METABOLIC AND HORMONAL RESPONSES TO EXERCISE IN TYPE 1 DIABETIC PATIENTS DURING CONTINUOUS SUBCUTANEOUS, AS COMPARED TO CONTINUOUS INTRAPERITONEAL, INSULIN INFUSION

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SUMMARY - This study was performed to determine whether metabolic and hormonal responses during moderate exercise differ between continuous intraperitoneal insulin infusion (CIPII) and continuous subcutaneous insulin infusion (CSII). In seven Type 1 diabetic patients, treatment was changed from CSII to CIPII. Prior to the change, these patients performed an ergometer exercise at 60% of VO2 max for 40 min followed by a 200-min rest. About one year later, when the procedure was repeated during CIPII, HbA1c had improved from 8.5 to 7.1%. Arterial blood glucose, venous lactate and hormonal responses were analysed. Although a regimen with a higher basal insulin infusion rate was applied during the exercise test on CIPII, corresponding venous insulin levels were lower (28.0 ± 2.2 vs. 48.1 ± 7.9 pmol L−1, p = 0.04). Exercise caused a more marked decline in blood glucose during CIPII, with nadir blood glucose at the end of exercise (3.6 ± 0.4 vs. 5.1 ± 0.4 mmol L−1, p = 0.005). Both exercise tests yielded significant and similar increases in plasma levels of adrenaline, noradrenaline, cortisol and growth hormone. A significant rise in plasma glucagon (15.1 ± 4.5 pg mL−1, p = 0.01) was observed during CIPII, but not during CSII (7.4 ± 3.5 pg mL−1, n.s.). It is concluded that patients on CIPII should reduce their insulin infusion rate during exercise. CIPII appears to have favourable effects on counterregulatory capacity; in particular, a more prominent glucagon response to exercise may prove important.

Key-words: Type 1 diabetes, exercise, insulin infusion, pump treatment, subcutaneous, intra-peritoneal, glucagon.

RÉSUMÉ - Réponses métaboliques et hormonales à un exercice chez des diabétiques type 1 durant une infusion continue d’insuline sous-cutanée ou intrapéritonéale.

Cette étude a été réalisée afin de déterminer si les réponses métaboliques et hormonales durant un exercice modéré diffèrent selon que l’infusion continue d’insuline est réalisée par voie sous-cutanée (CSII) ou intrapéritonéale (CIPII). Chez sept patients diabétiques de type 1, le traitement fut modifié de CSII à CIPII. Avant cette modification, ces patients réalisèrent un exercice sur ergomètre à 60 % de VO2 max pendant 40 minutes suivies de 200-minutes de repos. Environ un an plus tard, l’épreuve fut répétée sous CIPII, a ce moment l’HbA1c avait été améliorée (7,1 vs 8.5 %). Sur sang artérialisé ont été mesurés la glycémie, l’acide lactique, les réponses hormonales. Quoiqu’un débit basal d’insuline plus élevé sous CIPII ait été appliqué durant l’exercice, les insulinémies furent mesurées plus basses (28.0 ± 2.2 vs 48.1 ± 7.9 pmol L−1, p = 0.04). L’exercice a entraîné une chute glycémique plus marquée sous CIPII, avec un nadir en fin d’épreuve (3.6 ± 0.4 vs 5.1 ± 0.4 mmol L−1, p = 0.005). Les deux épreuves s’accompagnaient d’une élévation similaire des taux plasmatiques d’adrénaline, de noradrénaline, de cortisol et d’hormone de croissance. Une élévation comparable de glucagon (15.1 ± 4.5 pg ml L−1, p = 0.01) fut observée durant l’infusion CIPII, mais non durant la voie CSII (7.4 ± 3.5 pg ml L−1, n.s.). Il est conclu que les patients sous CIPII (pompe péritonéale) doivent réduire le débit d’insuline en cours d’exercice musculaire. La voie CIPII semble avoir des effets favorables sur les capacités de contre-régulation, en particulier, une meilleure réponse du glucagon après exercice.

Mots-clés : Diabète type 1, exercice, infusion d’insuline, voie sous-cutanée, voie intrapéritonéale, glucagon.
According to the literature, hypoglycaemia induced by exercise in Type 1 diabetic patients on conventional insulin therapy can only be prevented by a marked reduction of the insulin dose prior to exercise [1, 2], with a risk of post-exercise hyperglycaemia [3]. The same principles apply to patients on continuous subcutaneous insulin infusion (CSII) [1, 4, 5]. The blood glucose fall induced by exercise in Type 1 diabetic patients may have several explanations, e.g. enhanced insulin absorption from subcutaneous tissue [6], increased tissue sensitivity to insulin [7], or inability to increase hepatic glucose output to match the enhanced fuel demands of working muscle. The hypoglycaemic effect of exercise in normal man is compensated for by an enhanced secretion of glucagon and adrenaline [8]. In Type 1 diabetic patients, glucagon secretion during exercise appears to be normal. The glycaemic effect of exercise during intraperitoneal (i.p.) insulin infusion has hitherto only been studied in an acute experimental setting [9]. However, the blood glucose lowering effect of exercise was not observed in that study. Continuous i.p. insulin infusion (CIPII) has been thought to reduce the risk of severe hypoglycaemic events [10, 11]. The mechanism behind this effect is somewhat unclear, but may involve such factors as lower insulin depot via portal insulin absorption, yielding higher hepatic insulinisation at lower peripheral insulinaemia. Therefore, the present study was designed to assess the clinical relevance of the above findings by comparing glycaemic and hormonal responses to a 40-min bicycle exercise test at 60% of VO$_{2\text{max}}$ during CSII and CIPII in Type 1 diabetic patients. As prevailing insulin concentration may influence glucagon secretion, we were also interested in determining whether glucagon response to exercise was different.

## PATIENTS AND METHODS

Seven Type 1 diabetic patients (5 men and 2 women), mean age 42 (36-50) years, body mass index 25 ± 2 kg m$^{-2}$, duration of disease 15 (2-30) years, glycated haemoglobin (HbA1c) 8.5 ± 0.8% (ref. < 5.2%), participated in the study. All patients had meal-stimulated C-peptide < 0.2 nM. Four had non-proliferative retinopathy and one microalbuminuria. None had clinical signs of neuropathy and none had any other signs of late diabetic complications. Some relevant anthropometric data for these patients are included in Table I. Prior to the study, all patients had been treated with continuous subcutaneous insulin infusion (Minimed, model 506, Sylmar, USA) for at least six months. The patients were offered i.p. insulin treatment with an implantable insulin pump (Minimed, model 2001, Sylmar, USA) since their metabolic control was unsatisfactory (HbA1c > 7.2%; i.e. 2.0% > non-diabetic range) and/or blood glucose monitoring displayed instability. The patient’s blood glucose stability (SD$_{BG}$) was determined from a calculation of the standard deviation of 70 values of home monitoring of blood glucose, according to a method evaluated in our laboratory [12]. The incidence of biochemical hypoglycaemia, i.e. blood glucose <3.0 mmol L$^{-1}$ according to home blood glucose monitoring, was determined from the same time period used for the SD$_{BG}$ calculation. Three of the patients had a reduced insulin infusion rate during the early night both on CSII and CIPII. However, for all three the time interval exceeded 4 h from going back to the regular daytime insulin infusion rate prior to the exercise test. On a separate occasion during CSII, patients in fasting state were exposed to an i.v. bolus of insulin (0.05 U kg$^{-1}$) in order to induce hypoglycaemia. The

### Table I. Clinical data for the seven patients with Type 1 diabetes. Data are expressed as the mean ± SEM, unless otherwise stated.

<table>
<thead>
<tr>
<th></th>
<th>CSII</th>
<th>CIPII</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (% ref. &lt;5.2 %)</td>
<td>8.5 ± 0.3</td>
<td>7.1 ± 0.2</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.1 ± 4.3</td>
<td>74.6 ± 3.7</td>
<td>0.56</td>
</tr>
<tr>
<td>Basal rate infusion (U h$^{-1}$)</td>
<td>1.13 ± 0.31</td>
<td>1.37 ± 0.24</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Bolus doses per day (U 24 h$^{-1}$)</td>
<td>10.0 ± 1.4</td>
<td>7.3 ± 1.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Insulin dose per day (U 24 h$^{-1}$)</td>
<td>36.1 ± 2.8</td>
<td>38.4 ± 2.9</td>
<td>0.06</td>
</tr>
<tr>
<td>SD$_{BG}$ (mmol L$^{-1}$)</td>
<td>5.1 ± 0.6</td>
<td>3.5 ± 0.2</td>
<td>0.02</td>
</tr>
<tr>
<td>No. of blood glucose &lt; 3.0 mmol L$^{-1}$ during the month SD$_{BG}$ was calculated (range)</td>
<td>3.8 (0-12)</td>
<td>0.7 (0-4)</td>
<td>0.07</td>
</tr>
<tr>
<td>Basal blood pressure (mmHg)</td>
<td>129 ± 2/81 ± 3</td>
<td>124 ± 6/80 ± 3</td>
<td>0.69/p 0.82</td>
</tr>
<tr>
<td>Blood pressure at the end of exercise (mmHg)</td>
<td>163 ± 9/75 ± 5</td>
<td>167 ± 8/81 ± 5</td>
<td>0.66/p 0.48</td>
</tr>
<tr>
<td>Basal pulse rate (beat min$^{-1}$)</td>
<td>65 ± 4</td>
<td>68 ± 6</td>
<td>0.51</td>
</tr>
<tr>
<td>Pulse rate at the end of exercise (beat min$^{-1}$)</td>
<td>137 ± 5</td>
<td>135 ± 5</td>
<td>0.71</td>
</tr>
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</table>
patients’ glucagon response to hypoglycaemia was evaluated at the time of this test (Fig. 1). The study protocol was approved by the local ethics committee, and all patients gave their informed consent to participate.

**Study protocol** – The patients were studied on two occasions at the Department of Clinical Physiology, Karolinska Hospital, Stockholm. The first test was performed after the decision was made to change to CIPII while the patients were still being treated on CSII. The second test was intended to be performed about 6 to 9 months later. However, at this time CIPII therapy was affected with problems worldwide due to increased insulin aggregation in the system leading to decreased delivery rates. Unfortunately, none of the pumps were found to function accurately at this time. The problems were solved temporarily by special rinsing procedures, and in some instances by changing the catheters. Adequate delivery (refill difference, i.e. the amount programmed related to the delivered amount) was tested at the refill procedure, which was performed every 4 to 5 weeks. At the scheduled time, all patients had a refill difference above 10% (range 12.6-69.1). For this reason, the second test was performed later than planned [a mean 15 (11-19) months], at which time the refill difference was less than 10% (range 1.0-6.0).

In all patients, on a separate occasion, maximal oxygen uptake (VO$_{2\text{max}}$) was determined on a bicycle ergometer, as previously described [13]. VO$_{2\text{max}}$ was measured continuously with a breath-by-breath data collection technique (Med-Graphics Inc., St. Paul, MN, USA) and calculated at each 20-s interval. No symptomatic hypoglycaemic episode was allowed during the 24 h preceding each test. After an overnight fast, the patients arrived at the Department of Clinical Physiology at 08.00. An arterial catheter was inserted into the patients’ left brachioradial artery, and a venous catheter into the brachioradial vein on the same side. During the test day, the patient’s regular basal insulin infusion was maintained, and the pre-breakfast bolus was not given. After 15 to 30 min of rest, a bicycle ergometer exercise at 60% of VO$_{2\text{max}}$ was conducted for 40 min, unless symptomatic hypoglycaemia occurred, in which case cycling was stopped early. The time when the test was stopped was indicated as zero (Fig. 2). After the exercise test, the patients rested in supine position for 200 min. They were allowed to drink water, but had no other oral consumption.

Arterial blood samples for analysis of blood glucose were obtained immediately before and after cycling, then at 20 min and thereafter every 15 min. Venous blood samples for analyses of plasma concentrations of adrenaline, C-peptide, cortisol, free insulin, glucagon, growth hormone, lactate and noradrenaline were obtained immediately before and after cycling and then at 20, 50, 80, 110, 140, 170 and 200 min. Blood pressure and pulse were recorded at the same time-points at which venous blood samples were taken.

**ANALYSES**

HbA1c was analysed by a cation-exchange chromatographic method by fast, protein, liquid chromatography (normal ref. < 5.2%) [14]. Blood glucose was determined by a glucose oxidase method (Beckman Glucostat, CA, USA), plasma lactate by the method of Noll et al. [15], and plasma-free insulin according to Nakagawa et al., using commercial radioimmunoassay kits (Pharmacia Diagnostics AB, Uppsala, Sweden) after precipitation of antibody-bound insulin with 25% polyethylene glycol immediately following blood collection [16]. Plasma adrenaline and noradrenaline were analysed by HPLC with electrochemical detection [17]. Plasma C-peptide [18], plasma cortisol [19] and plasma growth hormone [20] were analysed by radioimmunoassays. Glucagon samples were obtained in prechilled test-tubes containing 0.084 mL EDTA (0.34 mol L$^{-1}$) and aprotinin (250 kallikrein-inhibiting U mL$^{-1}$ blood, Bayer, Leverkusen, Germany). Glucagon levels were measured with a double-antibody radioimmunoassay in duplicate using guinea pig anti-human glucagon antibodies.
specific for pancreatic glucagon, $^{125}\text{I}-\text{glucagon as tracer and glucagon standard (Linco, St Charles, MO, USA)}$ [21].

**Statistical analyses** – All results are expressed as the mean ± SEM unless otherwise stated. After validation for normal distribution using the Shapiro-Wilk’s test, analysis of variance (ANOVA) with repeated measures and Student’s two-tailed-test for paired observations were used for statistical evaluation, when applicable. $P$-values less than 0.05 were considered significant.

**RESULTS**

The shift from CSII to CIPII reduced HbA1c and improved the stability index as reflected by SDBG (Table I). The change to CIPII was associated with an increase in the basal insulin infusion rate (Table I) and a tendency to an increase in the total 24-hour insulin dose, whereas the mean sum of the bolus doses 24 h$^{-1}$ tended to decrease. The proportion of basal vs. bolus was high already on CSII (i.e. 72%), and this proportion was slightly increased to 81% while on CIPII (Table I). Despite a higher basal rate of insulin on CIPII (Table I), the pre-breakfast plasma venous insulin level was about 50% lower than that during CSII (28.0 ± 2.2 vs. 48.1 ± 7.9 pmol L$^{-1}$, $p = 0.043$).

Insulin concentrations were not altered by exercise (Fig. 2).

The workload expressed as VO$_{2\text{max}}$ was probably nearly identical between the two tests, as evidenced by almost identical increases in plasma lactate and pulse rate (Fig. 3 and (Table I). There was no correlation between blood glucose fall and workload. However, patients who displayed hypoglycaemia during exercise had the largest workloads.

Both exercise tests yielded significant rises in plasma levels of adrenaline, cortisol and growth hormone (Table II). The glucagon level was significantly raised only while on CIPII (Table II). The incremental area under the curve 0-60 min of plasma glucagon was also larger during CIPII (23.4 ± 6.2 vs. 10.3 ± 3.8 pg ml$^{-1}$ h$^{-1}$, $p = 0.04$). No correlation was found between the peak levels of adrenaline and glucagon ($r^2 = 0.22$), and there was no correlation between glucagon response and blood glucose level ($r^2 = 0.02$ during CSII and $r^2 = 0.04$ during CIPII) (Fig. 4).

**DISCUSSION**

Previous studies have shown that CIPII may improve metabolic control and glycaemic stability in Type 1 diabetic patients [10, 11], and the present study confirms these findings. In our experience, these improvements were obtained with a slightly higher 24-h
insulin dose, but more importantly with a larger basal rate infusion. This point is noteworthy since no preferable relation of basal/bolus infusion was indicated in previous reports [10, 11]. Notably, the frequency of biochemical hypoglycaemia did not increase during CIPII, despite improvement in metabolic control. None of our patients reported any episodes of severe hypoglycaemia during the year preceding the change to CIPII or during CIPII, despite the fact that several regularly performed moderate physical exercise such as jogging. Physical activity is a common cause of hypoglycaemia, and there is no uniform strategy to prevent its occurrence.

It is well-established that the prevailing portal insulin concentration is the most important factor regulating hepatic glucose output during exercise [22, 23]. In the present experimental setting, we were aware that a higher basal rate of insulin was given during the CIPII test. As a majority of insulin delivered into the peritoneal cavity reaches the portal system, the portal insulin concentration was certainly higher in the test during CIPII than with CSII. Assuming that nearly all

**TABLEAU II. Changes in hormone levels from preexercise to postexercise.**

<table>
<thead>
<tr>
<th></th>
<th>CSII</th>
<th>CIPII</th>
<th>Changes between clamps, CSII and CIPII</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenaline, nmol/l</td>
<td>0.43 (+0.16 ± 0.70) p = 0.009</td>
<td>0.81 (+0.11 ± 1.50) p = 0.03</td>
<td>-0.14 (-0.62 ± 0.34) p = 0.49</td>
</tr>
<tr>
<td>Noradrenaline, nmol/l</td>
<td>4.02 (+1.94 ± 6.09) p = 0.006</td>
<td>3.75 (+1.57 ± 5.93) p = 0.006</td>
<td>+0.59 (+0.15 ± 1.32) p = 0.09</td>
</tr>
<tr>
<td>Glucagon, pg/ml</td>
<td>7.4 (-1.2 ± 16.0) p = 0.08</td>
<td>15.1 (+4.3 ± 26.0) p = 0.01</td>
<td>-7.7 (-16.3 ± 0.9) p = 0.07</td>
</tr>
<tr>
<td>Cortisol, nmol/l</td>
<td>92.9 (+10.4 - 175.3) p = 0.03</td>
<td>135.1 (+30.4 - 239.9) p = 0.02</td>
<td>-42.3 (-176.4 - 91.8) p = 0.47</td>
</tr>
<tr>
<td>Growth hormone, mg/ml</td>
<td>11.9 (+3.8 ± 19.9) p = 0.01</td>
<td>9.4 (± 0.6 ± 19.4) p = 0.03</td>
<td>+2.4 (-3.3 ± 8.2) p = 0.34</td>
</tr>
<tr>
<td>C-peptide, nmol/l</td>
<td>-0.01 (-0.08 ± 0.05) p = 0.59</td>
<td>-0.02 (-0.05 ± 0.01) p = 0.19</td>
<td>±0 (-0.08 ± 0.09) p = 0.91</td>
</tr>
</tbody>
</table>

Data are means of differences (n) with 95% confidence interval (range), and p-values denoting the statistical significance of difference (n).
insulin delivered into the peritoneal cavity reaches the portal system [24] and that hepatic extraction is 50% [25], the portal venous insulin concentration during the CIPPII test could be calculated as 56 pmol L⁻¹ vs. 40 pmol L⁻¹ during the CSII test, since 15-20% of insulin is destroyed on first pass traverses of the splanchnic bed [26]. If so, the CIPPII regimen would result in a portal venous insulin level about 40% higher and a peripheral venous insulin level about 40% lower than that of the CSII regimen. Therefore, it is not surprising that a more pronounced lowering of blood glucose was recorded during the CIPPII test. Furthermore, better insulin sensitivity, probably associated with improvements of metabolic control [27], would add to this effect. Our results differ somewhat from those of Gooch et al. [9] since exercise in their experimental design (using an i.p. infusion of insulin) did not cause any blood glucose fall at all. The most likely explanation for this discrepancy relates to differences in the insulin doses given. In the study by Gooch et al., the amount of insulin administered was probably suboptimal in relation to clinical practice, but more optimal for exercise (only about 50% of the dose given in the present study). In the absence of any hypoglycaemic reaction in their study, there was no difference in the stress hormone response.

It is well-known that exercise in Type 1 diabetic patients, as in normal man, is a prominent stimulus for the release of several blood glucose-raising hormones, i.e. adrenaline, glucagon, cortisol and growth hormone. Glucagon is the most important one for the stimulation of hepatic glucose output [22, 28]. Significant increases in all these hormones were observed during exercise, partly because of the exercise itself, but also because of a lowering of blood glucose. Glucagon response was only significantly increased in the CIPPII test, which is interesting since it is well known that the alpha cell is insensitive to hypoglycaemia in Type 1 diabetic patients after the first 1 to 2 years [29]. Thus, the difference in glucagon is unlikely to have been due to lower blood glucose levels per se. Moreover, no relationship was found between glucagon response and blood glucose level (Fig. 4). We previously showed that the prevailing level of circulating insulin may modulate glucagon release, so that insulin may suppress glucagon secretion in the basal state as well as during hypoglycaemia [30]. Therefore, the lower peripheral concentrations of insulin in the CIPPII test (Table II) might account for enhanced glucagon response to exercise.

These differences in blood glucose and glucagon were probably not attributable to differences in work-load between the two tests as nearly identical rises were observed in lactate and noradrenaline levels and in heart rate reaction in the two studies.

In conclusion, patients on CIPPII should reduce their insulin infusion rate during exercise. CIPPII appears to have favourable effects on counterregulatory capacity; in particular, a more prominent glucagon response to exercise may prove important.

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