

# Influence of Short-Term Submaximal Exercise on Parameters of Glucose Assimilation Analyzed With the Minimal Model

J.F. Brun, R. Guinrand-Hugret, C. Boegner, O. Bouix, and A. Orsetti

After exercise, glucose uptake in tissues increases by insulin-dependent and -independent mechanisms. We evaluated whether these two effects of exercise on glucose disposal can be detected with the minimal model technique. Seven healthy volunteers were submitted at random order to two frequently sampled intravenous glucose tolerance tests (FSIVGTTs), one at rest and the other 25 minutes after a 15-minute exercise test. This exercise included 5 minutes of increasing workload on a cycloergometer followed by 10 minutes at 85% of the maximal theoretic heart rate. Bergman's minimal model of insulin action was used to analyze the two FSIVGTTs and produced the following parameters: coefficient of glucose tolerance ( $K_g$ ), ie, the slope of the exponential decrease in glycemia between 4 and 19 minutes after intravenous glucose; insulin sensitivity ( $S_i$ ); and glucose effectiveness at basal insulin ( $S_g$ ).  $S_g$  was divided into its two components: basal insulin effectiveness ([BIE]  $S_i \times$  basal insulin) and glucose effectiveness at zero insulin ([GEZI]  $S_g -$  BIE). After the exercise bout, subjects had an increased  $K_g$  ( $3.44 \pm 0.44$  v  $2.06 \pm 0.28 \times 10^{-2} \cdot \text{min}^{-1}$ ,  $P < .02$ ),  $S_i$  ( $11.43 \pm 1.27$  v  $6.23 \pm 0.97 \times 10^{-4} \mu\text{U}/\text{mL} \cdot \text{min}^{-1}$ ,  $P < .01$ ), and  $S_g$  ( $4.40 \pm 0.55$  v  $2.81 \pm 0.36 \times 10^{-2} \cdot \text{min}^{-1}$ ,  $P < .02$ ). The increase in  $S_g$  was mainly explained by a 60% increase in GEZI ( $3.6 \pm 0.57$  v  $2.25 \pm 0.36 \times 10^{-2} \cdot \text{min}^{-1}$ ,  $P < .02$ ), but also by an increase in BIE ( $0.80 \pm 0.12$  v  $0.47 \pm 0.08 \times 10^{-2} \cdot \text{min}^{-1}$ ,  $P < .05$ ). Thus, a FSIVGTT sensitively detects an acute increase in glucose assimilation after exercise, as demonstrated by an increase in  $K_g$  and its two components  $S_i$  and GEZI. GEZI seems to provide a measurement of the non-insulin-mediated recruitment of glucose transporters in exercised muscles. In addition, FSIVGTT protocols have to be carefully standardized for previous exercise, since minimal model measurements are sensitive to these acute effects of muscular activity.

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CONARD AND FRANCKSON were the first to show that glucose uptake was markedly increased during exercise.<sup>1</sup> More recently, this fact has been largely confirmed<sup>2</sup> and explained by an acute effect of contractile activity that stimulates glucose transport by a mechanism that seems independent of insulin.<sup>3</sup> Further studies in rodents showed that exercise enhances glucose transport activity by two apparently independent processes. One increases transport independently of insulin, by a mechanism that differs from the insulin-stimulated glucose transport pathway (since its maximal effects are additive to those of insulin). Exercise has an additional effect: it increases sensitivity of muscular glucose transport to insulin. The increased insulin sensitivity ( $S_i$ ) is not detectable in animal experiments until after the effect of exercise on insulin-independent glucose transport has partially reversed.<sup>4</sup> It is reduced by incubation of muscles with high concentrations of glucose.<sup>5</sup> Most of the effects of exercise on glucose uptake by muscle appear to be explained by recruitment of GLUT-4 glucose transporters to the plasma membrane from intracellular stores.<sup>6-8</sup> It has been suggested that two distinct pools of GLUT-4 transporters exist at the intracellular level: one insulin-recruitable and another exercise-recruitable.<sup>6</sup>

In humans, modifications of  $S_i$  after exercise have been measured with the glucose clamp technique.<sup>9</sup> The non-insulin-dependent component of glucose uptake, ie, non-insulin-mediated glucose uptake (NIMGU),<sup>10</sup> is less frequently measured during clamp experiments because more sophisticated procedures (eg, tracer experiments<sup>10</sup> or multiple-step hyperinsulinemia<sup>11</sup>) should be used with the clamp. The minimal model technique, which consists of analysis of the frequently sampled intravenous glucose tolerance test (FSIVGTT), is simpler than clamp procedures and allows a precise, reproducible measurement of the different components of glucose utilization. This technique is based on the assumption that glucose disposal after

an intravenous bolus can be described by two mechanisms: insulin action (ie, the combination of insulin circulating levels and  $S_i$ ) and glucose effectiveness ([ $S_g$ ] ie, the ability of the body to decrease blood glucose independent of any change in circulating insulin).<sup>12-13</sup>  $S_g$  includes basal insulin effectiveness (BIE) and a parameter termed glucose effectiveness at zero insulin (GEZI), which is closely related to NIMGU.<sup>14</sup>

To what extent these model parameters are representative of recruitment of the various pools of glucose transporters after exercise is not known. In this study, we investigated the effects of a single submaximal exercise bout on minimal model parameters of glucose assimilation calculated from a FSIVGTT to determine: (1) if this technique detects exercise-induced modifications in glucose assimilation parameters, (2) which among these model parameters are modified, and (3) whether previous exercise may be a cause of artifacts in minimal model measurements.

## SUBJECTS AND METHODS

### Subjects

Seven voluntary subjects were included in the study. Characteristics of these subjects are listed in Table 1. The mean age was 29.6 years (range, 23 to 39). There were three men and four women; the body mass index (BMI) was  $22.8 \pm 1.11 \text{ kg}/\text{m}^2$  (mean  $\pm$  SEM). All subjects were healthy and exercised only during leisure time. None had a family history of diabetes.

From the Prediabetes Unit, Service d'Exploration Physiologique des Hormones, Lapeyronie Hospital, Montpellier; and Département de Physiologie, Institut de Biologie, Faculté de Médecine, Montpellier, France.

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Address reprint requests to J.F. Brun, MD, PhD, Service d'Exploration Physiologique des Hormones, Lapeyronie Hospital, 34295 Montpellier, Cédex 5, France.

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**Table 1. Sex, Age, Weight, Height,  $W_{170}$ ,  $W_{85\%}$ , and BMI of the Seven Subjects**

Subject No.	Sex/Age (yr)	Weight (kg)	Height (m)	$W_{170}$ (W/kg)	$W_{85\%}$ (W/kg)	BMI (kg/m <sup>2</sup> )
1	F/32	58	1.6	1.94	1.55	22.7
2	M/23	57	1.7	1.4	1.4	19.7
3	M/27	83	1.68	2.25	1.32	29.4
4	F/39	62	1.66	3.92	1.61	22.5
5	M/27	65	1.71	2	1.69	22.2
6	F/33	55	1.55	2.22	1.82	22.9
7	F/26	56	1.67	1.84	1.79	20.1

### Exercise Test

At random order after overnight fasting, the seven subjects underwent a FSIVGTT either in the basal condition or after a standardized exercise protocol. The 15-minute FSIVGTT sample was drawn 10 minutes after the end of exercise, so that glucose injection started 25 minutes after cycling ended. This exercise test was performed on a cycloergometer (Bodyguard; Jonas Oglænd, Sandnes, Norway). Heart rate was monitored by ECG. Subjects were asked to exercise at an increasing workload for 5 minutes, followed by 10 minutes at 85% of the theoretic maximal heart rate for age (using the tables of the American Heart Association). Individual responses of these subjects to exercise are listed in Table 1. Physical working capacity ( $W_{170}$ )<sup>15</sup> was used as an index of subjects' aerobic performance during this exercise: this is the workload (in watts per kilogram body weight) that can be performed at a heart rate of 170 beats/min calculated by least-square fitting from measurements of heart rate at different workloads during the first 5 minutes of the test (Table 1). Since  $W_{170}$  is sensitive to age (which influences the maximal heart rate), we also indicated the subject's power at 85% of predicted maximal heart rate, corrected for the individual's weight ( $W_{85\%}$ ).

### FSIVGTT

Although no alimentary restriction was imposed, subjects were asked to fast for 12 hours before beginning the test at 9 AM. Either 10 minutes after exercise or after rest, a cannula was placed in the cephalic vein at the level of the cubital fossa for blood sampling at various times, while glucose injection was performed in the contralateral cephalic vein. Glucose (0.5 g/kg, 30% solution) was slowly injected over 3 minutes. Insulin (0.02 U/kg body weight, ie, 1 or 2 U) was injected intravenously immediately after time 19 minutes. Blood samples were drawn twice before the glucose bolus and at 1, 3, 4, 8, 10, 15, 19, 20, 22, 30, 41, 70, 90, and 180 minutes after glucose injection. Times 1 and 3 minutes were used for determination of the insulin early secretory phase.<sup>16</sup> Times 10, 20, and 30 minutes were used for calculation of the coefficient of glucose tolerance ( $K_{g10-30}$ ). The other times were necessary for minimal model calculations.<sup>17</sup>

### Laboratory Measurements

All samples were analyzed for plasma insulin content by radioimmunoassay (kit SB-INSI-5; International Compagnie Oris Industrie SA, Gif-sur-Yvette, France) and for plasma glucose content with a Beckman glucose analyzer (Beckman Instruments, Brea, CA). The within-assay coefficient of variation for insulin was determined by repetitive measurements of the same sample and was between 8.6% (low values) and 9.7% (high values). The between-assay coefficient of variation for insulin was between 12.5% (low values) and 14.4% (high values). The sensitivity (lowest detectable value) was 2  $\mu$ U/mL.

### $K_g$

The least-square slope of the log of the absolute glucose concentration between 4 and 19 minutes after the glucose bolus was used as an index of glucose tolerance ( $K_{g4-19}$ ). Concentrations between 10 and 30 minutes were used for calculating  $K_{g10-30}$ .<sup>18</sup> This  $K_g$  value was classically proposed as a measurement of glucose assimilation by tissues,<sup>18</sup> while it depends on the balance between glucose production and glucose uptake.  $K_g$  is dependent on three factors: insulin release,  $S_i$ , and  $S_g$  independent of insulin.  $K_{g10-30}$  may be influenced by the insulin injection at 19 minutes, but  $K_{g4-19}$  cannot be influenced by this injection.

### Measurement of $S_i$ and $S_g$

Minimal model analysis of the IVGTT was performed according to the method reported by Bergman et al<sup>12</sup> and Yang et al<sup>13</sup> using the software TISPAG from the Department of Physiology, University of Montpellier I (Montpellier, France),<sup>19,20</sup> which uses a nonlinear least-square estimation. This program produced the values for  $S_i$  and  $S_g$ .  $S_i$  and  $S_g$  are calculated from the equations  $dG(t)/dt = -[p1 + X(t)]G(t) + p1Gb$ ,  $G(0) = G_0$ ,  $dX(t)/dt = -p2X(t) + p3[I(t) - Ib]$ , and  $X(0) = 0$ , where  $G(t)$  and  $I(t)$  are plasma glucose and insulin concentrations,  $X(t)$  is the insulin in a compartment remote from plasma (insulin action), and  $p1$  to  $p3$  are model parameters.  $G_0$  is the glucose concentration that would be obtained immediately after injection if there was instantaneous mixing in the extracellular fluid compartment.  $G_b$  and  $I_b$  are basal values of glucose and insulin. Parameter  $p1$  represents  $S_g$ , ie, the fractional disappearance rate of glucose independent of any insulin response, and  $p3$  and  $p2$  determine the kinetics of insulin transport, respectively, into and out of the remote insulin compartment where insulin action is expressed.  $S_i$  is an index of the influence of plasma insulin to change the glucose effect per se on glucose concentration. Thus,  $S_i$  is equal to  $-p3/p2$ .

$S_g$  was divided into its two components<sup>14</sup>: the contribution of hyperglycemia per se to tissue glucose utilization and the effect of basal insulin on glucose uptake. The basal insulin component of  $S_g$  is BIE and can be calculated as the product of basal insulin  $I_b$  and  $S_i$ :  $BIE = I_b \times S_i$ . Thus, the contribution of non-insulin-dependent glucose uptake (GEZI) to glucose uptake is the difference between total  $S_g$  and the BIE:  $GEZI = S_g - (I_b \times S_i)$ .

Control values for minimal model parameters in 11 sedentary subjects (eight women and three men; BMI, <24 kg/m<sup>2</sup>; age, 25 to 52 years) were as follows:  $S_g$ ,  $3.12 \pm 0.16 \times 10^{-2} \cdot \text{min}^{-1}$ ;  $S_i$ ,  $6.86 \pm 0.75 \times 10^{-4} \mu\text{U/mL} \cdot \text{min}^{-1}$ ; GEZI,  $2.46 \pm 0.19 \times 10^{-2} \cdot \text{min}^{-1}$ ; and BIE,  $0.53 \pm 0.06 \times 10^{-2} \cdot \text{min}^{-1}$ . The validity of our procedure using a reduced number of samplings has been tested on 10 IVGTTs with values of  $S_i$  between 0.56 and  $16.94 \times 10^{-4} \mu\text{U/mL} \cdot \text{min}^{-1}$ . We compared the results produced by the software with results produced by a classic protocol that included 26 samples (1, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 24, 25, 27, 30, 40, 50, 60, 70, 90, 100, 120, 140, 160, and 180 minutes) with results produced by the reduced number of samples proposed by Steil and Bergman<sup>17</sup> and used here. Values of  $S_g$  ( $r = .996$ , slope = 0.966, intercept = 0.046) and  $S_i$  ( $r = .971$ , slope = 0.875, intercept = 0.983) were highly correlated. The mean relative deviation (defined as the percentage of difference between parameters calculated from the full sample protocol and parameters calculated from the reduced sample protocol) was  $-1.95\% \pm 1.15\%$  for  $S_g$  and  $2.55\% \pm 4.23\%$  for  $S_i$ .

### Assessment of $\beta$ -Cell Function

First-phase insulin secretion<sup>16</sup> was calculated as the sum of insulin concentrations at 1 and 3 minutes after the end of glucose injection ( $I_{1+3}$ ). The incremental insulin value over baseline (difference between  $I_b$  and the maximal insulin value during the

first phase) was also calculated. Since exogenous insulin was added after time 19 minutes, second-phase insulin secretion could not be measured.

### Statistics

Results are presented as the mean  $\pm$  SEM. Modifications of parameters of glucose assimilation induced by exercise were investigated with the Wilcoxon rank-sum test for paired data. Significance was defined as  $P$  less than .05. To evaluate the contribution of each minimal model parameter to glucose assimilation changes, a stepwise correlation analysis was performed among  $\Delta$  values of  $K_g$ ,  $I_{1+3}$ ,  $S_i$ , GEZI, and BIE.

### RESULTS

Blood glucose values remained stable between -15 and 0 minutes and returned to baseline at 180 minutes. Values did not differ significantly and were, respectively,  $4.7 \pm 0.44$ ,  $4.63 \pm 0.53$ , and  $4.90 \pm 0.45$  mmol/L (resting session) and  $4.84 \pm 0.36$ ,  $4.91 \pm 0.32$ , and  $4.87 \pm 0.44$  (exercise session). The variation of glycemia between -15 and 0 minutes was  $-0.05 \pm 0.06$  mmol/L (resting session) and  $0.06 \pm 0.09$  (exercise session), ie, there was no significant difference and a mean change of approximately 1%. Insulinemia was also unchanged between -15 and 0 minutes and returned to baseline at 180 minutes (respectively,  $7.8 \pm 2.1$ ,  $8.1 \pm 1.64$ , and  $9.85 \pm 3.27$   $\mu$ U/mL for the resting session  $\nu$   $9.5 \pm 2.92$ ,  $9.14 \pm 3.31$ , and  $11 \pm 5.23$  for the exercise session). The insulin to glucose ratio did not change between -15 and 0 minutes and returned to baseline at 180 minutes (respectively,  $0.088 \pm 0.01$ ,  $0.102 \pm 0.01$ , and  $0.106 \pm 0.01$  [ $\mu$ U/mL]/[mg/dL] for the resting session  $\nu$   $0.116 \pm 0.01$ ,  $0.1 \pm 0.01$ , and  $0.126 \pm 0.02$  for the exercise session).

Figure 1 shows glucose concentrations after intravenous glucose injection. At 4 minutes, postexercise values are higher than resting values ( $P < .02$ ). At 30 minutes, postexercise values are less than resting values ( $P < .02$ ). Figure 2 shows insulinemia values after FSIVGTT, which are not significantly different at rest and after exercise. Minimal model parameters are listed in Table 2. After the exercise

bout, subjects had an increased  $K_{g4-19}$  ( $+83.9\% \pm 23.9\%$ ,  $P < .02$ ), increased  $K_{g10-30}$  ( $+90.6\% \pm 38.7\%$ ,  $P < .05$ ), increased  $S_i$  ( $+119\% \pm 51.6\%$ ,  $P < .02$ ), and increased  $S_g$  ( $+69.8\% \pm 20.4\%$ ,  $P < .02$ ). Changes in  $p_2$  and  $p_3$  were not significant. Insulin first-phase response ( $I_{1+3}$ ) did not significantly change. As shown in Fig 3, the increase in  $S_g$  was explained by an increase of GEZI ( $+76.02\% \pm 34.7\%$ ,  $P < .02$ ) and BIE ( $+134.3\% \pm 72.3\%$ ,  $P < .05$ ). The increase of GEZI represented 58.46% ( $\pm 12.33\%$ ) of total  $S_g$  increase.

$\Delta K_{g4-19}$  (ie, difference between  $K_{g4-19}$  at rest and post-exercise) was correlated to  $\Delta$ GEZI ( $r = .981$ ,  $P < .01$ ), but not to  $\Delta S_i$ ,  $\Delta I_{1+3}$ , or  $\Delta$ BIE. A stepwise correlation analysis was performed to determine which modification of a minimal model parameter statistically explained the  $K_{g4-19}$  increase. The first determinant of  $\Delta K_{g4-19}$  was  $\Delta$ GEZI, which explained 96% of the total variance of  $\Delta K_{g4-19}$ . The stepwise correlation analysis chose as a second determinant of  $\Delta K_{g4-19}$  value  $\Delta$ BIE (which was not significantly correlated with  $\Delta K_{g4-19}$ :  $r = .624$ , NS). A combination of these two parameters explained 99% of the variance of  $\Delta K_{g4-19}$ :  $\Delta K_{g4-19} = -0.477 + 0.807\Delta$ GEZI +  $0.80\Delta$ BIE ( $r = .995$ ,  $P < .01$ ).

$\Delta S_i$  and  $\Delta I_{1+3}$  were not significantly correlated with  $\Delta K_{g4-19}$ , and their inclusion in the stepwise analysis did not markedly improve the equation.

### DISCUSSION

This study shows highly significant increases in both  $S_i$  and non-insulin-mediated glucose disposal after exercise ( $S_g$  and its component, GEZI). The latter appears to be the most important determinant of the acute increase in glucose tolerance observed in these experimental conditions.

The stimulatory effect of muscular activity on glucose uptake has been studied with various procedures. In animal experiments, tissue samples removed from exercised muscles allow studies on the biochemical modifications in muscle cells.<sup>3-8</sup> This technique cannot be widely used in humans for ethical reasons. The euglycemic clamp technique associ-

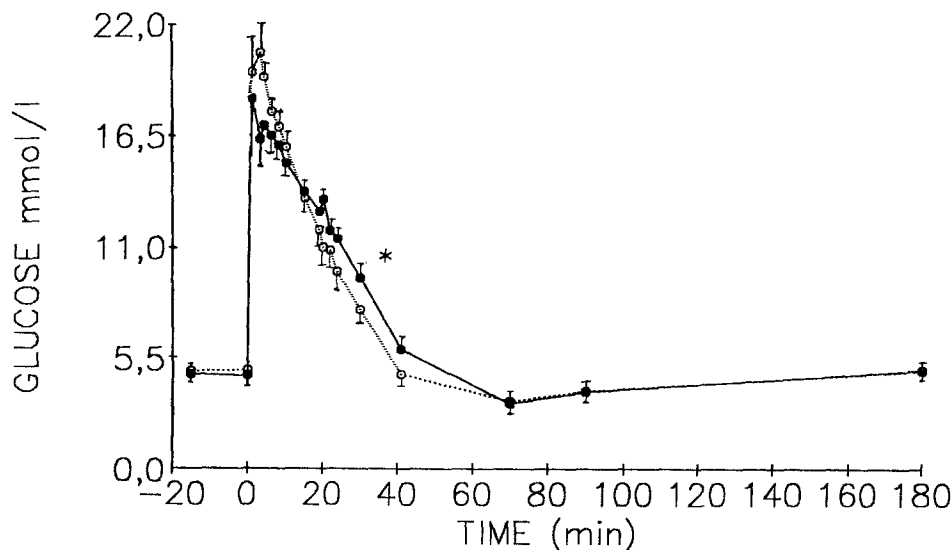


Fig 1. Glucose levels throughout the FSIVGTT. (●) After rest; (○) immediately after exercise. The only significant difference is at time 30 minutes: glycemia is lower for exercise ( $P < .01$ ).

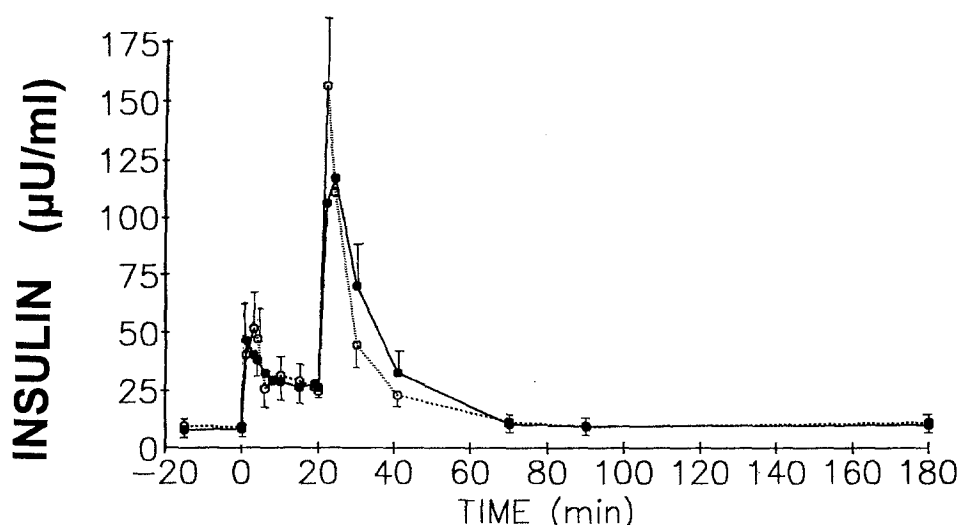


Fig 2. Insulin levels throughout the FSIVGTT. (●) After rest; (○) immediately after exercise. There was no significant difference between the two sessions.

ated with infusions of labeled glucose or indirect calorimetry has been used in animals and humans for assessing modifications of  $S_i$  and insulin responsiveness that result from various kinds of exercise. For instance, Bogardus et al<sup>21</sup> showed that a glycogen-depleting exercise increased insulin-stimulated glucose disposal. Annunzi et al<sup>9</sup> combined clamp and leg catheterization to show that local rather than systemic factors are responsible for changes in  $S_i$  during recovery from physical exercise. On the whole, most clamp studies focus on insulin-mediated glucose uptake, whereas NIMGU remains more difficult to measure with this procedure. Actually, non-insulin-dependent effects of muscle contraction on glucose uptake may be obscured to some extent by the stimulatory effect of the high insulin levels required by clamp experiments. The parameter GEZI of the minimal model has been reported to provide a measurement of NIMGU,<sup>14</sup> although, as discussed later, GEZI is not exactly equivalent to NIMGU. Interestingly, GEZI in this study is the parameter of glucose assimilation that exhibits the most important increase after cycling.

$S_i$ , determined from the FSIVGTT by fitting the experimental values to the equations of the minimal model, is useful for differentiating sensitivities among a normal population<sup>22</sup> and for detecting insulin resistance in obese or diabetic subjects.<sup>22</sup> Its equivalence with similar indices measured with the glucose clamp technique has been demonstrated in dogs<sup>23</sup> and humans.<sup>24</sup> Reproducibility of  $S_i$  measurements has been demonstrated.<sup>25</sup> A limitation of the minimal model procedure involves cases in which no insulin response occurs during IVGTT or in which this response is too low; in such cases, the assumptions of the model are no longer valid, and alternative protocols using insulin or

tolbutamide injection at minute 20 are required.<sup>13,26-28</sup> In this report, we used the insulin protocol as described by Yang et al.<sup>13</sup> Increasing the insulin levels above baseline has been shown to improve the reliability of this procedure.<sup>13,24</sup>

Relatively few studies have used the minimal model in exercise physiology. Exercise training has been shown to prevent the decline of  $S_i$  in the elderly.<sup>29</sup> A strenuous marathon session impairs glucose tolerance mainly by reducing insulin secretion without any significant effect on  $S_g$  and  $S_i$ .<sup>30</sup> A higher value of  $S_i$  has been found for 12 hours versus 84 hours after acute aerobic exercise.<sup>31</sup> Trained runners had higher  $S_i$  and  $S_g$  than sedentary subjects when tested either 16 hours or 1 week after the last training session.<sup>32</sup> In trained sportsmen suffering from exercise hypoglycemia, we reported increased values of both  $S_g$  and GEZI.<sup>20</sup> Therefore, exercise seems to induce a relatively long-lasting improvement of both  $S_g$  and  $S_i$ , but we were not aware of reports of short-term effects (within the first hours) of exercise on minimal model parameters. One of the aims of this study was to investigate these modifications of  $S_i$  and  $S_g$  shortly after muscular activity.

Applicability of the minimal model for a situation such as postexercise is dependent on some assumptions that deserve comment. One of the major assumptions for validity of the procedure is that glucose and insulin levels are at a steady state when a perturbation (glucose injection and insulin release) occurs.<sup>12</sup> Obviously, previous exercise has induced a transient modification of glycoregulatory parameters. However, several lines of evidence indicate that glucose assimilation has reached a stable situation that fulfills the conditions required for validity of the model.

First, since the -15-minute sample of the FSIVGTT is drawn 10 minutes after cycling was stopped, the glucose

Table 2. Acute Influence of Exercise on Parameters of Glucose Assimilation (mean  $\pm$  SEM)

	$K_{g4-19}$ ( $\times 10^{-2} \cdot \text{min}^{-1}$ )	$K_{g10-30}$ ( $\times 10^{-2} \cdot \text{min}^{-1}$ )	$S_g$ ( $\times 10^{-2} \cdot \text{min}^{-1}$ )	$S_i (\times 10^{-4})$ ( $\mu\text{U}/\text{mL} \cdot \text{min}^{-1}$ )	p2	p3	$I_{1+3}$ ( $\mu\text{U}/\text{mL}$ )	$\Delta\text{INS}$	BIE ( $\times 10^{-2} \cdot \text{min}^{-1}$ )	GEZI ( $\times 10^{-2} \cdot \text{min}^{-1}$ )
Rest	$2.06 \pm 0.28$	$2.33 \pm 0.39$	$2.81 \pm 0.36$	$6.23 \pm 0.97$	$5.89 \pm 2.17$	$25.73 \pm 4.42$	$80.86 \pm 12.65$	$40.14 \pm 7.42$	$0.47 \pm 0.08$	$2.25 \pm 0.36$
Exercise	$3.44 \pm 0.44$	$3.57 \pm 0.38$	$4.4 \pm 0.55$	$11.43 \pm 1.27$	$7.88 \pm 3.52$	$98.39 \pm 46.12$	$91.57 \pm 22.45$	$52.14 \pm 12.57$	$0.8 \pm 0.12$	$3.6 \pm 0.57$
P	<.02	<.05	<.02	<.02	NS	NS	NS	NS	<.05	<.02

Abbreviation:  $\Delta\text{INS}$ , insulin first phase expressed as the increment between  $I_b$  and maximal insulin peak value.

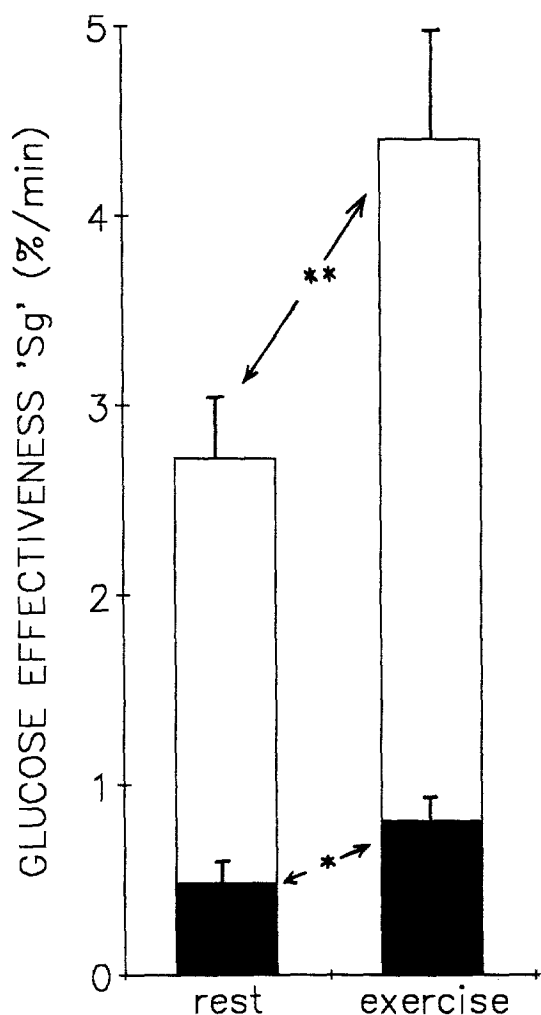


Fig 3. Comparison of  $S_g$  after rest and after exercise.  $S_g$  is higher after exercise ( $P < .02$  Wilcoxon rank-sum test), and its two components (■, BIE; □, GEZI) are increased. \* $P < .05$ ; \*\* $P < .02$ .

infusion starts 25 minutes after the end of exercise. In this kind of short-term, submaximal exercise protocol, modifications of blood parameters during recovery are transient, and blood glucose and insulin levels rapidly return to baseline values before the end of these 25 minutes. This fact can be verified by examining closely for variations of glycemia, insulinemia, and the insulin to glucose ratio at -15, 0, and 180 minutes of the test. As shown earlier, there is no significant change in glycemia, with a mean fluctuation of approximately 1%. For insulinemia and the insulin to glucose ratio, there is also no significant fluctuation. A steady state for glycemia and insulinemia is likely to exist, as is required for measurements of minimal model parameters.

Another question, related to the previous one, is whether one can assume that changes in  $S_g$  and  $S_i$  are sufficiently slow for  $S_i$  and  $S_g$  to be considered as almost constant during the test. The minimal model procedure measures only an average glucose assimilation over the whole period of 180 minutes, and if there were wide variations of glucose

disposal during these 180 minutes, the accuracy of these measurements could probably be impaired. However, we think that several lines of evidence indicate that the decline of  $S_g$  and  $S_i$  is probably small over the 180 minutes of the test and cannot impair the validity of the procedure. Theoretically, one could expect that just after this exercise session, values of glucose assimilation that have been increased by muscular contractions progressively decline toward preexercise values. During the period of recovery, immediately after cycling, some rapid changes in glucose disposal parameters could not be excluded. However, our measurement is not made at this time, but instead during the period that follows recovery between 30 and 210 minutes, and is characterized by a steady state as indicated earlier. This steady state indicates that there is a good balance between glucose output and glucose uptake. This fact, together with the lack of a report indicating strong acute changes in either output or uptake of glucose during this period that follows recovery, makes it unlikely that  $S_g$  and/or  $S_i$  undergo important, short-term modifications. If such modifications occurred, they would probably induce some modifications of blood glucose levels. After such a short-term exercise bout, between 30 and 210 minutes, the only predictable modification of  $S_i$  and  $S_g$  is a progressive decline toward preexercise values. We do not know exactly the rate of this decline, but if we combine information from previous reports, this rate is probably markedly lower than the coefficient of variation of the method, which is close to 20% for both  $S_i$ <sup>25</sup> and  $S_g$ . This rate of decline is small compared with the marked increase induced by the previous exercise. Previous studies in healthy young men<sup>21,33,34</sup> have shown that the rate of glucose disposal at submaximal plasma insulin concentration during a euglycemic clamp is increased for at least 16 to 48 hours after a bout of exercise. The increase in glucose assimilation induced by muscular contraction is a long-lasting phenomenon (several hours). Although minimal model reports on this topic are few, it has been reported that  $S_i$  and  $S_g$  remain increased either 16 hours or 1 week after the last training session.<sup>32</sup> Between 12 and 84 hours after exercise, using results reported by Prigeon and Porte,<sup>31</sup> one can calculate a rate of decrease of 0.19%/h for  $S_i$  (and a nonsignificant trend of 0.07%/h for  $S_g$ ). Given the order of magnitude of  $S_i$  and  $S_g$  in our study, if we assume that they remain elevated more than 12 hours later, the percentage of decrease over the 180 minutes of the FSIVGTT is surely less than the sensitivity of the method.

Results presented earlier confirm that exercise acutely improves  $K_g$ , as previously shown by Conard and Franckson<sup>1</sup> and others.<sup>35</sup>  $K_g$  is not a minimal model parameter, since it is produced by a simpler model of glucose kinetics, but it is frequently calculated together with  $S_i$  and  $S_g$  in reports of minimal models, because it gives an evaluation of the overall process of glucose assimilation. We calculated two values of  $K_g$ :  $K_{g10-30}$ , which is used in previous reports on  $K_g$  and exercise,<sup>1,35</sup> and  $K_{g4-19}$ , which rules out the influence of exogenous insulin administered just before time 20 minutes. Both are increased after exercise. This does not seem related to modifications of insulin release, which are a

major determinant of  $K_g$  but are not significantly modified by our short-term exercise protocol. The other determinants of  $K_g$  are  $S_i$  and  $S_g$  independent of insulin, which can both be calculated with minimal model analysis. Non-insulin-dependent  $S_g$  (ie, the parameter  $p1$  of the minimal model) is increased ( $P < .02$ ) after exercise, and this increase is explained by an increase of its two components, GEZI (which represents NIMGU) and BIE (which measures insulin action in the absence of changes in insulinemia). The increase in BIE is not a minor component of  $S_g$  improvement (41.5%), but GEZI seems to be statistically the major determinant of the overall increase in  $K_g$ .  $S_i$  is markedly increased, but this increase seems to explain only a portion of  $K_g$  improvement after cycling.

The exact physiologic meaning of an increase in GEZI should be discussed. GEZI has been reported to be equivalent to NIMGU.<sup>14</sup> Actually, there are some differences between GEZI and NIMGU. First, GEZI is a fractional clearance (ie, independent of blood glucose levels), and NIMGU is a rate of glucose uptake at a given level of blood glucose. In addition, GEZI, as defined in this model,<sup>12,22</sup> depends on the effect of glucose on both glucose production and glucose uptake, whereas NIMGU depends only on glucose uptake. Thus, an important question for the interpretation of our results is which percentage of  $S_g$  (and of GEZI) corresponds to the ability of glucose to increase peripheral glucose uptake, and which percentage represents the ability of glucose to suppress hepatic glucose production (HGP). Based on analysis of previous reports, Ader et al<sup>36</sup> postulate (in resting subjects) that 54% of  $S_g$  is explained by the effect of glucose on glucose uptake, whereas 46% results from glucose-mediated suppression of HGP. However, more recently, Kahn et al<sup>14,37</sup> present GEZI as a measurement equivalent to NIMGU. They indicate that the close relationship between GEZI and NIMGU is supported by the fact that GEZI represents 77% of  $S_g$ , ie, almost the same percentage as the 83% of whole-body glucose uptake in the basal state that is due to NIMGU.<sup>37</sup> The discrepancy between these evaluations can be largely explained by methodologic aspects: most of the previous studies on HGP during clamp experiments with tracer infusions have been recently criticized.<sup>38-40</sup> Consistent with the assumptions of Kahn et al,<sup>14,37</sup> Finegood and Tzur<sup>41</sup> recently reported convincing evidence that variations of  $S_g$  are a better reflection of the sensitivity to glucose of glucose uptake than of the sensitivity to glucose of glucose production. They have compared, in normal dogs and low-dose streptozotocin-treated dogs, values of  $S_g$  measured with the minimal model and hepatic versus peripheral glucose disposal measured with 3-[<sup>3</sup>H]glucose infusion. They show that  $S_g$  is well correlated with the sensitivity of glucose disposal to changes in glucose, and that it is independent of the sensitivity of the liver to suppression by glucose. The finding reported by Pacini and Cobelli<sup>42</sup> that there is minimal suppression of HGP during IVGTT is also consistent with this opinion: if HGP remains unchanged during IVGTT, it is likely to have a minor influence on the dynamic adaptation to a glucose injection measured by  $S_g$  (and GEZI). Although this domain requires

further investigation, all these data lead us to think that variations of GEZI can be considered as reflecting mainly modifications of peripheral glucose uptake. Therefore, given that exercise is well known to increase non-insulin-mediated glucose disposal,<sup>3,6-8</sup> it seems logical to assume that a postexercise increase in NIMGU is the major mechanism of the increase in GEZI. Since muscular contractions have been reported to increase GLUT-4 glucose transporters in muscles independently of insulin itself, we suggest that modifications of  $S_g$  and its component GEZI after exercise mostly reflect this non-insulin-mediated mobilization of glucose transporters. The finding of high values of  $S_g$  in trained sportsmen<sup>32</sup> and even more so in sportsmen suffering from exercise hypoglycemia<sup>20</sup> is in agreement with this assumption.

Although this experiment shows marked changes in glucose disposal, we cannot detect a clear modification of first-phase insulin release. This is surprising, since exercise generally impairs insulin secretion.<sup>43</sup> For instance, Pestell et al<sup>30</sup> showed that after a strong marathon session there was a reduction in insulin release, which resulted in impaired glucose tolerance, while  $S_i$  and  $S_g$  remained at preexercise values. The significant difference was found for second-phase insulin secretion, but there was also a tendency toward a reduction in the first phase.<sup>30</sup> As for our exercise protocol, second-phase insulin secretion cannot be measured, since we inject insulin before time 20 minutes. A study including a greater number of subjects might indicate an effect of such an exercise session on first-phase insulin release. However, our individual results (increase of  $I_{1+3}$  in three subjects and decrease in four) suggest that this effect, if it can be observed, is far from being constant and is probably less important than the increase in both  $S_g$  and  $S_i$  clearly observed in this group. This exercise session was probably not sufficient to impair first-phase insulin secretion.

One of the goals of this experiment was to determine whether, with FSIVGTT, significant changes in  $S_g$  and/or  $S_i$  could be detected after exercise, ie, if this procedure was sensitive enough to evidence the increases in glucose assimilation rates that have been described with other procedures. Actually, we did not directly compare the modifications of minimal model parameters used with measurements of glucose uptake on biopsies or on the whole body with tracer procedures. This was not the purpose of the study, which was only related to minimal model parameters. From the literature reviewed earlier, it was logical to speculate that both  $S_g$  and  $S_i$  would increase after exercise, but this theoretically predictable point had to be experimentally verified. Clearly, our results show that the minimal model procedure can detect those modifications and is thus sensitive for measuring these events.

Another potentially interesting finding is that exercise induces marked changes from the resting state, and thus is likely to result in artifacts for the minimal model technique. This study was not designed to define precisely which recommendations should be given for avoiding these artifacts. However, when considering our results and those of the few minimal model reports related to exercise, one can

suggest that patients be screened for any strenuous exercise session during the previous week and should not undertake a long walk or bicycle ride just before coming to the hospital unit for the IVGTT. A more precise study on this point is needed to improve the reliability of the minimal model procedure in clinical practice.

A last point that should be briefly discussed is the potential interest of the minimal model technique in exercise physiology and sports medicine. Previous reports have mainly investigated the delayed, long-lasting effects of exercise on  $S_g$  and  $S_i$ .<sup>29-32</sup> It appears, on the whole, that high values of  $S_i$  and/or  $S_g$  are a biologic characteristic of exercised subjects. However, our study suggests that markedly increased  $S_i$  and  $S_g$  may be found after muscular activity even in untrained subjects. We think that it will be interesting to compare the effects of training and of short-term exercise to determine whether increased  $S_i$  and/or  $S_g$  are markers of fitness. Improved glucose assimilation may be expected to have some positive effects for

aerobic muscular performance, since glucose is the major fuel in high-intensity exercise.<sup>43</sup> Other potential applications, such as exercise hypoglycemia,<sup>20</sup> also require further investigation. To provide further clarification of these fields, it was necessary to perform the experiment presented here, although some of the findings were predictable, to some extent.

In conclusion, this study shows that: (1) exercise increases both  $S_i$  and  $S_g$ ; (2) the acute effect of short-term submaximal exercise on glucose assimilation in sedentary subjects is mainly explained by an increase in non-insulin-mediated glucose disposal, which can be measured with the parameter GEZI of the minimal model; and (3) previous exercise may markedly modify the minimal model parameters and should be considered as a source of artifacts in FSIVGTTs. Whether measurement of  $S_i$ ,  $S_g$ , and GEZI in sports medicine can provide useful information on muscular glucose metabolism requires further study, but is an attractive hypothesis.

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