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Pilot Study of Pioglitazone and Exercise Training Effects on Basal Myocardial Substrate Metabolism and Left Ventricular Function in HIV-Positive Individuals with Metabolic Complications

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Abstract

Background—Individuals with HIV infection and peripheral metabolic complications have impaired basal myocardial insulin sensitivity that is related to left ventricular (LV) diastolic dysfunction. It is unknown whether interventions shown to be effective in improving peripheral insulin sensitivity can improve basal myocardial insulin sensitivity and diastolic function in people with HIV and peripheral metabolic complications.

Objective—In a pilot study, we evaluated whether the peroxisome proliferator-activated receptor-gamma (PPAR- γ) agonist pioglitazone or combined endurance and resistance exercise training improves basal myocardial insulin sensitivity and diastolic function in HIV+ adults with peripheral metabolic complications.

Design—Twenty-four HIV+ adults with metabolic complications including peripheral insulin resistance were randomly assigned to 4 months of pioglitazone (PIO; 30 mg/d) or supervised, progressive endurance and resistance exercise training (EXS; 90–120 min/d, 3 d/wk). Basal myocardial substrate metabolism was quantified by radioisotope tracer methodology and positron emission tomography (PET) imaging, and LV function was measured by echocardiography.

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Results—Twenty participants completed the study. Neither PIO nor EXS resulted in a detectable improvement in basal myocardial insulin sensitivity or diastolic function. Post hoc analyses revealed sample sizes of more than 100 participants are needed to detect significant effects of these interventions on basal myocardial insulin sensitivity and function.

Conclusions—PIO or EXS alone did not significantly increase basal myocardial insulin sensitivity or LV diastolic function in HIV+ individuals with peripheral metabolic complications.

Keywords

exercise; HIV; insulin resistance; left ventricular dysfunction; metabolic syndrome

Despite advances in combination antiretroviral therapy (cART) that reduce morbidity and mortality, individuals infected with HIV are at a greater risk for left ventricular (LV) dysfunction^{1–3} than the general population. Approximately 50% of HIV-infected people treated with cART develop a cluster of peripheral metabolic complications that include traditional cardiovascular disease risk factors such as peripheral insulin resistance,^{4,5} abdominal adiposity,⁶ dyslipidemia,^{7–9} and elevated blood pressure¹⁰; these are all components of the metabolic syndrome.¹¹ Even in the absence of severe HIV disease (eg, AIDS-related cardiomyopathy), individuals with well-controlled HIV infection have diastolic function abnormalities that are associated with basal myocardial insulin resistance,¹² suggesting that myocardial metabolic abnormalities may play a role in the development of LV dysfunction in these individuals.

Myocardial insulin resistance, especially in the presence of metabolic inflexibility,^{13,14} may result in contractile dysfunction of the heart.¹⁵ Although myocardial insulin resistance may result in both systolic and diastolic contractile abnormalities,^{16,17} disruptions in myocardial glucose metabolism may be more likely to manifest through diastolic function due to the importance of ATP in cross bridge cycling, specifically during relaxation.¹⁸ Abnormalities in diastolic function are of clinical importance, as mild abnormalities in diastolic function frequently lead to overt heart failure.¹⁹ In addition, myocardial insulin resistance may limit the heart's tolerance to ischemia, impair cardiac energetics and function,^{20,21} and predict worse outcomes following myocardial infarction.²² Thus, these reports suggest a need to identify treatments that improve both peripheral and myocardial insulin sensitivity in both HIV+ and HIV– men and women with peripheral metabolic complications. However, the quantification of myocardial glucose uptake and insulin sensitivity is challenging and expensive and can be confounded by large intersubject variability. Before conducting a large intervention trial with myocardial insulin sensitivity as the outcome, we collected preliminary data to assess measurement variability, feasibility, and sensitivity.

Exercise training and thiazolidinediones (eg, rosiglitazone, pioglitazone) represent potential treatments for myocardial insulin resistance and LV dysfunction in HIV+ individuals. Thiazolidinediones are synthetic activators of the nuclear transcription factor peroxisome proliferator-activated receptor-gamma (PPAR γ) and potent insulin sensitizers, likely acting through the upregulation of glucose transporters²³ and/or by increases in circulating adiponectin.²⁴ In HIV- individuals with diabetes, rosiglitazone improved myocardial insulin sensitivity^{25,26}; however, there have been no studies examining the effect of thiazolidinediones on myocardial insulin sensitivity and LV function in HIV+ people.

Exercise training (both resistance and endurance exercise) is a well-established intervention for improving peripheral insulin sensitivity^{27,28} in HIV- individuals, and it improves cardiovascular function and reduces the risk of cardiovascular disease in HIV+ people.^{29,30} Exercise training-induced improvements in insulin action are mediated by different mechanisms than those affected by thiazolidinediones. Exercise training activates muscle

PPAR- δ and 5' adenosine monophosphate-activated protein kinase (AMPK).^{31,32} Exercise training improved myocardial glucose metabolism in older HIV- men,³³ however it is not known whether exercise training improves myocardial insulin sensitivity and LV function in HIV+ people with metabolic complications.

Recently, we reported that 4 months of pioglitazone alone or combined with exercise training significantly improved peripheral insulin sensitivity in HIV+ men and women with peripheral metabolic complications.³⁴ In the current pilot study, we expanded these findings and examined the independent effects (pioglitazone vs combined endurance and resistance exercise training) on basal myocardial insulin sensitivity and LV function in HIV+ men and women with metabolic complications that included peripheral insulin resistance. We hypothesized that both pioglitazone alone and exercise training alone would increase basal myocardial insulin sensitivity and diastolic function but, compared to each other, neither intervention would be superior. Evidence for the efficacy of each intervention would provide preliminary data for larger, randomized, controlled clinical trials.

METHODS

Participants

Participants were recruited from the AIDS Clinical Trials Unit and Infectious Diseases Clinics at Washington University School of Medicine in St. Louis, Missouri. This was a prospective, 2-group, random assignment study. The purpose was to determine the effectiveness of 4 months of pioglitazone (PIO; 30 mg/d) or combined endurance and resistance exercise training (EXS) on basal myocardial insulin sensitivity and LV function in HIV-infected people with metabolic complications that included peripheral insulin resistance. Metabolic complications (MC) were defined as peripheral insulin resistance (fasting plasma glucose 100–126 mg/dL or 140 mg/dL at 2 hours following a 75 g oral glucose tolerance test or fasting plasma insulin 13 μ U/mL) and 2 of the following criteria: (1) abdominal obesity (either a waist circumference >102 cm for men and > 88 cm for women or body mass index [BMI] 30 kg/m²), (2) hypertriglyceridemia (fasting plasma triglycerides 150 mg/dL), (3) low high-density lipoprotein (HDL) cholesterol (fasting plasma HDL 40 mg/dL for males and 50 mg/dL for females), or (4) elevated blood pressure (SBP 130 or DBP > 85 mmHg or presence of hypertension medication) (Table 1). These criteria represent a modification of the ATP-III definition for the metabolic syndrome.¹¹ We broadened the insulin resistance/glucose intolerance criteria because HIV+ people frequently have normal fasting glucose but elevated fasting insulin levels.^{4,35}

Before enrollment, volunteers received a physical examination, including a medical history, fasting blood chemistry, lipid/lipoprotein and serum endocrine profile, a 2-hour 75-g oral glucose tolerance test with insulin monitoring, resting blood pressures (3 $\times$ at rest), urine drug and pregnancy screens, and plasma HIV RNA quantitation (Roche Amplicor HIV-1 Monitor; Roche Diagnostics Corp., Indianapolis, IN). Volunteers were excluded if they were taking medications or dietary supplements that could affect metabolism (β -blocker, β -agonist, Ca²⁺ channel blocker, corticosteroid) or if they had a neuromuscular (severe peripheral neuropathy) or other disorder that might affect metabolism or ability to exercise. All participants consumed fewer than 3 alcohol-containing beverages per week, did not have active hepatitis C or B infection, were not using recreational drugs (except marijuana) for 6 months prior to enrollment, and were weight stable (less than 2% weight change in the 3 months prior to the study). None of the participants took anabolic agents or appetite stimulants for at least 6 months prior to study. None participated regularly in physical activities that would constitute exercise training. Several participants randomized to PIO (but not EXS) were co-enrolled in our previously published study.³⁴

The primary outcomes were basal myocardial insulin sensitivity (fasting myocardial glucose utilization rate per unit fasting plasma insulin) and diastolic function (myocardial wall velocity during diastole averaged from the lateral and septal wall measured by tissue Doppler imaging echocardiography) (Table 2). Secondary outcomes included myocardial fatty acid utilization and oxidation, systolic function (myocardial wall velocity during systole averaged from the lateral and septal wall measured by tissue Doppler imaging echocardiography), and early to late filling velocity (E/A ratio) during diastole measured by Doppler echocardiography (Table 2). Tertiary outcomes are reported in Tables 1 and 2. This study was registered at clinicaltrials.gov (NCT 00656851).

Interventions

Participants were randomly assigned (1:1) to 4 months of pioglitazone (PIO) or exercise training (EXS). In the PIO group, each participant was given a 1-month supply of PIO tablets (30 mg/d) by a research pharmacist during each monthly visit. Participants were instructed to take one tablet each day with food at lunchtime to minimize any potential interactions with antiviral medications, which were typically taken in the morning. For the first month, participants used a glucometer to monitor their random fasting blood glucose concentrations to protect against hypoglycemia.

Participants in the EXS group received a 4-month supervised progressive exercise training program consisting of 1.5 to 2 h/d, 3 d/wk of supervised, progressive, combined aerobic conditioning and resistance training. Details of the exercise program have been described.³⁴ Briefly, endurance exercise intensity was based on a percent predicted maximum heart rate (max HR = 220 - age) targeting a HR range of 50% to 85% HR reserve (ie, moderate to high intensity) during endurance exercise. The trainer progressively increased the exercise intensity as the participant adapted. Endurance exercise involved stationary cycling, treadmill walking/jogging, stair-stepper climbing, or elliptical device training. The exercise program was individualized to each participant's baseline physical fitness level, which was determined by a peak exercise test.

The resistance exercise component consisted of 4 upper and 3 lower body exercises that were based on the participant's baseline voluntary maximum strength (1 repetition maximum [1-RM]). Over the 4 months of exercise, the trainer monitored the participant's exercise response and progressively increased the intensity (ie, % of 1-RM), increased the number of sets, and reduced the number of repetitions.

Experimental Procedures

Body composition assessment—Fat and fat-free mass were quantified using a Hologic Discovery (version 12.4; Waltham, MA) enhanced-array dual-energy X-ray absorptiometer (DXA). Abdominal subcutaneous (SAT) and visceral adipose tissue (VAT) volumes and right and left thigh muscle and SATs were visualized using ¹H-magnetic resonance imaging (1.5-T whole body Siemens Sonata; Siemens Medical Systems, Erlangen, Germany) and their volumes were quantified using Analyze software (Mayo Clinic, Rochester, MN) as described.³⁶

Myocardial metabolism—Participants were admitted to the Washington University Clinical Research Unit at 1800h (6:00 p.m.) the night prior to the study and were provided a standardized meal containing 12 kcal/kg body weight and 55% carbohydrate, 30% fat, and 15% protein. At 1900h (7:00 p.m.), they ingested a high-carbohydrate beverage (*Ensure* [80 g carbohydrates, 12.2 g fat, and 17.6 g protein]; Ross Laboratories, Columbus, OH) to ensure adequate muscle and hepatic glycogen stores. They fasted overnight (12 hours). In the morning, an 18-gauge catheter was inserted into an antecubital vein for radio-

pharmaceutical infusion, and a second catheter was inserted into a contralateral hand vein (heated to 55°C [131°F]) for arterialized venous blood sampling. To standardize for potential circadian variations, positron emission tomography (PET) imaging started at 0800h (8:00 a.m.)³⁷ using a commercially available tomograph (Siemens ECAT 962 HR+; Siemens Medical Systems, Iselin, NJ). Blood pressure and HR were monitored throughout the imaging study. PET imaging quantified myocardial blood flow after ¹⁵O-water injection, myocardial oxygen consumption (MVO₂) after 1-¹¹C-acetate injection, myocardial glucose extraction fraction and utilization (GLUT) after 1-¹¹C-glucose injection, and fatty acid extraction fraction, utilization, oxidation, and esterification after 1-¹¹C-palmitate injection. All PET procedures have been previously described and validated.^{38–40} During the PET, arterialized venous blood samples were obtained at predetermined intervals for plasma substrate (glucose, fatty acids, and lactate), insulin, and radiolabeled metabolite concentrations. Validated compartmental models were used to calculate myocardial substrate kinetic rates.^{39–41}

Echocardiography

Immediately after PET imaging, a complete 2-dimensional Doppler and tissue Doppler echocardiographic examination were conducted (Sequoia Cypress; Acuson-Siemens, Mountain View, CA). Left ventricular (LV) end-diastolic and end-systolic volumes and LV mass were determined according to recommendations of the American Society of Echocardiography.⁴² Pulsed-wave Doppler mitral inflow velocities of early LV filling (E) and atrial filling (A) were obtained at the mitral leaflet tips in the apical 4-chamber view for calculating E/A ratio. Tissue Doppler imaging was performed in the apical 4-chamber view to determine the peak systolic shortening velocity (S') and early diastolic myocardial relaxation velocity (E') for regional assessment of systolic and diastolic function, respectively. E' and S' were calculated by averaging the velocities of the lateral and septal base.

Plasma Analyses

Plasma glucose concentration was measured using an automated glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). Plasma insulin was quantified using a chemiluminescent immunometric method (Immulite; Siemens, Los Angeles, CA). Peripheral insulin resistance was evaluated using homeostatic model assessment of insulin resistance (HOMA-IR).⁴³ Fasting plasma lipid/lipoproteins were quantified as previously described.⁴⁴

Statistical Analysis

Statistical comparisons were performed using SAS version 9.3 (SAS Inc., Cary, NC). Differences in continuous variables (myocardial substrate kinetics, LV function) between time point and groups were determined using 2-way (Group x Time) analysis of variance (ANOVA) and post hoc analysis by Tukey honestly significant difference (HSD) test. A *P* value <.05 was considered statistically significant.

RESULTS

Twenty-four eligible volunteers agreed to enroll; 20 completed the 4-month intervention and all testing (PIO: *n* = 12; 42 ± 7 years; EXS: *n* = 8; 41 ± 6 years). Four EXS participants dropped out due to noncompliance for personal reasons. For PIO, 25% of the participants were women; 42% were African American, and 58% were Caucasian. For EXS, all participants were men; 38% were African American, 25% were eastern Indians, and 37% were Caucasian. The percentage of participants using nucleoside reverse transcriptase inhibitors (thymidine analogue and others), non-nucleoside reverse transcriptase inhibitors, and protease inhibitors (ritonavir-boosted or unboosted) was similar between groups (Table

1). No medication changes occurred during the study. There were no baseline differences between groups with respect to demographics, body composition, peripheral metabolism, myocardial metabolism, or LV function (Tables 1 and 2).

Effects of PIO

Safety—No serious adverse events or complications occurred. No participant developed heart failure, serious edema, or rapid weight gain. There were no significant changes in CD4+ T-cell count or plasma viral load.

Body composition—There were no effects of PIO on whole-body fat or fat-free mass or visceral or subcutaneous adipose tissue (Table 1).

Peripheral metabolic complications—Fasting plasma glucose and insulin levels trended lower ($P > .05$) after PIO, and all other peripheral metabolic parameters were unchanged (Table 1).

Myocardial metabolism—Myocardial oxygen consumption decreased slightly but not significantly with PIO. Basal myocardial insulin sensitivity (myocardial glucose utilization/unit plasma insulin) did not change in response to PIO. Myocardial fatty acid oxidation and utilization rates increased slightly, but not significantly, in response to PIO (Table 2).

LV function—Resting systolic and diastolic function were unchanged after PIO ($P > .05$) (Table 2).

Effects of Exercise Training

During the 4-month intervention, participants attended a median 43 exercise sessions (range, 23–52) (90% compliance), completed a median 21 hours (10–42 hours) hours of aerobic exercise in their target HR zone, and expended a median 78 Joules (37–152 J) of energy during aerobic exercise. Median rate of energy expenditure during aerobic exercise was 46 kJ/min (38–63 kJ/min).

Exercise tolerance—Whole-body peak oxygen consumption increased but not significantly after EXS ($P > .05$) (Table 1).

Body composition—Visceral adipose tissue, fat-free mass, total fat mass, and subcutaneous fat content were unchanged after EXS (Table 1).

Peripheral metabolic complications—There were small improvements in fasting plasma glucose, insulin, triglycerides, and total and low-density lipoprotein levels with EXS, but these differences were not significant (Table 1).

Myocardial metabolism—Basal myocardial insulin sensitivity (myocardial glucose utilization/unit plasma insulin) nonsignificantly increased ($P > .05$) after EXS. Myocardial fatty acid oxidation and utilization rates increased but not significantly ($P > .05$) with EXS (Table 2).

LV function—Resting systolic and diastolic function were unchanged after EXS (Table 2).

Post hoc power analyses for primary outcome variables—Based on the measurement variability, power analysis estimates indicate that sample sizes of $n = 15,198$ (PIO) and $n = 162$ (EXS) may be required to detect a significant effect ($\beta = 0.8$, $P < .05$) on

basal myocardial glucose utilization/insulin. Likewise, to detect a significant effect ($\beta = 0.8$, $P < .05$) of PIO or EXS on myocardial wall velocity measured at the lateral wall and septum during diastole, sample sizes of $n = 9,076$ (PIO) and $n = 250$ (EXS) might be required.

DISCUSSION

Although these preliminary findings suggest that neither pioglitazone nor combined endurance and resistance exercise training improved basal myocardial insulin sensitivity or LV function in HIV+ individuals with peripheral metabolic complications, several factors need to be mentioned. Given the magnitude of the variability observed in the PET-based measures of myocardial metabolism, the number of participants was inadequate to detect an improvement. Potential improvements in myocardial insulin sensitivity may be more readily detected under euglycemic-hyperglycemic conditions rather than basal conditions. Despite some reports in type 2 diabetes,^{25,26} we found no evidence that 4 months of pioglitazone adversely affected LV function or compromised myocardial metabolism. Given these factors, future studies of similar interventions focused on altering or improving myocardial metabolism and function in HIV-infected adults will require more than 160 participants and much more refined PET-based measurement procedures (eg, dobutamine stress, hyperinsulinemia).

The participants enrolled in the current study had lower basal myocardial insulin sensitivity compared to their HIV+ and HIV- peers who do not have peripheral metabolic complications,¹² so the potential for intervention-induced improvement existed. No standard value is used to classify an individual as having basal myocardial insulin resistance as there is for peripheral insulin resistance,⁴³ but in our experience, basal myocardial glucose utilization per unit insulin <15 nmol/g/min/ μ U might represent a threshold value. Again, myocardial glucose utilization quantified under hyperinsulinemic conditions might reduce measurement variability and provide a better classification for myocardial insulin sensitivity.

Several reports indicate that exercise training reduces cardiovascular disease risk profiles in people with HIV,⁴⁵⁻⁴⁷ however no study has examined the effect of exercise training on LV function or myocardial metabolism in HIV-infected adults with impaired LV diastolic function. The lack of an effect noted here might be explained by an insufficient exercise-training stimulus. However, exercise training was supervised, monitored, and progressively increased as each participant adapted to exercise. The lack of improvement in LV function may be closely linked to basal myocardial insulin sensitivity,¹² such that an improvement in myocardial insulin sensitivity is required to achieve an improvement in LV function. It is also possible that HIV infection itself, which is known to be associated with decreased diastolic function,⁴⁸ may have constrained any potential beneficial effect of exercise training on LV function.

CONCLUSION

These findings suggest that the effect of pioglitazone or exercise training on heart metabolism and LV function may be relatively small in HIV-infected adults with peripheral insulin resistance and LV diastolic dysfunction and that an exceptionally large number of participants will need to be studied in order to adequately test the hypothesis that pioglitazone or exercise training or a combination of both improves myocardial insulin sensitivity or LV function in HIV+ individuals with cardiovascular disease risk factors. Future studies examining myocardial insulin sensitivity in HIV-infected people with peripheral metabolic complications may benefit from using the hyperinsulinemic clamp procedure to detect any improvements in myocardial insulin sensitivity from insulin-sensitizing agents or behavioral interventions.

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Table 1

Baseline and postintervention total and regional body composition parameters

Parameter	Pioglitazone (n = 12)			Exercise training (n = 8)		
	Baseline	Post	Within-group P value	Baseline	Post	Between-group P value
Weight, kg	92.6 (18.8)	91.3 (19.0)	.99	94.5 (9.0)	94.2 (9.4)	.98
BMI, kg/m ²	30.4 (5.7)	29.7 (5.9)	.99	29.9 (2.3)	29.8 (2.1)	1.0
Fat mass, kg	26.9 (13.6)	25.8 (9.7)	.99	25.1 (5.1)	25.7 (6.1)	1.0
Fat free mass, kg	65.2 (10.7)	64.7 (11.7)	.99	67.1 (5.4)	64.5 (8.6)	1.0
Trunk fat mass, kg	16.3 (7.2)	15.4 (5.3)	.98	15.9 (3.0)	15.6 (3.8)	.99
Limb fat mass, kg	10.4 (6.8)	10.1 (5.3)	.99	9.0 (3.4)	9.8 (2.9)	.99
VAT, cm ³	1,764 (665)	1,750 (728)	.99	1,918 (557)	1,675 (593)	.89
SAT, cm ³	2,603 (1,509)	2,380 (1,119)	.96	2,276 (492)	2,245 (654)	.99
Hematocrit, %	40 (2)	38 (3)	.73	40 (4)	41 (3)	.32
CD4+ T-cell count, cells/ μ L	638 (246)	609 (245)	.99	372 (118)	366 (153)	.97
Glucose, mg/dL	102.4 (15.3)	95.3 (12.8)	.63	91.9 (9.5)	86.8 (8.2)	.90
Insulin, μ U/mL	20.5 (25.7)	11.4 (9.6)	.51	14.8 (8.4)	11.8 (7.6)	.98
HOMA	6.1 (10.4)	2.8 (2.7)	.53	3.3 (1.7)	2.6 (1.6)	1.0
Triglycerides, mg/dL	199.3 (119.2)	182.3 (90.7)	.97	184.8 (58.0)	147.3 (56.0)	.83
Total cholesterol, mg/dL	191.8 (32.4)	171.8 (16.8)	.32	186.4 (29.8)	159.1 (32.8)	.23
LDL cholesterol, mg/dL	114.7 (35.8)	96.6 (17.1)	.37	111.5 (26.1)	90.0 (24.0)	.39
HDL cholesterol, mg/dL	38.9 (11.0)	38.8 (12.4)	1.0	38.1 (8.4)	39.8 (21.8)	1.0
FFA, μ mol/L	588 (173)	564 (12)	.99	616 (157)	583 (168)	.99
VO _{2peak} , mL/kg/min	24.3 (5.2)	25.3 (6.0)	1.0	23.6 (5.6)	26.0 (7.9)	.96

Note: Values are given as mean (SD). FFA = plasma free fatty acid; HDL = high-density lipoprotein; HOMA = homeostatic model of assessment; LDL = low-density lipoprotein; SAT = abdominal subcutaneous adipose tissue volume; VAT = visceral adipose tissue volume; VO_{2peak} = peak volume of oxygen consumption.

Table 2

Baseline and postintervention myocardial metabolism and function

Parameter	Pioglitazone (n = 12)			Exercise training (n = 8)		
	Baseline	Post	Within-group P value	Baseline	Post	Within-group P value
MVO ₂	5.0 (1.3)	4.5 (1.1)	.67	4.2 (1.2)	4.1 (0.5)	.84
MBF	0.6 (0.1)	0.6 (0.2)	.87	0.5 (0.1)	0.5 (0.1)	.03
<i>Myocardial metabolism</i>						
Glucose extraction fraction, %	2 (2)	2 (2)	.99	2 (2)	3 (3)	.99
Glucose uptake, mL/mg/min	0.02 (0.01)	0.02 (0.01)	1.0	0.02 (0.01)	0.01 (0.02)	.97
Glucose utilization, nmol/g/min	109.6 (70.5)	109.1 (55.2)	1.0	106.7 (69.0)	87.2 (97.4)	.95
Glucose utilization/insulin, nmol/g/min/ μ U	14.9 (22.1)	15.7 (12.4)	1.0	11.9 (11.0)	21.7 (40.8)	.84
Fatty acid extraction fraction- oxidation, %	32 (9)	35 (11)	.84	33 (37)	37 (8)	.86
Fatty acid extraction fraction- esterification, %	7 (7)	4 (5)	.34	4 (3)	7 (6)	.84
Fatty acid extraction fraction-total, %	39 (4)	39 (10)	1.0	37 (8)	43 (8)	.40
Fatty acid oxidation, nmol/g/min	92.4 (27.5)	110.1 (31.7)	.62	106.3 (49.6)	97.5 (36.6)	.96
Fatty acid utilization, nmol/g/min	119.3 (39.8)	129.3 (34.5)	.94	119.8 (48.7)	130.4 (55.2)	.97
<i>Cardiac function</i>						
Rate pressure product	8,267 (1,833)	8,297 (2,052)	1.0	7,409 (1,806)	6,667 (1,733)	.86
EDV, units	105 (29)	103 (26)	1.0	125 (17)	126 (22)	1.0
EF, %	61 (5)	60 (5)	.92	62 (8)	62 (5)	1.0
LVM, M-mode	180.4 (37.7)	182.1 (40.9)	1.0	212.4 (21.5)	214.6 (22.1)	1.0
HR, bpm	66 (12)	61 (6)	.67	61 (17)	53 (7)	.62
SBP, mmHg	126 (12)	122 (14)	.95	125 (16)	126 (23)	1.0
DBP, mmHg	73 (9)	73 (9)	1.0	71 (7)	75 (12)	.91
Aortic TVI	21.9 (2.4)	24.2 (2.9)	.90	25.0 (4.2)	25.8 (2.1)	.99
E/A	1.4 (0.6)	1.4 (0.5)	1.0	1.4 (0.3)	1.5 (0.2)	.99
DT, ms	199 (56)	213 (22)	.84	212 (32)	178 (17)	.52
IVRT, ms	81 (10)	85 (12)	.83	79 (4)	75 (5)	.95
S', cm/s	8.5 (0.8)	8.5 (1.0)	1.0	8.6 (0.7)	7.2 (0.4)	.58
E', cm/s	12.7 (1.8)	12.8 (1.6)	1.0	13.1 (2.4)	13.6 (0.4)	.98

Note: Values are given as mean (SD). aortic TVI = tissue velocity index; DBP = diastolic blood pressure; DT = deceleration time; E' = myocardial wall velocity during systole averaged at the lateral wall and septum; E/A = early to late diastolic filling rate; EDV = end diastolic volume; EF = ejection fraction; IVRT = isovolumic relaxation time; LVM = left ventricular mass; MBF = myocardial blood flow; MVO₂ = myocardial oxygen consumption; S' = myocardial wall velocity during systole averaged at the lateral wall and septum; SBP = systolic blood pressure; TVI = time-velocity integral.