and 77 ± 49 nmol/mL after acipimox, and the ejection fraction was 35% ± 12%. The M/B ratio of ^{18}F-FDG SPECT images was comparable in patients with and without diabetes mellitus (Fig. 3). Examples of the image quality obtained with ^{18}F-FDG SPECT after oral administration of acipimox are presented in Figure 4.

Myocardial Viability

Figure 5 shows the number of viable and nonviable dysfunctional myocardial segments as assessed by ^{18}F-FDG SPECT in patients with and without diabetes mellitus. The 2 patients with poor ^{18}F-FDG image quality were excluded from the analysis of myocardial viability. The number of dysfunctional segments was comparable in patients with and without diabetes mellitus (10.2 ± 5.4 vs. 8.3 ± 4.1, not statistically significant). According to metabolic imaging with ^{18}F-FDG SPECT, patients with diabetes had more dysfunctional but viable myocardial tissue than did patients without diabetes. Patients with diabetes had, on average, 5.3 ± 4.4 dysfunctional but viable segments, whereas those without diabetes had 3.3 ± 3.3 viable segments ($P < 0.05$).

Results in Patients with NIDDM versus IDDM

Patients with IDDM had clinical characteristics similar to those of patients with NIDDM (Table 2). Glucose levels were comparable in patients with IDDM and NIDDM (10.1 ± 4.8 mmol/L vs. 7.6 ± 2.6 mmol/L at baseline, $P = 0.06$, and 8.6 ± 3.2 mmol/L vs. 7.8 ± 3.0 mmol/L at the time of ^{18}F-FDG injection, $P = 0.49$). At baseline, free fatty acid levels were comparable in patients with IDDM and NIDDM (242 ± 189 nmol/mL vs. 404 ± 305 nmol/mL, $P = 0.13$). However, after the administration of acipimox,

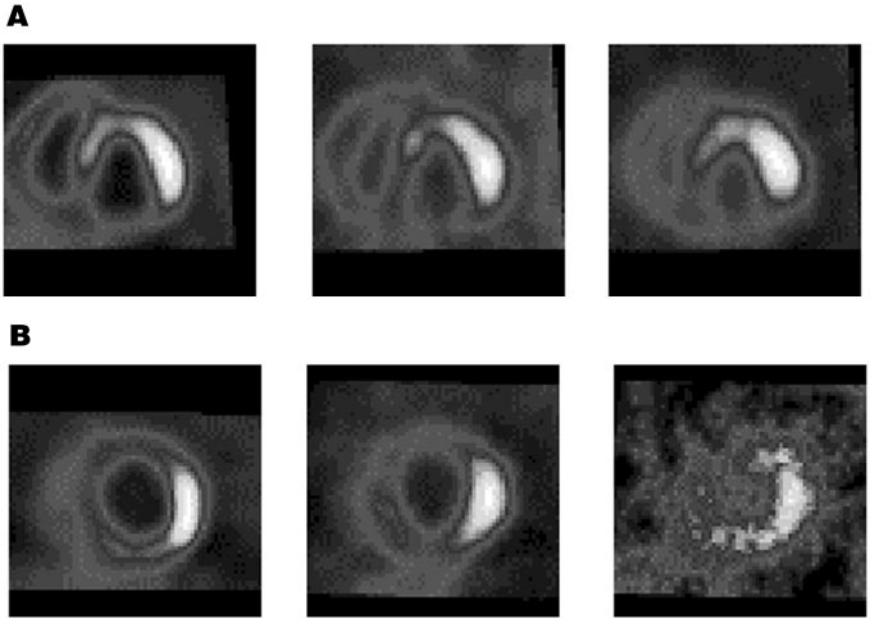

FIGURE 4. Examples of image quality obtained with ^{18}F-FDG SPECT after oral administration of acipimox. (A) Baseline ^{99m}Tc-tetrofosmin (left), dual-isotope simultaneous acquisition (DISA) ^{99m}Tc-tetrofosmin (middle), and DISA ^{18}F-FDG (right) short-axis images of patient with NIDDM. All images are of good quality; this patient had M/B ratio of 4.2. (B) Baseline ^{99m}Tc-tetrofosmin (left), DISA ^{99m}Tc-tetrofosmin (middle), and DISA ^{18}F-FDG (right) short-axis images of patient with IDDM. ^{18}F-FDG images are of poor quality. This patient had M/B ratio of 2.1.

TABLE 2
Clinical Characteristics of the 34 Patients with Diabetes Mellitus

Characteristic	Patients with NIDDM (n = 22)	P	Patients with IDDM (n = 12)
Men/women	19 (86%)/3 (14%)	NS	11 (92%)/1 (8%)
Age (y)	60 ± 8	NS	57 ± 9
Hypertension	4 (18%)	NS	1 (8%)
Hypercholesterolemia	12 (55%)	NS	5 (42%)
Smoking history			
Previous	7 (32%)	NS	5 (42%)
Current	8 (36%)	NS	2 (17%)
Family history of CAD	13 (59%)	NS	9 (75%)
Previous MI	19 (86%)	NS	12 (100%)
Multivessel disease	19 (86%)	NS	11 (92%)
LV ejection fraction (%)	34 ± 14	NS	30 ± 14

Data presented are mean value ± SD or number of patients.
NS = not statistically significant; CAD = coronary artery disease; MI = myocardial infarction.

at the time of ^{18}F-FDG injection, free fatty acid levels were lower in patients with IDDM than in those with NIDDM (27 ± 17 nmol/mL vs. 102 ± 116 nmol/mL, $P < 0.05$). Region-of-interest analysis demonstrated that the type of diabetes (IDDM vs. NIDDM) had no influence on ^{18}F-FDG image quality (Fig. 6). Also, patients with IDDM and NIDDM had a comparable number of dysfunctional segments (10.4 ± 5.8 vs. 10.1 ± 5.1, $P = 0.81$). Patients with IDDM and NIDDM had a comparable number of dysfunctional but viable segments (6.5 ± 4.8 vs. 4.6 ± 3.9, $P = 0.37$).

DISCUSSION

Noninvasive assessment of myocardial viability in patients with ischemic cardiomyopathy has major implications for clinical decision making. When a substantial amount of dysfunctional but viable myocardium is present, coronary revascularization may improve LV function and long-term survival. Currently, both the number of patients with heart failure due to coronary artery disease and the prevalence of diabetes mellitus are increasing rapidly (*17,18*). Diabetes mellitus is a well-known risk factor for coronary artery disease. Patients with diabetes have a 4-fold increased risk for development of heart failure after myocardial infarction (*19*). The assessment of myocardial viability is particularly relevant in these patients, since coronary revascularization in patients with diabetes mellitus is associated with a high morbidity and mortality (*3*). Currently, ^{18}F-FDG PET is considered the gold standard for the assessment of myocardial viability (*4–7*). Recently, ^{18}F-FDG metabolic imaging has become widely available with the introduction of ^{18}F-FDG SPECT using dedicated collimators (*20–25*). The image quality of ^{18}F-FDG imaging is influenced by metabolic conditions (*8,9*). Several protocols were introduced to lower free fatty acid levels, which appear the main determinant of image quality during ^{18}F-FDG imaging (*8*). ^{18}F-FDG imaging after oral glucose loading is practical, but the image quality varies substantially, with 20%–30% of the images being uninterpretable (particularly in patients with diabetes). The hyperinsulinemic–euglycemic clamp ensures excellent image quality but is labor intensive and time consuming. Recently, ^{18}F-FDG SPECT after oral administration of nicotinic acid derivatives (acipimox) has been suggested as a clinically useful protocol that increases patient throughput in busy nuclear cardiology laboratories (*8,9*). Acipimox is a nicotinic acid derivative that inhibits lipolysis and decreases plasma concentrations of free fatty acids (*12–14*). Two preliminary studies showed that ^{18}F-FDG imaging using acipimox was of good quality (*8,9*). However, the image quality with this protocol in patients with diabetes is unclear; this patient subset is the most challenging for obtaining good image quality.

The present study assessed the feasibility and image quality of ^{18}F-FDG SPECT after oral administration of acipimox for the assessment of myocardial viability in patients with diabetes mellitus. Metabolic conditions (plasma

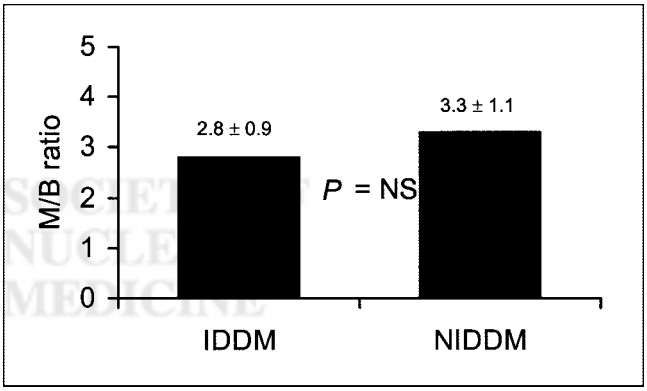

FIGURE 6. Region-of-interest analysis demonstrated that type of diabetes, IDDM vs. NIDDM, had no influence on ^{18}F-FDG image quality. NS = not statistically significant.

substrate levels) were monitored. As anticipated, baseline glucose levels were higher in patients with diabetes. In patients with plasma glucose levels > 9 mmol/L, additional insulin was added. An oral dose of acipimox effectively lowered the free fatty acid concentrations in both patient groups. No serious side effects of acipimox were observed. The image quality was comparable in patients with and without diabetes mellitus, and the type of diabetes mellitus (IDDM or NIDDM) did not influence ^{18}F-FDG image quality. These findings demonstrate that ^{18}F-FDG SPECT after oral administration of acipimox is a safe and clinically useful method for the assessment of myocardial viability and offers good image quality, even in patients with diabetes mellitus.

Acipimox is currently not available in the United States. Recently, Vitale et al. (*26*) studied 10 patients with ischemic LV dysfunction and NIDDM using ^{18}F-FDG PET. In that study, ^{18}F-FDG imaging was performed after administration of niacin (a nicotinic acid), yielding suboptimal results. However, nicotinic acid derivatives (e.g., acipimox), are known to be 20 times as potent as nicotinic acids, which may explain the lesser results in the study by Vitale et al. using niacin (*12*,*26*).

Of interest, patients with diabetes had more dysfunctional but viable myocardial tissue than did patients without diabetes. This observation is in line with our previous work (*27*). The reason for this finding is unclear. Further studies including follow-up data on functional recovery (the final proof of myocardial viability) are needed to elucidate this issue.

Some limitations of the present study need to be addressed. First, although the same 16-segment model was used for analysis, some misalignment between echocardiograms and SPECT images may have occurred. Second, the findings in our study did not include the results of recovery of function after revascularization. Previous studies by Altehoefer et al. (*28*) and by Zanco et al. (*29*) demonstrated that in patients with left bundle branch block, regional ^{18}F-FDG uptake in the septum may be affected without a correlating change in perfusion. This is a limitation of ^{18}F-FDG imaging that should be considered in the evaluation of myocardial viability.

CONCLUSION

^{18}F-FDG SPECT metabolic imaging after acipimox is safe and practical for routine assessment of viability in patients with ischemic cardiomyopathy. Image quality is good, even in patients with diabetes, although additional insulin is sometimes needed.

REFERENCES

1. Shindler DM, Kostis JB, Yusuf S, et al. Diabetes mellitus, a predictor of morbidity and mortality in the Studies of Left Ventricular Dysfunction (SOLVD) Trials and Registry. *Am J Cardiol.* 1996;77:1017–1020.
2. Dries DL, Sweitzer NK, Drazner MH, Stevenson LW, Gersh BJ. Prognostic impact of diabetes mellitus in patients with heart failure according to the etiology of left ventricular systolic dysfunction. *J Am Coll Cardiol.* 2001;38:421–428.
3. Herlitz J, Wognsen GB, Emanuelsson H, et al. Mortality and morbidity in diabetic and nondiabetic patients during a 2-year period after coronary artery bypass grafting. *Diabetes Care.* 1996;19:698–703.
4. Tamaki N, Ohtani H, Yamashita K, et al. Metabolic activity in the areas of new fill-in after thallium-201 reinjection: comparison with positron emission tomography using fluorine-18-deoxyglucose. *J Nucl Med.* 1991;32:673–678.
5. Tillisch J, Brunken R, Marshall R, et al. Reversibility of cardiac wall motion abnormalities predicted by positron tomography. *N Engl J Med.* 1986;314:884–888.
6. Lucignani G, Paolini G, Landoni C, et al. Presurgical identification of hibernating myocardium by combined use of technetium-99m hexakis 2-methoxyisobutylisonitrile single photon emission tomography and fluorine-18 fluoro-2-deoxy-D-glucose positron emission tomography in patients with coronary artery disease. *Eur J Nucl Med.* 1992;19:874–881.
7. Eitzman D, Al-Aouar Z, Kanter H, et al. Clinical outcome of patients with advanced coronary artery disease after viability studies with positron emission tomography. *J Am Coll Cardiol.* 1992;20:559–565.
8. Knuuti MJ, Ykii-Jarvinen H, Voipio-Pulkki LM, et al. Enhancement of myocardial [fluorine-18]fluorodeoxyglucose uptake by a nicotinic acid derivative. *J Nucl Med.* 1994;35:989–998.
9. Bax JJ, Veening MA, Visser FC, et al. Optimal metabolic conditions during fluorine-18 fluorodeoxyglucose imaging; a comparative study using different protocols. *Eur J Nucl Med.* 1997;24:35–41.
10. Kam BL, Valkema R, Poldermans D, et al. Feasibility and image quality of dual-isotope SPECT using ^{18}F-FDG and ^{99m}Tc-tetrofosmin after acipimox administration. *J Nucl Med.* 2003;44:140–145.
11. Bourdillon PD, Broderik TM, Sawada SG, et al. Regional wall motion index for infarct and non-infarct region after reperfusion in acute myocardial infarction: comparison with global wall motion index. *J Am Soc Echocardiogr.* 1989;2:398–407.
12. Fuccella LM, Goldaniga G, Lovisolo P, et al. Inhibition of lipolysis by nicotinic acid and by acipimox. *Clin Pharmacol Ther.* 1980;28:790–795.
13. Musatti L, Maggi E, Moro E, Valzelli G, Tamassia V. Bioavailability and pharmacokinetics in man of acipimox, a new antilipolytic and hypolipemic agent. *J Int Med Res.* 1981;9:381–386.
14. Nuutila P, Knuuti MJ, Raitakari M, et al. Effect of antilipolysis on heart and skeletal muscle glucose uptake in overnight fasted humans. *Am J Physiol.* 1994;267:E941–E946.
15. van Lingen A, Huijgens PC, Visser FC, et al. Performance characteristics of a 511-keV collimator for imaging positron emitters with a standard gamma-camera. *Eur J Nucl Med.* 1992;19:315–321.
16. Schinkel AFL, Bax JJ, Elhendy A, et al. Assessment of viable tissue in Q-wave regions by metabolic imaging using single-photon emission computed tomography in ischemic cardiomyopathy. *Am J Cardiol.* 2002;89:1171–1175.
17. McCullough PA, Philbin EF, Spertus JA, et al. Confirmation of a heart failure epidemic: findings from the Resource Utilization Among Congestive Heart Failure (REACH) study. *J Am Coll Cardiol.* 2002;39:60–69.
18. Burke JP, Williams K, Gaskill SP, Hazuda HP, Haffner SM, Stern MP. Rapid rise in the incidence of type 2 diabetes from 1987 to 1996: results from the San Antonio Heart Study. *Arch Intern Med.* 1999;159:1450–1456.
19. Abbott RD, Donahue RP, Kannel WB, Wilson PW. The impact of diabetes on survival following myocardial infarction in men vs women: The Framingham Study. *JAMA.* 1988;260:3456–3460.
20. Sandler MP, Videlefsky S, Delbeke D, et al. Evaluation of myocardial ischemia using a rest metabolism/stress perfusion protocol with fluorine-18 deoxyglucose/technetium-99m MIBI and dual-isotope simultaneous-acquisition single-photon emission computed tomography. *J Am Coll Cardiol.* 1995;26:870–878.
21. Martin WH, Delbeke D, Patton JA, et al. FDG-SPECT: correlation with FDG-PET. *J Nucl Med.* 1995;36:988–995.
22. Chen EQ, MacIntyre WJ, Go RT, et al. Myocardial viability studies using fluorine-18-FDG SPECT: a comparison with fluorine-18-FDG PET. *J Nucl Med.* 1997;38:582–586.
23. Bax JJ, Cornel JH, Visser FC, et al. Prediction of improvement of contractile function in patients with ischemic ventricular dysfunction after revascularization by fluorine-18 fluorodeoxyglucose single-photon emission computed tomography. *J Am Coll Cardiol.* 1997;30:377–383.
24. Sandler MP, Bax JJ, Patton JA, et al. Fluorine-18-fluorodeoxyglucose cardiac imaging using a modified scintillation camera. *J Nucl Med.* 1998;39:2035–2043.
25. Srinivasan G, Kitsiou AN, Bacharach SL, Bartlett ML, Miller-Davis C, Dilsizian V. [^{18}F]fluorodeoxyglucose single photon emission computed tomography: can it replace PET and thallium SPECT for the assessment of myocardial viability? *Circulation.* 1998;97:843–850.
26. Vitale GD, deKemp RA, Ruddy TD, Williams K, Beanlands RS. Myocardial

glucose utilization and optimization of ^{18}F-FDG PET imaging in patients with non-insulin-dependent diabetes mellitus, coronary artery disease, and left ventricular dysfunction. *J Nucl Med.* 2001;42:1730–1736.
27. Bax JJ, Visser FC, Poldermans D, et al. Feasibility, safety and image quality of cardiac FDG studies during hyperinsulinaemic-euglycaemic clamping. *Eur J Nucl Med.* 2002;29:452–457.
28. Altehoefer C, vom Dahl J, Bares R, Stocklin GL, Bull U. Metabolic mismatch of septal beta-oxidation and glucose utilization in left bundle branch block assessed with PET. *J Nucl Med.* 1995;36:2056–2059.
29. Zanco P, Desideri A, Mobilia G, et al. Effects of left bundle branch block on myocardial FDG PET in patients without significant coronary artery stenoses. *J Nucl Med.* 2000;41:973–977.