Prevalence of Hypoglycemia Following Pre-exercise Carbohydrate Ingestion Is Not Accompanied By Higher Insulin Sensitivity

Roy L.P.G. Jentjens, and Asker E. Jeukendrup

Pre-exercise carbohydrate feeding may result in rebound hypoglycemia in some but not all athletes. The aim of the present study was to examine whether insulin sensitivity in athletes who develop rebound hypoglycemia is higher compared with those who do not show rebound hypoglycemia. Twenty trained athletes ($\overline{VO}_{2\text{max}}$ of $61.8 \pm 1.4$ ml · kg$^{-1}$ · min$^{-1}$) performed an exercise trial on a cycle ergometer. Forty-five minutes before the start of exercise, subjects consumed 500 ml of a beverage containing 75 g of glucose. The exercise trial consisted of 20 min of submaximal exercise at $74 \pm 1$% $\overline{VO}_{2\text{max}}$ immediately followed by a time trial. Based upon the plasma glucose nadir reached during submaximal exercise, subjects were assigned to a Hypo group (<3.5 mmol/L) and a Non-hypo group ($\geq$3.5 mmol/L). An oral glucose tolerance test was performed to obtain an index of insulin sensitivity (ISI). The plasma glucose nadir during submaximal exercise was significantly lower ($p < .01$) in the Hypo-group ($n = 10$) compared with the Non-hypo group ($n = 10$) (2.7 $\pm$ 0.1 vs. 4.1 $\pm$ 0.2 mmol/L, respectively). No difference was found in ISI between the Hypo and the Non-hypo group (3.7 $\pm$ 0.4 vs. 3.8 $\pm$ 0.5, respectively). The present results suggest that insulin sensitivity does not play an important role in the occurrence of rebound hypoglycemia.

Key Words: glucose ingestion, cycling, insulin response, OGTT

Introduction

Several studies have shown that carbohydrate (CHO) ingestion in the hour before exercise can result in hyperglycemia and hyperinsulinemia, which is followed by a rapid decline in blood glucose at the onset of exercise (2, 14, 31), often referred to as rebound hypoglycemia. A decrease in blood glucose concentration has been associated with the onset of fatigue during prolonged exercise (7). However, hypoglycemia following pre-exercise CHO feeding has been reported in some studies (6, 14, 20, 28, 29, 35, 39, 42) but not in others (5, 8, 13, 17, 19, 27, 30, 31, 33, 34, 37, 40). Furthermore, only two studies have found decreased performance when CHO was ingested prior to exercise (14, 23), whereas the majority of studies have found either
no change (5, 11, 12, 19, 43) or improved performance (17, 25, 41, 44, 45). The reason for the discrepancies among studies may be related to differences in experimental design, including variations in training status of the subjects, subject nutritional state, the type and duration of exercise, choice of performance measurement, exercise intensity, and timing, amount, and type of CHO ingested.

In a series of experiments in our laboratory, we have attempted to systematically examine the effects of the amount of CHO ingestion (21), the timing of CHO feeding (36), the type of CHO intake (22), and the intensity of exercise (1) on CHO metabolism and exercise performance, when other factors such as those described above were controlled. The main conclusion from these studies was that none of the factors investigated affected performance. Furthermore, altering the timing of CHO ingestion (15, 45, or 75 min before the onset of exercise), the amount of CHO intake (25, 75, or 200 g of CHO), the type of CHO consumed (glucose, trehalose, or galactose), or the exercise intensity performed (40, 65, or 80% maximum work rate [Wmax]) did not result in rebound hypoglycemia, when average group data were examined. However, within each study, rebound hypoglycemia was observed in some individuals. For instance, hypoglycemia was reported in 3 to 4 subjects \((n = 8)\) when subjects performed exercise at intensities varying between 40 and 80% Wmax (1). Furthermore, the occurrence of hypoglycemia tended to be higher when a high glycemic index (GI) CHO was ingested compared with a low or moderate GI CHO (4 subjects after glucose; 1 subject after trehalose; 0 subjects after galactose \((n = 8)\)) (22). When the timing of CHO ingestion was delayed from 15 to 45, or 75 min before the start of exercise, more subjects developed rebound hypoglycemia (2 vs. 3 vs. 5 subjects, respectively \((n = 8)\)) (36). Varying the amount of CHO intake between 25 and 200 g of CHO induced hypoglycemia in 4 to 6 subjects \((n = 9)\), while hypoglycemia was prevented when no CHO was ingested (21). It is clear from the studies above that the number of individuals who develop rebound hypoglycemia is partly related to the GI of the ingested CHO (22) and the timing of CHO intake prior to exercise (36). However, it is still not known why rebound hypoglycemia occurs in some individuals but not in others. Recently, Kuipers et al. (29) have suggested that the occurrence of rebound hypoglycemia in trained athletes is related to a high insulin sensitivity. Long-term exercise training induces an increase in insulin sensitivity (for reviews, see 4, 18); hence, trained subjects have a higher insulin sensitivity than untrained subjects (10, 24, 38). In the present study we investigated the prevalence of hypoglycemia in 20 trained subjects with a wide range of physical fitness who were likely to have a wide range of insulin sensitivity. The aim of the present study was to examine whether the insulin sensitivity of trained subjects is higher in subjects who develop rebound hypoglycemia compared with subjects who do not show rebound hypoglycemia.

### Methods

#### Subjects

Twenty trained male subjects (age: 27.9 ± 1.6 years; height: 180 ± 2 cm; body mass: 73.9 ± 1.3 kg; maximal oxygen uptake \((\dot{V}O_{2\text{max}})\): 61.8 ± 1.4 ml · kg⁻¹ · min⁻¹) were recruited to take part in this study. Most of the subjects who participated were either cyclists or triathletes \((n = 17)\). The other subjects \((n = 3)\) were active in sports like running, weight training, cricket, and swimming and did not have a history of
endurance training. The aim was to recruit 20 trained individuals of a wide fitness range, as reflected by a wide range of \( \dot{V}O_{2\text{max}} \). Prior to participation, each of the subjects was fully informed of the purpose and the risks associated with the procedures, and a written informed consent was obtained. All subjects were nonsmokers and healthy as assessed by a General Health Questionnaire. The study was approved by the Ethics Committee of the School of Sport of Exercise Sciences of the University of Birmingham, United Kingdom.

**General Design**

Each subject reported to the laboratory on 4 different occasions. On the first visit, Wmax and \( \dot{V}O_{2\text{max}} \) were determined. Because this study was part of a large project, where the effect of pre-exercise CHO feeding on cycling performance was investigated, all subjects performed a time trial (TT). On a second visit, subjects performed a familiarization TT to become familiar with the TT procedure and to ensure that they could complete the required exercise. The performance results of the TT are not included in the present study because this was not the aim of study. During the experimental trial, subjects ingested a 75-g glucose drink 45 min prior to the start of a 20-min steady state (SS) exercise bout on a cycle ergometer, which was immediately followed by a simulated TT. Furthermore, on a separate visit, all subjects underwent an oral glucose tolerance test (OGTT) in order to obtain an index of insulin sensitivity (32).

**Preliminary Testing**

At least 1 week before the start of the experimental exercise trials, subjects were asked to perform a graded exercise test to volitional exhaustion in order to determine Wmax and \( \dot{V}O_{2\text{max}} \). This test was performed on an electromagnetically braked cycle ergometer (Lode Excalibur Sport, Groningen, The Netherlands), modified to the configuration of a racing bicycle with adjustable saddle height and handlebar position. On arrival to the laboratory, subjects’ body mass (Seca Alpha, Hamburg, Germany) and height were recorded to the nearest 0.1 kg and 0.1 cm, respectively. In addition, body fat was estimated from skinfold thickness measurements at four sites of the body (biceps, triceps, subscapular, and supra-iliac) according to the method of Durnin and Womersley (9). Subjects then started cycling at 95 W for 3 min followed by incremental steps of 35 W every 3 min until exhaustion. Heart rate (HR) was recorded continuously by a radiotelemetry heart rate monitor (Polar Vantage NV, Kempele, Finland). Wmax was calculated from the last completed work rate, plus the fraction of time spent in the final non-completed work rate multiplied by the work rate increment. The results were used to determine the work rates corresponding to 65 and 80% Wmax, which were later employed in the experimental exercise trials. Breath by breath measurements were performed throughout exercise using an online automated gas analysis system (Oxycon Alpha, Jaeger, Wuerzburg, Germany). The volume sensor was calibrated using a 3-L calibration syringe, and the gas analyzers were calibrated using a 4.11% CO\(_2\) : 16.48% O\(_2\) : 79.41% N gas mixture. Oxygen uptake was considered to be maximal (\( \dot{V}O_{2\text{max}} \)) when at least two of the three following criteria were met: (a) a leveling off of \( \dot{V}O_{2} \) with increasing workload (increase of no more than 2 ml · kg\(^{-1}\) · min\(^{-1}\)), (b) a HR within 10 beats · min\(^{-1}\) of predicted maximum (HR 220 – age), and (c) a respiratory exchange ratio (RER)
1.05. \( \bar{V} \text{O}_2 \) was calculated as the average oxygen uptake over the last 60 s of the test.

### Experimental Exercise Trial

Subjects were asked to avoid vigorous exercise and to abstain from alcohol 24 h prior to each testing day. Subjects reported to the Human Performance Laboratory in the morning (between 7:00 to 9:00 AM) after an overnight fast (10 to 12 h). On subjects’ arrival to the laboratory, a flexible 21-gauge Teflon catheter (Quickcath, Baxter BV, Norfolk, UK) was inserted in an antecubital vein and attached to a three-way stopcock (Sims Portex, Kingsmead, UK) for blood sampling. The catheter was kept patent by flushing with 1.0–1.5 ml of isotonic saline (0.9% Baxter, Norfolk, UK) after each sample collection. Blood samples were transferred into precooled EDTA-containing tubes and kept on ice until further centrifugation. After collection of a 5-ml fasting blood sample (referred to as \( t = -45 \) min), subjects ingested an experimental CHO solution containing 75 g of glucose (D-Glucose monohydrate, Meritose 200, Amylum UK) made up with distilled water to a beverage volume of 400 ml. Another 100 ml of a non-energy liquid orange flavor (Lucozade placebo drink, SmithKline Beecham, UK) was added to the drink, which increased the total volume to be consumed to 500 ml.

All drinks were served in plastic nontransparent drink bottles at refrigerator temperature and had to be consumed within a 5-min period. After consumption of the CHO drink, subjects rested quietly in the laboratory for 45 min. Exactly 45 min after consumption of the CHO drink, subjects mounted the cycle ergometer and began exercise. The exercise protocol consisted of 20 min of submaximal steady state exercise (SS) at 65% \( W_{\text{max}} \) \((74 \pm 1\% \ \bar{V} \text{O}_2_{\text{max}})\), immediately followed by a TT. Body mass was recorded before and after each exercise trial, to the nearest 0.1 kg using a platform scale (Seca Alpha, Germany). Before the start of exercise, another 5 ml of blood was taken \((t = 0)\). Additional blood samples were obtained at 5-min intervals until the end of SS. Furthermore, every 5 min during SS, subjects were asked to rate their perceived exertion for whole body and legs on a scale from 6 to 20 using the Borg category scale (3). \( \bar{V} \text{O}_2 \), carbon dioxide production (\( \text{VCO}_2 \)), and RER were measured throughout the entire duration of SS using an online automated gas analysis system (Oxycon Alpha, Jaeger, Wuerzberg, Germany), and averages were taken of each 5-min period. HR was recorded in 30-s intervals throughout SS using a radiotelemetry heart rate monitor (Polar Vantage NV, Kempele, Finland) and later averaged for 5-min periods.

After SS, a simulated TT was performed as previously described by Jentjens et al. (21). Subjects were instructed to complete a predetermined amount of work (equal to approximately 40 min of exercise at 80% \( W_{\text{max}} \)) as fast as possible. In the present study, the total amount of work that had to be completed was 702 ± 25 kJ. Subjects did not receive any information regarding work rate, pedaling rate, HR, or time. All timekeeping devices (e.g., clocks, stop watches) were kept out of sight of the subjects during the performance test. The only information subjects received was the amount of work performed and the percentage of work performed relative to the preset amount of work (0% at start, 100% at completion of the trial). Blood samples (5 ml) were taken at 25%, 50%, 75%, and 100% of completion of TT. HR was recorded continuously in 30-s intervals and later averaged for the duration of time needed to complete the TT. All exercise tests were performed under normal and
standard environmental conditions (20 ± 1 °C dry bulb temperature and 60 ± 2% relative humidity). During the exercise trials (SS and TT), subjects were cooled with standing floor fans in order to minimize thermal stress, and water was available ad libitum. After the exercise trials, subjects were divided into two groups: a “Hypo-group”, in which subjects were assigned who had developed rebound hypoglycemia during SS exercise (plasma glucose <3.5 mmol/L) (21), and a “Non-hypo” group in which subjects were assigned who did not develop rebound hypoglycemia.

**OGTT Trials**

Subjects reported to the Human Performance Laboratory in the morning (between 7:00 and 9:00 AM) after an overnight fast (10 to 12 h) and having refrained from any strenuous activity or drinking any alcohol in the previous 24 h. On arrival to the laboratory, a flexible 21-gauge Teflon catheter (Quickcath, Baxter BV, Norfolk, UK) was inserted in an antecubital vein and attached to a three-way stopcock (Sims Portex, Kingsmead, UK) for blood sampling. The catheter was kept patent by flushing with 1.0 to 1.5 ml of isotonic saline (0.9% Baxter, Norfolk, UK) after each sample collection. A resting blood sample (2 ml) was collected into a heparin-coated syringe and immediately centrifuged. Immediately after the resting blood sample was taken (t = 0), subjects received a solution containing 75 g of glucose (D-Glucose monohydrate, Meritose 200, Amylum UK) made up with distilled water to a beverage volume of 500 ml. Subsequent blood samples were taken at 10-min intervals during the first hour, and at 15-min intervals during the second hour after glucose ingestion. Blood samples were analyzed for plasma glucose and insulin concentrations. The plasma glucose and insulin concentrations at t = 0, 30, 60, 90, and 120 min were used to determine the insulin sensitivity index (ISI), according to the following formula (32):

\[
\text{ISI} = \frac{10000}{\sqrt{\frac{(\text{FPG} \times \text{FPI}) \cdot (\text{mean OGTT insulin concentration})}{\text{mean OGTT glucose concentration}}}}
\]

in which FPG is the fasting plasma glucose concentration, FPI is the fasting plasma insulin concentration, and 10000 simply represents a constant that allows one to obtain numbers ranging from 0 to 12. Square-root conversion was used to correct the nonlinear distribution of values. The above index of whole-body insulin sensitivity is highly correlated \((r = 0.73, p < .0001)\) with the direct measure of whole-body insulin sensitivity derived from an euglycemic insulin clamp (32).

**Analyses**

Blood samples collected during exercise trials were transferred into pre-chilled EDTA-containing tubes (100 μL of 0.2 M EDTA) and centrifuged at 2300 × g for 10 min at 4 °C. Aliquots of plasma were stored at −20 °C until further analysis for glucose, insulin, and lactate. The blood samples collected during the OGTT were transferred into prechilled 2-ml micro tubes (Alpha Laboratories Ltd., Hampshire, UK) and subsequently centrifuged at 15,000 rpm for 2 to 3 min using a micro centrifuge. Aliquots of plasma were stored at −20 °C for later analysis of glucose and insulin. Glucose (Glucose HK kit, Proc. No.17-UV, Sigma-Aldrich, Dorset, UK)
and lactate (Lactate kit, Proc. No. 735, Sigma-Aldrich, UK) were analyzed on a semi-automatic analyzer (COBAS BIO, Roche, Basel, Switzerland). Plasma insulin was determined by radioimmunoassay using a commercially available kit (Insulin $^{125\text{I}}$ RIA 100 kit, ICN Pharmaceuticals, Inc., Costa Mesa, CA, USA).

**Statistics**

Analysis of variance (ANOVA) for repeated measures was used to compare differences in blood related parameters over time between the two groups. A Tukey post hoc was applied in the event of a significant $F$ ratio. Greenhouse-Geisser epsilon correction was used to adjust the significance level of the test statistics for violation in the assumed sphericity. Where appropriate, comparison of variables between the two groups was conducted using unpaired $t$ tests. Furthermore, where appropriate, post hoc power analyses were performed. Data evaluation was performed using Statistical Program for the Social Sciences (SPSS) for Windows version 10.05 (1999) software package (Chicago, USA). All data are reported as means ± SEM. Statistical significance was set at $p < .05$.

**Results**

**Subject Characteristics**

The subject characteristics for both the Hypo group and the Non-hypo group are shown in Table 1. The individual plasma glucose nadir during SS exercise was significantly lower ($p < .001$ and Power = 100%) in the Hypo group compared with

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hypo group ($n = 10$)</th>
<th>Non-hypo group ($n = 10$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.8 ± 3.0</td>
<td>25.9 ± 2</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>182 ± 2</td>
<td>178 ± 2</td>
</tr>
<tr>
<td>Body mass (kg)</td>
<td>74.7 ± 2.3</td>
<td>72.9 ± 1.4</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>14.2 ± 1.7</td>
<td>13.4 ± 0.9</td>
</tr>
<tr>
<td>$\dot{V}O_{2\text{max}}$ (ml · kg$^{-1}$ · min$^{-1}$)</td>
<td>60.5 ± 1.8</td>
<td>63.0 ± 2.1</td>
</tr>
<tr>
<td>Wmax (W)</td>
<td>356 ± 11</td>
<td>352 ± 10</td>
</tr>
<tr>
<td>HRmax (beats · min$^{-1}$)</td>
<td>187 ± 2</td>
<td>194 ± 2*</td>
</tr>
<tr>
<td>Glucose nadir$^\dagger$ (mmol/L)</td>
<td>2.7 ± 0.1</td>
<td>4.1 ± 0.2*</td>
</tr>
<tr>
<td>Insulin sensitivity index</td>
<td>3.7 ± 0.4</td>
<td>3.8 ± 0.5</td>
</tr>
</tbody>
</table>

*Note.* Values are means ± SEM. $\dot{V}O_{2\text{max}}$, maximal oxygen uptake expressed per kilogram body mass; Wmax, maximal work rate; HRmax, maximal heart rate. Hypo group: subjects who developed rebound hypoglycemia. Non-hypo group: subjects who did not develop rebound hypoglycemia. $^\dagger$Individual glucose nadir determined during cycling exercise at 65% Wmax, after ingestion of a 75 g glucose drink 45 min before the start of exercise.
the Non-hypo group (2.7 ± 0.1 mmol/L vs. 4.1 ± 0.2 mmol/L, respectively). However, there was no difference in ISI between the Hypo and the Non-hypo groups (3.7 ± 0.4 vs. 3.8 ± 0.5, respectively; \( p = .82 \) and Power = 6%). Furthermore, there were no differences in \( \text{VO}_{2\text{max}} \), Wmax, age, height, body mass, or body fat between both groups. Maximal HR (HRmax) was significantly lower in the Hypo-group (\( p = .028 \)) compared with the Non-hypo group.

**Exercise Trials**

**Plasma Glucose and Insulin Responses.** Plasma glucose and insulin concentrations at rest and during exercise are shown in Figures 1 and 2, respectively. Fasting plasma glucose concentrations were similar in the Hypo and the Non-hypo groups. At the start of exercise, 45 min after glucose ingestion, plasma glucose was significantly lower (\( p = .016 \)) in the Hypo group compared with the Non-hypo group. In addition, the plasma glucose concentrations during SS exercise were significantly lower (\( p = .01 \)) in the Hypo group compared with plasma glucose concentrations in the Non-hypo group. Plasma glucose in the Non-hypo group declined from 5.7 ± 0.3 mmol/L at the start of exercise to a glucose nadir of 4.4 ± 0.2 mmol/L at 15 min of SS exercise (\( p = .035 \)). However, plasma glucose concentrations during SS exercise were not statistically different from plasma glucose at rest. In the Hypo group, plasma glucose concentrations decreased from 4.2 ± 0.4 mmol/L at the onset of exercise to a glucose nadir of 3.2 ± 0.1 mmol/L at 15 min of SS exercise (\( p = .009 \)). Plasma glucose concentrations were significantly lower during SS exercise compared with the plasma glucose concentration at rest (\( p = .012 \)). After the drop in

![Figure 1 — Plasma glucose concentrations at rest, during submaximal exercise (SS), and during time trial performance (TT) after ingestion of 75 g of glucose 45 min prior to SS. Hypo group: subjects who developed rebound hypoglycemia. Non-hypo group: subjects who did not develop rebound hypoglycemia. \( * \)Hypo group significantly different compared with Non-hypo group (\( p < .05 \)); \( ^{b} \)Hypo group significantly different compared with Non-hypo group; (\( p < .01 \)). Values are means ± SEM.](image-url)
plasma glucose during SS exercise, plasma glucose then gradually rose until the end of the TT. In both the Hypo and the Non-hypo groups, plasma glucose concentrations during TT were significantly higher compared with plasma glucose concentrations during SS ($p < .001$ and $p = .024$) but were not different compared with corresponding plasma glucose concentrations at rest. There were no differences in plasma glucose concentrations between both groups at any of the time points during TT.

There were no differences in plasma insulin concentrations between both groups at any of the time points. However, plasma insulin concentrations were significantly higher at the onset of SS exercise compared with resting values ($p < .001$). In addition, plasma insulin remained higher ($p = .008$) during the first 5 min of SS exercise compared with plasma insulin at rest. Thereafter, plasma insulin declined to fasting levels at 10 min into SS exercise and remained relatively constant until the end of exercise.

**Plasma Lactate.** The plasma lactate concentrations at rest and during exercise are presented in Figure 3. There were no differences in plasma lactate concentrations between both groups at any of the time points. Plasma lactate increased ($p < .001$) from 0.9 to 1.0 mmol/L before the start of exercise ($t = 0$) to values ranging from 2.6 to 4.1 mmol/L during SS exercise. Furthermore, plasma lactate concentrations during TT were significantly higher ($p < .001$) compared with SS exercise (8.0 ± 0.4 vs. 3.3 ± 0.2 mmol/L, respectively).

**$\dot{V}_{O_2}$, RER, HR, and RPE.** Respiratory data, HR, and RPE are shown in Table 2. There were no significant differences in $\dot{V}_{O_2}$ and RPE for either whole body or legs between both groups. There was no significant interaction between group and time for RER. However, there was a main effect of time ($p = .001$). RER gradually
declined throughout the 20 min SS exercise in both the Hypo group and the Non-hypo group \((p = .034\) and \(p < .001\), respectively). HR during SS exercise was not different between both groups. The overall mean values for the Hypo group and the Non-hypo group were 153 ± 2 and 151 ± 2 beats · min⁻¹, respectively. As expected, there was a significant rise in HR during SS exercise in both groups (main effect of time; \(p = .000\)).

**OGTT**

The plasma glucose and insulin concentrations obtained during the OGTT are shown in Figures 4 and 5, respectively. There were no differences in fasting plasma glucose and insulin concentrations between the Hypo and the Non-hypo groups. After ingestion of 75 g of glucose, plasma glucose and insulin concentrations followed a similar pattern in both groups during a 120-min rest period. There were no differences in plasma glucose and insulin concentrations between the two groups at any of the time points. Because plasma glucose and insulin concentrations were the same in the Hypo and Non-hypo groups, no difference was found in ISI between both groups (Table 1). Furthermore, no correlation was found between the plasma glucose nadir during SS exercise and ISI (Figure 6).
Discussion

Numerous studies have shown that pre-exercise CHO feedings can result in rebound hypoglycemia 15 to 30 min after the onset of exercise studies (6, 14, 20, 28, 29, 35, 39, 42). In contrast, several other studies did not find hypoglycemia during exercise when glucose was ingested in the hour before exercise (5, 8, 13, 17, 19, 27, 30, 31, 33, 34, 37, 40). Although the contradictory findings may be partly explained by
Table 2: Average Oxygen Uptake (\( \dot{V}O_2 \)), Respiratory Exchange Ratio (RER), Heart Rate (HR), and Rating of Perceived Exertion for Whole Body (RPE Overall) and Legs (RPE Legs) During Cycling Exercise at 65% Maximum Work Rate After Ingestion of 75 g of Glucose 45 Minutes Before the Start of Exercise

<table>
<thead>
<tr>
<th>Variable</th>
<th>Time (min)</th>
<th>0–5</th>
<th>5–10</th>
<th>10–15</th>
<th>15–20</th>
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<tr>
<td>( \dot{V}O_2 ) (ml/min)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypo</td>
<td>3370 ± 128</td>
<td>3381 ± 127</td>
<td>3392 ± 126</td>
<td>3377 ± 132</td>
<td></td>
</tr>
<tr>
<td>Non-hypo</td>
<td>3304 ± 127</td>
<td>3305 ± 114</td>
<td>3309 ± 104</td>
<td>3352 ± 113</td>
<td></td>
</tr>
<tr>
<td>RER</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Hypo*</td>
<td>1.04 ± 0.02</td>
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<tr>
<td>Non-hypo*</td>
<td>1.05 ± 0.02</td>
<td>1.01 ± 0.02</td>
<td>1.00 ± 0.02</td>
<td>1.00 ± 0.01</td>
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<tr>
<td>HR (bpm)</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Hypo#</td>
<td>146 ± 2</td>
<td>157 ± 3</td>
<td>159 ± 3</td>
<td>160 ± 3</td>
<td></td>
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<tr>
<td>Non-hypo#</td>
<td>144 ± 3</td>
<td>156 ± 3</td>
<td>158 ± 3</td>
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<tr>
<td>RPE overall</td>
<td></td>
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<tr>
<td>Hypo</td>
<td>11.3 ± 0.5</td>
<td>11.2 ± 0.5</td>
<td>11.2 ± 0.5</td>
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<tr>
<td>Non-hypo</td>
<td>10.6 ± 0.6</td>
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<td>11.7 ± 0.5</td>
<td>12.4 ± 0.4</td>
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<tr>
<td>RPE legs</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hypo</td>
<td>12.1 ± 0.6</td>
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<td>11.6 ± 0.6</td>
<td>12.1 ± 0.6</td>
<td></td>
</tr>
<tr>
<td>Non-hypo</td>
<td>11.6 ± 0.8</td>
<td>11.8 ± 0.5</td>
<td>12.2 ± 0.7</td>
<td>12.6 ± 0.7</td>
<td></td>
</tr>
</tbody>
</table>

Note. Data are presented as means ± SEM; \( n = 10 \) for both groups. Hypo: subjects who developed rebound hypoglycemia. Non-hypo: subjects who did not develop rebound hypoglycemia. Perceived exertion for whole body and legs was rated on a scale from 6 to 20 using the Borg category scale (3). *Significant main effect of time \((p < .05)\); #significant main effect of time \((p < .01)\).

differences in research designs among these studies, this does not explain why some individuals develop rebound hypoglycemia and others do not, as was shown in recent studies from our laboratory (1, 21, 22, 36) and the work of Kuipers et al. (29). It has been suggested that rebound hypoglycemia in trained individuals is due to a high insulin sensitivity (29). Insulin sensitivity is higher in trained compared with untrained subjects (10, 24, 38), and therefore well-trained subjects may have an increased risk to develop rebound hypoglycemia (29). The aim of the present study was to investigate if the prevalence of rebound hypoglycemia in trained individuals is accompanied by a higher insulin sensitivity. The main finding of this study was that subjects who developed rebound hypoglycemia did not have a higher insulin sensitivity compared with subjects who did not show rebound hypoglycemia.
In the present study, subjects were assigned to a Hypo group (plasma glucose <3.5 mmol/L) or a Non-hypo group (plasma glucose ≥3.5 mmol/L) based on their plasma glucose nadir during SS exercise. During the first 20 min of SS exercise, 50% of the subjects ($n = 10$) developed rebound hypoglycemia, following ingestion of 75 g glucose 45 min prior to exercise. This finding is in agreement with the results of a recent study by Kuipers et al. (29), who investigated 19 subjects, with similar characteristics as those in the present study, who consumed 50 g of glucose 30 min before exercise at 60% Wmax. The subjects in their Hypo-group ($n = 6$) (plasma glucose concentration <3.0 mmol/L) showed a significantly lower plasma glucose concentration at the onset of exercise ($6.0 \pm 0.4$ vs. $7.8 \pm 0.5$ mmol/L, respectively) and had a significantly lower plasma glucose nadir during exercise compared with the subjects in their Non-hypo group ($n = 13$; $2.6 \pm 0.1$ vs. $4.4 \pm 0.2$ mmol/L, respectively). The lower plasma glucose concentrations in the Hypo group were found without any differences in plasma insulin concentrations between the Hypo and Non-hypo groups. These results are in close agreement with the present findings, although in our study plasma glucose concentrations at the onset of exercise were approximately 25% lower and plasma insulin concentrations were 50% higher compared with those of Kuipers et al. (29). Of note, in the present study, plasma glucose concentrations in the Hypo-group were below 3.5 mmol/L at 5 min into SS exercise and remained stable at this level throughout SS exercise, whereas plasma glucose concentrations in the study of Kuipers et al. (29) gradually dropped and reached a nadir approximately 20 min after the onset of exercise. The small differences in glucose and insulin responses between our study and Kuipers et al.’s (29)

Figure 6 — Scatter plot of plasma glucose nadir during submaximal exercise (SS) and insulin sensitivity index (ISI). The dotted line represents the cutoff point for plasma glucose to be defined as rebound hypoglycemia (<3.5 mmol/L). Hypo group: subjects who developed rebound hypoglycemia. Non-hypo group: subjects who did not develop rebound hypoglycemia.
might be explained by differences in research design (i.e., fasted vs. not fasted, 75 g vs. 50 g of glucose, CHO ingestion 45 min vs. 30 min before exercise, exercise at 65% vs. 60% Wmax, respectively). Kuipers et al. (29) suggested that the lower plasma glucose concentrations at the onset of exercise with similar plasma insulin concentrations in the Hypo group compared with the Non-hypo group was due to a higher insulin sensitivity in the Hypo group. Unfortunately, no measurement of insulin sensitivity was obtained in their study. Therefore, in the present study we measured insulin sensitivity by using an OGTT. However, the present findings do not support the hypothesis of Kuipers et al. (29), because we did not find a difference in ISI between the Hypo and Non-hypo groups (3.7 ± 0.4 vs. 3.8 ± 0.5, respectively).

It might be argued that the difference in ISI between the two groups was too small to detect with the present method. However, despite a wide range of ISI between subjects, no link between insulin sensitivity and rebound hypoglycemia was found (Figure 6). The range of ISI seemed to be similar among subjects in the Hypo and Non-hypo groups (2.1 to 6.0 vs. 2.6 to 7.4, respectively), which also suggests that the prevalence of rebound hypoglycemia in trained individuals cannot be explained by a higher insulin sensitivity. It is therefore unlikely that a more accurate method to determine whole body insulin sensitivity would have changed our conclusion. The wide ISI range of our subjects was most likely due to a large range of fitness levels. The $\bar{V}\bar{O}_{2\text{max}}$ of the subjects ranged from 53 to 74 ml/kg/min and Wmax ranged from 3.9 to 5.4 W/kg. When subjects were ranked according to their $\bar{V}\bar{O}_{2\text{max}}$, the average $\bar{V}\bar{O}_{2\text{max}}$ of the 10 subjects with the highest $\bar{V}\bar{O}_{2\text{max}}$ was 67 ± 1 ml/kg/min, while the 10 remaining subjects had an average $\bar{V}\bar{O}_{2\text{max}}$ of 57 ± 1 ml/kg/min ($p < .001$). In accordance with this, the ISI of the subjects with the highest $\bar{V}\bar{O}_{2\text{max}}$ values was significantly higher ($p = .026$) compared with the ISI of the subjects with moderate $\bar{V}\bar{O}_{2\text{max}}$ values (4.4 ± 0.5 vs. 3.0 ± 0.2, respectively). Although the purpose of the present study was not to investigate the ISI between groups of trained subjects differing in $\bar{V}\bar{O}_{2\text{max}}$, this is the first time that differences in ISI between moderately and well-trained subjects were determined by an OGTT using the method of Matsuda and Defronzo (32). This method has been recently validated in sedentary subjects by comparing it against the direct measurement of insulin sensitivity obtained with the euglycemic insulin clamp technique and showed a strong correlation ($r = 0.73, p < .0001$). Although some authors have criticized the OGTT because of its poor reproducibility (16, 26), the ISI obtained from an OGTT according to the new validated method of Matsuda and Defronzo (32), may be a valuable tool when comparing ISIs between different groups of subjects. The advantage of the OGTT for measuring insulin sensitivity compared with other methods for measuring insulin sensitivity is that this test can be performed in most exercise laboratories and does not require expensive equipment and qualified medical staff.

In the present study, there was no difference in RPE between the Hypo group and the Non-hypo group (Table 2), despite significantly lower plasma glucose concentrations during SS exercise (Table 2 and Figure 2) in the Hypo group. This suggests that subjects did not experience any detrimental effects of hypoglycemia, most probably because hypoglycemic plasma glucose levels only existed for a relatively short period of time. In addition, none of the other variables measured were different between the two groups (Table 2). It should be noted that we were not able to calculate total CHO oxidation, since RER reached values above 1.0, and the substrate equations of Frayn (15) do not account for the extra CO$_2$ production that occurs during excessive H$^+$ buffering. However, $\bar{V}\bar{O}_2$, RER, and plasma lactate
concentrations during SS exercise were similar for the Hypo group and the Non-hypo group, which suggests a similar type of fuel selection.

In conclusion, this study shows that the prevalence of rebound hypoglycemia in trained individuals is not accompanied by higher insulin sensitivity. The present results suggest that the magnitude of insulin sensitivity does not play an important role in the occurrence of rebound hypoglycemia in trained individuals, and hence it is still not clear why some individuals develop rebound hypoglycemia and others do not.

**References**


**Acknowledgments**

The authors would like to thank Miss C. Cale, Miss C. Gutch, and Mr L. Moseley for their help with the data collection. Miss C. Cale was funded by a grant from the Physiological Society, and Miss C. Gutch was funded by a grant from the Wellcome Trust.