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Pioglitazone Improves Cardiac Function and Alters Myocardial Substrate Metabolism Without Affecting Cardiac Triglyceride Accumulation and High-Energy Phosphate Metabolism in Patients With Well-Controlled Type 2 Diabetes Mellitus

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Background—Cardiac disease is the leading cause of mortality in type 2 diabetes mellitus (T2DM). Pioglitazone has been associated with improved cardiac outcome but also with an elevated risk of heart failure. We determined the effects of pioglitazone on myocardial function in relation to cardiac high-energy phosphate, glucose, and fatty acid metabolism and triglyceride content in T2DM patients.

Methods and Results—Seventy-eight T2DM men without structural heart disease or inducible ischemia as assessed by dobutamine stress echocardiography were assigned to pioglitazone (30 mg/d) or metformin (2000 mg/d) and matching placebo for 24 weeks. The primary end point was change in cardiac diastolic function from baseline relative to myocardial metabolic changes, measured by magnetic resonance imaging, proton and phosphorus magnetic resonance spectroscopy, and [¹⁸F]-2-fluoro-2-deoxy-D-glucose and [¹¹C]palmitate positron emission tomography. No patient developed heart failure. Both therapies similarly improved glycemic control, whole-body insulin sensitivity, and blood pressure. Pioglitazone versus metformin improved the early peak flow rate ($P=0.047$) and left ventricular compliance. Pioglitazone versus metformin increased myocardial glucose uptake ($P<0.001$), but pioglitazone-related diastolic improvement was not associated with changes in myocardial substrate metabolism. Metformin did not affect myocardial function but decreased cardiac work relative to pioglitazone ($P=0.006$), a change that was paralleled by a reduced myocardial glucose uptake and fatty acid oxidation. Neither treatment affected cardiac high-energy phosphate metabolism or triglyceride content. Only pioglitazone reduced hepatic triglyceride content ($P<0.001$).

Conclusions—In T2DM patients, pioglitazone was associated with improvement in some measures of left ventricular diastolic function, myocardial glucose uptake, and whole-body insulin sensitivity. The functional changes, however, were not associated with myocardial substrate and high-energy phosphate metabolism. (*Circulation*. 2009;119:2069-2077.)

Key Words: diabetes mellitus ■ cardiomyopathy ■ metabolism ■ magnetic resonance imaging ■ tomography

Cardiac disease is the leading cause of mortality in type 2 diabetes mellitus (T2DM).¹ In asymptomatic patients, cardiac abnormalities exist, even in the absence of coronary artery disease (CAD) or hypertension, due to diabetic cardiomyopathy.^{2,3} Increased left ventricular (LV) diastolic stiff-

ness is a common and early finding.³ Although diabetic cardiomyopathy is a multicausal condition, evidence obtained from animal studies indicates that diabetes-related metabolic abnormalities are the major contributors to the observed cardiac defects.³ Thus, increased nonesterified fatty acid

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(NEFA) fluxes that result in myocardial triglyceride accumulation, the formation of toxic intermediates, mitochondrial dysfunction, and oxidative stress have been implicated.³ Although NEFAs are the preferred cardiac substrate under physiological conditions, the heart should be able to readily switch to glucose oxidation during stress or ischemia.

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Because of prolonged exposure to an abnormal metabolic environment, the diabetic heart may lose its flexibility to switch between NEFA and glucose as substrates as required by the circumstances.⁴ Consequently, the initially adaptive mechanism will transform into a maladaptive vicious circle that leads to altered high-energy phosphate metabolism and contractile dysfunction.^{3,5} Mechanistic *in vivo* studies in humans are limited, but similar mechanisms have been proposed to underlie human diabetic cardiomyopathy.^{2,6–9}

By targeting lipotoxicity and insulin resistance, the blood glucose-lowering agent pioglitazone may favorably influence cardiac risk in T2DM.^{10,11} In the PROactive Study (PROspective pioglitazone Clinical Trial In macroVascular Events), pioglitazone reduced cardiovascular disease in high-risk patients with T2DM.¹² However, although pioglitazone improved cardiac function in experimental diabetic cardiomyopathy,^{13,14} its use in patients may result in heart failure due to fluid retention.¹⁵ Inasmuch as the majority of patients in the PROactive study had CAD and longstanding diabetes, it is feasible that cardiac inability to accommodate metabolic changes may have contributed to the pioglitazone-related heart failures. Indeed, substrate manipulation in heart failure due to CAD decreased myocardial efficiency and cardiac function,¹⁶ which reveals the close connection of metabolism and function in the compromised heart. At present, however, it is unknown whether interventions aimed at altering cardiac metabolism will lead to changes in function in the nonischemic diabetic heart. We studied the effect of pioglitazone versus metformin on myocardial function, dimensions, and perfusion in association with cardiac glucose and fatty acid metabolism, as well as triglyceride content and high-energy phosphate metabolism, using magnetic resonance imaging (MRI), magnetic resonance (MR) spectroscopy, and positron emission tomography (PET). To avoid confounding by ischemia, we performed the studies in patients with well-controlled T2DM of short duration and with verified absence of cardiac ischemia.

Methods

Study Design and Patients

The PIRAMID (Pioglitazone Influence on tRiglyceride Accumulation in the Myocardium In Diabetes) study was a 24-week prospective, randomized, double-blind, double-dummy with active comparator, 2-center parallel-group intervention. Men with uncomplicated T2DM, 45 to 65 years of age, were eligible. Inclusion criteria were a glycohemoglobin level of 6.5% to 8.5% at screening, body mass index [weight/(length²)] of 25 to 32 kg/m², and blood pressure not exceeding 150/85 mm Hg (with or without the use of antihypertensive drugs). Exclusion criteria were any clinically significant disorder, particularly any history or complaints of cardiovascular or liver disease or diabetes-related complications, and prior use of thiazo-

lidinediones or insulin. Written informed consent was obtained from all participants. The protocol was approved by the medical ethics committee of both centers, and the study was performed in full compliance with the Declaration of Helsinki.

Study Procedures

Participants underwent a 2-step screening procedure that consisted of a medical history, physical examination, ECG, Ewing tests to exclude autonomic neuropathy, and fasting blood and urine analysis (screening visit 1), as well as dobutamine stress echocardiography to exclude cardiac ischemia or arrhythmias (screening visit 2). After successful screening, participants entered a 10-week run-in period during which their previous blood glucose-lowering agents (metformin monotherapy 39.8%, sulfonylurea monotherapy 25.6%, and metformin and sulfonylurea combination therapy 34.6%) were washed out; they were transferred to glimepiride monotherapy, which was titrated until a stable dose was reached during the 8 weeks before randomization. Mean glycohemoglobin levels at screening and at the end of the run-in period were comparable (data not shown). All patients underwent MRI; the first 60 patients underwent both MRI and PET examinations (see below). Because of the demanding protocol, phosphorus MR (³¹P-MR) spectroscopy was offered as an optional test.

Patients were randomized to pioglitazone (15 mg once daily, titrated to 30 mg once daily after 2 weeks) or metformin (500 mg twice daily, titrated to 1000 mg twice daily) and matching placebo, to be taken in addition to glimepiride throughout the study. A randomization code list, with a block size of 4, was generated by the trial pharmacist (Amsterdam). Treatments were allocated chronologically and stratified for study center. All study investigators and study personnel were unaware of treatment assignment for the duration of the study. If recurrent hypoglycemia occurred, the glimepiride dose was lowered in a stepwise fashion to levels of nonoccurrence. Back titration to pioglitazone 15 mg once daily or metformin 500 mg twice daily was made if persistent, study drug-related side effects occurred. Patients were assessed in the fasting state at 2- to 8-week intervals for 24 weeks and underwent outcome measurements at baseline and at study termination as outlined below. They were requested to adhere to prestudy lifestyle and dietary habits throughout the study.

Cardiac MRI Protocol

MR assessments were performed after an overnight fast at a single site (Leiden) with a 1.5-T whole-body MR scanner (Gyroscan ACS/NT15; Philips, Best, the Netherlands). During MR examinations, blood samples were collected to determine substrates, and blood pressure and heart rate were monitored. Rate-pressure product was calculated as the product of systolic blood pressure and heart rate. The entire heart was imaged in the short-axis orientation with ECG-gated breath-hold balanced steady state free-precession imaging.¹⁷ Measures of systolic function were LV ejection fraction and cardiac index (cardiac index=cardiac output/body surface area). LV end-diastolic volume, LV end-systolic volume, and stroke volume were cardiac dimensions. An ECG-gated gradient echo sequence with velocity encoding was performed to measure blood flow across the mitral valve for the determination of LV diastolic function parameters, including peak filling rates of the early filling phase (E) and atrial contraction (A), and their ratio (E/A) was calculated. Also, the peak (E-dec_{peak}) and mean (E-dec_{mean}) deceleration gradients of E were calculated.¹⁷ LV filling pressures (E/Ea) were estimated.¹⁸ Images were analyzed quantitatively with dedicated software (MASS and FLOW, Medis, Leiden, the Netherlands).

Cardiac and Hepatic Proton MR Spectroscopy

Cardiac and hepatic proton MR spectroscopy (¹H-MRS) was performed as described previously.^{17,19} Briefly, myocardial ¹H-MRS spectra were obtained from the interventricular septum carefully to avoid contamination from epicardial fat. Spectroscopic data acquisition was double-triggered with ECG triggering and respiratory navigator echoes to minimize motion artifacts. Water-

suppressed spectra were acquired to measure myocardial triglyceride content, and spectra without water suppression were acquired and used as an internal standard.¹⁷ ¹H]-MRS data were fitted by use of Java-based MR user interface software (jMRUI version 2.2, Leuven, Belgium), as described previously.¹⁹ Myocardial triglyceride content relative to water was calculated as (signal amplitude of triglyceride)/(signal amplitude of water)×100.^{17,19} ¹H]-MRS of the liver was performed with an 8-mL voxel positioned in the liver, with care taken to avoid gross vascular structures and adipose tissue depots. The twelfth thoracic vertebra was used as a landmark to ensure the same voxel position during both visits. Sixty-four averages were collected with water suppression.¹⁹

Phosphorus MRS

A 100-mm-diameter surface coil was used to acquire ECG-triggered [³¹P]-MR spectra of the LV anterior wall with subjects in the supine position. Volumes of interest were selected by image-guided spectroscopy with 3D-ISIS. Shimming was performed automatically, and tuning and matching of the [³¹P] surface coil were performed manually. Technical details of data acquisition and spectral quantification were similar to those described previously.²⁰ In brief, spectroscopic volume size was typically 7×7×7 cm. Acquisitions were based on 192 averaged free induction decays, and total acquisition time was 10 minutes. [³¹P]-MR spectra were quantified automatically in the time domain by use of prior spectroscopic knowledge and were corrected for partial saturation effects and for the ATP contribution from blood in the cardiac chambers. The phosphocreatine/ATP ratios of the spectra were calculated and used as a parameter to represent myocardial high-energy phosphate metabolism.²¹

PET Imaging Protocol

PET examinations were performed after an overnight fast at a single center (Amsterdam) with an ECAT EXACT HR+ scanner (Siemens/CTI, Knoxville, Tenn). Patients received 2 venous catheters, 1 in the antecubital vein and 1 in the vein of the opposite hand, the latter being wrapped in a heated blanket to obtain arterialized blood. During procedures, patients were monitored by telemetry, and blood pressure was measured at 5-minute intervals. PET was used to measure myocardial blood flow with H₂¹⁵O; myocardial fatty acid uptake, β -oxidation, and esterification with [¹¹C]palmitate; and myocardial metabolic rate of glucose uptake (MMRglu) with [¹⁸F]-2-fluoro-2-deoxy-D-glucose (¹⁸FDG). Perfusion and NEFA metabolism were assessed in the fasting state, whereas MMRglu was measured during a euglycemic-hyperinsulinemic clamp procedure (see below). After a 10-minute transmission scan, H₂¹⁵O was injected (t=10 minutes), and a 10-minute dynamic emission scan (40 frames) was acquired. Subsequently, a 30-minute dynamic emission scan (34 frames) was performed after [¹¹C]palmitate injection (t=35 minutes). Next, the clamp procedure was begun (t=65 minutes), as described previously,²² to approximate an isometabolic steady state and measure whole-body insulin sensitivity. At steady state (approximately t=155 minutes), after a new transmission scan was performed, ¹⁸FDG was injected, and a 60-minute dynamic emission scan (40 frames) was acquired. Blood samples were collected during [¹¹C]palmitate and ¹⁸FDG scans at predefined time points to measure glucose, NEFA, lactate, lipids, and insulin levels. In addition, ¹¹CO₂ was measured during the [¹¹C]palmitate scan.⁹

PET Image Analysis

PET data were quantitatively reconstructed with filtered backprojection, with all appropriate corrections applied. To generate myocardial time-activity curves, regions of interest were defined on resliced LV short-axis (summed) [¹¹C]palmitate and ¹⁸FDG images and subsequently projected onto the dynamic images. Regions of interest were drawn as described previously²³ and grouped for further analysis. Myocardial segments exposed to liver spill-in were omitted from the analysis of [¹¹C]palmitate data. Additional regions of interest were defined in left and right ventricular chambers for [¹¹C]palmitate and H₂¹⁵O image-derived input functions. A separate

aorta ascendance region of interest was defined for ¹⁸FDG image-derived input functions.

Myocardial blood flow was determined with the standard single-tissue compartment model.²⁴ [¹¹C]palmitate time-activity curves were analyzed with a 3-tissue plasma input kinetic model, which, together with plasma NEFA concentrations, enabled calculation of myocardial fatty acid uptake, oxidation, and esterification.²⁵ The [¹¹C]palmitate image-derived input function was corrected for ¹¹CO₂ metabolites and the difference between plasma and whole-blood concentrations, as described elsewhere.⁹ This model is similar to that described by Bergmann et al²⁶ but has a reduced number of parameters, thereby increasing the precision of derived estimates (see online-only Data Supplement for details). MMRglu was calculated by multiplying the net influx constant for ¹⁸FDG, K_i, by the mean plasma glucose concentration. For determination of K_i, Patlak graphic analysis was used.²⁷

Study End Points

The primary end point was change from baseline to follow-up (24 weeks) in diastolic function as operationalized by the 4 parameters, ie, the E-dec_{peak} and E-dec_{mean}, early peak filling rate, and E/A ratio. Secondary efficacy measures included difference in cardiac dimensions, systolic function parameters, and myocardial metabolism and perfusion variables, as described above, as well as differences in hepatic and myocardial triglyceride content, body mass index, blood pressure, glycohemoglobin (reference values 4.3% to 6.1%), plasma lipids, and whole-body insulin sensitivity. Exploratory analyses included changes in the relation of LV end-diastolic volume and estimates of LV filling pressure, including N-terminal pro-brain natriuretic peptide, the ratio of early diastolic velocity (E) and early diastolic tissue velocity (Ea), and high-energy phosphate metabolism (phosphocreatine/ATP ratio). Blood samples for end-point measurements were analyzed at a central laboratory (Amsterdam).

Statistical Analysis

Because at the time of study design, no data were available relative to the effect of thiazolidinediones on MR-measured cardiac function, we based our sample-size calculations on previous MR studies.² To detect a subtle 15% (SD 20%) difference in the diastolic functional parameter of early peak filling rate with 90% power, ≈80 randomized patients were needed (primary end point). The sample size for the PET measurements was based on available PET studies.⁶ We calculated that 60 randomized patients would be necessary to detect a difference of 20% (SD 25%; estimated dropout rate 20%) in cardiac metabolism with 80% power. Values are shown as mean±SE or median (interquartile range) when nonnormally distributed. Between-group comparisons were performed with ANCOVA with adjustments for treatment group and baseline values. Within-group changes from baseline were assessed with independent paired *t* tests or Wilcoxon signed-rank tests. Correlations were calculated by Pearson's or Spearman's correlation analyses, as appropriate. All statistical tests were 2-sided, and significance was considered at the level of 0.05. Analyses were done with SPSS software version 15.0 (SPSS Inc, Chicago, Ill). This study was initiated, designed, performed, analyzed, and submitted for publication by the investigators at both centers, without any interference from the funding source.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Figure 1 shows the trial flowchart. At baseline, the study groups were well matched (Tables 1 and 2). Glimepiride dose adjustment was needed in 4 patients randomized to pioglitazone and in 3 assigned to metformin. Two patients required metformin back titration. No clinically evident fluid retention or heart failure occurred during the study.

At 24 weeks, pioglitazone and metformin similarly improved glycemic control versus baseline (Table 2). Pioglitazone

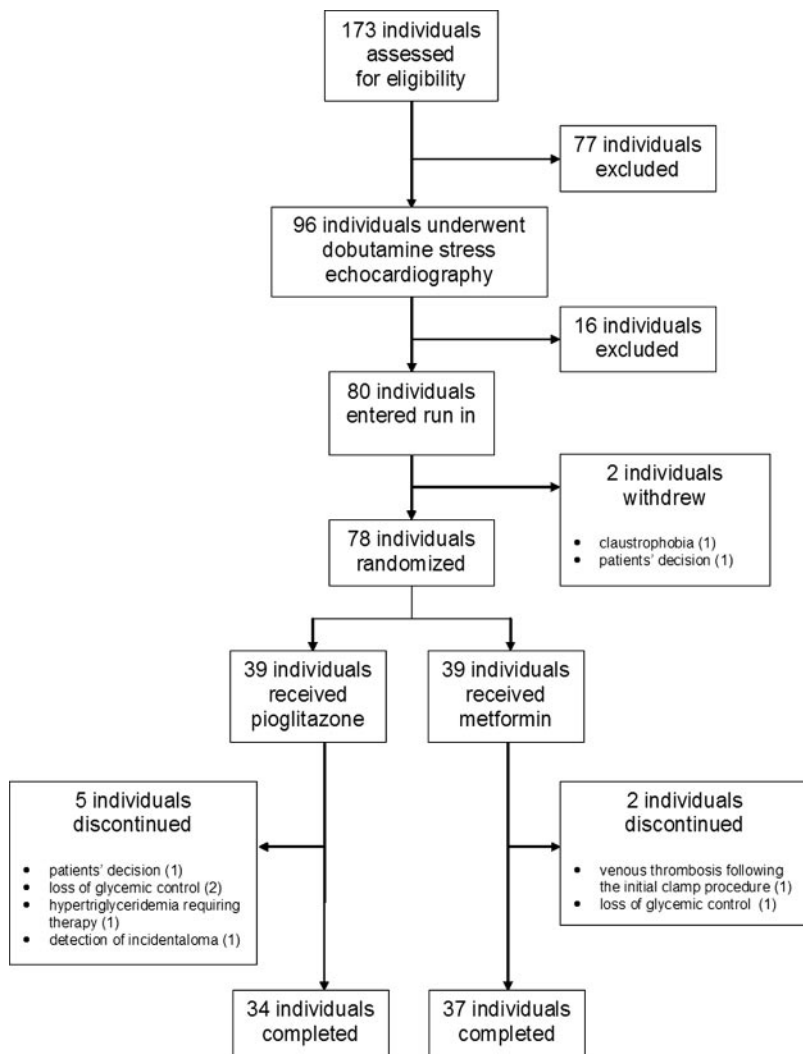


Figure 1. Trial profile.

zone versus metformin significantly increased HDL, whereas metformin decreased total cholesterol and LDL cholesterol levels (Table 2). Pioglitazone but not metformin induced weight gain relative to baseline (from 91 ± 2 to 94 ± 2 kg versus 92 ± 2 to 92 ± 3 kg; between-group $P < 0.001$). Both pioglitazone and metformin significantly improved whole-body insulin sensitivity, by a median 35.1% and 29.6%, respectively, which was paralleled by reduced NEFA levels during hyperinsulinemia that were more suppressed by pioglitazone (Table 2); however, neither treatment affected fasting NEFA levels. Metformin increased and pioglitazone decreased fasting lactate levels (Table 2). In both groups, similar decreases in systolic blood pressure and rate-pressure product were observed, whereas diastolic blood pressure and heart rate remained unchanged (Table 3).

At follow-up, pioglitazone increased indices of diastolic function, including $E\text{-dec}_{\text{peak}}$, $E\text{-dec}_{\text{mean}}$, and the early peak filling rate (Table 3). Pioglitazone-treated patients showed an increase in LV end-diastolic volume, whereas N-terminal pro-brain natriuretic peptide levels and E/E_a remained unchanged (Tables 2 and 3). In contrast to metformin, pioglitazone shifted the relations of LV end-diastolic volume and estimates of LV filling pressure toward improved compliance

(Figure 2A and 2B). Metformin had no significant effect on the diastolic cardiac parameters measured. Comparisons between groups of diastolic function parameters revealed a significant difference in early peak filling rate, whereas only a trend was observed for $E\text{-dec}_{\text{mean}}$ (Table 3). A significant between-group difference in stroke volume, cardiac index, and cardiac work was observed, whereas ejection fraction remained unaltered in both groups (Table 3).

PET examinations were successful in 54 subjects (90%). At follow-up, pioglitazone significantly increased and metformin markedly decreased MMR_{glu} from baseline (between-group $P < 0.001$; Figure 2C and 2D). At 24 weeks, pioglitazone and metformin therapy did not significantly change myocardial fatty acid uptake from baseline, whereas only metformin significantly reduced myocardial fatty acid oxidation (Figure 2D). Myocardial fatty acid esterification was negligible in both groups; however, increases from baseline were observed after pioglitazone and to a lesser extent after metformin therapy (Figure 2C and 2D). These minor changes measured by PET were not detected by the $[^1\text{H}]\text{-MRS}$ measurements, because myocardial triglyceride content remained unchanged in both groups (pioglitazone $0.77 \pm 0.05\%$ versus $0.82 \pm 0.07\%$; metformin $0.87 \pm 0.08\%$

Table 1. Patient Characteristics at Baseline*

	Pioglitazone (n=39)	Metformin (n=39)
Age, y	56.8±1.0	56.4±0.9
Time since diagnosis of diabetes, y	4 (3–6)	3 (1–5)
Current smoker, n (%)	10 (26)	7 (18)
Body mass index, kg/m ²	28.2±0.5	29.3±0.6
Waist circumference, cm	103.8±1.5	104.9±1.8
Concomitant medication, n (%)		
Statin	19 (48.7)	19 (48.7)
Any antihypertensive medication	19 (48.7)	15 (38.5)
β-Blocker	5 (12.8)	2 (5.1)
Diuretic	6 (15.4)	6 (15.4)
ACE inhibitor	9 (23.1)	9 (23.1)
ARB	6 (15.4)	3 (7.7)
Calcium antagonist	1 (2.6)	3 (7.7)

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

Values are presented as mean±SE, median (interquartile range), or No. and % of total.

*No statistically significant differences were found between treatment groups.

versus 0.89±0.07%; between-group *P*=0.774). In contrast, pioglitazone but not metformin decreased hepatic triglyceride content (pioglitazone 5.9% [2.6% to 17.4%] versus 4.1% [1.9% to 12.3%]; metformin 7.7% [3.7% to 23.9%] versus 10.7% [5.1% to 22.0%]; between-group *P*<0.001). Phosphocreatine/ATP ratio was successfully obtained on both study occasions from 22 patients (n=13 in the pioglitazone group), which was similar at baseline in both groups and was not influenced by either treatment (pioglitazone 2.02±0.06 ver-

sus 1.99±0.11; metformin 2.19±0.10 versus 2.04±0.07; between-group *P*=0.976). Phosphocreatine/ATP ratio of the remaining participants either could not be collected at baseline or at follow-up or appeared to be of insufficient spectral quality (Cramér-Rao SD >20%). Metformin but not pioglitazone slightly increased myocardial blood flow from baseline (metformin 0.86±0.05 to 0.93±0.04 g·mL⁻¹·min⁻¹; pioglitazone 0.94±0.04 versus 0.92±0.03 g·mL⁻¹·min⁻¹; between-group *P*=0.254). No associations were observed between pioglitazone-related changes in diastolic function and alterations in myocardial NEFA metabolism, MMRglu, or phosphocreatine/ATP ratio (data not shown).

Discussion

Pioglitazone but not metformin improved LV diastolic function and compliance in men with well-controlled, uncomplicated T2DM and verified absence of cardiac ischemia. Although both treatments improved whole-body insulin sensitivity, pioglitazone and metformin induced differential alterations in myocardial substrate utilization. These changes in substrate utilization did not affect high-energy phosphate metabolism or myocardial triglyceride content, but only pioglitazone significantly lowered hepatic triglyceride content. The effects of pioglitazone on diastolic function were not related to myocardial metabolism.

Thiazolidinedione-related improvements in cardiac diastolic function have been reported by some studies^{28,29} but not by others.^{30,31} These contrasting findings may be due to differences in study populations, severity and duration of diabetes, comorbid conditions (including preexistent cardiac dysfunction and CAD), medication use, and the use of echocardiography versus MRI in small populations. The relatively normal cardiac function at baseline may explain the seemingly

Table 2. Biochemical and Metabolic Characteristics and Whole-Body Insulin Sensitivity at Baseline and 24 Weeks

	Pioglitazone			Metformin			<i>P</i> (Between Groups)
	Baseline	24 Weeks	<i>P</i>	Baseline	24 Weeks	<i>P</i>	
Fasting							
HbA _{1c} , %	7.1±0.2	6.5±0.1	<0.001	7.0±0.1	6.3±0.1	<0.001	0.146
Plasma glucose, mmol/L	8.4 (7.2–10.3)	7.6 (6.7–9.4)	0.002	8.2 (6.8–9.1)	6.8 (5.8–7.4)	0.001	0.141
NEFA, mmol/L	0.45 (0.41–0.59)	0.46 (0.34–0.57)	0.369	0.53 (0.39–0.77)	0.49 (0.39–0.56)	0.136	0.933
Insulin, pmol/L	58 (38–83)	49 (34–70)	0.106	80 (31–99)	59 (32–98)	0.377	0.151
Lactate, mmol/L	1.2 (1.0–1.5)	1.0 (0.8–1.2)	0.001	1.1 (1.0–1.5)	1.5 (1.2–1.8)	0.012	0.001
Total cholesterol, mmol/L	4.5±0.1	4.6±0.2	0.374	4.9±0.2	4.5±0.2	0.001	0.042
LDL cholesterol, mmol/L	2.5±0.1	2.5±0.1	0.380	2.9±0.1	2.6±0.2	0.001	0.107
HDL cholesterol, mmol/L	1.07 (0.94–1.28)	1.23 (0.99–1.46)	0.003	1.13 (0.90–1.42)	1.02 (0.86–1.26)	0.133	0.009
Triglycerides, mmol/L	1.4 (1.0–2.2)	1.4 (0.9–2.3)	0.926	1.5 (0.9–2.1)	1.7 (0.9–2.3)	0.519	0.596
NT-proBNP, ng/L	24 (20–38)	26 (19–40)	0.731	32 (18–43)	33 (20–43)	0.134	0.505
During hyperinsulinemia							
NEFA, mmol/L	0.07 (0.05–0.13)	0.04 (0.02–0.05)	<0.001	0.09 (0.04–0.16)	0.06 (0.03–0.14)	0.006	0.036
Insulin, pmol/L	572 (503–620)	521 (447–590)	0.014	614 (540–710)	520 (472–601)	<0.001	0.292
Lactate, mmol/L	1.1 (1.0–1.3)	1.1 (1.0–1.2)	0.070	1.0 (0.9–1.3)	1.4 (1.2–1.7)	<0.001	0.001
M/I value, (mg/kg·min)/(pmol/L)	0.46 (0.28–0.73)	0.54 (0.43–0.97)	0.001	0.45 (0.19–0.80)	0.58 (0.35–1.00)	0.033	0.501

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; NT-proBNP, N-terminal pro-brain natriuretic peptide; and M/I value, whole-body insulin sensitivity adjusted during steady state.

Data are mean (SE) or median (interquartile range).

Table 3. Hemodynamic Parameters and Cardiac Dimensions and Function at Baseline and 24 Weeks

	Pioglitazone			Metformin			<i>P</i> (Between Groups)
	Baseline	24 Weeks	<i>P</i>	Baseline	24 Weeks	<i>P</i>	
Hemodynamics							
Systolic blood pressure, mm Hg	130±2	125±2	0.036	126±2	121±2	0.026	0.486
Diastolic blood pressure, mm Hg	77±1	74±1	0.064	74±1	73±1	0.118	0.971
Heart rate, beats/min	65±1	63±1	0.235	65±1	64±1	0.061	0.904
Rate pressure product, (beats/min) · mm Hg	8508±256	7853±195	0.040	8206±215	7744±193	0.009	0.771
Cardiac function and dimensions							
LV mass, g	108±2	105±3	0.171	107±3	103±3	0.066	0.542
LV end-systolic volume, mL	66±3	66±3	0.821	60±2	59±2	0.704	0.911
LV end-diastolic volume, mL	160±4	166±5	0.045	152±4	148±4	0.148	0.003
Stroke volume, mL	94±3	99±3	0.016	92±3	89±2	0.095	0.001
Ejection fraction, %	59±1	60±1	0.228	61±1	60±1	0.574	0.533
Cardiac index, L · min ⁻¹ · m ⁻²	2.9±0.1	2.9±0.1	0.845	2.9±0.1	2.7±0.1	0.019	0.008
Cardiac work, mm Hg · L ⁻¹ · min ⁻¹	57±2	57±2	0.898	55±2	50±2	0.002	0.006
E peak filling rate, mL/s	422±15	440±14	0.067	409±14	407±13	0.890	0.047
E-dec _{peak} , mL/s ² × 10 ⁻³	3.5±0.2	3.8±0.2	0.034	3.5±0.2	3.5±0.2	0.792	0.106
E-dec _{mean} , mL/s ² × 10 ⁻³	2.3±0.1	2.4±0.1	0.080	2.3±0.1	2.2±0.1	0.498	0.064
E/A peak flow	1.07±0.05	1.09±0.05	0.583	1.01±0.04	1.01±0.03	0.939	0.348
E/Ea	9.2 (7.4–11.4)	9.1 (6.6–12.0)	0.695	9.3 (6.3–12.3)	10.3 (8.3–11.8)	0.203	0.254

Data are mean±SE, except for E/Ea, which is median (interquartile range).

modest pioglitazone-induced diastolic functional improvements in patients in the present study. Given the absence of treatment-related effects on the MR estimate of LV filling pressure (E/Ea) in both treatment groups, we hypothesize that pioglitazone-improved LV compliance accounts for the ob-

served favorable changes in the transmitral filling pattern. The most important finding in LV functional change, however, was the pioglitazone-related increase in LV end-diastolic volume at similar estimates of LV filling pressure, which is compatible with an improved LV compliance.^{32,33} These data

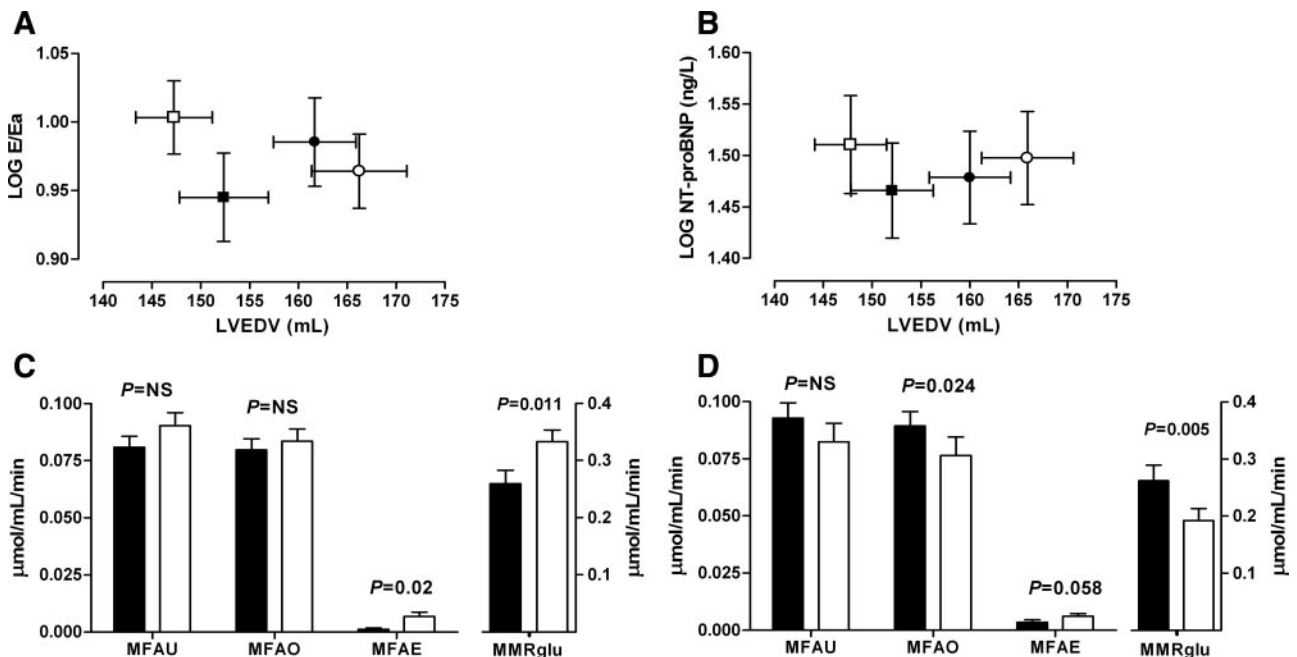


Figure 2. Relations of LV end-diastolic volume (LVEDV) and estimates of LV filling pressure, including E/Ea (A) and N-terminal pro-brain natriuretic peptide (NT-proBNP; B), before (black) and after (white) 24 weeks of treatment with pioglitazone (circles) or metformin (squares). Myocardial fatty acid uptake (MFAU), oxidation (MFAO), and esterification (MFAE) and the metabolic rate of glucose uptake (MMRglu) in patients with T2DM before (black) and after (white) 24 weeks of treatment with pioglitazone (C) or metformin (D). Probability values for between-group differences: MFAU, *P*=0.056; MFAO, *P*=0.091; MFAE, *P*=0.467; and MMRglu, *P*=0.001. Myocardial fatty acid metabolism was assessed during fasting, and myocardial glucose metabolism was assessed during hyperinsulinemia.

are in line with earlier findings in diabetic rats showing that pioglitazone improved diastolic function by reducing myocardial collagen content and by favorably affecting matrix remodeling.^{13,34} A more recently described mechanism possibly underlying the observed LV compliance improvement may be the pioglitazone-induced inhibition of macrophage chemotaxis, cardiac macrophage expression of proinflammatory genes, and secretion of the inflammatory glycoprotein osteopontin, which is associated with myocardial fibrosis and stiffness.³⁵

Only pioglitazone increased stroke volume, as reported by others, possibly owing to a decrease in peripheral resistance.³⁶ Metformin trended to decrease cardiac index, which is compatible with the reported metformin-related effects on cardiac sympathovagal balance.³⁷ Both treatments induced similar decreases in systolic blood pressure and rate-pressure product, whereas diastolic blood pressure and heart rate remained unchanged. Although previous studies showed comparable decreases in systolic blood pressure after thiazolidinedione therapy, the observation that systolic blood pressure was also reduced by metformin suggests that part of the changes in systolic blood pressure may be attributed to an initial stress response rather than to the effect of therapy.³⁸

The present study is timely in light of the ongoing debate on the safety profile of thiazolidinediones.^{39,40} During this short-term trial, we observed no cardiac events or heart failure. In the PROactive Study population, the majority of whom had a history of CAD, pioglitazone use was associated with an increased risk of heart failure. The present data indicate that when pioglitazone is used in patients with uncomplicated T2DM without cardiac ischemia, it may reverse the process of cardiac concentric remodeling, which is among the hallmarks of diabetic cardiomyopathy, by shifting the LV end-diastolic pressure-volume relation toward improved compliance. However, it is conceivable that in patients with compromised hearts, in particular those with (ischemic) dilated cardiomyopathy, pioglitazone may actually promote the risk of overt heart failure.

Cardiac glucose uptake was assessed under hyperinsulinemic euglycemic conditions to standardize metabolic conditions and to improve the signal-to-noise ratio. Because NEFA substrate metabolism was measured in the fasting state, direct reciprocal associations of cardiac glucose and NEFA metabolism were limited. Both treatments induced significant albeit different changes in cardiac substrate metabolism. Pioglitazone increased MMRglu, which may be due to the simultaneous reduction of competing substrates, in particular NEFA, but also may be due to direct enhancement of myocardial insulin signaling and expansion of the available pool and translocation of GLUT-4 receptors in the heart.³¹

Metformin significantly lowered MMRglu and myocardial fatty acid oxidation. These changes were paralleled by an increase in plasma lactate, although NEFA levels decreased during hyperinsulinemia and remained unchanged during fasting. Others have shown a trend toward MMRglu decline but no changes in lactate levels in 9 patients after 26-week metformin therapy.⁴¹ The normal human heart may be regarded as a metabolically flexible omnivore that utilizes the most energy-efficient substrate available. Although NEFAs

are the preferential substrate because they have the highest ATP yield, during stress, increased workload, and ischemia, the heart can switch to energetically more favorable substrates, including glucose and lactate.³ Because myocardial lactate uptake has been shown to be directly proportional to circulating lactate levels,⁴² it might be speculated that metformin could have increased myocardial lactate utilization, as was previously shown for skeletal muscle.⁴³ However, the observed decreases in cardiac glucose and NEFA metabolism in the metformin group might also be linked to the treatment-related reduction in cardiac work, because less ATP needs to be generated to maintain adequate high-energy phosphate levels.

Unexpectedly, and contrary to findings from animal studies, we found no association between treatment-related cardiac functional and metabolic changes. Few and partly conflicting data exist on NEFA uptake/utilization in the human (pre)diabetic heart and its relation to cardiac function.^{44,45} On the basis of animal studies, it was proposed that the diabetic heart primarily relies on the abundantly supplied NEFA in the presence of myocardial insulin resistance.⁴⁶ Chronically elevated NEFA utilization may lead to impaired β -oxidation, accumulation of toxic intermediates, production of reactive oxygen species, mitochondrial dysfunction, and finally, cardiac functional abnormalities. Because glucose oxidation relative to NEFA oxidation requires less oxygen per mole of ATP produced, therapies that enhance myocardial glucose utilization, including insulin and thiazolidinediones, have been advocated in T2DM patients with cardiac ischemia. However, it is unknown whether enforced myocardial glucose use is beneficial in all circumstances.

Similarly, rosiglitazone increased MMRglu in T2DM patients with CAD without affecting echocardiographically measured function.³¹ Additionally, indirect stimulation of myocardial glucose metabolism by acute deprivation of NEFA by acipimox in heart failure patients resulted in depressed cardiac work and efficiency.¹⁶ These findings support the notion that compromised hearts may lose their flexibility to respond to imposed changes in substrate availability and readily switch to another substrate. In contrast, it is likely that the myocardiums of patients with uncomplicated T2DM of short duration still possesses sufficient oxidative capacity to benefit from NEFA as the preferential myocardial substrate. Forced glucose utilization in these patients will not necessarily lead to improved cardiac function. Because changes in myocardial metabolism and function in the pioglitazone-treated patients were not related, it is unlikely that the improvement in diastolic function originated from altered metabolism.

Because we did not measure myocardial oxygen consumption, no calculation of treatment-related changes in cardiac efficiency can be made. Nevertheless, because resting perfusion is tightly coupled to oxidative metabolism, the unchanged cardiac work and resting perfusion after pioglitazone may suggest that cardiac efficiency was unaffected by this therapy. In contrast, metformin significantly reduced cardiac work and increased resting perfusion, both of which effects appear compatible with an actual reduction in cardiac efficiency. These changes, however, did not translate into a decrease in phosphocreatine/ATP ratio, which implies an

adaptive cardiac response sufficient to preserve high-energy phosphate metabolism. Additional studies addressing the effects of these pharmacological interventions relative to myocardial energetics and efficiency in T2DM are warranted.

Pioglitazone decreased hepatic but not myocardial triglyceride content, which indicates differential regulation of various body lipid compartments. We recently found an independent association between diastolic function and myocardial triglyceride content in T2DM patients,⁴⁷ which confirms and extends previous data from McGavock et al.⁸ However, as noted earlier, because myocardial triglyceride content was not altered by pioglitazone, the improvements in LV filling dynamics and compliance were likely caused by other mechanisms.^{13,34,35} The actual mechanisms by which pioglitazone improved LV diastolic function and compliance, however, could not be identified in the present study with the present technology. Further studies are therefore warranted to define those mechanisms.

The major asset of the present study is the combined use of PET, MRI/[¹H]-MRS, and [³¹P]-MR to evaluate the cardiac effects of pioglitazone and metformin. The relatively short intervention time and the exclusion of women and patients with ischemia, however, are limitations that preclude generalization of the results.

Conclusions

Only pioglitazone improved LV diastolic function and compliance, whereas both pioglitazone and metformin altered myocardial substrate metabolism, likely owing to treatment-specific changes in plasma substrate levels. Pioglitazone-related improvement in diastolic function was not associated with concomitant alterations in myocardial substrate metabolism. Treatment with pioglitazone in patients with uncomplicated, well-controlled T2DM and absence of cardiac ischemia might be beneficial, as demonstrated by the improved diastolic function and LV compliance, in the presence of unaltered myocardial high-energy phosphate metabolism.

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Disclosures

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References

1. Grundy SM, Howard B, Smith S Jr, Eckel R, Redberg R, Bonow RO. Prevention Conference VI: diabetes and cardiovascular disease: executive summary: conference proceeding for healthcare professionals from a special writing group of the American Heart Association. *Circulation*. 2002;105:2231–2239.
2. Diamant M, Lamb HJ, Groeneveld Y, Endert EL, Smit JW, Bax JJ, Romijn JA, de Roos A, Radder JK. Diastolic dysfunction is associated with altered myocardial metabolism in asymptomatic normotensive

- patients with well-controlled type 2 diabetes. *J Am Coll Cardiol*. 2003;42:328–335.
3. Boudina S, Abel ED. Diabetic cardiomyopathy revisited. *Circulation*. 2007;115:3213–3223.
4. Taegtmeyer H, Goffman L, Sharma S, Razeghi P, van Arsdall M. Linking gene expression to function: metabolic flexibility in the normal and diseased heart. *Ann N Y Acad Sci*. 2004;1015:202–213.
5. Goffman LS, Wilson CR, Sharma S, Burgmaier M, Young ME, Guthrie PH, Van Arsdall M, Adroge JV, Brown KK, Taegtmeyer H. Activation of PPARgamma enhances myocardial glucose oxidation and improves contractile function in isolated working hearts of ZDF rats. *Am J Physiol Endocrinol Metab*. 2005;289:E328–E336.
6. Mäki M, Nuutila P, Laine H, Voipio-Pulkki LM, Haaparanta M, Solin O, Knuuti JM. Myocardial glucose uptake in patients with NIDDM and stable coronary artery disease. *Diabetes*. 1997;46:1491–1496.
7. Iozzo P, Chareonthaitawee P, Dutka D, Betteridge DJ, Ferrannini E, Camici PG. Independent association of type 2 diabetes and coronary artery disease with myocardial insulin resistance. *Diabetes*. 2002;51:3020–3024.
8. McGavock JM, Lingvay I, Zib I, Tillery T, Salas N, Unger R, Levine BD, Raskin P, Victor RG, Szczepaniak LS. Cardiac steatosis in diabetes mellitus: a ¹H-magnetic resonance spectroscopy study. *Circulation*. 2007;116:1170–1175.
9. Herrero P, Peterson LR, McGill JB, Matthew S, Lesniak D, Dence C, Gropler RJ. Increased myocardial fatty acid metabolism in patients with type 1 diabetes mellitus. *J Am Coll Cardiol*. 2006;47:598–604.
10. Hardie DG. Role of AMP-activated protein kinase in the metabolic syndrome and in heart disease. *FEBS Lett*. 2007;582:81–89.
11. Diamant M, Heine RJ. Thiazolidinediones in type 2 diabetes mellitus: current clinical evidence. *Drugs*. 2003;63:1373–1405.
12. Dormandy JA. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitazone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet*. 2005;366:1279–1289.
13. Tsuji T, Mizushige K, Noma T, Murakami K, Ohmori K, Miyatake A, Kohno M. Pioglitazone improves left ventricular diastolic function and decreases collagen accumulation in prediabetic stage of a type II rat. *J Cardiovasc Pharmacol*. 2001;38:868–874.
14. Kim SK, Zhao ZS, Lee YJ, Lee KE, Kang SM, Choi D, Lim SK, Chung N, Lee HC, Cha BS. Left-ventricular diastolic dysfunction may be prevented by chronic treatment with PPAR-alpha or -gamma agonists in a type 2 diabetic animal model. *Diabetes Metab Res Rev*. 2003;19:487–493.
15. Fang ZY, Schull-Meade R, Downey M, Prins J, Marwick TH. Determinants of subclinical diabetic heart disease. *Diabetologia*. 2005;48:394–402.
16. Tuunanen H, Engblom E, Naum A, Nägren K, Hesse B, Airaksinen KE, Nuutila P, Iozzo P, Ukkonen H, Opie LH, Knuuti J. Free fatty acid depletion acutely decreases cardiac work and efficiency in cardiomyopathic heart failure. *Circulation*. 2006;114:2130–2137.
17. van der Meer RW, Hammer S, Smit JW, Frölich M, Bax JJ, Diamant M, Rijzewijk LJ, de Roos A, Romijn JA, Lamb HJ. Short-term caloric restriction induces accumulation of myocardial triglycerides and decreases left ventricular diastolic function in healthy subjects. *Diabetes*. 2007;56:2849–2853.
18. Paelinck BP, de Roos A, Bax JJ, Bosmans JM, van Der Geest RJ, Dhondt D, Parizel PM, Vrints CJ, Lamb HJ. Feasibility of tissue magnetic resonance imaging: a pilot study in comparison with tissue Doppler imaging and invasive measurement. *J Am Coll Cardiol*. 2005;45:1109–1116.
19. van der Meer RW, Doornbos J, Kozerke S, Schär M, Bax JJ, Hammer S, Smit JW, Romijn JA, Diamant M, Rijzewijk LJ, de Roos A, Lamb HJ. Metabolic imaging of myocardial triglyceride content: reproducibility of ¹H MR spectroscopy with respiratory navigator gating in volunteers. *Radiology*. 2007;245:251–257.
20. Lamb HJ, Doornbos J, den Hollander JA, Luyten PR, Beyerbach HP, van der Wall EE, de Roos A. Reproducibility of human cardiac ³¹P-NMR spectroscopy. *NMR Biomed*. 1996;9:217–227.
21. Bottomley LA. MR spectroscopy of the human heart: the status and the challenges. *Radiology*. 1994;191:593–612.
22. DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol*. 1979;237:E214–E223.
23. Knaapen P, Boellaard R, Götte MJ, Dijkmans PA, van Campen LM, de Cock CC, Luurtsema G, Visser CA, Lammertsma AA, Visser FC. Per-

- fusible tissue index as a potential marker of fibrosis in patients with idiopathic dilated cardiomyopathy. *J Nucl Med.* 2004;45:169–175.
24. Hermansen F, Rosen SD, Fath-Ordoubadi F, Kooner JS, Clark JC, Camici PG, Lammertsma AA. Measurement of myocardial blood flow with oxygen-15 labelled water: comparison of different administration protocols. *Eur J Nucl Med.* 1998;25:751–759.
 25. Jong HWAM, Rijzewijk LJ, Lubberink M, Meer van der RW, Lamb HJ, Smit JWA, Diamant M, Lammertsma AA. Kinetic models for analysing myocardial [¹¹C]palmitate data. *Eur J Nucl Med Mol Imaging.* Published online before print January 27, 2009. doi: 10.1007/s00259-008-1035-3. Available at: <http://www.springerlink.com/content/520vx7166551n025/>. Accessed April 3, 2009.
 26. Bergmann SR, Weinheimer CJ, Markham J, Herrero P. Quantitation of myocardial fatty acid metabolism using PET. *J Nucl Med.* 1996;37:1723–1730.
 27. Patlak CS, Blasberg RG. Graphical evaluation of blood-to-brain transfer constants from multiple-time uptake data: generalizations. *J Cereb Blood Flow Metab.* 1985;5:584–590.
 28. Horio T, Suzuki M, Suzuki K, Takamisawa I, Hiuge A, Kamide K, Takiuchi S, Iwashima Y, Kihara S, Funahashi T, Yoshimasa Y, Kawano Y. Pioglitazone improved LV diastolic function in patients with essential hypertension. *Am J Hypertens.* 2005;18:949–957.
 29. von Bibra H, Diamant M, Scheffer PG, Siegmund T, Schumm-Draeger PM. Rosiglitazone, but not glimepiride, improves myocardial diastolic function in association with reduction in oxidative stress in type 2 diabetic patients without overt heart disease. *Diab Vasc Dis Res.* 2008;5:310–318.
 30. St John Sutton M, Rendell M, Dandona P, Dole JF, Murphy K, Patwardhan R, Patel J, Freed M. A comparison of the effects of rosiglitazone and glyburide on cardiovascular function and glycaemic control in patients with type 2 diabetes. *Diabetes Care.* 2002;25:2058–2064.
 31. Lautamäki R, Airaksinen KE, Seppänen M, Toikka J, Luotolahti M, Ball E, Borra R, Härkönen R, Iozzo P, Stewart M, Knuuti J, Nuutila P. Rosiglitazone improves myocardial glucose uptake in patients with type 2 diabetes and coronary artery disease: a 16-week randomised, double-blind, placebo-controlled study. *Diabetes.* 2005;54:2787–2794.
 32. van Heerebeek L, Hamdani N, Handoko ML, Falcao-Pires I, Musters RJ, Kupreishvili K, Jsselmuiden AJ, Schalkwijk CG, Bronzwaer JG, Diamant M, Borbély A, van der Velden J, Stienen GJ, Laarman GJ, Niessen HW, Paulus WJ. The failing diabetic heart: importance of fibrosis, advanced glycation endproducts and myocyte stiffness. *Circulation.* 2008;117:43–51.
 33. Solomon SD, St John Sutton M, Lamas GA, Plappert T, Rouleau JL, Skali H, Moyé L, Braunwald E, Pfeffer MA; Survival And Ventricular Enlargement (SAVE) Investigators. Ventricular remodeling does not accompany the development of heart failure in diabetic patients after myocardial infarction. *Circulation.* 2002;106:1251–1255.
 34. Shiomi T, Tsutsui H, Hayashidani S, Suematsu N, Ikeuchi M, Wen J, Ishibashi M, Kubota T, Egashira K, Takeshita A. Pioglitazone, a peroxisome proliferator-activated receptor-gamma agonist, attenuates left ventricular remodeling and failure after experimental myocardial infarction. *Circulation.* 2002;106:3126–3132.
 35. Caglayan E, Stauber B, Collins AR, Lyon CJ, Yin F, Liu J, Rosenkranz S, Erdmann E, Peterson LE, Ross RS, Tangirala RK, Hsueh WA. Differential roles of cardiomyocyte and macrophage peroxisome proliferator-activated receptor gamma in cardiac fibrosis. *Diabetes.* 2008;57:2470–2479.
 36. Ghazali MN, Perez JE, Antonucci TK, Driscoll JH, Huang SM, Faja BW, Whitcomb RW. Cardiac and glycaemic benefits of troglitazone treatment in NIDDM: the Troglitazone Study Group. *Diabetes.* 1997;46:433–439.
 37. Manzella D, Grella R, Esposito K, Giugliano D, Barbagallo M, Paolisso G. Blood pressure and cardiac autonomic nervous system in obese type 2 diabetic patients: effect of metformin administration. *Am J Hypertens.* 2004;17:223–227.
 38. Wulffélé MG, Kooy A, de Zeeuw D, Stehouwer CD, Gansevoort RT. The effect of metformin on blood pressure, plasma cholesterol and triglycerides in type 2 diabetes mellitus: a systematic review. *J Intern Med.* 2004;256:1–14.
 39. Lincoff AM, Wolski K, Nicholls SJ, Nissen SE. Pioglitazone and risk of cardiovascular events in patients with type 2 diabetes mellitus: a meta-analysis of randomized trials. *JAMA.* 2007;298:1180–1188.
 40. Singh S, Loke YK, Furberg CD. Long-term risk of cardiovascular events with rosiglitazone: a meta-analysis. *JAMA.* 2007;298:1189–1195.
 41. Hällsten K, Virtanen KA, Lönnqvist F, Janatuinen T, Turiceanu M, Rönnemaa T, Viikari J, Lehtimäki T, Knuuti J, Nuutila P. Enhancement of insulin-stimulated myocardial glucose uptake in patients with type 2 diabetes treated with rosiglitazone. *Diabet Med.* 2004;21:1280–1287.
 42. Herrero P, Dence CS, Coggan AR, Kisrieva-Ware Z, Eisenbeis P, Gropler RJ. L-3-¹¹C-Lactate as a PET tracer of myocardial lactate metabolism: a feasibility study. *J Nucl Med.* 2007;48:2046–2055.
 43. Stumvoll M, Nurjhan N, Perriello G, Dailey G, Gerich JE. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. *N Engl J Med.* 1995;333:550–554.
 44. Turpeinen AK, Kuikka JT, Vanninen E, Uusitupa MI. Abnormal myocardial kinetics of ¹²³I-heptadecanoic acid in subjects with impaired glucose tolerance. *Diabetologia.* 1997;40:541–549.
 45. Knuuti J, Takala TO, Nägren K, Sipilä H, Turpeinen AK, Uusitupa MI, Nuutila P. Myocardial fatty acid oxidation in patients with impaired glucose tolerance. *Diabetologia.* 2001;44:184–187.
 46. Carley AN, Severson DL. Fatty acid metabolism is enhanced in type 2 diabetic hearts. *Biochim Biophys Acta.* 2005;1734:112–126.
 47. Rijzewijk LJ, van der Meer RW, Smit JW, Diamant M, Bax JJ, Hammer S, Romijn JA, de Roos A, Lamb HJ. Myocardial steatosis is an independent predictor of diastolic dysfunction in type 2 diabetes mellitus. *J Am Coll Cardiol.* 2008;52:1793–1799.

CLINICAL PERSPECTIVE

Cardiac disease is the leading cause of mortality in type 2 diabetes mellitus. The blood glucose-lowering thiazolidinedione pioglitazone has been associated with improved cardiac outcome but also with an elevated risk of congestive heart failure. Use of metformin, at present the drug of choice in the treatment of type 2 diabetes mellitus, showed improved outcome in the United Kingdom Prospective Diabetes Study but has been related to adverse cardiac events in other studies. Using magnetic resonance imaging and proton and phosphorus magnetic resonance spectroscopy, as well as [¹⁸F]-2-fluoro-2-deoxy-D-glucose and [¹¹C]palmitate positron emission tomography, this randomized, controlled, double-blinded study investigated the effects of 24-week treatment with pioglitazone or metformin on myocardial function and metabolism in men with well-controlled, uncomplicated type 2 diabetes mellitus who had no clinical evidence of myocardial ischemia. The major findings revealed that pioglitazone but not metformin improved left ventricular diastolic function and cardiac compliance. In addition, pioglitazone and metformin showed differential action on myocardial substrate metabolism; however, this did not translate into alterations in myocardial high-energy phosphate metabolism or myocardial triglyceride content. Both agents improved whole-body insulin sensitivity. None of the treatments were associated with clinically evident edema or congestive heart failure. These data suggest that for male patients with well controlled, uncomplicated type 2 diabetes mellitus without cardiac ischemia, treatment with pioglitazone may be a good safe option because it may favorably influence myocardial function.

Supplemental material

For [^{11}C]palmitate kinetic analysis, a modification of the three tissue plasma input model as proposed by Schelbert ¹ and Bergmann ² was used which is shown in Figure X. The first tissue compartment is the cytosol and the third is the mitochondrion. The second compartment describes the slow turnover pool of esterified [^{11}C]palmitate. A total of three rate constants between the compartments were used. The first, k_{p1} , simply reflects myocardial perfusion and capillary permeability for [^{11}C]palmitate. This perfusion phase is followed by two elimination phases. The first elimination phase is considered to represent beta-oxidation, k_{13} , and it is clinically the most important. The parameter k_{12} mainly reflects esterification into a slow turnover pool.³ Spill-over of activity from the left ventricle pool into the myocardium was also included in the model.

The model is an optimized trade-off between detail in tracer physiology and accuracy of parameter estimation. To this end, back-diffusion of unaltered [^{11}C] Palmitate (k_{1p}) was omitted since it mathematically cannot be estimated independently from the parallel oxidation-path (k_{13} , k_{3p}). Furthermore, the transfer rate from the esterification pool back to the cell k_{21} was fixed to zero based on earlier findings that this rate is orders of magnitude smaller than the influx k_{12} in the pool.^{3,4} Finally, k_{3p} was fixed equal to k_{13} , based on the assumption that no $^{11}\text{CO}_2$ is accumulated in the cell.

As input to the model, [^{11}C]palmitate concentrations were determined by correcting venous whole-blood samples for plasma /whole blood concentration ratios and $^{11}\text{CO}_2$ levels.

Oxidation and esterification were described using mathematical indices MFAO and MFAE that can directly be calculated from the model ^{3,4}: $\text{MFAO} = C_{\text{NEFA}} \times k_{p1} \times k_{13}/(k_{12} + k_{13})$, $\text{MFAE} = C_{\text{NEFA}} \times k_{p1} \times k_{12}/(k_{12} + k_{13})$, where C_{NEFA} is the plasma fatty acid concentration [mmol/mL]. The total fatty acid utilization MFAU was defined as the sum of MFAO and MFAE.

Supplemental references

1. Schelbert HR. Features of positron emission tomography as a probe for myocardial chemistry. *Eur J Nucl Med.* 1986;12:s2–s10
2. Bergmann SR, Weinheimer CJ, Markham J, Herrero P. Quantitation of myocardial fatty acid kinetics using PET. *J Nucl Med.* 1996;37:1723–1730.
3. A.K. Turpeinen, J.T. Kuikka, E. Vanninen, M. I.J. Uusitupa. Abnormal myocardial kinetics of 123I-heptadecanoic acid in subjects with impaired glucose tolerance. *Diabetologia.* 1997;40:541-9.
4. DeGrado TR, Holden JE, Ng CK, Raffel DM, Gatley SJ. Quantative analysis of myocardial kinetics of 15-*p*-[Iodine-125]Iodophenylpentadecanoic acid. *J Nucl Med.* 1989;30:1211–1218.

Supplemental figure

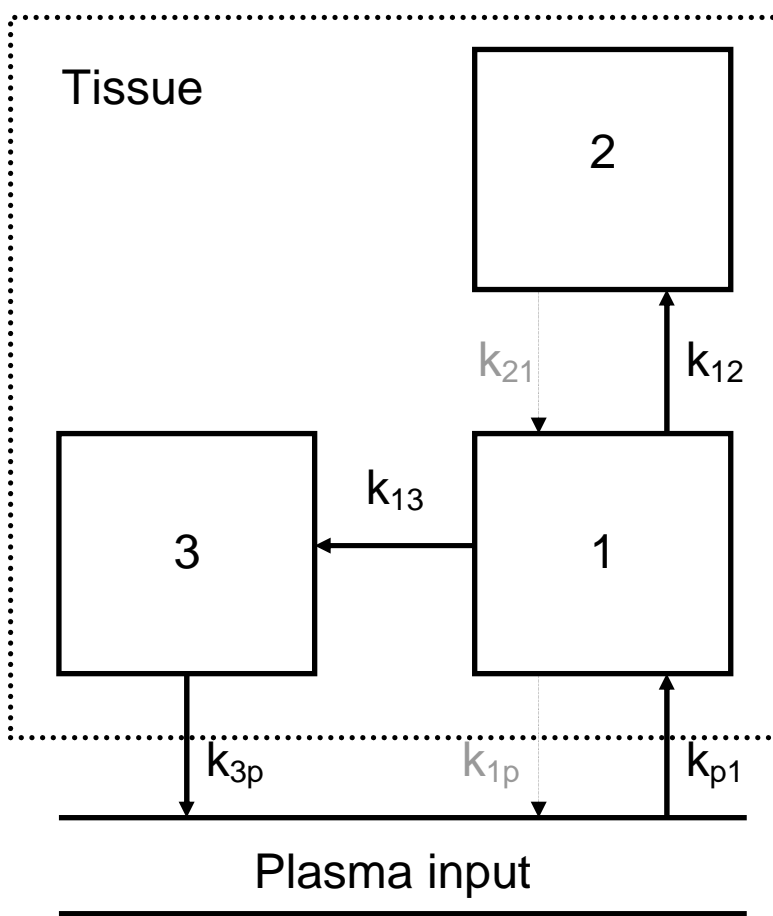


Fig X: Modified Bergmann model for myocardial $[^{11}\text{C}]$ palmitate kinetics