Effect of intermittent high-intensity compared with continuous moderate exercise on glucose production and utilization in individuals with type 1 diabetes

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Guelfi KJ, Ratnam N, Smythe GA, Jones TW, Fournier PA. Effect of intermittent high-intensity compared with continuous moderate exercise on glucose production and utilization in individuals with type 1 diabetes. Am J Physiol Endocrinol Metab 292: E865–E870, 2007; doi:10.1152/ajpendo.00533.2006.—Previously, the decline in glycemia in individuals with type 1 diabetes has been shown to be less with intermittent high-intensity exercise (IHE) compared with continuous moderate-intensity exercise (MOD) despite the performance of a greater amount of total work. The purpose of the present study was to determine whether this lesser decline in glycemia can be attributed to a greater increment in endogenous glucose production (Ra) or attenuated glucose utilization (Rd). Nine individuals with type 1 diabetes were tested on two separate occasions, during which either a 30-min MOD or IHE protocol was performed under conditions of a euglycemic clamp in combination with the infusion of [6,6-2H]glucose. MOD consisted of continuous cycling at 40% V̇O₂peak whereas IHE involved a combination of continuous exercise at 40% V̇O₂peak interspersed with additional 4-s maximal sprint efforts performed every 2 min to simulate the activity patterns of intermittent sports. During IHE, glucose Ra increased earlier and to a greater extent compared with MOD. Similarly, glucose Rd increased sooner during IHE, but the increase by the end of exercise was comparable with that elicited by MOD. During early recovery from IHE, Ra rapidly declined, whereas it remained elevated after MOD, a finding consistent with a lower glucose infusion rate during early recovery from IHE compared with MOD (P < 0.05). The results suggest that the lesser decline in glycemia with IHE may be attributed to a greater increment in Ra during exercise and attenuated Rd during exercise and early recovery.

glycemia; hypoglycemia; physical activity

FOR INDIVIDUALS WITH TYPE 1 DIABETES, participation in exercise generally increases the risk of experiencing hypoglycemia both during exercise (31, 36) and for up to 3 h of recovery (22). Consequently, these individuals may fear or be discouraged from physical activity (13) despite the well-established benefits of exercise (18, 27, 28). Although hypoglycemia is a legitimate fear, the American Diabetes Association Position Statement on Physical Activity/Exercise and Diabetes (43) states that complication-free individuals with type 1 diabetes can safely enjoy the benefits of physical activity by balancing exogenous insulin administration and carbohydrate intake to maintain glucose levels within the euglycemic range. However, effective adjustment of these parameters requires an understanding of the metabolic and hormonal responses to exercise (43). For this reason, much research has focused on investigating the glucoregulatory responses to exercise.

It is well established that continuous exercise of moderate-intensity causes a decline in blood glucose levels (31, 36), whereas sustained high-intensity exercise [~15 min at >80% maximal oxygen uptake (V̇O₂max)] stimulates a progressive rise in glycemia during exercise and prolonged hyperglycemia during recovery (30, 34). On the other hand, the response of blood glucose levels to a combination of moderate and high-intensity exercise, a pattern of physical activity referred to as intermittent high-intensity exercise (IHE), is less well understood. IHE involves repeated bouts of short, intense activity, interrupting longer periods of lower-intensity activity or rest. This type of exercise characterizes most team and field sports and accounts for much of the selection of activities participated in by individuals with type 1 diabetes (32), as well as spontaneous play in children (1).

Recently, the glucoregulatory responses to IHE that reflect the work-to-recovery ratios observed in team and field sports have been compared with continuous moderate-intensity exercise (MOD) (15). The experimental design simulated a “real-life” situation in which the participants injected their normal morning dose of insulin and consumed their typical breakfast prior to the performance of exercise ~3.5 h later. It was found that the decline in glycemia was less with IHE compared with MOD both during exercise and throughout the first hour of recovery. This was despite the performance of a greater amount of total work with IHE. The authors hypothesized that the lesser decline in glycemia with IHE may have resulted from a greater increase in hepatic glucose production and attenuated glucose utilization. Since this issue has not previously been addressed, the purpose of the present study was to compare the effect of IHE and MOD on the rate of glucose production and utilization during and after exercise in individuals with type 1 diabetes.

EXPERIMENTAL PROCEDURES

Participants. Nine healthy, physically active male (n = 5) and female (n = 4) volunteers with type 1 diabetes [age 22.6 ± 5.7 yr, body mass index (BMI) 24.6 ± 2.2 kg/m², peak oxygen uptake
plasma glucose in response to adjustments in the glucose infusion rate (11). For the next 150 min the participant remained rested in a seated position to allow for isotope equilibration, with stable enrichment confirmed via blood sampling in the final 30 min of this period. While they rested, expired air was collected from each participant via a mask connected to a \( V_{\text{max}} \) Spectra respiratory analysis system (SensorMedics) for at least 10 min for the determination of baseline rates of \( O_2 \) consumption and \( CO_2 \) production.

After this equilibration period, blood was sampled for baseline measurements and the participant moved to an adjacent Front Access Cycle ergometer (Repeco). The rate of constant infusion resulted in free insulin levels of 5.5 mmol/l, with no difference between trials (Fig. 1A). Although tracer methodology is not typically applied to the type of exercise, there was no statistical difference between trials. During early recovery, GIR remained elevated following both protocols but was significantly higher after MOD compared with IHE at 5 min of recovery (\( P = 0.049 \)). During later recovery from MOD, GIR returned to baseline but remained slightly elevated after IHE, although there was no difference between trials.

**Glucose \( R_g \) and \( R_d \).** Isotopic enrichment was stable prior to the commencement of exercise and remained relatively constant for the duration of the experiment (coefficient of variation = 7.8%). With the onset of exercise, endogenous \( R_d \),
progressively increased to peak at the cessation of exercise (Fig. 2A). However, the rise in $R_a$ commenced sooner and was of a greater magnitude during IHE compared with MOD, with the latter difference reaching statistical significance at 15 min of exercise ($P = 0.05$). Postexercise, $R_a$ rapidly declined but remained above baseline levels for the first hour of recovery. During the second hour of recovery, $R_a$ returned to baseline with MOD but remained slightly elevated after IHE. Basal glucose $R_d$ was equivalent in both trials and progressively increased during exercise to a similar extent; however, the rise commenced earlier during IHE (Fig. 2B). Immediately postexercise, $R_a$ declined to baseline with IHE, whereas it remained elevated after MOD. During later recovery from IHE, $R_d$ rose again above baseline, whereas after MOD $R_d$ remained at baseline from 30 min. At 2 h postexercise, $R_d$ was significantly higher after IHE compared with MOD ($P = 0.045$).

**Total work, heart rate, and oxygen consumption.** A greater amount of total work was performed during IHE compared with MOD (2,882 ± 385 vs. 2,199 ± 289 J/kg, $P = 0.000$). This greater amount of total work was reflected by the response of heart rate and oxygen consumption to exercise, which increased to a greater extent during IHE (Table 1). The higher average rate of oxygen consumption during IHE corresponded to ~55% of $V_O_2$ peak compared with 40% during MOD.

**Metabolites and hormones.** Blood lactate increased during both exercise protocols, but the increase was greater with IHE compared with MOD ($P = 0.000$; Fig. 3A). In contrast, the levels of circulating FFAs were not different between MOD and IHE, remaining stable during exercise but increasing after 2 h of recovery (Fig. 3B). Epinephrine levels were not significantly increased in response to MOD or IHE, and there was no difference between protocols (Fig. 3C). On the other hand, norepinephrine increased during both exercise protocols, with a greater increase in response to IHE compared with MOD ($P = 0.012$; Fig. 3D). Growth hormone levels also rose during IHE, remaining elevated for the first 15 min of recovery, but did not change in response to MOD (Fig. 3E), whereas cortisol levels were not altered by either protocol (Fig. 3F). Like cortisol, glucagon did not change during exercise, although a decline was observed after 60 min of recovery from IHE, resulting in a significant difference from MOD at this time ($P = 0.027$; Fig. 3G). Despite this difference in glucagon at 60 min of recovery, no difference in the ratio of glucagon to insulin was observed (Fig. 3H).

**DISCUSSION**

This study compared the effect of IHE and MOD on the rate of glucose production and utilization during and after exercise in individuals with type 1 diabetes. It was found that IHE stimulated a more rapid and greater magnitude of increase in $R_a$ compared with MOD. Similarly, $R_d$ increased sooner during IHE, but by the end of exercise the total increase was comparable to MOD. During early recovery from exercise, $R_a$ rapidly declined following IHE, whereas it remained elevated after MOD. Throughout the second hour of recovery, $R_a$ and $R_d$ returned to baseline following MOD but remained slightly
The GIR required to maintain euglycemia was significantly lower at this time following IHE.

The more rapid increase in Ra and Rd in response to IHE was consistent with the higher workload associated with this exercise protocol, as indicated by the greater amount of total work performed and elevation in heart rate and oxygen consumption. Since the only difference between the two exercise protocols was accounted for by the added 4-s maximal efforts involved in IHE, it is likely that these short, intense bouts were responsible for the early differences in Ra and Rd. Although the response of Ra and Rd to an isolated short bout of high-intensity exercise has not previously been investigated, it is well established that both Ra and Rd increase with exercise intensity as a result of a greater reliance on carbohydrate oxidation (37). It is also well established that, during more sustained high-intensity exercise (10–15 min at >80% \( \dot{V}O_2 \max \)), the increase in Ra is disproportionately greater than the increase in Rd (30, 34). Although maximal efforts of only 4 s in duration are unlikely to stimulate an equivalent response, it is likely that the greater rise in Ra during IHE compared with MOD can be attributed to the repeated bouts of maximal exercise.

The mechanism by which the repeated bouts of high-intensity exercise involved in IHE stimulated a different response of Ra and Rd to exercise is likely related to the exercise-mediated changes in counterregulatory hormone levels. First, the greater early rise in Ra during IHE is likely attributed to the larger rise in hormone concentrations. The elevated after IHE. Associated with the changes early in recovery, the GIR required to maintain euglycemia was significantly lower at this time following IHE.

Table 1. Effect of MOD and IHE on heart rate and \( \dot{V}O_2 \)

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Baseline</th>
<th>Exercise</th>
<th>Recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>MOD</td>
<td>70±17</td>
<td>117±12†</td>
</tr>
<tr>
<td></td>
<td>IHE</td>
<td>67±11</td>
<td>153±18*†</td>
</tr>
<tr>
<td>( \dot{V}O_2 ), ml·kg⁻¹·min⁻¹</td>
<td>MOD</td>
<td>3.4±0.7</td>
<td>15.9±1.9*†</td>
</tr>
<tr>
<td></td>
<td>IHE</td>
<td>3.3±0.8</td>
<td>23.0±4.4*†</td>
</tr>
</tbody>
</table>

Results are expressed as means ± SD. MOD, moderate-intensity exercise; IHE, intermittent high-intensity exercise; \( \dot{V}O_2 \), oxygen consumption. *Statistically significant difference \((P < 0.05)\) between MOD and IHE; †Statistically significant difference \((P < 0.05)\) from baseline (0 min).
in norepinephrine during this protocol, since the catecholamines have been previously implicated as potent stimulators of hepatic glucose output during exercise (17), although other studies do not support this suggestion (7). On the other hand, the earlier rise in $R_d$ during IHE might be explained by the higher intensity of exercise. High-intensity exercise typically stimulates a greater release of $\text{Ca}^{2+}$ from the sarcoplasmic reticulum and activation of AMPK (5), both factors that mediate skeletal muscle contraction-stimulation of glucose transport (42). Despite this earlier rise in $R_d$, the total increase by the end of both exercise protocols was comparable. This may be the result of a greater reliance on muscle glycogen breakdown and, hence, increased glycolytic flux during IHE, which has been implicated as a factor that attenuates glucose $R_d$ via glucose 6-phosphate-mediated inhibition of glucose utilization (39). It is also possible that the greater rise in norepinephrine toward the end of IHE may have attenuated the increase in glucose uptake during this type of exercise (20), as may lactate (24). Growth hormone is also elevated at this time, and although some studies have demonstrated an acute effect on glucose utilization (25, 26), most consider the effects of growth hormone on glucose turnover to take several hours to become evident (9). Furthermore, it is unlikely that insulin, glucagon, cortisol, or FFAs contributed to the differences observed in $R_d$ and $R_d$ during exercise, since the peripheral circulating levels of these variables were equivalent during both protocols. However, this does not preclude the possibility that different levels of these glucoregulatory factors, particularly glucagon, were present in the portal vein (38).

The exercise-induced changes in counterregulatory hormone levels might also assist in explaining, in part, the different pattern of response of $R_d$ at the cessation of exercise. The rapid decline in $R_d$ following IHE may be attributed to the above-mentioned higher levels of norepinephrine at this time via attenuated glucose uptake (20). Regardless, the rapid decline in $R_d$ after IHE was surprising given that the repeated maximal sprint bouts would be expected to deplete muscle glycogen to a greater extent (14) and thus stimulate a higher rate of glucose uptake for glycogen resynthesis during recovery (29). Perhaps the high levels of norepinephrine, growth hormone, and lactate during early recovery were sufficient to counter any stimulatory effect of low glycogen levels on glucose uptake. Consistent with this interpretation, it is possible that, during the second hour of recovery, when the levels of norepinephrine, lactate, and growth hormone had returned to baseline, the raised $R_d$ after IHE was a manifestation of increased glucose requirements for glycogen resynthesis.

The different pattern of response of $R_d$ and $R_d$ to IHE and MOD was relatively consistent with the changes in GIR required to maintain euglycemia. Although visual inspection of the results suggests that the increase in GIR during exercise peaked earlier and began to decline toward the end of IHE, while continuing to progressively increase during MOD, these differences were not statistically significant. On the other hand, during early recovery from IHE, the significantly lower GIR compared with MOD was consistent with the rapid decline in $R_d$ after IHE. Finally, the increase in GIR during the second hour of recovery from IHE might be explained partly by the rise in $R_d$ at that time. Of note, there was no significance difference in the area under the curve for GIR during exercise or recovery (results not shown).

The above-mentioned changes in $R_d$, $R_d$, and GIR in response to MOD and IHE explain only in part the previous observation that blood glucose levels decline less during and for the first hour after IHE compared with MOD (15). On the basis of this earlier study, a lower GIR was expected during IHE compared with MOD. However, as previously mentioned, no statistical difference was observed in the GIR during exercise. On the other hand, the lower GIR during early recovery from IHE is consistent with the findings of the previous study (15). Conversely, after 2 h of recovery from IHE (which was not previously investigated), the continued elevation of GIR suggests that the decline in blood glucose levels might not be less at this time after IHE if carbohydrates are not administered in the meantime.

The lack of complete consistency between the findings of the present study and the previous observation that blood glucose levels decline less with IHE compared with MOD is likely explained by differences in experimental design and the physiological conditions of study participants. First, the participants in the present study were fasted overnight, but in a postprandial state previously (15). Lower preexercise hepatic glycogen levels resulting from fasting in the present study may have impaired the exercise-induced rise in hepatic glucose production (40). Second, the circulating levels of insulin in the present study were marginally higher, which may have further attenuated the exercise-induced increase in glucose production while also enhancing glucose uptake (3). Another factor to consider is the infusion of exogenous glucose, which has been shown to attenuate glucose production and increase uptake during exercise (23). Finally, since blood glucose levels were kept stable in the present study, but allowed to decline in the real-life study (15), this might account for some of the differences in results, since the actual change in glucose level itself may be important in stimulating glucoregulatory responses (33). Thus it is advisable that future studies be conducted without glucose clamping to further elucidate the response of glucose production and utilization to these two types of exercise.

In summary, this study shows that the high-intensity bouts associated with IHE stimulate a more rapid and greater increment in endogenous glucose production during exercise than MOD alone. During early recovery from exercise, glucose utilization declines rapidly following IHE, whereas it remains elevated after MOD despite the performance of more total work. Consistent with these findings, a lower GIR required to maintain euglycemia was observed immediately following IHE compared with MOD. These events assist in explaining, in part, the previous observation that the decline in blood glucose is less with IHE compared with MOD in individuals with type 1 diabetes despite the performance of a greater amount of total work.

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REFERENCES


