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A Single Bout of Exercise at Higher Intensity Enhances Glucose Effectiveness in Sedentary Men

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Objective: Previous studies have shown that glucose effectiveness and insulin sensitivity are acutely enhanced by exercise at various intensities. The aim of this study was to determine the effects of a single bout of exercise at intensities recommended by the American Diabetes Association (ADA) and the American College of Sports Medicine (ACSM) on glucose uptake-specific glucose effectiveness (S_G^{2*}) and insulin sensitivity (S_I^{2*}). S_G^{2*} and S_I^{2*} were estimated by a two-compartment minimal model.

Design: Six healthy men (age, 28.5 ± 2.0 yr) performed a stable-labeled frequently sampled iv glucose tolerance test (FSIGT) under three separate conditions: without any prior exercise, and immediately after single 20-min bouts of cycle ergometer exercise at an intensity of 50% and 70% of maximal oxygen uptake ($\dot{V}O_{2max}$). The exercise intensities were close to the lower and upper boundaries recommended by the ADA and ACSM.

Results: Glucose disappearance constant (K_G), S_G^{2*}, and S_I^{2*} increased after exercise in an intensity-dependent manner. Increases in S_G^{2*} (+237.1 ± 50.5%), S_I^{2*} (+225.6 ± 51.9%), and K_G (+151.7 ± 16.5%) following exercise at 70% $\dot{V}O_{2max}$ were statistically significant ($P < 0.05$), whereas those at 50% $\dot{V}O_{2max}$ were not.

Conclusions: In conclusion, a single bout of exercise acutely improves S_I^{2*} and S_G^{2*} in individuals with normal glucose tolerance in an intensity-dependent manner. (***J Clin Endocrinol Metab* 90: 4035–4040, 2005**)

EXERCISE IS WELL known to improve glucose tolerance through its acute and chronic effects (1). Effectiveness of exercise prescription has been proposed not only for obesity, hypertension, and hypertriglyceridemia, but also for diabetes mellitus. For individuals with type 2 diabetes mellitus, exercise intensities between 50 and 70% of maximal oxygen uptake ($\dot{V}O_{2max}$) have been recommended by the American Diabetes Association (ADA) (2). The American College of Sports Medicine (ACSM) also recommends a range of exercise intensities corresponding to 50–85% of $\dot{V}O_{2max}$ as a standard guideline for adequate glycemic control (3).

Insulin sensitivity was found to increase after a single bout of exercise at 85% of maximal theoretic heart rate (HR) (70–80% $\dot{V}O_{2max}$, as predicted by age) at 70% $\dot{V}O_{2max}$ and at 150 W (64 ± 1% $\dot{V}O_{2max}$) (4–6). However, relatively mild exercise at lactate threshold (LT) (45.4 ± 3.1% $\dot{V}O_{2max}$) did not improve insulin sensitivity (7). In addition to insulin sensitivity, overall glucose tolerance is influenced by glucose effectiveness, which is the combined ability of glucose *per se* to stimulate its own uptake and suppress its own production (8–10). Applying minimal model analysis of an iv glucose tolerance test, it has been demonstrated that glucose effectiveness is enhanced after a single bout of exercise at 45% and 70–80% $\dot{V}O_{2max}$ levels (4, 7). Thus, exercise at recommended intensity levels is hypothesized to acutely enhance both insulin sensitivity and glucose effectiveness.

Minimal model analysis has been widely used to assess both insulin sensitivity and glucose effectiveness. However, this classical method could not single out the estimates of glucose uptake alone from the combined ability of insulin or glucose *per se* to stimulate glucose uptake and suppress glucose production (11–15). A recently proposed stable-labeled two-compartment minimal model enabled us to single out the estimates of the glucose uptake-specific insulin sensitivity (S_I^{2*}) and glucose effectiveness (S_G^{2*}) (16, 17). The purpose of the present study was to investigate the effects of a single bout of exercise on S_G^{2*} and S_I^{2*} at two different levels of exercise intensity within the recommended ranges suggested by the ADA and ACSM.

Subjects and Methods

Subjects

Six healthy men (23–35 yr old) participated in this study. Physical characteristics of these participants are listed in Table 1. All participants were healthy and relatively active only during their leisure time. Before the onset of the study, the nature, purpose, and risk of the study were

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Abbreviations: AMPK, AMP-activated protein kinase; EGP, endogenous glucose production; FSIGT, frequently sampled iv glucose tolerance test; GLUT-4, glucose transporter-4; HR, heart rate; LT, lactate threshold; RPE, rating of perceived exertion; S_G^{2*}, glucose uptake-specific glucose effectiveness; S_I^{2*}, glucose uptake-specific insulin sensitivity; $\dot{V}_E$, ventilation; $\dot{V}O_2$, oxygen consumption; $\dot{V}O_{2max}$, maximal oxygen uptake; VT, ventilatory threshold.

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TABLE 1. Characteristics of the participants at baseline

Characteristic	Value
Age (yr)	28.5 ± 2.0
Height (cm)	173.7 ± 2.5
Weight (kg)	69.1 ± 2.4
Body mass index (kg/m^2)	22.9 ± 0.5
Body fat (%)	21.2 ± 1.9
$\dot{V}O_{2max}$ (ml/kg/min)	45.2 ± 2.7
O_2 uptake at VT (ml/kg/min)	22.9 ± 1.3 (50.7 ± 3.0% $\dot{V}O_{2max}$)
50% $\dot{V}O_{2max}$ (ml/kg/min)	22.6 ± 1.3
70% $\dot{V}O_{2max}$ (ml/kg/min)	31.6 ± 1.9
Workload at maximal work load (W)	245.0 ± 16.7
Workload at VT (W)	115.0 ± 11.4
Workload at 50% $\dot{V}O_{2max}$ (W)	107.5 ± 9.8
Workload at 70% $\dot{V}O_{2max}$ (W)	155.0 ± 12.0

Values are means ± SE; n = 6 participants.

fully explained to all participants, and informed written consent was obtained. All individuals were free from diabetes, and none were taking any medications. All participants were asked not to change their normal dietary habits, and not to change their levels of spontaneous physical activity. The protocol was approved by the local ethical committee of the Jichi Medical School and was conducted in accordance with the Helsinki Declaration.

Preliminary testing

Before starting the experimental program, the participants underwent a symptom-limited graded exercise test. After a 2-min warm-up exercise on a Monark cycle ergometer (818E, Monark, Stockholm, Sweden) at 0 W, the power output was set at 15 W and then increased 15 W every minute until the participant demonstrated symptoms for termination of the exercise test (3). For detection of $\dot{V}O_{2max}$ and ventilatory threshold (VT), oxygen consumption ($\dot{V}O_2$), carbon dioxide production, and ventilation ($\dot{V}E$) were measured by standard techniques of open-circuit spirometry using Mijnhardt Oxycon System (Oxycon-alpha, Bunnik, The Netherlands) during the exercise test. $\dot{V}O_{2max}$ was chosen as the highest $\dot{V}O_2$ value in the series of minute-by-minute $\dot{V}O_2$ values. VT was determined as a nonlinear increase in $\dot{V}E$ when plotted against $\dot{V}O_2$ or a simultaneous breakpoint in $\dot{V}E/\dot{V}O_2$ and the partial pressure of oxygen in end-tidal expired air (18). Calculation of carbohydrate oxidation rates was assessed from gas exchange measurements according to the nonprotein respiratory quotient technique (19). The values were then converted into kilocalories.

Experimental design

Participants consumed a diet containing 58.5 ± 0.8% carbohydrate, 14.5 ± 0.3% protein, and 27.2 ± 0.6% fat calories on 3 consecutive days previous to each frequently sampled iv glucose tolerance tests (FSIGT). A 12- to 13-h fast was imposed on the participants. They were admitted to the hospital one night before each FSIGT and woke up at 0700 h.

At 0800 h, the participants rested in a sitting position for 30 min. The participants then exercised on a cycle ergometer for 30 min (from 0830–0900 h) at a workload of either 107.5 ± 24.0 W or 155.0 ± 29.5 W on separate days that elicited 53.9 ± 6.1% and 74.6 ± 8.2% of $\dot{V}O_{2max}$, respectively. These intensities correspond to the "moderate" and "hard" intensities according to the most recent position statement by the ADA (20), and both are within the ACSM-recommended range of exercise intensities for diabetes mellitus (3). In this study, we adopted 30 min as the exercise time based on recommendations of the ADA (2) and ACSM (3). Throughout each exercise of 50% $\dot{V}O_{2max}$ and 70% $\dot{V}O_{2max}$, expiratory gases of the participants were sampled breath-by-breath and averaged over 30 sec. All metabolic measurements of expiratory gases were determined by the same respirometry system. HR was recorded at every 1-min interval during exercise. The participants were asked to provide their ratings of perceived exertion (RPE) every 2 min during exercise using the 15-point Borg scale (21).

The FSIGT was performed three times with an interval of at least 1 wk between tests: 1) 30 min after the exercise at 50% $\dot{V}O_{2max}$, 2) 70% $\dot{V}O_{2max}$, and 3) without any prior exercise (nonexercise trial). These three trials were randomly assigned to each participant.

FSIGT

Each FSIGT started at 0930 h (min 0) regardless of exercise, as previously described (22). In brief, four baseline samples were taken at min −20, −10, −3, and immediately before the glucose injection from an antecubital vein in one arm, which was kept in a radiant warmer at 70 C to provide an arterialized blood source. In our experience, the procedure to warm the sampling arm guarantees taking blood samples from well-mixed circulation as assumed in minimal model analysis. Glucose isotopically labeled with [6,6-$^2H_2$]glucose (Aldrich, Milwaukee, WI) was then administered in the contralateral antecubital vein (300 mg/kg body weight) within 1 min, and subsequent blood samples for glucose and insulin were taken until min 180. Regular insulin (Humulin; Shionogi, Osaka, Japan) was administered from min 20–25 at doses of 20 mU/kg (nonexercise trial), 16.5 ± 1.6 mU/kg (50% $\dot{V}O_{2max}$ trial), and 13.8 ± 2.0 mU/kg (70% $\dot{V}O_{2max}$ trial), respectively. Because insulin sensitivity is known to increase after a bout of exercise, the doses of insulin injection after the exercise trials were individually reduced to minimize hypoglycemia, considering the results of previous FSIGTs in the present study.

Analytic methods of glucose

Plasma glucose concentrations were measured in triplicate using the glucose oxidase method. The immunoreactive insulin levels were measured in duplicate using a Phadeseph insulin RIA kit (Shionogi). Deuterated glucose was analyzed as a pentaacetate derivative by use of the method of Wolfe, as previously described (23, 24). The measurement error associated with the labeled glucose measurement was assumed to be independent, and Gaussian, with a zero mean and a coefficient of variation of 3.0%.

Calculations of $S_G{}^{2*}$ and $S_I{}^{2*}$

The indices of $S_G{}^{2*}$ and $S_I{}^{2*}$ specific for glucose uptake were estimated by a two-compartment minimal model (16, 17). Endogenous glucose production (EGP) was estimated by nonparametric deconvolution (16). The insulin area above the basal during 10 and 20 min immediately after the administration of glucose was calculated according to a previously described method (25). The glucose disappearance constant (K_G) was calculated as the slope of the least squares regression line related to the natural logarithm of the glucose concentration to the time when samples were drawn between min 10–19 after glucose load.

Statistics

All values are shown as the means ± SE. Data were analyzed using the SPSS for Macintosh package (SPSS, Inc., Chicago, IL). Statistical comparisons of percent $\dot{V}O_{2max}$, HR, glucose, insulin, exogenous glucose, endogenous glucose, and EGP among nonexercise, 50% $\dot{V}O_{2max}$, and 70% $\dot{V}O_{2max}$ trials over time were performed by a mixed design two-way ANOVA with repeated measures. After significant interactions, one-way ANOVA were employed each time (28 points) to compare and contrast the effect of trials. If a significant difference was detected, these were further evaluated by *post hoc* Tukey's test and a Bonferroni-corrected 95% confidence interval. The comparison of energy expenditure from carbohydrate oxidation and average of RPE during 30 min exercise between the 50 and 70% $\dot{V}O_{2max}$ trials was performed using Student's *t* test. A one-way ANOVA was used to test for statistically significant differences in $S_G{}^{2*}$, $S_I{}^{2*}$, insulin area, K_G, and basal EGP among the three trials. When appropriate, Tukey's test and a Bonferroni-corrected 95% confidence interval were used *post hoc*. Statistical significance was set at $P < 0.05$.

Results

Measurements during a single bout of exercise

Mixed design two-way ANOVA with repeated measures for percent $\dot{V}O_{2max}$ and HR showed significant trial-by-time

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interactions as well as three trials and time effects. The average values of absolute work rate performed during the 50% and 70% $\dot{V}O_{2max}$ trials were 107.5 ± 9.8 and 155.0 ± 12.0 W, which corresponded to 53.9 ± 6.1% and 74.6 ± 8.2% $\dot{V}O_{2max}$, respectively. HR increased progressively to 133.0 ± 17.3 and 165.0 ± 17.6 beats per minute at the end of the 50% and 70% $\dot{V}O_{2max}$ trials, respectively. Average RPE during the 70% $\dot{V}O_{2max}$ exercise (14.7 ± 0.9) was significantly higher ($P < 0.05$) than during 50% $\dot{V}O_{2max}$ (12.8 ± 0.8). An energy expenditure by carbohydrate oxidation during the 70% $\dot{V}O_{2max}$ trial (397.6 ± 66.6 kcal) was 68% greater ($P < 0.05$) than the 50% $\dot{V}O_{2max}$ trial (236.8 ± 36.7 kcal). During and after the exercise, nobody reported chest pain and extreme fatigue.

FSIGT

The plasma glucose, insulin, exogenous glucose, and endogenous glucose during FSIGT in three trials are illustrated in Fig. 1. According to mixed design two-way ANOVA with repeated measures for the plasma concentrations of glucose, insulin, exogenous glucose, and endogenous glucose, trial-by-time interactions as well as a trial effect were significant in the 70% $\dot{V}O_{2max}$ trial but not significant in the 50% $\dot{V}O_{2max}$ trial. The plasma glucose concentration was significantly lower in the 70% $\dot{V}O_{2max}$ trial than the nonexercise trial from min 10–33, respectively. As can be seen in Fig. 1A, plasma glucose in the 70% $\dot{V}O_{2max}$ trial returned to the basal level at min 36 in the experiment. Plasma glucose in the 50% $\dot{V}O_{2max}$ trial returned to the basal level at min 40, and in the nonexercise trial it came back to the basal level at min 50. The plasma insulin at min 24 during FSIGT was significantly lower in the 70% $\dot{V}O_{2max}$ trial than the nonexercise and 50% $\dot{V}O_{2max}$ trials (Fig. 1B). The exogenous and endogenous glucose concentrations were significantly lower in the 70% $\dot{V}O_{2max}$ trial than the nonexercise trial from 14–33 min and from 3–33 min, respectively (Fig. 1, C and D). Endogenous glucose concentration during the last 120 min of FSIGT was higher in the 50% and 70% $\dot{V}O_{2max}$ trials than the nonexercise trial, but the differences were not statistically significant.

Minimal model analysis

Among the nonexercise, 50% $\dot{V}O_{2max}$ and 70% $\dot{V}O_{2max}$ trials, a significant main effect was demonstrated by an intensity-dependent increase in S_I^{2*}, S_G^{2*}, and K_G, respectively (Table 2). The S_I^{2*} was significantly higher in the 70% $\dot{V}O_{2max}$ trial than the nonexercise trial, whereas S_G^{2*} in the 70% $\dot{V}O_{2max}$ trial was significantly higher than the other two trials.

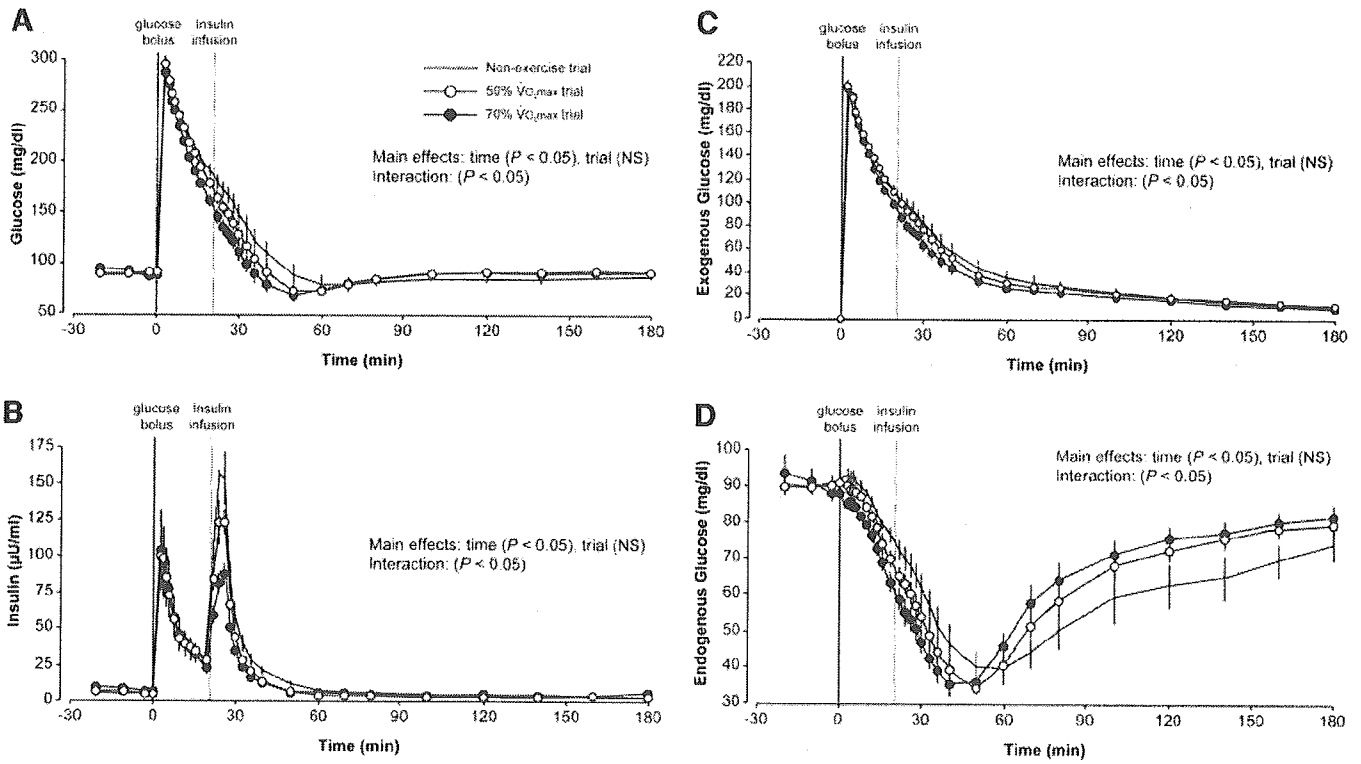

FIG. 1. Time courses of plasma glucose (A), insulin (B), exogenous glucose (C), and endogenous glucose (D) concentration during the iv glucose tolerance test under control (nonexercise trial) and after 50% (50% $\dot{V}O_{2max}$ trial) and 70% $\dot{V}O_{2max}$ (70% $\dot{V}O_{2max}$ trial) exercise. *Vertical dotted line* indicates the initiation of insulin infusion. Main effects for time, trials, as well as time by trial interaction are indicated in each subpanel. Values are means ± SE. A, Plasma glucose concentration in 70% $\dot{V}O_{2max}$ trial was significantly lower ($P < 0.05$) as compared with nonexercise trial at min 10, 12, 14, 16, 19, 22, 24, 26, 28, 30, and 33. B, Plasma insulin concentration in 70% $\dot{V}O_{2max}$ trial was significantly lower ($P < 0.05$) as compared with nonexercise trial at min −10, 22, 24, 26, 28, 30, 33, 36, 40, and 50 and with 50% $\dot{V}O_{2max}$ trial at 24 min. Also, the plasma insulin concentration in 50% $\dot{V}O_{2max}$ trial was significantly lower as compared with nonexercise trial at min 24. C, Exogenous glucose concentration in 70% $\dot{V}O_{2max}$ trial was significantly lower ($P < 0.05$) as compared with nonexercise trial at min 14, 16, 19, 22, 24, 26, 28, 30, and 33. D, Endogenous glucose concentration in 70% $\dot{V}O_{2max}$ trial was significantly lower ($P < 0.05$) as compared with nonexercise trial at min 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 24, 26, 28, 30, and 33.

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TABLE 2. Metabolic parameters of participants

	Nonexercise trial	50% $\dot{V}O_{2max}$ trial	70% $\dot{V}O_{2max}$ trial
S_G^{2*} [$\times 10^2$ dl/kg/min]	0.53 ± 0.12	0.72 ± 0.08	1.02 ± 0.11[a,b]
S_I^{2*} [$\times 10^4$ dl/kg/min/(μU/ml)]	9.36 ± 1.24	13.61 ± 1.37	18.34 ± 3.20[a]
Insulin area (μU/ml/min)			
0–10 min	600.2 ± 92.5	604.0 ± 68.0	610.2 ± 151.4
0–20 min	887.4 ± 131.9	903.5 ± 100.3	887.8 ± 196.1
K_G (%/min)	2.40 ± 0.28	2.98 ± 0.20	3.48 ± 0.30[a]
Basal EGP (mg/kg/min)	1.49 ± 0.10	1.65 ± 0.06	1.90 ± 0.11[a]

Values are means ± SE; n = 6 participants.
[a] Significantly different from nonexercise trial, $P < 0.05$.
[b] Significantly different from 50% $\dot{V}O_{2max}$ trial, $P < 0.05$.

K_G was also significantly greater in the 70% $\dot{V}O_{2max}$ trial than the nonexercise trial. The integrated area of plasma insulin during the first 10 and 20 min remained unchanged among the three trials.

EGP

Basal EGP in the 70% $\dot{V}O_{2max}$ trial (1.90 ± 0.11 mg/kg/min) was significantly higher than that in the nonexercise trial (1.49 ± 0.10 mg/kg/min), but did not differ from that in the 50% $\dot{V}O_{2max}$ trial (1.65 ± 0.06 mg/kg/min) (Table 2). After the glucose bolus, EGP was similarly suppressed, followed by its overshoot (Fig. 2). EGP at around 70 min in the experiment tended to be higher in the 50% and 70% $\dot{V}O_{2max}$ trials than the nonexercise trial ($P = 0.056$).

Discussion

In this study, workloads corresponding to 50% and 70% $\dot{V}O_{2max}$ in a symptom-limited graded exercise test were adopted as a target exercise intensity. Oxygen uptake throughout the 30-min constant-load exercise averaged 53.9 ± 2.5% and 74.6 ± 3.3% $\dot{V}O_{2max}$ at 50% and 70% $\dot{V}O_{2max}$ intensities, respectively. This indicates that the participants exercised approximately at our intended target intensities. The major finding of the present study was that both S_G^{2*} and S_I^{2*}, glucose uptake-specific indices analyzed by a two-compartment minimal model, were enhanced immediately after a single bout of exercise in an exercise intensity-dependent manner. Nearly 2-fold increases in S_G^{2*} and S_I^{2*} after the exercise at the 70% $\dot{V}O_{2max}$ were statistically significant, whereas the changes at 50% $\dot{V}O_{2max}$ were modest.

Applying an original minimal model approach, several previous studies evaluated an acute effect of exercise on glucose effectiveness. Brun *et al.* (4) reported that glucose effectiveness and insulin sensitivity markedly increased at min 25 after 15-min hard exercise at 85% of estimated maximum HR that corresponded to about 70–80% $\dot{V}O_{2max}$, as predicted by age. Sakamoto *et al.* (7) observed a significant increase in glucose effectiveness without improvement of insulin sensitivity 25 min after 60 min of mild exercise at LT intensity (45.4 ± 3.1% $\dot{V}O_{2max}$). Using the stable-labeled two-compartment minimal model, the present study demonstrated that the exercise at 70% $\dot{V}O_{2max}$ level improved S_I^{2*} and S_G^{2*}.

It is worth mentioning that the effects of acute exercise analyzed by minimal model approach require cautious interpretation. First, additional insulin infusion is imposed on endogenous insulin secretion to estimate the minimal model parameters accurately, and the dose of insulin was empirically reduced to avoid hypoglycemia after a bout of exercise. The effect of insulin dose on insulin sensitivity and glucose effectiveness estimated by the minimal model technique has been evaluated (26, 27). According to studies on a "single"-compartment minimal model, lower dose of insulin resulted in higher insulin sensitivity and lower glucose effectiveness. The effect of insulin dynamics on the glucose effectiveness is most likely a consequence of single-compartment undermodeling. Monte Carlo simulation on a "two"-compartment model of glucose kinetics with various insulin response patterns revealed that glucose effectiveness is influenced by the early insulin response (0–20 min) but not by the late one (20–180 min) (28). The early insulin response remained unchanged irrespective of exercise in the present study. Col-

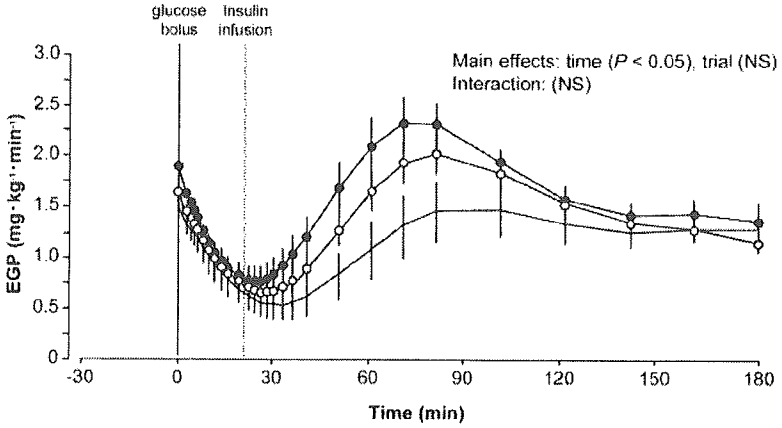

FIG. 2. Time course of EGP during the iv glucose tolerance test under control (nonexercise trial) and after 50% (50% $\dot{V}O_{2max}$ trial) and 70% $\dot{V}O_{2max}$ (70% $\dot{V}O_{2max}$ trial) exercise. *Vertical dotted line* indicates the initiation of insulin infusion. Values are means ± SE.

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lectively, the present finding of the increased S_G^{2*} after a single bout of exercise seems robust against the use of variable dose of exogenous insulin, whereas the increased S_I^{2*} after exercise may, at least partly, reflect the reduced dose of exogenous insulin.

Secondly, an inherent assumption of parameter estimation of the model is that its parameters are constant during the FSIGT, although it is uncertain whether this assumption holds during the 3-h period after a bout of exercise. In fact, muscle glucose transport (29) and AMP-activated protein kinase (AMPK) activity (30, 31) can be changed during the FSIGT, depending on insulin dose and/or exercise intensity. In the present study, a 30-min interval was set between the end of exercise and FSIGT. As a result, plasma concentrations of glucose and insulin immediately before the glucose bolus were comparable among the three trials ($P > 0.1$), suggesting that the changes in glucose and insulin kinetics induced by a bout of exercise were restored in part to resting levels. In addition, minimal model analysis of exogenous glucose, which was simulated by increases in S_G^{2*} and S_I^{2*} through changing parameters (k_{21}, k_{12}, k_{02}, k_b, k_s, and v_1 in Ref. 17) in linear or stepwise manner *in silico*, resulted in enhanced S_G^{2*} and S_I^{2*}. Therefore the results of the present study suggest that S_G^{2*} and S_I^{2*} were increased after a bout of exercise.

Glucose effectiveness and insulin sensitivity seem to be separately regulated and functionally distinct (10). Insulin-stimulated recruitment of glucose transporter (GLUT-4) to the plasma membrane and activation of glycogen synthase in muscle are the major mechanisms responsible for the enhanced insulin-stimulated glucose transport and metabolism (32). In contrast, the physiological basis for the effect of exercise on glucose effectiveness remains vague, although several factors have been proposed. First, muscle contraction stimulates AMPK, particularly its α2 isoform, which induces translocation of GLUT-4 to the plasma membrane and enhances cellular glucose uptake (33–35). Recent studies have provided evidence that the activation of α2-AMPK by muscle contraction depends on exercise intensities. Activity of skeletal muscle α2-AMPK was 3- to 4-fold higher immediately after high-intensity exercise (75% $\dot{V}o_{2max}$ for 60 min), whereas no activation was observed after low-intensity exercise (50% $\dot{V}o_{2max}$ for 90 min) (30). Similarly, the effect of exercise intensity on α2-AMPK activity was examined by 20-min cycle ergometer exercise at low (40 ± 2% $\dot{V}o_2$ peak), medium (59 ± 1% $\dot{V}o_2$ peak), and high (79 ± 1% $\dot{V}o_2$ peak) intensities. α2-AMPK activity increased 5-fold from low to medium intensity, and it increased further from medium to high intensity (36). Cycling for 30 min at a workload requiring 62.8 ± 1.3% of peak O_2 uptake significantly enhanced α2-AMPK activity after 5 min (2-fold), and the activity further elevated after 30 min (3-fold) of exercise (37). Collectively, at least 60% of $\dot{V}o_{2max}$ as a threshold intensity of exercise may be required to stimulate α2-AMPK activity in human skeletal muscle. It seems possible that the activation of α2-AMPK contributes to the increased S_G^{2*} in the 70% $\dot{V}o_{2max}$ trial of the present study.

Secondly, increased blood flow that enhances glucose delivery to peripheral tissue might contribute to the increased glucose effectiveness after exercise. Glucose uptake in muscle is stimulated by increased blood flow in the absence of insulin (38). Leg blood flow and glucose effectiveness increased immediately even after mild exercise at LT intensity (45.4 ± 3.1% $\dot{V}o_{2max}$) for 60 min (7). Thirdly, decreasing muscle glycogen content after exercise may play a role, because the activation of AMPK and its associated increases in muscle glucose uptake are affected by glycogen content (32). In the present study, the amount of carbohydrate oxidized during the 70% $\dot{V}o_{2max}$ exercise was significantly greater than the 50% $\dot{V}o_{2max}$ exercise (236.8 ± 36.7 kcal and 397.6 ± 66.6 kcal), and it might be related to the intensity-dependent increase in S_G^{2*} after the exercise. Finally, in addition to changes in intracellular location of GLUT-4, its content may also increase after exercise. Studies performed in rodent skeletal muscle have indicated that GLUT-4 mRNA and protein are rapidly increased after intensive exercise (39). Consistently, exercise for 60 min on a cycle ergometer at a power output requiring 73 ± 4% peak oxygen uptake acutely increased GLUT-4 gene expression in human skeletal muscle (29).

In previous studies, an increase in glucose effectiveness after an acute bout of moderate exercise disappeared after several hours (40, 41). No effects in insulin sensitivity and glucose effectiveness were observed 11 h after a single bout of exercise at the LT level (60 min) or the 4 mM lactate level (36 ± 1 min) (40). In contrast, 11 h after the exhaustive exercise bout (96 ± 7 min), insulin sensitivity and glucose effectiveness were still higher than these indices without any prior exercise. Therefore, the effects of an acute exercise at higher intensity on insulin sensitivity and glucose effectiveness may persist at least 11 h after the exercise (40). It remains to be determined how long the acute effect of higher intensity exercise on S_I^{2*} and S_G^{2*} lasts. In addition, although the effects of a single bout of the 50% $\dot{V}o_{2max}$ exercise on S_I^{2*} and S_G^{2*} were not statistically significant in the present study, habitual exercise at lower intensities seems to be beneficial to improve these indices. In fact, cycle ergometer exercise at LT (49.1 ± 2.8% $\dot{V}o_{2max}$) for 60 min/d, 5 d/wk for 12 wk enhanced S_I^{2*} and S_G^{2*} (42).

Combination of two-compartment minimal model analysis and deconvolution technique provides a reliable profile of EGP (16). During exercise, EGP is shown to be increased by an exercise intensity-dependent manner, and the increase in EGP is restored to basal levels at around 30 min (43). In the present study, basal EGP at the time of glucose bolus was the highest after exercise at the 70% $\dot{V}o_{2max}$ among the three experimental trials. During the first 30 min after glucose load, when plasma glucose concentration was elevated above the basal level (Fig. 1A), EGP in the three experimental conditions was similarly suppressed (Fig. 2). During this period, plasma glucose and insulin, both of which are capable of suppressing EGP, were lower after the 70% $\dot{V}o_{2max}$ exercise (Fig. 1, A and B). Therefore, these results suggest that a single bout of high-intensity exercise may also increase hepatic insulin sensitivity and/or glucose effectiveness to suppress EGP as well as S_I^{2*} and S_G^{2*}. The suppression of EGP was followed by its overshoot, which was earlier and greater after the exercise, presumably reflecting differences in plasma glucose level and/or the reduced exogenous insulin dose in the FSIGTs after the exercise trials.

In conclusion, a single bout of exercise acutely improved

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S_I^{2*} and S_G^{2*} for ordinary men with normal glucose tolerance in an intensity-dependent manner, and an exercise intensity toward the higher ends of the ranges recommended by the ADA 1993 and ACSM 2000 has a greater potential. The beneficial effect of such exercise for glucose-intolerant participants remains to be studied.

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