Enhancement of Myocardial [Fluorine-18]Fluorodeoxyglucose Uptake by a Nicotinic Acid Derivative

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Recently, the euglycemic hyperinsulinemic clamp technique was shown to give excellent image quality during metabolic steady-state conditions. Acipimox is a new potent nicotinic acid derivative that rapidly reduces serum free fatty acid (FFA) levels by inhibiting lipolysis in peripheral tissue. **Methods:** To compare the effects of acipimox administration and insulin clamp on [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) uptake and myocardial glucose utilization, five nondiabetic and seven type II diabetic patients who had had previous myocardial infarctions were studied twice: once during a clamp study and once after the administration of acipimox (2 × 250 mg orally). All patients also underwent resting SPECT perfusion imaging prior to PET scans. **Results:** The patients tolerated acipimox well. Although fasting plasma glucose levels were higher in diabetic patients (9.2 ± 3.4 versus 5.5 ± 0.3 m*M*, p = 0.03), they were decreased both during clamping and after acipimox; during imaging, no significant differences between the groups and approaches were detected. By visual analysis, the image quality and myocardial [^{18}F]FDG uptake patterns were similar during clamping and after acipimox. Compared with the relative [^{18}F]FDG uptake values obtained during clamping, acipimox yielded similar results in normal, mismatch and scar segments (r = 0.88, p = 0.0001). Similar rMGU values were also obtained during both approaches. **Conclusion:** Thus, PET imaging with [^{18}F]FDG after the administration of acipimox is a simple and feasible method for clinical viability studies both in nondiabetic and diabetic patients. It results in excellent image quality and gives rMGU levels similar to the insulin clamp technique.

Key Words: myocardial glucose metabolism; PET; glucose-insulin clamp; acipimox; coronary artery disease

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PET imaging of the heart with [^{18}F]fluorodeoxyglucose ([^{18}F]FDG) is a clinically feasible method to assess myocardial viability in patients with impaired left ventricular function (*1–5*). In the fasting state, the heart prefers to use free fatty acids (FFA) for energy production, and myocardial glucose uptake is low (*6*). Therefore, the [^{18}F]FDG uptake is low, and the image quality is poor when PET imaging is performed in the fasting state (*7*). In addition, significant myocardial heterogeneity in the myocardial glucose utilization (rMGU) in fasting subjects has been observed (*8*), which limits the specificity of detecting myocardial ischemia by [^{18}F]FDG studies. To stimulate rMGU in viability studies, oral glucose loading is commonly used. This leads to unstable metabolic conditions (*9*) and unsatisfactory image quality in one quarter to one fifth of the patients with coronary artery disease (CAD) (*7*). The image quality is especially poor in patients with impaired glucose tolerance or diabetes (*10*). Therefore, alternative methods have been proposed. The euglycemic hyperinsulinemic clamp is an elegant technique that provides excellent image quality in all patients but is rather complicated and time-consuming for clinical use (*9,11–14*). Also, insulin bolus injections have been used in selected patients (*11*), but no direct comparisons of this method to glucose loading or insulin clamping are available.

Acipimox is a potent nicotinic acid derivative, which decreases FFA concentrations by inhibiting lipolysis (*15*), and it has been successfully used to treat hyperlipidemia. After a single oral dose of acipimox, serum FFA levels decrease within 2 hr. Because high FFA levels inhibit glucose utilization in the human heart (*16*) and skeletal muscles (*16,17*), an acute reduction of arterial FFA levels can be assumed to result in a significant increase in myocardial glucose utilization. The administration of nicotinic acid was shown to decrease circulating FFA levels and increase myocardial extraction of glucose (*18*). However, the efficacy of acipimox in stimulating rMGU is not known. Besides this, it is not clear whether the drug leads to similar tracer distribution in the myocardium than that obtained during the postprandial state or during insulin clamping. In addition, acipimox has vasodilatory effects (*19*) that might also change the myocardial perfusion distribution and thus

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TABLE 1
Summary of Clinical Data

Group	Patient no.	Age (yr)	Weight	BMI	fP-gluk	Infarction	NYHA class (angina)	Angiography (Location of stenoses)	EF
Group A,	1	53	78	23	5.4	ANT	2	LAD (99%), RCA (50%), LCX (50%)	56%
nondiabetic	2	51	82	26	5.9	ANT	3	LAD (75%), RCA (75%)	27%
patients	3	42	75	28	5.2	ANT	2	LAD (100%)	37%
	4	41	90	28	5.8	ANT	1	LAD (75%), RCA (50%), LCX (50%)	30%
	5	49	93	26	5.3	LAT	2	LAD (99%), RCA (50%), LCX (50%)	37%
Group B,	6	64	76	28	8.6	ANT	3	LAD (100%), RCA (75%), LCX (99%)	51%
diabetic	7	65	84	27	7.3	INF	3	LAD (50%), RCA (99%), LCX (25%)	65%
patients	8	59	75	26	7.8	INF	3	LAD (60%), RCA (100%), LCX (100%)	42%
	9	62	85	29	11.6	ANT	3	LAD (50%), RCA (99%), LCX (75%)	54%
	10	71	90	34	5.9	POST	2	LAD (75%), LCX (50%)	61%
	11	56	87	30	15.7	ANT+INF	3	LAD (99%), RCA (100%), LCX (75%)	40%
	12	55	75	25	7.7	ANT	2	LAD (99%), RCA (70%), LCX (75%)	35%

ANT = anterior; BMI = body mass index; fP-gluk = fasting plasma glucose level; EF = ejection fraction percent in isotope ventriculography; INF = inferior; LAD = left anterior descending coronary artery; LAT = lateral; LCX = left circumflex coronary artery; NYHA = New York Heart Association Classification; POST = posterior; RCA = right coronary artery.

alter regional myocardial glucose metabolism in patients with CAD.

The purpose of this study was to evaluate the acute effects of acipimox on myocardial glucose uptake and to assess whether acipimox could be used to enhance myocardial PET imaging with [^{18}F]FDG. The distribution of myocardial perfusion, [^{18}F]FDG uptake and rMGU after acipimox administration in the fasting state was compared with the results achieved during euglycemic hyperinsulinemic clamping in nondiabetic and type II diabetic patients who had had previous myocardial infarctions and had impaired left ventricular function.

METHODS

Subjects

Five male nondiabetic patients (age 47 ± 5 yr, mean ± s.d.) with angiographically confirmed stable CAD and a previous Q-wave infarction participated in the study (Group A). In addition, seven patients (six males and one female, age 62 ± 6 yr) with noninsulin-dependent (type II) diabetes, stable coronary artery disease and a previous myocardial infarction were included in the study (Group B). The clinical data of the patients is summarized in Table 1. Three of the diabetic patients were receiving oral antidiabetic agents; one, both oral medication and insulin treatment; and three patients, no antidiabetic medication. The mean interval between the infarction and the PET study was 22 mo (range 4–120 mo). The left ventricular ejection fraction averaged 37% ± 13% in the nondiabetic patients and 49% ± 11% in the diabetic patients (no significant difference between groups), as determined by radionuclide ventriculography. None of the subjects had overt heart failure at the time of the study.

To localize normal, infarcted and possibly ischemic areas, all patients underwent coronary angiography, radionuclide ventriculography, echocardiography and SPECT perfusion imaging at rest. The angiographies were performed within 4 mo of the PET study (mean time interval 2.3 ± 1.6 mo), and the echocardiographies and radionuclide ventriculographies were performed within 2 wk of the PET studies. Each subject gave written informed consent. The study protocol was accepted by the ethical committee of the Turku University Central Hospital.

Study Design

Two PET studies in each patient were performed in random order within 2 wk. All antianginal medication, except nitrates and oral antidiabetic agents, was withdrawn at least 24 hr prior to the PET studies. All studies were performed after a 12-hr overnight fast. To study the potential effect of acipimox on regional myocardial perfusion, SPECT perfusion studies in Group A were performed twice: in the fasting state with and without acipimox before each PET imaging, as described later. In Group B, only one perfusion study was performed before starting the clamping.

Acipimox Study. In the acipimox study, 250 mg of acipimox (Olbetam, Farmitalia Carlo Erba, Milan, Italy) were given orally to patients 1.5 hr before SPECT tracer injection and imaging (Fig. 1A). To prevent the vasodilatory effects of acipimox (*19*), all patients were concomitantly given 500 mg of aspirin with the first acipimox dose. At the end of the SPECT imaging, another 250 mg of acipimox were given, and 1.5 hr later, [^{18}F]FDG was injected. Dynamic PET imaging was performed for 60 min. In Group B, a similar time schedule was used, except no perfusion imaging was performed.

Clamp Study. On the clamp study day, the SPECT perfusion imaging was performed in the fasting state before starting the clamp in the both patient groups (Fig. 1B). After the collection of SPECT data, intravenous insulin and glucose infusions were started, as previously described (*9*), and the plasma glucose level was stabilized during the preinjection period of 60 min. Fluorine-18-FDG was injected, and dynamic imaging was performed for 60 min.

Infusions and Blood Sampling. Two catheters were inserted, one in an antecubital vein for the infusion of glucose and insulin and the injection of [^{18}F]FDG and another in a vein of the contralateral hand, which was warmed (70°C) for sampling of arterialized venous blood. In the beginning of the clamp procedure, the

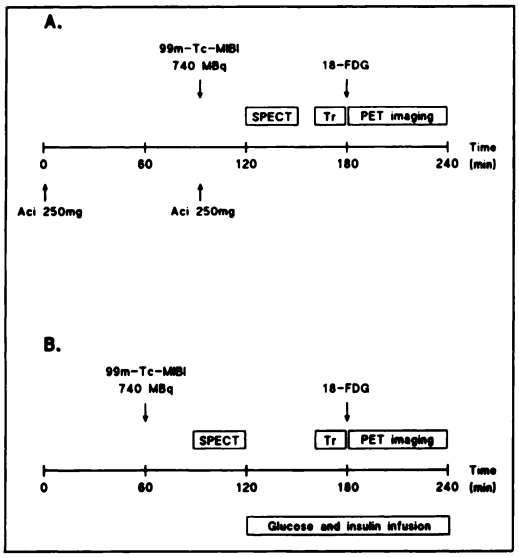

FIGURE 1. (A) Protocol for acipimox study. (B) Protocol for insulin clamp study. Aci = acipimox; Tr = transmission imaging.

serum insulin level was raised by a primed-continuous infusion of insulin (*20*). The rate of the insulin infusion was 1 mU/kg/min. During hyperinsulinemia, normoglycemia was maintained with 20% glucose infused at an appropriate rate. The rate of the glucose infusion was adjusted according to plasma glucose determinations, which were performed every 10 min from arterialized venous blood. Blood samples were taken at 30-min intervals for a determination of serum insulin and FFA concentrations. In the acipimox study, the glucose and insulin infusions were replaced with a saline infusion. The heart rate and systolic blood pressure were monitored during the SPECT and PET studies to calculate the rate-pressure product.

Measurement of rMGU

Preparation of [^{18}F]FDG. This was synthesized with an automatic apparatus by a modified method of Hamacher et al. (*21*). The ^{18}F-F$^-$ had a specific activity of 150 Ci/μmole (*22*); the radiochemical purity exceeded 99%.

Image Acquisition, Processing and Corrections. The imaging procedure and analysis were described in detail previously (*9*). The patients were positioned supine in an eight-ring ECAT 931/08-12 tomograph (Siemens/CTI, Knoxville, TN) with a measured axial resolution of 6.7 mm and 6.5 mm in the plane. At 60 min after starting the insulin clamping or 90 min after the acipimox dose, 7.1 ± 1.3 mCi (260 ± 50 MBq) of [^{18}F]FDG was injected intravenously over 30 sec (mean dose in Group A, 7.6 ± 1.0 mCi in the clamp studies and 7.8 ± 0.9 mCi in the acipimox studies; mean dose in Group B, 6.5 ± 1.3 and 7.0 ± 1.4 mCi, respectively, no significant difference between doses). Dynamic imaging was started simultaneously and continued for 60 min. The myocardium was divided into eight segments (*9*), and fractional utilization constants of [^{18}F]FDG (K_i) and rates of rMGU were calculated segmentally. The lumped constant in the myocardium was assumed to be 0.67 (*23*). In addition to a calculation of the quantitative values, relative [^{18}F]FDG uptake values in the last 10-min frame images were determined by normalization so that the uptake level of the segment with maximum counts at rest in a SPECT perfusion image was used as a reference region. The radioactivity levels in blood and in each myocardial segment at the end of the study were computed to allow a comparison of tracer distribution independently of the measurement of [^{18}F]FDG kinetics by dynamic imaging.

Coronary Angiography

All patients underwent selective coronary angiography by standard techniques. A 50% or greater reduction in the diameter in a major epicardial branch was considered significant. The cine tapes were blindly analyzed by an experienced radiologist.

SPECT Perfusion Imaging

Technetium-99m-labeled methoxyisobutylisonitrile was used for the SPECT perfusion studies. The studies consisted of imaging at rest 30 min after tracer injection (20 mCi, 740 MBq). A Siemens-Orbiter SPECT gamma camera (Siemens Gammasonics, Des Plaines, IL) was used for SPECT. The tomographic images of the heart were reconstructed in 6-mm thick transaxial slices and three perpendicular planes. The radioactivity in the eight anatomic segments was assessed qualitatively, and the distribution of tracer uptake in different myocardial areas was compared between the approaches. The results from images were scored according to the following scale: 1, normal; 2, clear but modest defect; 3, notable defect; and 4, complete defect.

Echocardiography

Two-dimensional echocardiography (Acuson 128XP/5, Acuson, Mountain View, CA) was performed according to the semiquantitative method recommended by the American Society of Echocardiography Committee on Standards (*24*), but the segmental subdivision was modified to correspond with the PET studies. The segmental left ventricular wall motion and thickening was scored according to the following scale: 1, normal; 2, hypokinetic; 3, akinetic; and 4, dyskinetic. In addition, wall segments were considered to be thinned if the wall thickness was reduced by 25% or more compared with the adjacent normal segments.

Radionuclide Ventriculography

A gated blood-pool radionuclide ventriculography was performed in two views. Six hundred cycles (≈10 min) were collected after the injection of 740 MBq (20 mCi) of ^{99m}Tc-labeled human serum albumin. A left anterior oblique view was used for ejection fraction calculations. A Siemens-Orbiter gamma camera was used and ejection fractions were calculated with the Gamma-11 program (Nuclear Diagnostics, Stockholm, Sweden).

Alignment of Myocardial Segments with Different Methods

The SPECT and PET transaxial slices were visually aligned and compared with each other, and the results of the transaxial images were assigned to the eight segments with the help of a heart map phantom (*9*). The wall motion abnormalities by echocardiography were also localized in the segmental heart map phantom. All results were first localized by the physician who performed each study. The segmental scores from each method were finally aligned and pooled together by the first author.

Analytic Procedures

The plasma glucose level was determined in duplicate by the glucose oxidase method (*25*) using an Analox GM7 (Analox Instruments, Copenhagen, Denmark) glucose analyzer. The serum insulin level was measured by radioimmunoassay (*26*) and serum FFA level, with fluorometric methods (*27*).

Statistical Analysis

Independent samples were compared by analysis of variance. Paired samples were compared by paired-comparisons t-tests. All

TABLE 2
Summary of Results in Both Patient Groups During Insulin Clamp and After Acipimox*

	Group A (nondiabetic patients, n = 5)			Group B (diabetic patients, n = 7)		
	Insulin clamp	p value	Acipimox	Insulin clamp	p value	Acipimox
Metabolic and physiologic characteristics						
Glucose (m*M*)	5.0 ± 0.4	NS	5.2 ± 0.3	5.1 ± 0.3	NS	6.2 ± 1.4
Insulin (mU/liter)	74 ± 9	0.0001	6 ± 5	75 ± 14	0.0001	9 ± 7
FFA (μM)	230 ± 106	NS	198 ± 42	174 ± 34	NS	161 ± 36
RP (mmHg/min)	7600 ± 1700	NS	6900 ± 1300	7800 ± 1000	NS	7100 ± 600
Radioactivity levels in						
Myocardium (μCi/ml)	0.93 ± 0.34	0.013	1.44 ± 0.51	1.01 ± 0.55	NS	1.13 ± 0.55
Blood (μCi/ml)	0.08 ± 0.03	0.011	0.17 ± 0.03	0.11 ± 0.03	0.006	0.19 ± 0.04
Ratio (myocardium/blood)	13.8 ± 8.8	NS	8.2 ± 2.3	9.2 ± 3.5	NS	6.4 ± 4.1
Quantitative results						
K_i ($g_p/ml_m/min$)	0.085 ± 0.038	NS	0.087 ± 0.023	0.105 ± 0.044	NS	0.074 ± 0.048
MGU (μmole/100 g/min)	57 ± 23	NS	61 ± 14	74 ± 32	NS	57 ± 27

*Note that no significant differences were detected between the patients groups in any of the parameters, except fasting glucose values.
MGU = myocardial glucose utilization; RP = rate-pressure product; FFA = free fatty acids; NS = not significant.

results are expressed as the mean values ± s.d. Pearson's correlation coefficients were calculated where appropriate.

RESULTS

Metabolic and Physiologic Characteristics During Insulin Clamping and After Acipimox

In diabetic patients (Group B), the fasting glucose values were higher than in the nondiabetic (Group A) patients (9.2 ± 3.4 versus 5.5 ± 0.3 m*M*, p = 0.03). During insulin clamping, the plasma glucose levels were adjusted by a variable glucose infusion. The target value was 5 m*M* and similar values were obtained in both patient groups during PET imaging (5.1 ± 0.3 m*M* in Group B and 5.0 ± 0.4 m*M* in Group A, not significant). After the administration of acipimox, the plasma glucose level decreased significantly in Group B (decrease from 9.2 ± 6.2 m*M* to 6.2 ± 1.4 m*M*, p = 0.01), and the differences in glucose values after the administration of acipimox were not significant between the patient groups during PET imaging (Table 2).

The serum fasting insulin concentrations averaged 9 ± 7 mU/liter in Group A and 19 ± 9 mU/liter Group B (p = 0.06). During insulin clamping, the respective values were 74 ± 9 mU/liter and 75 ± 14 mU/liter (not significant) (Figs. 2 and 3). After acipimox, the serum insulin concentrations remained at fasting levels in both groups (6 ± 5 and 9 ± 7 mU/liter, not significant).

No significant differences between the approaches and the patient groups were detected in serum FFA concentrations during PET imaging. In Group A, the serum FFA levels were 741 ± 271 μM before the clamp studies and 478 ± 121 μM before acipimox administration (not significant). Both during clamping and after the administration of acipimox, the FFA levels decreased and were comparable in both patient groups (Table 2, Figs. 2 and 3).

The rate-pressure products were similar between the study groups, two approaches or during the PET (Table 2) and SPECT studies (during insulin clamping, SPECT 8100 ± 1700 and during acipimox, SPECT 8100 ± 1200, not significant).

Segment Classification by Echocardiogram, Coronary Angiogram and SPECT

By definition, 96 segments were identified in the 12 patients (40 segments in Group A and 56 in Group B). The segments were classified as normal, scar or potentially ischemic in each patient based on the results of the echocardiogram, coronary angiogram and SPECT perfusion imaging performed in the fasting state before clamping. The segment was classified as normal if it gave a normal result by echocardiogram and SPECT and was associated with 75% or less coronary stenoses.

In Group A, 28 segments were classified as normal. Seven of the remaining 12 segments were associated with severe SPECT perfusion defects and severe dysfunction (akinesis or dyskinesia) in the echocardiogram. In addition, these segments showed severe [^{18}F]FDG defects in the visual analysis of clamp PET study and were suggested to represent myocardial scar. The remaining five segments showed milder SPECT perfusion defects (score 2) and wall motion abnormalities (scores 2–3) and were associated with critical coronary stenoses (90%–100%). The segments showed normal or increased [^{18}F]FDG uptake during clamp, and these five "mismatch" segments were assumed to represent ischemic but viable myocardium.

In Group B, the accurate classification of the segments

into the three groups explained earlier was problematic. Because of the smaller number of clear scar regions, more diffuse CAD and many severe coronary stenoses (99%–100%), the classification of the segments into normal, scar and mismatch groups was believed to be inaccurate. Therefore, the analysis of the results and the comparison of approaches was based on the segment-to-segment comparison and correlation analysis.

Effects of Acipimox on Myocardial Perfusion

In the visual analysis of SPECT perfusion images, no significant differences in the distribution of tracer were detected in the studies performed in the fasting state before the clamp and after acipimox (Fig. 4). The concordance of segmental uptake scores between the two studies was 100%. Thus, no clinically significant effects of acipimox on myocardial perfusion was observed.

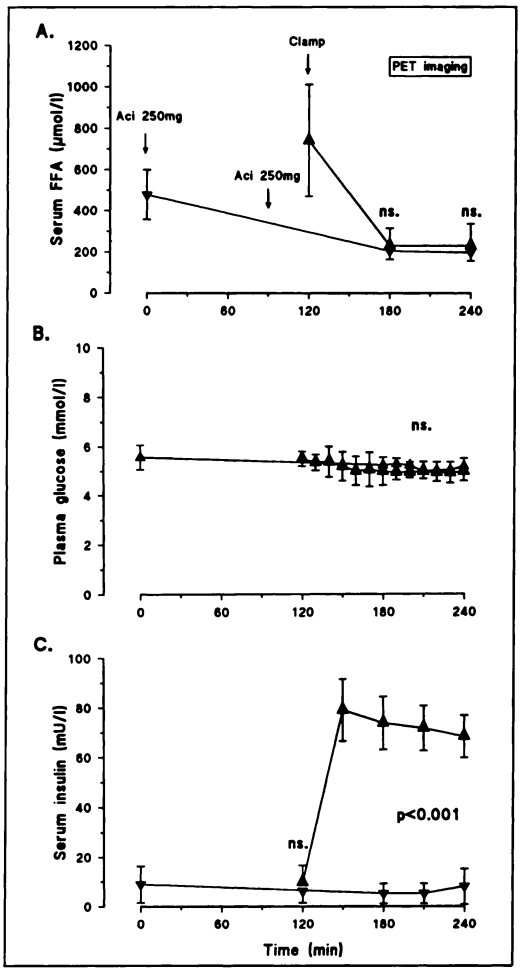

FIGURE 2. Serum FFA levels (A), plasma glucose (B) and serum insulin (C) levels during the PET studies in nondiabetic (Group A) patients (mean ± s.d.). △ = insulin clamp studies; ▼ = acipimox studies. The differences in FFA and glucose levels between the approaches were not significant, but higher serum insulin levels were obtained during clamping.

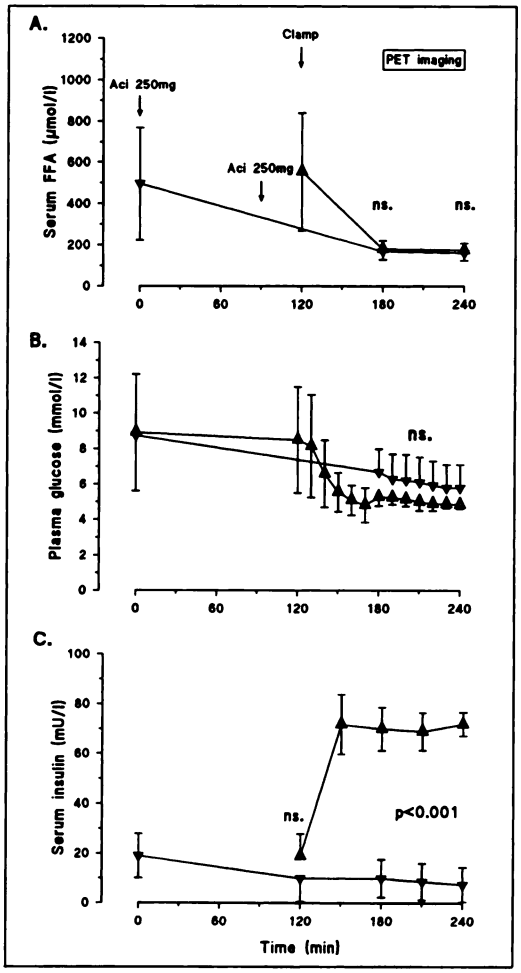

FIGURE 3. Serum FFA (A), plasma glucose (B) and serum insulin (C) levels during the PET studies in diabetic (Group B) patients (mean ± s.d.). △ = insulin clamp studies; ▼ = acipimox studies. The FFA and insulin values were comparable to those in nondiabetic patients. Note the significant decrease in plasma glucose levels both during insulin clamping and after administration of acipimox.

Side Effects of Acipimox

All patients developed a mild asymptomatic flush reaction 1 to 2 hr after the acipimox dose. No other side effects were observed.

Quality of PET Images During Clamping and After Acipimox Administration

In Group A, the visually observed image quality was comparable during both approaches (Fig. 5). As shown in Figure 6, the radioactivity at the end of the studies in the normal myocardial segments was significantly (56%) higher after acipimox than during clamping (Fig. 6A). However, the mean plasma radioactivity was also 110% higher in the acipimox studies (Fig. 6B). As a consequence, the mean ratio of radioactivity in normal myocardium and plasma was slightly but not significantly lower after acipimox compared with insulin clamping (Fig. 6C).

The image quality was also excellent in the Group B diabetic patients. The myocardium was acceptably visualized in all patients both during clamping and after acipi-

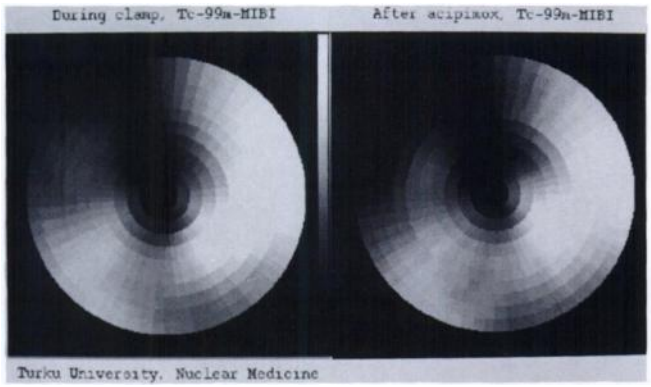

FIGURE 4. An example of polar tomograms of SPECT perfusion studies at rest. A similar tracer distribution was obtained during both approaches.

mox. Compared with the results in Group A patients, the visually observed image quality was found to be comparable between the approaches in most of the Group B patients (Fig. 7). In one diabetic patient, a slightly poorer image quality was obtained with acipimox compared with that in insulin clamping (Fig. 8). The mean radioactivity level in normal myocardium was also slightly higher after acipimox in Group B, but the difference was only 10% and not statistically significant (Fig. 9A). However, the mean plasma radioactivity was 73% higher in acipimox studies (Fig. 9B). Therefore, the mean ratio of radioactivity in the normal myocardium and plasma was lower after acipimox compared with that in insulin clamping (Fig. 9C), but the difference was not statistically significant.

Relative Myocardial [^{18}F]FDG Uptake in Normal and Abnormal Regions During Clamping and After Administration of Acipimox

There were no apparent differences in the size or intensity of the defects between the two approaches. All normal segments showed homogeneous accumulation of [^{18}F]FDG during the clamp and after acipimox, and all segments classified as scar had reduced (below normal range) [^{18}F]FDG uptake by both approaches. In the mismatch segments, the [^{18}F]FDG uptake was normal or above the reference segment in both studies. In one patient (Patient 6 in Group B), with an occluded left anterior descending artery and anterior wall motion abnormality, a large area of increased [^{18}F]FDG uptake (157% of normal) was detected after acipimox, but during clamping, the [^{18}F]FDG uptake was only moderately increased (110% of normal). The calculated relative [^{18}F]FDG uptake values correlated highly ($r = 0.88$, $p = 0.0001$) during both approaches in both patient groups (Fig. 10). When the segmental values were classified to normal or reduced according to the normal range of relative [^{18}F]FDG uptake (mean ± 2 s.d.), the results were concordant in all patients during clamping and after acipimox.

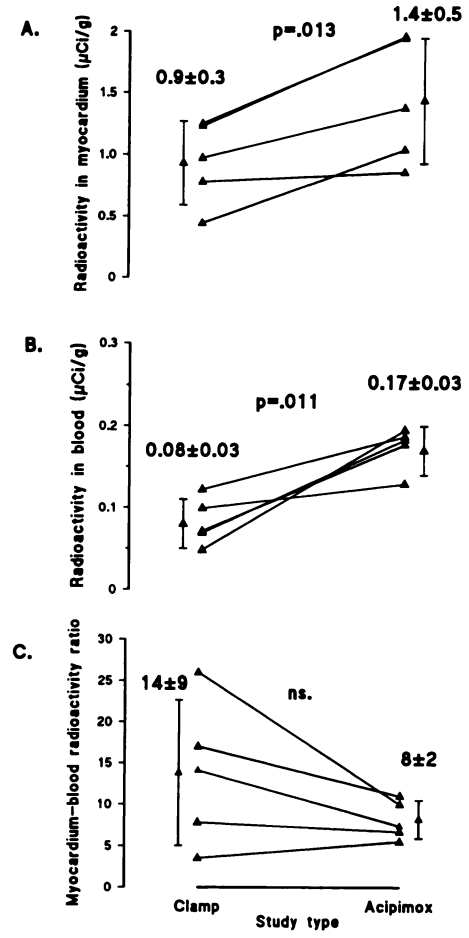

FIGURE 6. The radioactivity levels (mean ± s.d.) in myocardium (A), blood (B) and the myocardium-to-blood radioactivity ratios (C) during both approaches in nondiabetic (Group A) patients. In the acipimox studies, the mean radioactivity level in the myocardium was higher, but a higher radioactivity level in the blood was also obtained. As a consequence, the myocardium-to-blood radioactivity ratios were comparable during both approaches.

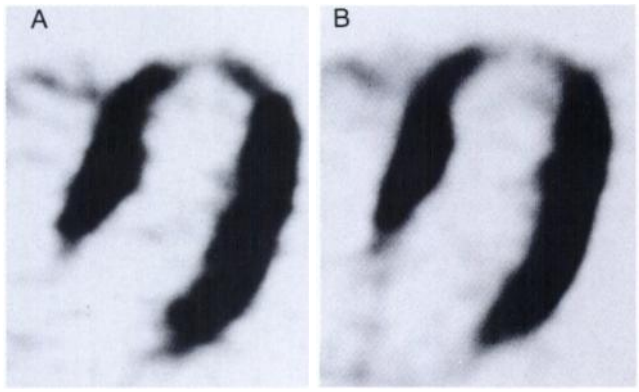

FIGURE 5. An example of transaxial images in a nondiabetic patient obtained during insulin clamping (A) and after acipimox in the fasting state (B) (50 min after [^{18}F]FDG injection). The image quality was comparable, and the distribution of [^{18}F]FDG uptake was similar during both approaches.

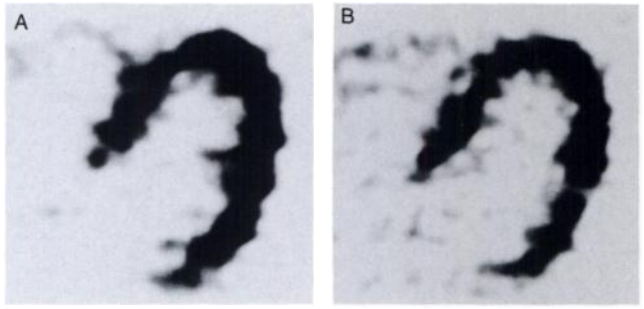

FIGURE 7. An example of transaxial images in a diabetic patient obtained during insulin clamping (A) and after acipimox in the fasting state (B) (50 min after [^{18}F]FDG injection). Comparable image quality was obtained by both approaches.

rMGU in Normal and Abnormal Regions During Clamping and After Administration of Acipimox

The rMGU values were similar in normal myocardium during both approaches in both patient groups (Table 2). Table 3 shows the K_i, rMGU and relative [^{18}F]FDG uptake values in Group A in different segment groups. No significant differences in any of the parameters was found between the approaches. There was no apparent difference in the variation of rMGU in the normal segments between the approaches (the average s.d. of rMGU was 41% during clamping and 35% after acipimox). In addition, the distribution of rMGU was similar in normal segments; in the septal segments, the rMGU was slightly lower than in the other segments.

DISCUSSION

The results of this study show that acipimox administration in the fasting state gives [^{18}F]FDG PET image quality comparable to that of the insulin clamp technique. In previous studies, the image quality was poor when patients were studied in the fasting state with [^{18}F]FDG (*7*). To enable an assessment of myocardial viability, rMGU is commonly stimulated by oral glucose loading. However, glucose load results in variable and unstable metabolic conditions (*9*), and the image quality is still often poor, especially in patients with impaired glucose tolerance or diabetes caused by a relative insulin deficiency (*7,9,10*). An alternative technique to improve the image quality is the euglycemic hyperinsulinemic clamp, which was shown (*9*) to give superior image quality during metabolic steady-state conditions. The insulin clamp method, however, is cumbersome and time consuming for routine clinical studies. This study shows that excellent image quality and rMGU levels comparable to those of the clamp method can be obtained in the fasting state by reducing serum FFA levels acutely by the oral administration of acipimox. The results of this study also show that patients with impaired glucose tolerance and type II diabetes can be successfully studied with [^{18}F]FDG PET after the administration of

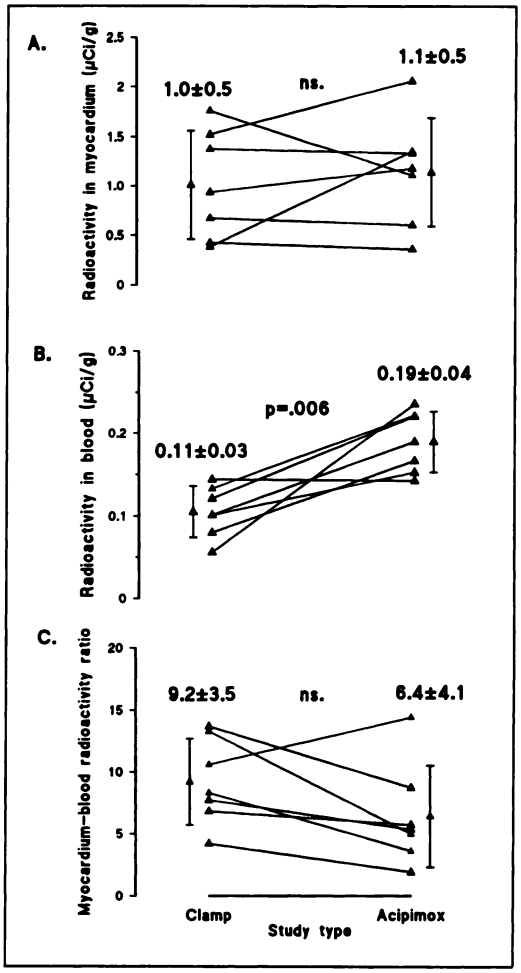

FIGURE 9. The radioactivity levels (mean ± s.d.) in myocardium (A), blood (B) and the myocardium-blood radioactivity ratios (C) during both approaches in diabetic (Group B) patients. Significantly higher radioactivity levels in blood were detected in acipimox studies. However, myocardium-to-blood radioactivity ratios were comparable during both approaches.

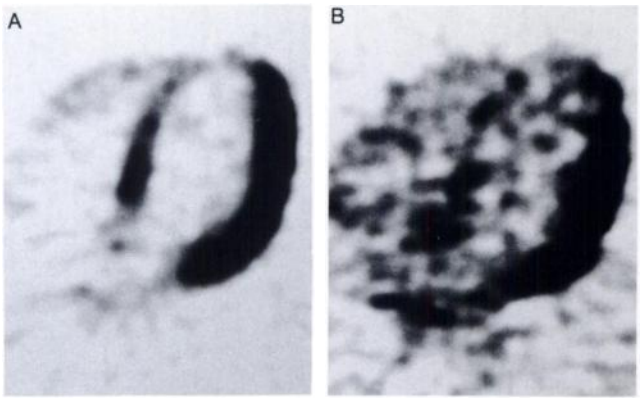

FIGURE 8. An example of transaxial images obtained during insulin clamping (A) and after acipimox in the fasting state (B) in the diabetic patient with the lowest myocardium-to-blood radioactivity ratio (Patient 12 in Table 1). Higher blood radioactivity levels were seen in the acipimox study compared with those in the insulin clamp method, but the distribution of [^{18}F]FDG uptake was similar in both studies.

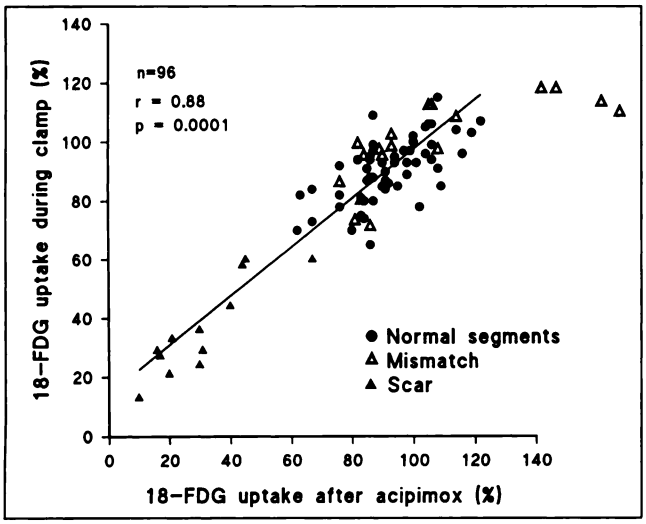

FIGURE 10. The relationship of segmental normalized [^{18}F]FDG uptake values during both approaches in all patients. Suggested classification of segments: ● = normal segments; △ = mismatch segments; ▲ = scar (match) segments; r = Pearson correlation coefficient.

acipimox. The dose of 2 × 250 mg of acipimox, when given together with aspirin, was well tolerated by all patients.

Acipimox is a new potent nicotinic acid derivative that inhibits lipolysis (*15*). After the oral administration of acipimox, serum FFA levels decrease to similar levels obtained during insulin clamping. In the human heart, high serum FFA levels (e.g., in the fasting state) inhibit glycolysis, thus lowering the uptake and phosphorylation rates of glucose (*16,28*). As shown in the present study, if these inhibitory effects are abolished, the glucose utilization rate in the myocardium is comparable to that obtained during the clamp technique. The mechanism of rMGU stimulation resembles that observed after glucose loading or during insulin clamping; insulin decreases blood FFA levels by the inhibition of lipolysis (*6,12,28*). In addition to this mechanism, insulin facilitates glucose transport to myocardial tissue and increases glycogen synthesis (*6*). The roughly similar rMGU values obtained during insulin clamping and after acipimox suggest that insulin stimulates rMGU mainly by decreasing FFA levels in the blood under physiologic conditions. Also, acipimox was previously shown to increase skeletal muscle glycogen synthase activity (*29*). A similar effect in the heart might also explain part of its effects on myocardial glucose uptake. These effects of acipimox concurrently result in the increased accumulation of [^{18}F]FDG to the myocardium and excellent PET image quality.

The relative [^{18}F]FDG uptake values were similar in normal and abnormal segment groups, and the correlation between [^{18}F]FDG uptake measured with the two approaches was good. In one diabetic patient with an occluded left anterior descending artery, an increase in [^{18}F]FDG uptake in the anterior wall was more prominent after acipimox than during clamping. However, the reason for this might be changes in the metabolism of that region during the 1-wk interval between the studies. Anyhow, in both studies, the segments were similarly classified as viable. Correspondingly, the observed rMGUs in normal and mismatch regions were comparable during clamping and after acipimox. In addition, the steady-state conditions required for the Patlak et al. (*30*) quantitative analysis were obtained in the fasting state, even after acipimox.

The [^{18}F]FDG uptake distribution in different anatomic regions and also the variabilities of rMGU values were similar after acipimox and during clamping. Earlier, it was shown (*9*) that insulin clamping gives a myocardial [^{18}F]FDG distribution similar to that obtained after glucose loading. The results of this study suggest that acipimox also mimics postprandial conditions sufficiently. In the previous study (*9*), better image quality, higher myocardial radioactivity levels and lower blood radioactivity levels were found during insulin clamping than after glucose loading. In this study, the tracer uptake to the myocardium was even higher after acipimox than during clamping in nondiabetic patients. This explains the excellent image quality in the acipimox studies. In peripheral muscle, however, the stimulatory effect of acipimox on glucose uptake in the fasting state seemed to be smaller than in the myocardium, whereas during the insulin clamping, the peripheral glucose level and [^{18}F]FDG disposal were greatly increased (*31*). Probably because of the less prominent increase in peripheral tissue glucose disposal, plasma radioactivity levels remained somewhat higher after acipimox than during insulin clamping.

TABLE 3
Fractional Glucose Utilization, Myocardial Glucose Utilization and Relative Fluorine-18-Labeled Fluorodeoxyglucose Uptake in Normal and Abnormal Segment Groups During Insulin Clamping and in the Fasting State After Acipimox Administration in Nondiabetic Patients

	K_i ($g_p/ml_m/min$)			rMGU (μmole/min/100g)			Relative [^{18}F]FDG uptake		
Segment group	Clamp	Acipimox		Clamp	Acipimox		Clamp	Acipimox	
Normal (n = 28)	0.079 ± 0.04	0.081 ± 0.02	NS	53 ± 23	57 ± 14	NS	92% ± 12%	94% ± 12%	NS
Visual mismatch (n = 5)	0.102 ± 0.03	0.095 ± 0.02	NS	66 ± 17	66 ± 9	NS	97% ± 15%	94% ± 15%	NS
Scar (n = 7)	0.036 ± 0.03	0.027 ± 0.01	NS	24 ± 18	19 ± 10	NS	41% ± 13%	32% ± 11%	NS

K_i = fractional glucose utilization; rMGU = myocardial glucose utilization; [^{18}F]FDG = [^{18}F]fluorodeoxyglucose; NS = not significant.

Uninterpretable images after glucose loading are especially common in diabetic patients (*10*). High plasma glucose levels are associated with a lower fractional FDG utilization (*32–34*). Impaired glucose tolerance is commonly observed in patients with coronary artery disease (*35*). This study shows that, in diabetic patients, the elevated fasting plasma glucose levels decrease after the administration of acipimox. Because skeletal muscle is responsible for about 70% of total body glucose disposal (*16*), even a modest increase in skeletal muscle glucose uptake can be suggested as a reason for this. In addition, acipimox decreases blood FFA levels, thus increasing rMGU. As a consequence, the image quality improves, and the analysis of images is feasible.

For rMGU calculations, it was assumed that the lumped constant (LC) remained unchanged during clamping and after acipimox. However, there are no data about the effects of insulin clamping or acipimox on the LC. Previous studies show that the nutritional state during physiologic conditions does not affect the LC (*32,33,36*). There were no significant differences in the rate-pressure products and, thus, in the myocardial workload between the two protocols. Moreover, the plasma glucose and FFA levels were similar.

This experience with oral administration of acipimox in stimulating [^{18}F]FDG uptake during PET imaging was encouraging. Acipimox enhanced myocardial [^{18}F]FDG uptake in the fasting state without altering perfusion distribution and the [^{18}F]FDG uptake patterns in normal and abnormal myocardial regions and was well tolerated. Image quality and results comparable to the insulin clamp technique were obtained in nondiabetic and diabetic patients by the administration of acipimox. This method obviated the need for insulin and glucose infusions and appeared to be a superior alternative to glucose loading or insulin clamping in stimulating rMGU, especially for clinical viability studies.

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