Pioglitazone Improves Left Ventricular Diastolic Function in Subjects With Diabetes

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OBJECTIVE

To examine the effect of pioglitazone on myocardial insulin sensitivity and left ventricular (LV) function in patients with type 2 diabetes (T2D).

RESEARCH DESIGN AND METHODS

Twelve subjects with T2D and 12 with normal glucose tolerance received a euglycemic insulin clamp. Myocardial glucose uptake (MGU) and myocardial perfusion were measured with [^{18}F]fluoro-2-deoxy-D-glucose and [^{15}O]H_2O positron emission tomography before and after 24 weeks of pioglitazone treatment. Myocardial function and transmitral early diastolic relation/atrial contraction (E/A) flow ratio were measured with magnetic resonance imaging.

RESULTS

Pioglitazone reduced HbA_{1c} by 0.9%; decreased systolic and diastolic blood pressure by 7 ± 2 and 7 ± 2 mmHg, respectively ($P < 0.05$); and increased whole-body insulin-stimulated glucose uptake by 71% (3.4 ± 1.3 to 5.8 ± 2.1 mg/kg · min; $P < 0.01$) in subjects with T2D. Pioglitazone enhanced MGU by 75% (0.24 ± 0.14 to 0.42 ± 0.13 μmol/min · g; $P < 0.01$) and myocardial perfusion by 16% (0.95 ± 0.16 to 1.10 ± 0.25 mL/min · g; $P < 0.05$). Measures of diastolic function, E/A ratio (1.04 ± 0.3 to 1.25 ± 0.4) and peak LV filling rate (349 ± 107 to 433 ± 99 mL/min), both increased ($P < 0.01$). End-systolic volume, end-diastolic volume, peak LV ejection rate, and cardiac output trended to increase (P not significant), whereas the ejection fraction (61 ± 6 to 66 ± 7%) and stroke volume increased significantly (71 ± 20 to 80 ± 20 L/min; both $P < 0.05$).

CONCLUSIONS

Pioglitazone improves whole-body and myocardial insulin sensitivity, LV diastolic function, and systolic function in T2D. Improved myocardial insulin sensitivity and diastolic function are strongly correlated.

The incidence of cardiovascular (CV) disease, including myocardial infarction, stroke, and heart failure, is increased two- to threefold in patients with type 2 diabetes (T2D) (1,2). Heart failure is an ominous sign in patients with diabetes, and 50% of those with T2D and heart failure die within 5 years (3). Diastolic dysfunction is a common abnormality in T2D found on echocardiography, yet most patients with T2D are asymptomatic (4–6).

Peripheral tissues, including skeletal (7) and cardiac (8,9) muscle, liver (10), and adipose tissue (11), are resistant to insulin in T2D. We and others have shown that pioglitazone is a potent insulin sensitizer in skeletal muscle, liver, and adipocytes (7,12–16). However, only one study examined the effect of pioglitazone on myocardial

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insulin sensitivity and demonstrated that pioglitazone increases myocardial insulin sensitivity and parameters of cardiac function, but no correlation between improved cardiac function and increase in myocardial insulin sensitivity was observed (8). The effect of pioglitazone on myocardial insulin sensitivity in T2D is of considerable clinical importance because myocardial insulin resistance has been implicated in the development of myocardial dysfunction and accelerated coronary atherosclerosis (4,5,17–19).

In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive), pioglitazone significantly reduced the main second end point (CV death, nonfatal myocardial infarction, nonfatal stroke) (hazard ratio 0.84; $P = 0.017$), although the decrease in primary end point (major adverse CV events plus peripheral vascular disease) did not reach statistical significance because of an increase in leg revascularization (20), which we now know is refractory to glucose-, lipid-, and blood pressure–lowering therapies (21–23). In PROactive, the incidence of heart failure in pioglitazone-treated subjects was stated to be increased (20), but heart failure was not adjudicated, and overall mortality and CV events tended to decline (not increase) in the pioglitazone-treated group with heart failure. Because heart failure is an ominous sign in T2D, with 5-year mortality of ~50% (24), that these subjects really had heart failure is unlikely. The recently published Insulin Resistance Intervention After Stroke trial results are consistent with those of PROactive (25). In 3,876 patients with recent stroke or transient ischemic attack, pioglitazone reduced the incidence of recurrent stroke and cardiovascular events by 24% ($P < 0.001$). No difference in incidence of heart failure ($P = 0.80$) or hospitalization for heart failure ($P = 0.35$) was observed.

In the current study, we used cardiac magnetic resonance imaging (MRI) to quantify LV diastolic and systolic function and the euglycemic insulin clamp with positron emission tomography (PET) to quantify whole-body (primarily reflects muscle) and myocardial insulin sensitivity before and after pioglitazone treatment. Contrary to common belief (13,26–29), we hypothesized that pioglitazone improves—not impairs—parameters of LV diastolic and systolic function.

RESEARCH DESIGN AND METHODS

Subjects

Twelve patients with T2D (age 51 ± 9 years, 10 males, 2 females, HbA_{1c} 6.8 ± 1.6%, diabetes duration 4.0 ± 3.1 years, BMI 30.8 ± 4.3 kg/m^2, 7 Mexican American, 5 Caucasian) without clinically manifested CV disease participated in the study (Table 1). Subjects with T2D were drug naïve ($n = 4$) or treated with metformin ($n = 7$) or metformin/sulfonylurea ($n = 1$). We did not observe any differences regarding the effect of pioglitazone on either diastolic function or myocardial insulin sensitivity between drug-naïve and metformin-treated subjects, but the number of subjects in each group was small. Other than having diabetes, all subjects were in good general health as determined by medical history, physical examination, screening blood tests, urinalysis, and a normal electrocardiogram. Body weight was stable (±3 lb) for at least 3 months before study entry. All subjects were normally active, and none participated in an excessively heavy exercise program. Other than metformin and/or sulfonylurea, no subject was taking any medication known to affect glucose metabolism. Ten subjects were taking a statin, and 10 were taking an antihypertensive medication (ACE inhibitor $n = 7$, angiotensin receptor blocker $n = 3$, calcium channel blocker $n = 1$).

Twelve healthy subjects with normal glucose tolerance (NGT) (age 47.7 ± 10.5 years, BMI 28.4 ± 0.4 kg/m^2, HbA_{1c} 5.5 ± 0.4%; eight males, four females, nine Mexican American, three Caucasian) served as the control group. The entry criteria for the control group were similar to those for the T2D group. The protocol was approved by institutional review board of the University of Texas Health Science Center (San Antonio, TX), and written informed consent was obtained from all subjects.

Table 1—Metabolic and cardiac MRI values obtained in control subjects with NGT and subjects with T2D before and after pioglitazone treatment

	NGT control	T2D baseline	T2DM after pioglitazone
Sex, *n*			
Male	9	10	10
Female	3	2	2
Age (years)	47.7 ± 10.5	50.7 ± 9.1	51.3 ± 9.1
BMI (kg/m^2)	28.4 ± 4.4	30.8 ± 4.3	31.3 ± 4.2
Body fat (%)	29.3 ± 8.6	31.9 ± 5.7	33.4 ± 6.1
HbA_{1c} (%)	5.5 ± 0.4	6.7 ± 1.3***	5.6 ± 0.8‡
Fasting plasma glucose (mg/dL)	93 ± 6	149 ± 48***	112 ± 23†
Fasting FFAs (mmol/L)	0.32 ± 0.1	0.52 ± 0.17***	0.30 ± 0.14‡
HDL cholesterol (mg/dL)	55.7 ± 9.8	38.8 ± 11.9***	41.5 ± 9.7†
Triacylglycerol (mg/dL)	128 ± 94	265 ± 155***	153 ± 74‡
Matsuda index of insulin sensitivity	8.7 ± 4.8	2.8 ± 1.9***	5.8 ± 3.4‡
Glucose infusion rate (mg/kg · min)	7.5 ± 2.8	3.4 ± 1.3***	5.8 ± 2.1‡
MGU (μmol/min · g)	0.38 ± 0.14	0.24 ± 0.14*	0.42 ± 0.13‡
Myocardial perfusion (mL/min · g)	0.83 ± 0.20	0.95 ± 0.16	1.10 ± 0.25†
Systolic function			
Resting heart rate (beats/min)	63.3 ± 6.8	78.1 ± 10.5**	71.3 ± 11.3
Cardiac index (L/min · m^2)	2.85 ± 0.32	2.90 ± 0.70	2.91 ± 0.74
EF (%)	64.2 ± 4.7	60.7 ± 6.3	65.6 ± 6.9†
Stroke volume/BSA (mL/m^2)	42.7 ± 5.0	37.7 ± 7.3*	41.7 ± 8.5†
Peak LV ejection rate/BSA (mL/s · m^2)	226 ± 36	224 ± 52	255 ± 54
Myocardial mass/BSA (g/m^2)	60.2 ± 9.4	64.1 ± 8.5	61.4 ± 8.6
Diastolic function			
Transmitral E/A flow ratio	1.48 ± 0.37	1.04 ± 0.28**	1.25 ± 0.38‡
ESV/BSA (mL/m^2)	26.4 ± 9.7	24.3 ± 5.4	21.2 ± 5.3
EDV/BSA (mL/m^2)	69.1 ± 10.3	61.9 ± 9.1*	62.9 ± 9.3
PLVFR/BSA (mL/s · m^2)	196 ± 33	171 ± 52*	212 ± 54‡

Data are mean ± SD. *$P < 0.05$; **$P < 0.01$; ***$P < 0.005$ determined by unpaired *t* test for T2D baseline vs. NGT control. †$P < 0.05$ and ‡$P < 0.01$ for T2D baseline vs. T2D after pioglitazone (determined by paired *t* test).

Study Design

At baseline, HbA_{1c} and fasting plasma glucose (FPG), insulin, and lipid concentrations were measured. At 8:00 A.M., after a 10-h overnight fast, a 2-h oral glucose tolerance test (OGTT) (75 g) was performed, with measurements of plasma glucose, insulin, and C-peptide every 15 min. DEXA (Hologic, Waltham, MA) was performed to determine total body fat and lean mass.

Cardiac MRI Studies

Within 1 week after the OGTT, subjects returned for a cardiac MRI study to assess cardiac morphology and function (30). Within 3–7 days after the MRI study, subjects returned for a euglycemic insulin clamp study to measure whole-body (primarily reflects skeletal muscle) insulin sensitivity (31).

MRI was performed on a 3.0-T system (TIM Trio; Siemens Healthcare, Malvern, PA) with a six-channel anterior phased-array torso coil and corresponding posterior coil elements (12 channels total). Axial and sagittal localizer views; standard cardiac two-, three-, and four-chamber views; and 7-mm-thick slices were obtained by using gradient echo sequence (2.2×1.3-mm^2 pixel area). Cine imaging with retrospective gating was used with a balanced steady-state free precession sequence (repetition time/echo time 2.44/1.22 ms). Acquisitions consisted of 25–30 cardiac phases (matrix 224×288, field of view [FOV] 336×430 mm^2, 1.5×1.5-mm^2 pixel area), which varied slightly by subject body size and heart rate. Contiguous short-axis slices were acquired during repetitive breath-holds at end expiration. Mitral inflow images were obtained by using phase-contrast gradient-echo sequence with through-plane velocity encoding (V_{enc} = 100 cm/s) at the mitral valve (flip angle 10°, repetition time/echo time 5.8/3.6 ms). Phase-contrast gradient-echo slice thickness was 8 mm (typical FOV 228×430 mm^2, matrix 192×102), producing $2.89 \times 2.89 \times 8.0$-$mm^3$ pixel volumes (30).

Euglycemic Insulin Clamp and PET

Cardiac PET study was performed in subjects with T2D while concurrently undergoing the insulin clamp. Subjects reported to the Research Imaging Institute at 7:00 A.M. after a 10-h overnight fast. PET scans were performed in two-dimensional imaging mode by using an ECAT 931-08/12 PET scanner (Control Technology Inc., Knoxville, TN) with a 10.5-cm axial FOV and resolution of $8.4 \times 8.3 \times 6.6$ mm^3 full width at half maximum. After optimization of subject position, a 20-min transmission scan was performed after exposure of a retractable ^{68}Ge ring source to correct emission data for tissue attenuation of γ-photons. Next, $[^{15}O]H_2O$ (10.5 MBq/kg) was administered through the catheter over 20 s, and the PET scan (10 mL/min) was performed to measure myocardial blood flow (MBF) as previously described (31).

Before the euglycemic insulin clamp (32), a catheter (for blood withdrawal) was placed in a vein on the dorsum of the hand, which rested in a box heated to 60°C (30). A second catheter for infusion of test substances was inserted into an antecubital vein. During the 30 min before the start of the insulin clamp, three baseline blood samples were drawn at 15-min intervals to allow sufficient time for decay of ^{15}O radioactivity. At time 0, a primed continuous insulin ($40\ mU \cdot m^{-2} \cdot min^{-1}$) infusion was started for 150 min, and blood samples were drawn at 5–30-min intervals. No glucose was infused until plasma glucose concentration declined to 100 mg/dL, at which level it was maintained by variable infusion of 20% glucose. At 90 min after the start of insulin, $[^{15}O]H_20$ was infused over 20 seconds for repeat measurement of MBF. At 105 min, $[^{18}F]$fluoro-2-deoxy-D-glucose ($[^{18}F]$FDG) (185 MBq) was infused, and a dynamic PET scan was performed for measurement of myocardial glucose uptake (MGU) as previously described (33). All radioactive tracers were produced at the onsite cyclotron radiochemistry facility.

Pioglitazone Treatment

After completion of the above studies, subjects with T2D were started on pioglitazone 15 mg/day. After 2 weeks, the dose was increased to 30 mg/day for 2 weeks. At week 4, the dose was increased to 45 mg/day and continued for an additional 20 weeks (total treatment period 24 weeks). Subjects received dietary counseling before initiation of pioglitazone therapy and were asked to consume a standard weight-maintaining American Diabetes Association diet throughout. Patients returned for follow-up every 2–4 weeks. After 24 weeks, baseline studies were repeated.

Data Analysis

MRI data were analyzed blindly by one of the investigators (G.D.C.), who used a commercial postprocessing package (cmr^{42}; Circle Cardiovascular Imaging, Calgary, AB, Canada). The cmr^{42} function module performed global and regional LV function analyses on slices acquired in short-axis orientation. LV volumes and myocardial mass were calculated with trabeculae and papillary muscles included. The cmr^{42} flow module computed velocity, flow, regurgitant volumes, and cardiac output. Ejection fraction (EF) was computed by using end-diastolic volume (EDV) and end-systolic volume (ESV). For determining differences between the control and pretreatment T2D groups, dimensional parameters were normalized to body surface area (BSA) by using the Mosteller equation (34). Ejection and filling functions were assessed from the respective maximal and average downslope and upslope of volume time curves to determine the peak LV ejection rate and peak LV filling rate (PLVFR).

PET sinograms were corrected for tissue attenuation and reconstructed through standard reconstruction algorithms. Image manipulation and data handling were performed by using MATLAB software (MathWorks, Natick, MA) (35). The input function for $[^{18}F]$FDG was derived from continuous monitoring of arterialized blood radioactivity. Whole blood was converted into plasma input by using a limited number of discrete plasma samples. Delay correction was performed. Arterial input for $[^{15}O]H_2O$ was obtained from the left atrium time-activity curve. The glucose infusion rate during the last 30 min of insulin clamp was stable in all studies and was averaged to obtain a measure of total-body insulin-mediated glucose disposal.

Statistical Analysis

Data are expressed as mean $\pm$ SD or as percentages. Statistical analyses were performed by using R version 3.2.1 statistical software with RStudio integrated development environment version 0.99.467. Unpaired two-sided Student *t* test was used to evaluate the null hypothesis of no difference between the baseline (prepioglitazone) T2D and control groups. Paired two-sided Student *t* test was used to evaluate the null hypothesis of no difference between the baseline (prepioglitazone) and posttreatment

pioglitazone studies in T2D. $P < 0.05$ was deemed significant.

RESULTS

The control and T2D groups were similar in age, BMI, body fat, and sex (Table 1). HbA_{1c}, FPG, and fasting plasma free fatty acids (FFAs) were lower in the control versus T2D group at baseline ($P < 0.005$). The Matsuda index of insulin sensitivity was greater in the control versus T2D group at baseline ($P < 0.001$) (Table 1).

EDV and ESV, normalized to BSA, were greater in control subjects (69.1 ± 10.3 mL/m^2 and 26.4 ± 9.7 mL/m^2, respectively; both $P < 0.05$) versus subjects with T2D (61.9 ± 9.1 mL/m^2 and 24.3 ± 5.4 mL/m^2, respectively). Early diastolic relaxation/atrial contraction (E/A) ratio was significantly higher ($P < 0.01$) in the control (1.48 ± 0.37) versus T2D (1.04 ± 0.28) group. PLVFR/BSA was significantly greater ($P < 0.05$) in control subjects (196 ± 33 mL/s · m^2) versus subjects with T2D (171 ± 52 mL/s · m^2).

In the subjects with T2D, pioglitazone reduced HbA_{1c} (6.7 ± 1.3 to 5.6 ± 0.8%; $P < 0.01$), FPG (149 ± 48 to 112 ± 23 mg/dL; $P < 0.05$), and fasting plasma FFAs (0.52 ± 0.17 to 0.30 ± 0.14 mmol/L; $P < 0.01$) (Table 1). Insulin-stimulated whole-body (primarily reflects skeletal muscle) glucose uptake increased from 3.4 ± 1.3 to 5.8 ± 2.1 mg/kg · min ($P < 0.01$), and the Matsuda index of insulin sensitivity during OGTT increased from 2.8 ± 1.9 to 5.8 ± 3.4 ($P < 0.01$). After pioglitazone treatment, MGU (measured with [^{18}F]FDG PET scan), increased from 0.24 ± 0.14 to 0.42 ± 0.13 μmol/min · g ($P < 0.01$), and MBF (measured with [^{15}O]H_2O PET scan) increased from 0.95 ± 0.16 to 1.10 ± 0.25 mL/min · g tissue ($P < 0.05$).

After pioglitazone treatment, both systolic (124 ± 12 to 117 ± 10 mmHg) and diastolic (80 ± 9 to 73 ± 9 mmHg) blood pressure were reduced ($P < 0.05$). Percent body fat and BMI increased slightly (P not significant) after pioglitazone (Table 1). Edema was observed in 2 of the 12 subjects treated with pioglitazone and was considered to be mild in both.

Also after pioglitazone treatment, parameters of systolic function (determined by cardiac MRI) improved. Stroke volume increased from 37.7 ± 7.3 to 41.7 ± 8.5 mL/m^2 ($P < 0.05$), and EF increased from 60.7 ± 5.1 to 65.6.0 ± 6.9% ($P < 0.05$). Resting heart rate decreased modestly (P not significant). Diastolic dysfunction improved after pioglitazone. Transmitral E/A ratio (1.04 ± 0.28 to 1.25 ± 0.38; $P < 0.01$) and PLVFR (171 ± 52 to 212 ± 54 mL/s · m^2; $P < 0.01$) both increased markedly. No significant differences in LV volumes or myocardial mass were found (Table 1).

Change in HbA_{1c} correlated inversely with insulin-stimulated glucose disposal during insulin clamp ($r = -0.47$; $P < 0.05$) and with the change in MGU ($r = -0.64$; $P = 0.02$) after pioglitazone treatment. The decrement in plasma FFAs also correlated with the change in MGU ($r = -0.67$; $P = 0.02$) (Supplementary Fig. 1).

Insulin-stimulated whole-body (muscle) glucose uptake during insulin clamp correlated positively and strongly with MGU ($r = 0.50$; $P = 0.01$) (Fig. 1*A*) and both measures of diastolic function (transmitral E/A ratio: $r = 0.52$; $P = 0.01$; PLVFR: $r = 0.55$; $P = 0.005$) (Fig. 1*A* and *B*). The Matsuda index of insulin sensitivity correlated positively with MGU ($r = 0.51$; $P = 0.01$).

The increase in E/A ratio after pioglitazone treatment was strongly correlated with the reduction in HbA_{1c} ($r = -0.74$; $P < 0.01$) (Fig. 2*A*), increase in MGU ($r = 0.51$; $P = 0.03$) (Fig. 2*B*), and increase in insulin-stimulated whole-body glucose uptake during insulin clamp ($r = 0.58$; $P = 0.047$) (Fig. 2*C*). The change in PLVFR after pioglitazone treatment correlated with change in HbA_{1c} ($r = -0.56$; $P < 0.05$) and tended to correlate with the change in MGU ($r = 0.51$; $P = 0.09$) and insulin-stimulated whole-body glucose uptake ($r = 0.46$; $P = 0.13$) during insulin clamp (Fig. 3*A–C*). The change in E/A ratio correlated strongly with PLVFR after pioglitazone treatment ($r = 0.69$; $P < 0.001$).

CONCLUSIONS

The current study provides three novel findings. To our knowledge, this study is

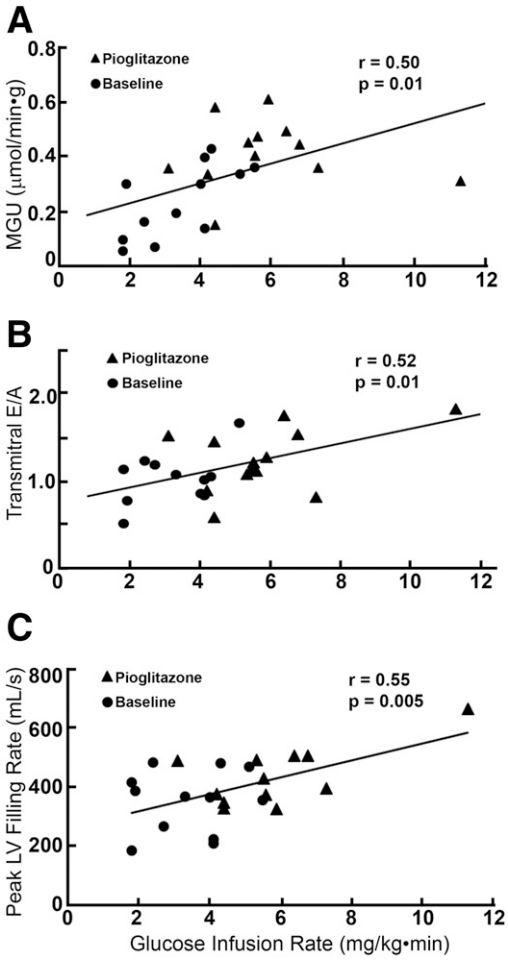

Figure 1—Correlation between insulin-stimulated whole-body glucose disposal (glucose infusion rate) and MGU (*A*), transmitral E/A ratio (*B*), and PLVFR (*C*) in subjects with T2D before (●) and after (▲) pioglitazone treatment.

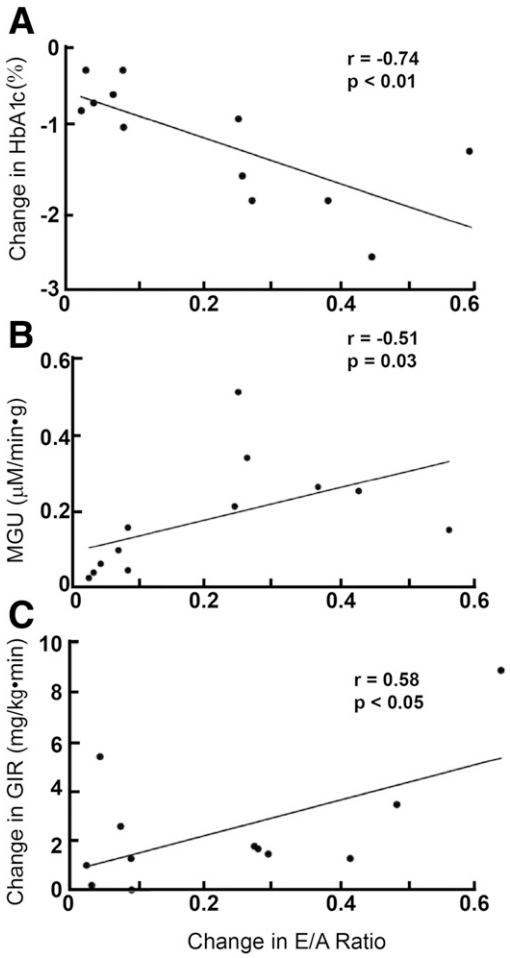

Figure 2—Correlation between the change in transmitral E/A ratio and change in HbA_{1c} (*A*), MGU (*B*), and glucose infusion rate (GIR) (*C*) during insulin clamp after pioglitazone treatment.

the first to *1*) simultaneously quantitate myocardial and skeletal muscle insulin resistance in the same subject and to document a strong correlation between the two; *2*) demonstrate that pioglitazone or any thiazolidinedione improves both diastolic and systolic function in patients with T2D without clinical CV disease; and *3*) demonstrate that the improvements in diastolic and systolic function are closely related to improved myocardial (and skeletal muscle) insulin sensitivity after pioglitazone treatment. Consistent with previous results (8), the current study demonstrates that pioglitazone does not exert any negative effects on cardiac function in patients with T2D without clinically manifest CV disease and that diastolic dysfunction is present early in the natural history of these patients.

Insulin resistance in skeletal muscle is a characteristic feature of T2D (7). Myocardial insulin resistance also has been demonstrated in individuals with T2D with and without coronary artery disease (8,9). Diastolic dysfunction and increased LV diastolic stiffness are commonly observed in T2D. These abnormalities are observed early in the natural history of T2D and have been related to underlying myocardial insulin resistance (4,5,19). FFAs are the major metabolic fuel for the heart; however, under conditions of ischemia, the heart switches to glucose utilization because of the higher ATP yield per amount of oxygen consumed (5). The diabetic heart has been postulated to lose its metabolic flexibility because of myocardial insulin resistance (18,19), and this is associated with myocardial lipid accumulation, inflammation, increased collagen formation, myocardial stiffness, and a noncompliant LV (4,5,8,19). Thiazolidinediones are potent insulin sensitizers in skeletal muscle (7,36), and both rosiglitazone (37) and pioglitazone (8) augment insulin-mediated MGU in patients with T2D. In the rosiglitazone study (37), no measures of myocardial function were performed, and in the pioglitazone study (8), no correlation between improved myocardial insulin resistance and cardiac function was observed. In diabetic rodents treated with pioglitazone, a reduction in myocardial collagen content was demonstrated in association with improved LV function (38). Collectively, these results suggest that pioglitazone improves LV diastolic dysfunction, but whether this improvement is related to the increase in myocardial insulin sensitivity/MGU is unclear. On the other hand, pioglitazone therapy is associated with fluid retention (39,40) and can lead to heart failure, especially in patients with T2D and underlying diastolic dysfunction (20), raising concern about the use of thiazolidinediones in T2D. However, salt and water retention with peroxisome proliferator–activated receptor-γ agonists is related to enhanced renal sodium reabsorption and, as demonstrated by the current results, not to a negative effect on the myocardium. To the contrary, pioglitazone improved all parameters of LV diastolic dysfunction, including the transmitral E/A ratio, PLVFR, and EDV (Table 1). Key parameters of systolic function also were enhanced with pioglitazone. Thus, in patients with T2D with diastolic dysfunction but without clinically evident CV disease, pioglitazone improved parameters of diastolic as well as systolic LV function. These findings are consistent with an echocardiographic study in patients with T2D (41). Of note, consistent with previous results (24,42), pioglitazone reduced both systolic and diastolic blood pressure while reducing heart rate. Thus, despite pioglitazone's renal sodium retentive effect, blood pressure dropped most likely secondary to vasodilation, leading to afterload reduction, and this could partly explain the beneficial effect of pioglitazone on both LV systolic and LV diastolic function.

Although the insulin sensitizing effect of thiazolidinediones on skeletal muscle is well established (7), the effect of thiazolidinediones on myocardial insulin sensitivity has been less well studied (8,33). In the current study, pioglitazone improved skeletal muscle and myocardial insulin sensitivity in subjects with T2D by 71% and 75%, respectively, and a strong correlation between the these increases was observed (P = 0.50 and $P < 0.01$,

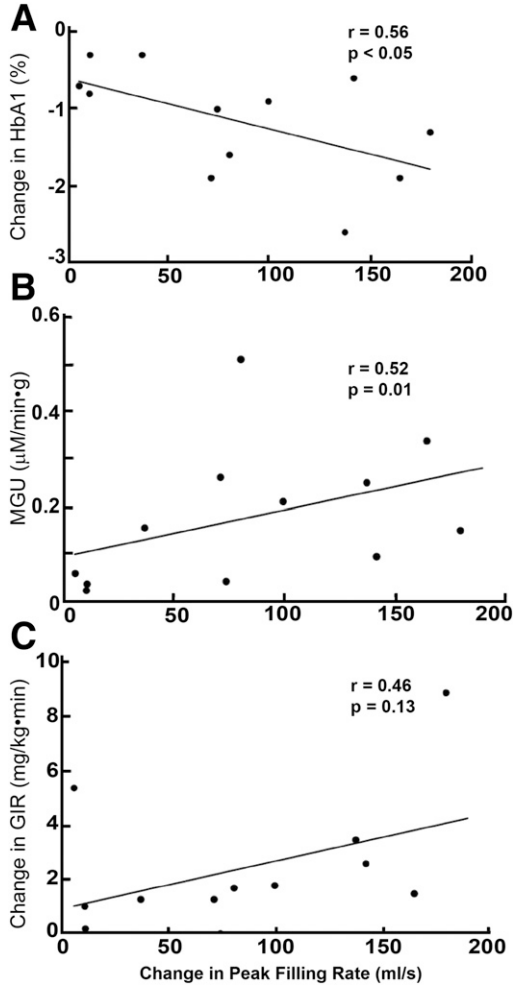

Figure 3—Correlation between the change in PLVFR and change in HbA_{1c} (*A*), MGU (*B*), and glucose infusion rate (GIR) (*C*) during insulin clamp after pioglitazone treatment.

respectively) (Fig. 1). The myocardial insulin sensitizing effect of pioglitazone is consistent with that reported previously (8,37), but these studies did not measure skeletal muscle insulin sensitivity. The current results indicate that both skeletal and cardiac muscle insulin resistance is characteristic of T2D. Of note, our results demonstrate for the first time to our knowledge a strong correlation between improved myocardial (and skeletal muscle) insulin sensitivity and improved diastolic dysfunction, as manifested by the increased E/A ratio (Fig. 2) and PLVFR (Fig. 3). The study by van der Meer et al. (8) also showed increases in myocardial insulin sensitivity and LV diastolic function in pioglitazone-treated patients but did not find a significant correlation between these two variables. These authors' failure to detect a correlation stands in contrast to the current results and may be explained by the higher daily dose of pioglitazone (45 vs. 30 mg) used in the current study or by the difference in study design and/or concomitant antidiabetic therapy (10-week washout followed by a switch to glimepiride monotherapy).

Both lipotoxicity and glucotoxicity contribute to skeletal muscle insulin resistance in T2D (7). The current results suggest that these same pathogenic factors also play a role in diabetic myocardial insulin resistance. Both the decrement in HbA_{1c} ($r = -0.64$; $P = 0.02$) and the decrement in plasma FFAs ($r = -0.67$; $P = 0.02$) correlated with enhanced insulin-stimulated myocardial glucose uptake after pioglitazone treatment (Supplementary Fig. 1). Similarly, improvements in E/A ratio and PLVFR were related to the reduction in HbA_{1c} ($r = -0.74$ and -0.56, respectively; both $P < 0.05$) (Figs. 2 and 3). In the current study, we observed a 21% increase in insulin-stimulated MBF after pioglitazone treatment, and thiazolidinediones have been shown to augment insulin signaling in skeletal muscle (43). Thus, multiple factors (improved glycemic control, reduced plasma FFAs, increased MBF, increased insulin signaling) could have contributed to the improvement in myocardial insulin sensitivity, whereas both amelioration of myocardial insulin resistance and decrease in blood pressure likely contributed to enhanced LV diastolic and systolic function.

The study has several limitations. First, the number of subjects was relatively small. Second, we specifically enrolled patients with T2D who did not have clinically manifest cardiac disease. Whether similar results would be observed in T2D with longer duration of diabetes and clinical evidence of cardiac dysfunction remains to be examined. Third, radiolabeled glucose was not used; therefore, insulin-stimulated whole-body (skeletal muscle) glucose uptake may have been underestimated in the subjects with T2D during baseline insulin clamp because of incomplete suppression of endogenous glucose production. However, even if endogenous glucose production continued at 0.5–1.0 mg/kg · min (the latter value is unlikely), pioglitazone treatment still would have significantly increased skeletal muscle insulin sensitivity.

In summary, the results demonstrate that 6 months of pioglitazone treatment in patients with T2D without clinically evident CV disease ameliorates myocardial insulin resistance, augments MBF, improves both LV diastolic and LV systolic function, and reduces blood pressure while decreasing heart rate. These observations indicate that *1*) LV diastolic dysfunction in T2D is closely correlated with myocardial insulin resistance and that both are improved by pioglitazone and *2*) pioglitazone exerts no negative effects on myocardial function and can be used safely in patients with T2D without clinically evident CV disease.

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