Abnormal oxygen uptake kinetic responses in women with type II diabetes mellitus

JUDITH G. REGENSTEINER,1,2,3 TIMOTHY A. BAUER,1 JANE E. B. REUSCH,4 SUZANNE L. BRANDENBURG,2 JEFFREY M. SIPPEL,5 ANDRIA M. VOGELSONG,1 SUSAN SMITH,1 EUGENE E. WOLFEL,3 ROBERT H. ECKEL,4 AND WILLIAM R. HIATT1,6
1Section of Vascular Medicine, Divisions of 2Internal Medicine, 3Cardiology, 4Endocrinology and 6Geriatrics, Departments of Medicine, University of Colorado Health Sciences Center, Denver, Colorado 80262; and 5Division of Pulmonary Medicine, University of Oregon Health Sciences Center, Portland, Oregon 97201

Regensteiner, Judith G., Timothy A. Bauer, Jane E. B. Reusch, Suzanne L. Brandenburg, Jeffrey M. Sippel, Andria M. Vogelsong, Susan Smith, Eugene E. Wolfel, Robert H. Eckel, and William R. Hiatt. Abnormal oxygen uptake kinetic responses in women with type II diabetes mellitus. J. Appl. Physiol. 85(1): 310–317, 1998.—Persons with type II diabetes mellitus (DM), even without cardiovascular complications have a decreased maximal oxygen consumption (VO2max) and submaximal oxygen consumption (VO2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women had a VO2max test. On two separate occasions, subjects performed 7-min bouts of constant-load bicycle exercise at workloads below and above the lactate threshold to enable measurements of VO2, oxygen consumption (V˙O2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women had a VO2max test. On two separate occasions, subjects performed 7-min bouts of constant-load bicycle exercise at workloads below and above the lactate threshold to enable measurements of VO2, oxygen consumption (V˙O2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women had a VO2max test. On two separate occasions, subjects performed 7-min bouts of constant-load bicycle exercise at workloads below and above the lactate threshold to enable measurements of VO2, oxygen consumption (V˙O2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women had a VO2max test. On two separate occasions, subjects performed 7-min bouts of constant-load bicycle exercise at workloads below and above the lactate threshold to enable measurements of VO2, oxygen consumption (V˙O2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women had a VO2max test. On two separate occasions, subjects performed 7-min bouts of constant-load bicycle exercise at workloads below and above the lactate threshold to enable measurements of VO2, oxygen consumption (V˙O2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women had a VO2max test. On two separate occasions, subjects performed 7-min bouts of constant-load bicycle exercise at workloads below and above the lactate threshold to enable measurements of VO2, oxygen consumption (V˙O2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women had a VO2max test. On two separate occasions, subjects performed 7-min bouts of constant-load bicycle exercise at workloads below and above the lactate threshold to enable measurements of VO2, oxygen consumption (V˙O2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women had a VO2max test. On two separate occasions, subjects performed 7-min bouts of constant-load bicycle exercise at workloads below and above the lactate threshold to enable measurements of VO2, oxygen consumption (V˙O2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women had a VO2max test. On two separate occasions, subjects performed 7-min bouts of constant-load bicycle exercise at workloads below and above the lactate threshold to enable measurements of VO2, oxygen consumption (V˙O2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women had a VO2max test. On two separate occasions, subjects performed 7-min bouts of constant-load bicycle exercise at workloads below and above the lactate threshold to enable measurements of VO2, oxygen consumption (V˙O2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women had a VO2max test. On two separate occasions, subjects performed 7-min bouts of constant-load bicycle exercise at workloads below and above the lactate threshold to enable measurements of VO2, oxygen consumption (V˙O2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women had a VO2max test. On two separate occasions, subjects performed 7-min bouts of constant-load bicycle exercise at workloads below and above the lactate threshold to enable measurements of VO2, oxygen consumption (V˙O2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women had a VO2max test. On two separate occasions, subjects performed 7-min bouts of constant-load bicycle exercise at workloads below and above the lactate threshold to enable measurements of VO2, oxygen consumption (V˙O2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women had a VO2max test. On two separate occasions, subjects performed 7-min bouts of constant-load bicycle exercise at workloads below and above the lactate threshold to enable measurements of VO2, oxygen consumption (V˙O2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women had a VO2max test. On two separate occasions, subjects performed 7-min bouts of constant-load bicycle exercise at workloads below and above the lactate threshold to enable measurements of VO2, oxygen consumption (V˙O2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women had a VO2max test. On two separate occasions, subjects performed 7-min bouts of constant-load bicycle exercise at workloads below and above the lactate threshold to enable measurements of VO2, oxygen consumption (V˙O2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women had a VO2max test. On two separate occasions, subjects performed 7-min bouts of constant-load bicycle exercise at workloads below and above the lactate threshold to enable measurements of VO2, oxygen consumption (V˙O2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women had a VO2max test. On two separate occasions, subjects performed 7-min bouts of constant-load bicycle exercise at workloads below and above the lactate threshold to enable measurements of VO2, oxygen consumption (V˙O2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, nondiabetic women, and 10 lean, nondiabetic women had a VO2max test. On two separate occasions, subjects performed 7-min bouts of constant-load bicycle exercise at workloads below and above the lactate threshold to enable measurements of VO2, oxygen consumption (V˙O2) during graded exercise compared with healthy controls. We evaluated the hypothesis that change in the rate of VO2 in response to the onset of constant-load exercise (measured by VO2-uptake kinetics) was slowed in persons with type II DM. Ten premenopausal women with uncomplicated type II DM, 10 overweight, non
Women who were current smokers were not accepted for study because smoking can impair cardiovascular exercise performance. Former smokers must have been abstinent for the past 2 yr.

Prenumepausal women between the ages of 30 and 50 yr were included in the study. Prenumepausal status was evaluated in all women by history of regular menstrual cycles and by measurements of serum follicle-stimulating hormone (FSH) levels. For the purpose of uniformity and to rule out effects of widely differing levels of female hormones on exercise as well as to minimize potential effects of progesterone on ventilation, women were tested in the midfollicular phase (days 6–10) of the menstrual cycle (14, 22).

Absence of comorbid conditions was confirmed by history, physical examination, and laboratory testing. Distal symmetrical neuropathy was evaluated by symptoms (numbness, paresthesia) and signs. Persons who had clinically evident distal symmetrical neuropathy were excluded from further study because of possible effects on exercise performance (10). Three subjects were excluded by using these criteria.

Through the use of resting echocardiographic criteria, persons were excluded who had the presence of global or regional contractile abnormalities (12). Exclusions occurred if 1) regional wall motion abnormalities suggested coronary disease, 2) left ventricular (LV) wall thickness was >1.3 cm (suggesting moderate LV hypertrophy), or 3) there was decreased contractility, i.e., fractional shortening <35%. Subjects were also excluded if they had evidence of ischemic heart disease by history or abnormal resting or exercise electrocardiogram (ECG) (≥1-mm flat or downsloping S-T segment depression). Persons with angina or any other cardiac or pulmonary symptoms potentially limiting exercise performance were excluded as well. Presence of systolic blood pressure >130 mmHg at rest or >190 mmHg with exercise or diastolic pressure >90 mmHg at rest or >100 mmHg with exercise was also grounds for exclusion. Persons with autonomic insufficiency, assessed by measuring variation in R-R intervals with cycled breathing and by the presence of a >20-mm fall in upright blood pressure without a change in heart rate, were excluded because of possible effects on exercise performance (9). Subjects with proteinuria (urine protein >200 mg/dl) or a creatinine >2.0 mg/dl, suggestive of renal disease, were excluded. Renal disease was grounds for exclusion because it can alter exercise performance (2).

Control subjects were screened identically to persons with type II DM. These subjects were taking no medications, had a normal Hb A1c, and had no history of any active medical problems.

Design (Study Protocol)

Subjects were evaluated over the course of six visits on separate days. Subjects made an initial visit to the General Clinical Research Center (GCRC) to have a history and physical examination, blood draws, and questionnaire administrations. A resting ECG was obtained, and a familiarization bicycle test was performed. During the two subsequent visits, a diet interview was administered and underwater weighing was performed. Three days before the fourth visit (to control for the effects of diet on exercise performance), subjects began receiving all meals from the GCRC. On the fourth visit, subjects performed a graded maximal bicycle exercise test to determine the lactate threshold and VO2max. On the fifth and sixth visits, four 7-min bouts of constant-load exercise were performed each day (with 15-min rest periods between bouts) so that three bouts at 20 W, three bouts at 30 W, and two bouts at 80 W were performed in total over the 2-day period. Performance of multiple bouts enabled averaging of VO2 kinetic data within a work load to reduce variability of results.

Graded Maximal Exercise Test

After subjects fasted overnight, VO2max and lactate threshold were determined during a graded bicycle protocol to exhaustion. Each test began with the subject seated at rest on the cycle ergometer (Cardio-2, Medical Graphics, Minneapolis, MN) breathing into a mouthpiece connected to a metabolic cart (CPX-D, Medical Graphics). All testing was done with the subject in the upright seated position. Three minutes of resting data were collected to obtain baseline measurements before exercise. The rest period was prolonged at the discretion of the investigator if additional time was required for adjustment to the mouthpiece and stabilization of physiological variables. To obviate the need to overcome inertia of the ergometer flywheel at the start of exercise, the flywheel was driven at 60 rpm during rest by an electric motor, which was turned off synchronous with the start of exercise. At the start of exercise, the work rate was increased in 10 W/min increments, and the incremental portion of the test was 12–15 min in duration. VO2max was defined as VO2 remaining unchanged or increasing <1 ml·kg⁻¹·min⁻¹ for 30 s or more despite an increment in workload (29).

VO2 and carbon dioxide production (VCO2) were measured, breath by breath, at rest and during exercise. Peak VO2 data were averaged over 30-s intervals. Arm blood pressure (by auscultation) and heart rate (by 12-lead ECG) were obtained every minute during exercise. Cardiac status was monitored throughout the test by 12-lead ECG. The respiratory exchange ratio was calculated as VCO2/VO2. VO2 was normalized on a per kilogram basis and per lean body mass as well as presented as milliliters per minute. Normalization by lean body mass was done to avoid confounding, which could result from differences in the fat mass between lean and overweight (type II DM and overweight control) subjects.

The slope of the increase in VO2 per increase in work rate (ΔVO2/Δwork rate) was analyzed by least squares linear regression excluding the first 2 min and last minute of graded exercise data as previously described (11).

Blood was drawn every minute during the first VO2max test to enable determination of the lactate threshold. The lactate threshold was defined as the point at which a net increase in venous lactate accumulation was observed during incremental maximal exercise. Venous lactate (mmol) vs. VO2 was plotted for determination of the lactate threshold for each patient. The VO2 at the lactate threshold was determined and recorded from each plot. Confirmation of the lactate threshold was performed by using ventilatory, data and the V-slope technique. VCO2 was plotted against VO2, and the ventilatory threshold was labeled where the slope of VCO2 vs. VO2 exceeded 1.0. In all cases, V-slope analyses confirmed lactate threshold measurements.

Constant-Load Exercise Tests

An overnight fast preceded each test day. Each test began with 3 min of resting baseline measurements as described in Graded Maximal Exercise Test. After this period, with the flywheel driven by the motor as described Graded Maximal Exercise Test, the preselected workload (20, 30, or 80 W) was then imposed and the subject maintained pedaling at 60 rpm for 7 min. This protocol allowed all subjects to reach steady-state VO2 at 20 and 30 W but not at 80 W, which was above the lactate threshold.
Kinetic Measurements During Constant-Load Exercise

\( \dot{V}O_2 \) kinetic measurements. Three phases to the response of \( \dot{V}O_2 \) from rest to moderate constant-load exercise were proposed by Whipp and Mahler (30). At the onset of exercise, \( \dot{V}O_2 \) from the lungs normally increases abruptly for the first 15 s (phase I) as pulmonary blood flow increases. Next, the \( \dot{V}O_2 \) increases exponentially in phase II with a time constant \( \tau \) of \( \sim 30-45 \) s representing further increases in blood flow and decreased venous \( O_2 \) content. Phase II ends as gas exchange approaches a steady state. PhaseIII is steady-state \( \dot{V}O_2 \) below the lactate threshold, but above the lactate threshold; phase III \( \dot{V}O_2 \) kinetic responses are not steady-state (phaseIII drift), and modeling is altered accordingly (30).

\( \dot{V}O_2 \) was measured breath by breath. After collection, the \( \dot{V}O_2 \) data were transferred to an ASCII file and filtered, and then a \( \dot{V}O_2 \) value was assigned to each second by extrapolation between breaths by using a program developed and validated at our laboratory. To dampen noise and enhance resolution of data, the data from repetitions within a workload were temporally aligned to a time at the start of exercise and superimposed to yield a single second-by-second averaged record of the tests for each subject at a given workload. The \( \tau \) and the actual change in \( \dot{V}O_2 \) from rest to steady-state \( \dot{V}O_2 \) were then calculated by using a statistical program as previously described (6). With use of this program, a single exponential curve was fit to the data from the onset of exercise to the end of the sixth minute of steady-state exercise in 20- and 30-W transitions. Because we expected that 80 W would constitute high-intensity exercise (i.e., above the lactate threshold) in the majority of patients (given the sedentary profile of the patients), we modified the modeling procedures for this workload to enable comparability between those for whom 80 W was above the lactate threshold and those still below the lactate threshold at 80 W. Thus, to minimize the impact of a phase III drift in \( \dot{V}O_2 \) (non-steady-state \( \dot{V}O_2 \) associated with constant-load exercise \( \dot{V}O_2 \) above the lactate threshold), 80-W transitions were analyzed by using a single exponential curve fit from the onset of exercise to the end of the third minute of exercise.

Heart rate kinetic measurements. Heart rate was monitored beat by beat from the R-R interval of the ECG signal (Quinton Q-plex). These data underwent analog-to-digital conversion and were subjected to kinetic analyses as described in Kinetic Measurements During Constant-Load Exercise.

Specific Methods

Echocardiographic measurements. Two-dimensional and Doppler echocardiography were performed by using standard methods (12) to exclude the presence of significant valvular pathology, LV global dysfunction and segmental wall motion abnormalities (Sonos 2500, Hewlett-Packard, Andover, MA). Chamber sizes, LV end-diastolic and diastolic chamber dimensions and wall thickness, fractional shortening, and the area-length method for measurement of cardiac volume (to measure ejection fraction) were quantitated by standard techniques for all individuals. All readings were done by one of the authors (E. E. Wolfel), a cardiologist who is skilled in these readings and who was blinded to the diagnostic status of the patient. Measurements of diastolic filling were assessed by analyzing mitral valve and pulmonary venous flow patterns by using Doppler techniques.

Dietary control. Three days before the fourth visit, subjects began diet regulation. The diet was administered until the sixth visit was completed. With the use of a diet interview administered during the third visit, subjects were given a diet composed of the percentage of each macronutrient that they customarily ate for all meals. Customary macronutrient pattern was used because a change in diet may affect the respiratory exchange ratio. Overnight fasting (from 10:00 PM the preceding night) was observed before the underwater weighing test day and each exercise test day.

Body composition and hydrodensitometry. Body composition and hydrodensitometry measurements were performed according to standard methods and were used to derive fat-free mass. Percent body fat was estimated from body density by using the revised equation of Brozek et al. (4). Body fat distribution was determined by using the waist-to-hip ratio, where the waist circumference was measured at one-half the distance from the xiphoid process to the navel and the hip circumference was measured at the level of the greater trochanter.

Tests of autonomic insufficiency. To evaluate autonomic insufficiency, we measured variation in R-R intervals with cycled breathing (7, 9). The method for obtaining R-R variability was as follows. The patient, while resting supine, breathed five times per minute, coordinating breaths with a visual electronic signal. This was repeated for 5 min. To obtain data, maximum inspiratory heart rate was subtracted from the minimum expiratory heart rate. Variations of >30 beats/min were considered normal, and values <20 beats/min were considered abnormal (7, 9). In addition, autonomic insufficiency was evaluated by measuring, in lying and standing subjects, heart rates and blood pressures (>20-mm fall in upright systolic blood pressure without a change in heart rate). Subjects who failed to meet these criteria were excluded from study. Three potential subjects were excluded in this way.

Blood collection and preparation. Blood was drawn at baseline for the measurement of glucose, insulin, and plasma FSH levels and of Hb A1c. Blood lactate concentrations were measured every minute during the graded exercise test to determine the lactate threshold in all subjects. In addition, lactate was measured at rest and at peak exercise during the constant-load tests. For the measurement of blood lactate concentration, a 20-gauge intravenous catheter was placed in a forearm vein, with a three-way stopcock to facilitate blood drawing, and patency was maintained with heparinized saline. For each sample, 50 µl of blood were withdrawn and immediately deproteinized in 3% perchloric acid and stored at room temperature.

Assay methods. Lactate concentration was assayed by a lactate dehydrogenase method (23). The lactate threshold was determined as the point at which blood lactate concentration began to progressively increase in the blood. Hb A1c was measured by glyc-deriv GHB columns (Isolab). Serum insulin concentrations were measured by radioimmunoassay (18, 32). Serum glucose concentrations were measured by the glucose oxidase method (17). Plasma FSH levels were measured by a chemiluminescence assay (19).

LOPAR questionnaire. This questionnaire has been modified for use in persons with type II DM and peripheral arterial disease as well as in sedentary controls (20, 21). The subjects were asked a series of questions to itemize their time (reporting specific activities) into work, leisure, and housework categories for the previous week. Questionnaire results were expressed in metabolic equivalents (METs) where 1 MET equals resting \( \dot{V}O_2 \) (3.5 ml·kg\(^{-1}\)·min\(^{-1}\)). Scores are reported in MET hours per week, derived by multiplying the amount of time spent performing an activity by the MET value of the activity. This questionnaire was primarily used in the present study to quantify the activity level of all participants.
pared the slopes of the D
shifted upward, reflecting the effect of obesity on the cal slopes (Fig. 1). Data from the overweight group were 1). Overweight and lean groups exhibited nearly identi-
values were over 1.10). Maximal heart rate also was not suggested a maximal effort in all three groups (all
in the other two groups whether expressed in milliliters
work rate measured by LOPAR. (Table 1).
LopAR, MET h/wk 223
6
6
6
6
36 6
37 6
42 7
6
3.0 2.0
6
82.3 16.7
6
30.8 3.6
33.1 6.3
6
47.7 4.8
47.2 4.9
6
11.8 7.1
28.1 16.4
6
5.3 0.5
9.0 0.4
6
216 67
210 60

Values are means ± SD for 10 subjects in each group. DM, diabetes mellitus; BMI, body mass index; FFM, fat-free mass; Hb A1c, glyco-
sylated hemoglobin; LOPAR, low-level physical activity recall; MET, metabolic equivalent. *P < 0.05 difference between lean control
group and other 2 groups; †P < 0.05 difference between group with type II DM and other 2 groups.

Data analysis. The three groups were compared by using a between-subjects ANOVA. The Student-Newman-Keuls test was used for post hoc analysis. Where data were nonparametric, the Kruskal-Wallis test was used to make between-group comparisons. Correlations were done by using Pearson's product-moment correlation.

RESULTS

Demographic Data

Ten subjects were enrolled in each group (Table 1). There were no significant differences among the three groups in age. The subjects with type II DM had been diagnosed with the disease an average of 3 yr. The group with type II DM and the overweight control group were not different with regard to weight, body mass index, or fat-free mass. However, these two groups differed from the lean control group in terms of the above measurements (Table 1). Fasting insulin, fasting glucose, and Hb A1c levels did not differ between the lean and overweight control groups. However, the group with type II DM had higher insulin, glucose, and Hb A1c levels than did the other two groups (all P < 0.05). Analysis of the physical activity recall revealed that there was no significant difference among the three groups in terms of habitual physical activity level measured by LOPAR. (Table 1).

Graded Maximal Exercise Test

Vo2max was lower in the group with type II DM than in the other two groups whether expressed in milliliters per minute or normalized to kilograms or kilograms of fat-free mass (Table 2). In addition, the maximal respiratory exchange ratio did not differ among groups and suggested a maximal effort in all three groups (all values were over 1.10). Maximal heart rate also was not different among groups.

To evaluate the Vo2/work rate relationship, we com-
pared the slopes of the ∆Vo2/∆work rate measured
during the graded test between the three groups (Fig. 1). Overweight and lean groups exhibited nearly identi-
cal slopes (Fig. 1). Data from the overweight group were shifted upward, reflecting the effect of obesity on the absolute Vo2/work rate. In contrast, data from the group with type II DM, which similarly shifted upward, revealed a decreased slope (P < 0.05).

Kinetic Responses to Constant-Load Exercise

Vo2 kinetics were slower in persons with type II DM
than in the lean and overweight control groups at the 20- and 30-W workloads (both P < 0.05, comparison
between persons with type II DM and the other two
groups) and tended to be slower at 80 W as well (P = 0.09; Figs. 2 and 3, Table 3). The heart rate kinetics were slower in persons with type II DM than in the other two groups at all three workloads (both P < 0.05,
comparison between persons with type II DM and the other 2 groups). The values of the overweight and lean control groups were not different from each other in terms of the VO₂ and heart rate kinetic measurements.

Steady-State Measurements During Constant-Load Exercise

Respiratory exchange ratios did not differ between groups during constant-load exercise workloads (Table 4). However, lactate concentrations were higher at 30 and 80 W (both P < 0.05) in the group with type II DM than in the other two groups. Lactate concentration was higher in the group with type II DM than in the lean group at 20 W and tended to be higher in persons with diabetes than in the overweight control group. Steady-state VO₂ did not differ between groups at any workload. However, steady-state VO₂ as a percentage of VO₂max was higher for the group with diabetes at all three constant-load workloads (Table 4).

Correlations Between Maximal and Steady-State Values

There was an inverse correlation across the three groups between the VO₂ t and VO₂max such that the shorter the t, the greater the VO₂max (r = −0.36, r = −0.38, and r = −0.38, all P < 0.05 for 20, 30, and 80 W, respectively). There was also an inverse correlation

Table 3. Oxygen uptake and heart rate kinetics during constant-load submaximal exercise

<table>
<thead>
<tr>
<th>VO₂ kinetics</th>
<th>Lean Control</th>
<th>Overweight Control</th>
<th>Type II DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-W t</td>
<td>21.4 ± 8.9</td>
<td>18.4 ± 9.9</td>
<td>42.6 ± 23.8*</td>
</tr>
<tr>
<td>30-W t</td>
<td>28.8 ± 5.3</td>
<td>27.8 ± 8.9</td>
<td>36.8 ± 6.2*</td>
</tr>
<tr>
<td>80-W t</td>
<td>42.8 ± 7.5</td>
<td>41.2 ± 8.2</td>
<td>55.7 ± 20.6</td>
</tr>
<tr>
<td>Heart rate kinetics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20-W t</td>
<td>8.5 ± 4.6</td>
<td>10.6 ± 8.2</td>
<td>23.8 ± 16.2*</td>
</tr>
<tr>
<td>30-W t</td>
<td>23.9 ± 13.8</td>
<td>14.2 ± 8.0</td>
<td>40.7 ± 11.9*</td>
</tr>
<tr>
<td>80-W t</td>
<td>41.2 ± 14.8</td>
<td>43.3 ± 11.3</td>
<td>72.3 ± 21.5*</td>
</tr>
</tbody>
</table>

Values are means ± SD. VO₂, *P < 0.05 difference between group with type II DM and other 2 groups.

Table 4. Exercise responses during constant-load submaximal exercise

<table>
<thead>
<tr>
<th>Workload</th>
<th>Lean Control</th>
<th>Overweight Control</th>
<th>Type II DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 W</td>
<td>RER 0.80 ± 0.04</td>
<td>0.82 ± 0.03</td>
<td>0.87 ± 0.10</td>
</tr>
<tr>
<td></td>
<td>Lactate, mmol</td>
<td>0.49 ± 0.19</td>
<td>0.69 ± 0.45</td>
</tr>
<tr>
<td></td>
<td>VO₂ss (ml·kg⁻¹·min⁻¹)</td>
<td>9.2 ± 1.6</td>
<td>7.8 ± 1.2</td>
</tr>
<tr>
<td></td>
<td>VO₂ss/VO₂max, %</td>
<td>37 ± 7</td>
<td>39 ± 9</td>
</tr>
<tr>
<td>30 W</td>
<td>RER 0.85 ± 0.05</td>
<td>0.85 ± 0.04</td>
<td>0.90 ± 0.10</td>
</tr>
<tr>
<td></td>
<td>Lactate, mmol</td>
<td>0.50 ± 0.21</td>
<td>0.84 ± 0.39</td>
</tr>
<tr>
<td></td>
<td>VO₂ss (ml·kg⁻¹·min⁻¹)</td>
<td>10.7 ± 1.5</td>
<td>9.5 ± 1.1</td>
</tr>
<tr>
<td></td>
<td>VO₂ss/VO₂max, %</td>
<td>44 ± 11</td>
<td>47 ± 9</td>
</tr>
<tr>
<td>80 W</td>
<td>RER 1.03 ± 0.08</td>
<td>0.99 ± 0.06</td>
<td>1.06 ± 0.11</td>
</tr>
<tr>
<td></td>
<td>Lactate, mmol</td>
<td>1.88 ± 1.10</td>
<td>2.08 ± 1.31</td>
</tr>
<tr>
<td></td>
<td>VO₂ss (ml·kg⁻¹·min⁻¹)</td>
<td>19.1 ± 3.9</td>
<td>17.2 ± 2.2</td>
</tr>
<tr>
<td></td>
<td>VO₂ss/VO₂max, %</td>
<td>77 ± 18</td>
<td>84 ± 13</td>
</tr>
</tbody>
</table>

Values are means ± SD. VO₂ss, steady-state VO₂; VO₂max, VO₂ as percentage of maximal VO₂ (VO₂max). *P < 0.05 difference between group with diabetes and lean group. †P < 0.05 difference between group with type II DM and other 2 groups.
between heart rate kinetics and $\dot{V}O_2^{\text{max}}$ such that the shorter the $\tau$ for heart rate kinetics, the greater the $V_2^{\text{max}}$ ($r = -0.59$, $r = -0.45$, and $r = -0.60$, all $P < 0.05$, for 20, 30, and 80 W, respectively).

**DISCUSSION**

In the present study, we found that women with type II DM had impaired maximal and submaximal cardiopulmonary responses to exercise, even though they had no evidence of clinical cardiovascular disease or diabetic complications. We had previously observed a lower $V_O_2$ response to submaximal workloads during submaximal graded exercise testing in persons with type II DM compared with controls (20). We reasoned that this finding might be due to slowed $V_2$ kinetic responses in subjects with type II DM. In the present study, constant-load testing was used to confirm that the $V_2$/workload relationship was impaired and that $V_2$ kinetic responses were in fact slowed in type II DM. In addition, the presence of slowed heart rate kinetics in the women with type II DM suggested that a cardiac component may be partially responsible for the abnormalities observed.

In the present study, to confirm our finding of slowed $V_2$ kinetics, we used multiple constant workloads, with each workload repeated several times over 2 days. We documented the consistent finding of slowed kinetics in persons with type II DM at the two workloads below the lactate threshold. However, at the one workload above the lactate threshold, persons with type II DM only tended to have slower kinetics than did controls. This may have been due in part to limitations in monoexponential modeling techniques at this workload.

Importantly, the presence of greater than ideal body weight could not account for the lower $V_2^{\text{max}}$, or slowed $V_2$, and heart rate kinetic responses observed in the study because the overweight and lean groups had similar responses. Overweight controls were not different in terms of weight and fat-free mass from subjects with type II DM. In addition, $V_2^{\text{max}}$, was lower in persons with type II DM than in controls, whether presented in milliliters per minute or milliliters per kilogram per minute. Differences in habitual physical activity level could also not account for the exercise differences observed between persons with type II DM and control subjects. The use of the LOPAR questionnaire revealed that physical activity levels did not significantly differ between groups.

The present study was performed in women only. The reason for studying women was that we observed that women with type II DM had a lower $V_2^{\text{max}}$ relative to their nondiabetic counterparts than did men with type II DM compared with nondiabetic men (unpublished observations). The reason for studying premenopausal women only was for greater homogeneity of the sample in terms of age. The finding of cardiopulmonary exercise abnormalities during maximal and submaximal exercise was especially interesting given that the women studied had only had the clinical diagnosis of diabetes for a relatively short time.

Whereas, in healthy individuals, $V_2$ kinetic measurements are thought to closely reflect the time course of changing $V_O_2$ of exercising muscles, persons with specific cardiovascular or cardiopulmonary diseases have rate-limiting effects in the oxygen delivery and utilization process (5, 25, 26, 31). In the healthy individual, where oxygen delivery is not rate limiting during submaximal exercise, $V_2$ kinetics reflect the oxidative rephosphate rate of phosphocreatine (i.e., primarily reflect muscle bioenergetics and oxygen diffusion at the tissue level) (31) and therefore the utilization aspects of $V_2$ during exercise. However, in disease states in which oxygen delivery is compromised, for example, by a limited cardiac output response, $V_2$ kinetics also reflect the ability of the cardiovascular system to deliver oxygen to working muscle and therefore may reflect impaired oxygen delivery (28). Consistent with this thinking is the finding that the $\tau$ of phase II of $V_2$ kinetics (rise to steady state) is prolonged in patient groups with abnormal cardiovascular responses to exercise, such as pulmonary vascular disease and cyanotic congenital heart disease (25, 26). Further evidence for a relationship between impaired oxygen delivery and slowed kinetics is the observation that patients with pulmonary vascular disease who underwent surgical procedures that improved pulmonary hemodynamics had faster $V_2$ kinetics after the procedure (25).

There is evidence to support the idea that both central (cardiac) and peripheral factors may be related to the exercise abnormalities associated with type II DM. Studies have not thoroughly assessed the ability of the person with diabetes to utilize oxygen during exercise. Allenberg et al. (1) and Lithell et al. (16) reported that citrate synthase activity in skeletal muscle increased markedly after exercise training in type II DM, thereby showing the normal response. In contrast, Simoneau and Kelley (27) recently reported a higher than normal ratio between glycolytic and oxidative enzyme activities that was explained not only by an increased activity for glycolytic enzymes but also by decreased maximum velocities for citrate synthase and cytochrome-c oxidase enzymes in the subjects with type II DM compared with lean and nondiabetic obese subjects. Another recent study investigated whether older persons with impaired glucose tolerance or type II DM had an increased frequency of mitochondrial DNA deletions in skeletal muscle compared with an age-matched nondiabetic control group (15). The authors found that one particular deletion (4,977 bp) as well as other deletions were significantly increased in the muscle tissue of subjects with type II DM or impaired glucose tolerance compared with nondiabetic individuals. Future studies should further explore the effects of type II DM on skeletal muscle metabolism.

There is also evidence suggesting that impaired myocardial function (and subsequently oxygen delivery) in persons with type II DM may play a critical role in the abnormal exercise performance observed in persons with type II DM compared with controls (13, 24). In the present study, the finding of slowed heart rate kinetics supports the likelihood of a cardiac factor...
as a component of the exercise abnormalities observed. In other studies, a reduced cardiac output during exercise has been reported in persons with type II DM vs. controls (13, 24). One study used right heart catheterization to show the presence of a reduced cardiac output in men with diabetes during submaximal workloads of supine bicycling exercise (13). Another study, which used noninvasive methods (24), also measured cardiac output during exercise in persons with diabetes and reported similar results. Methodological issues limit interpretation in both studies. For instance, subjects were included who were taking insulin and oral agents. Persons with both type II DM and type I DM were studied, although evidence suggests that these groups may show differing hemodynamic responses to exercise (8). Also, subjects were not separated according to physical activity levels or carefully matched for age, factors which can strongly affect exercise performance. Finally, the presence of autonomic dysfunction was not reported in the study. However, the suggestion from the literature is that some degree of LV dysfunction may occur in persons with diabetes.

To summarize, the results of the present study demonstrate that premenopausal women with uncomplicated diabetes have impaired VO2 responses to maximal and submaximal exercise. Further studies will be necessary to evaluate whether cardiac output, arteriovenous oxygen difference, and/or aspects of skeletal muscle metabolism are involved in causing the abnormalities observed. Understanding the magnitude and causes of the exercise impairments observed in this relatively healthy group of women with type II DM is important to potentially target appropriate interventions to improve exercise performance and thereby perhaps prevent increasing disability.

The authors thank Sheri Kozemchak and the other nurses of the General Clinical Research Center for their excellent work on this study. In addition, the authors thank the participants in the study, who gave generously of their time and effort. The authors thank the participants in the study, who gave generously of their time and effort. The authors thank the participants in the study, who gave generously of their time and effort. The authors thank the participants in the study, who gave generously of their time and effort.

This study was funded by a clinical research grant from the American Diabetes Association to J. G. Regensteiner and by the General Clinical Research Center RR 501RR-00051. W. R. Hiatt is the recipient of the National Institutes of Health Academic Award in Vascular Disease.

The study was presented in abstract form to the American Federation for Clinical Research in Washington, DC, in May 1997. Address for reprint requests: J. G. Regensteiner, Sect. of Vascular Medicine, Divs. of Internal Medicine and Cardiology, Univ. of Colorado Health Sciences Center, Box B-180, 4200 E. Ninth Ave., Denver, CO 80262 (E-mail: judy.regensteiner@uchsc.edu).

Received 9 December 1997; accepted in final form 10 March 1998.

REFERENCES


