Exercise in Insulin-dependent Diabetes Mellitus: The Effect of Continuous Insulin Infusion Using the Subcutaneous, Intravenous, and Intraperitoneal Sites

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The metabolic response to exercise in insulin-dependent diabetic (IDD) man was assessed during continuous insulin infusion using the subcutaneous (CSII), intravenous (CIVII), and intraperitoneal (CIPII) routes. During the basal period, plasma glucose levels were higher with CIPII (153 ± 17 mg/dl) than with CSII (117 ± 13 mg/dl) or CIVII (118 ± 17 mg/dl). Basal free insulin concentrations were similar for CSII (12.3 ± 10 μU/ml) and CIVII (12.4 ± 1.4 μU/ml) but lower in CIPII (8.5 ± 1.0 μU/ml, $P < 0.05$). Exercise on a stationary bicycle at 75 W for 60 min produced a decline of plasma glucose in each protocol that was significant only during CIVII (55 ± 11 mg/dl, $P < 0.01$). Insulin levels remained unchanged throughout the study period in all protocols. In normals, insulin values decreased during exercise and remained below basal levels through the recovery period ($P < 0.05$), while plasma glucose remained unchanged. Plasma glucagon and epinephrine levels were similar in all protocols and remained unchanged with exercise, while plasma norepinephrine tended to be higher than normal in all diabetic subjects. Significant differences between normal and diabetic subjects ($P < 0.05$) were observed for blood ketone bodies, while blood lactate, glycerol, and plasma FFA were similar. Normalization of intermediary metabolites occurred only with CIVII. Continuous insulin infusion provides near-normal glycemic and metabolic control before, during and following exercise in IDD man. However, to produce normal blood concentrations of intermediary metabolites during exercise, the insulin infusion rate may be excessive in terms of its hypoglycemic effect. CSII appears to be a safe, accessible, and adequate method for treating diabetic man during exercise. DIABETES CARE 6: 122–128, MARCH–APRIL 1983.

Moderate exercise in normal man produces stable glucose levels with reductions in the peripheral plasma insulin concentrations.[1–3] In diabetic man, the metabolic effects of exercise depend on the route of insulin administration, the level of metabolic control prior to exercise, and other variables. In the patient who is well controlled using subcutaneous depot insulin, hypoglycemia is a predictable consequence of exercise because of inappropriate hyperinsulinemia.[4,5] Conversely, in the underinsulinized state, exercise increases glucose production and lipolysis, worsening the hyperglycemia and ketosis.[5]

In considering the optimal site for insulin infusion for reversal of diabetes mellitus in exercising man, the venous drainage of the infused site becomes important. Previous studies using continuous subcutaneous (CSII)[6] and intravenous (CIVII)[3] insulin infusions have indicated that relatively stable plasma glucose levels are achievable during and after exercise. Intraperitoneal insulin (CIPII) delivery has recently gained great interest, since absorption occurs through the portal system[7] and is not accompanied by the degree of peripheral hyperinsulinemia that occurs with peripherally delivered insulin.

The present studies were designed to explore these issues by comparing the metabolic effects of insulin delivered by three routes (CSII, CIVII, and CIPII) in diabetic subjects before, during and following exercise.

METHODS

Subjects (*Table 1*). Five male IDD, exhibiting normal physical activity, aged 32–40 yr and a duration of diabetes of 7–30 yr were studied. All were from the Vanderbilt Diabetes

TABLE 1
Clinical background of subjects

Patient	D.W.	J.R.	B.H.	D.C.	B.G.
Age (yr)	36	32	32	40	32
Weight (kg)	82.7	62.3	65.5	84.5	65
Age at onset	16	2	25	12	10
Duration (yr)	20	30	7	28	22
HgbA (after stabilized)	6.7	9.0	8.4	9.7	7.8
Retinopathy	+*	+†	—	+†	—
Nephropathy	+‡	—	—	—	—
Neuropathy	—	—	—	—	—
Insulin dose (U)					
Conventional a.m.	34L	25N + 6R	20N + 4R	40N	15N + 5R
p.m.	5L + 5R	12N + 6R	8N + 4R	—	8N + 2R
Total	44	49	36	40	30
Pump					
Basal U/h	0.83	0.625	0.67	0.75	0.67
Meals B,L,D	8,10,10	6,4,5	6,7,7	5,5,5	6,4,6
Basal rate (mU/kg/h)	10	10	10.2	8.9	10.3
Pump model	Mill Hill AS-2C		Mill Hill AS-2C		AS-2C
Mean glucose§	130	95	125	100	90
Urine glucose¶ (24 h)	2 g	0	1 g	0	0

*Preproliferative changes.
†Background.
‡Proteinuria >1 g/24 h on 2 occasions.
§Mean of 6–10 glucose done in hospital after stabilization on CSII.
¶Quantitative 24 h urine glucose after stabilization on CSII.
N = NPH.
L = Lente.
R = Regular.
HgbA Normal Range = 6.2–8.0%.

Research and Training Center. Four healthy male volunteers aged 20–22 served as the normal controls.

Experimental design. All subjects were studied on the Clinical Research Center of the Vanderbilt Medical Center after giving informed consent following an explanation of the purpose, nature, and risks of the experiment. Each diabetic subject was first stabilized on CSII as an inpatient. The basal infusion rate for each subject was determined by maintaining the fasting plasma glucose between 70 and 120 mg/dl. Mealtime boluses were adjusted to maintain the 1- and 2-h postprandial glucoses less than 180 mg/dl. Once stabilized, the patients were then discharged on CSII and the blood glucose was monitored 4–9 times per day using Chemstrip bG glucose-oxidase strips (Bio-Dynamics/bmc division of Boehringer, Indianapolis, Indiana). The basal rate was similar for each patient with a mean of 9.9 ± 0.58 mU/kg/h (±SD).

The subjects were readmitted to the Clinical Research Center for each exercise protocol (CSII, CIVII, or CIPII). The studies were performed in random order at least 4–10 days after stabilization and with 3–10 days between each protocol study.

All studies were begun between 6:30 and 7:30 a.m., after a 12–14-h overnight fast. An indwelling catheter was inserted into a superficial forearm vein for blood sampling and kept patent with 0.9% saline infusion. For the CIVII protocol, a contralateral superficial forearm vein was used for insulin infusion. For the CIPII protocol, the intraperitoneal catheter was inserted using the method of Berger[8] as modified by Schade et al.[9] After a 60-min resting period, blood samples were obtained at 10-min intervals during a 30-min basal period and a 60-min exercise period on a bicycle ergometer (at 460 kpm/min or 75 W), followed by a 60-min recovery period. The cycle ergometer was set at a resistance to produce 75 W and exercise performed to reach 60% maximum heart rate for each individual (diabetic mean heart rate = 67 ± 5 beats/min, control = 64 ± 4 beats/min). Insulin replacement was maintained at the basal rate as determined by CSII for all 3 protocols. The insulin infusion was switched from the subcutaneous to the intravenous site (CIVII protocol) at least 90 min and to the intraperitoneal site (CIPII protocol) at least 3–14 h prior to the basal period.

The normal subjects were admitted to the Clinical Research Center after a 12-h fast and followed the same exercise protocol. None of the diabetic or control subjects were trained athletes.

Blood processing. Blood was collected in sodium EDTA tubes (15 mg/tube) and immediately placed on ice. Proteins in 1 ml whole blood were precipitated with 1:4 (vol/vol) ice-

cold perchloric acid (0.4 M) and were immediately centrifuged. The supernate was stored at −20°C for later enzymatic assay of lactate, β-hydroxybutyrate (βOHB), and glycerol.[10] The remainder of the blood was centrifuged immediately and an aliquot of the plasma was prepared for the assay of free insulin, by precipitating with (1:1 vol/vol) 25% polyethylene glycol. The supernate was stored at −20°C until later assayed using the sephadex antibody method.[11] Plasma glucose was determined using the glucose-oxidase method (Beckman glucose analyzer, Beckman Instruments, Fullerton, California), and plasma glucagon was assayed by radioimmunoassay using Unger's 30K antibody.[12] Plasma free fatty acids (FFA) were measured according to the method of Dole et al.[13] Fractionated catecholamines were estimated from plasma using radioenzymatic methods.[14]

Statistical methods. All data in the text, tables, and figures are presented as the mean ± SEM (standard error of the mean) unless otherwise designated. The paired and unpaired *t* tests are used where applicable.

RESULTS

Glucose (Figures 1 and 2)

For all protocols, the glucose concentrations remained stable during the 30-min basal period. The mean basal glucose values for the diabetics during all protocols (CSII = 117 ± 13, range 54–135; CIVII = 118 ± 17, range 35–110; and CIPII = 153 ± 17, range 126–227 mg/dl) were higher than normal (normal = 84 ± 3, range 79–91 mg/dl), but were only significant with CIPII ($P < 0.02$).

Exercise induced a maximum decline in mean plasma glucose in all diabetic subjects (CSII = 24 ± 10, CIVII = 55 ± 11, CIPII = 14 ± 19 mg/dl) by end-exercise (60 min) but were only significant with CIVII ($P < 0.01$). No changes occurred in the normals. Plasma glucose remained stable for all groups during the recovery period.

Hormones

Insulin (Figure 1). Basal insulin levels were 12.3 ± 1.5 μU/ml in normals, decreased to 9.71 ± 1.4 μU/ml ($P < 0.05$) during exercise, and remained lower than basal in the recovery period (10.5 ± 1.4 μU/ml, $P < 0.05$). Insulin concentrations in the diabetic subjects were comparable to the normal basal range for CSII (12.3 ± 1 μU/ml) and CIVII (12.4 ± 1.5 μU/ml), but were lower with CIPII (8.5 ± 1 μU/ml, $P < 0.05$ for both comparisons). Furthermore, these levels remained constant through the exercise and recovery periods.

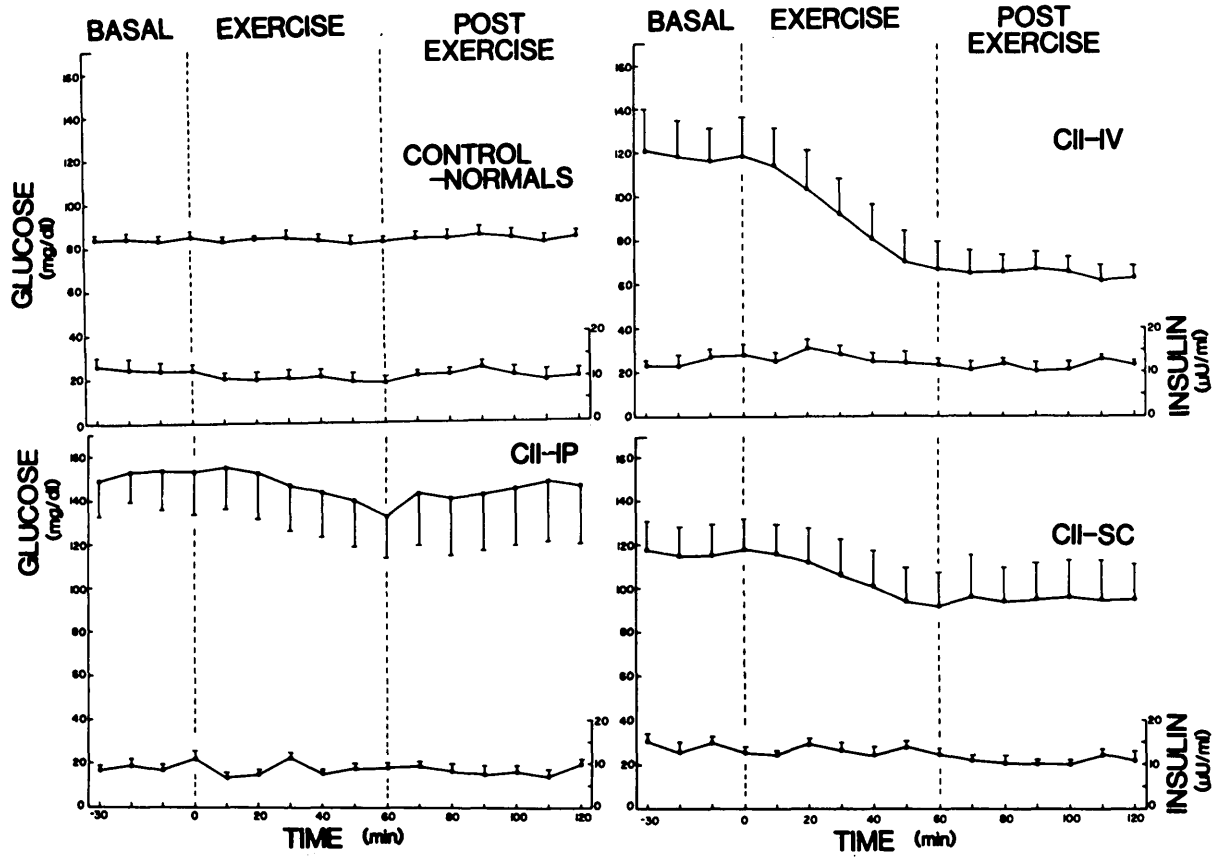

FIG. 1. Glucose and insulin values in all protocols represented as mean ± SEM. CII-SC = Continuous subcutaneous insulin infusion. CII-IV = Continuous intravenous insulin infusion. CII-IP = Continuous intraperitoneal insulin infusion.

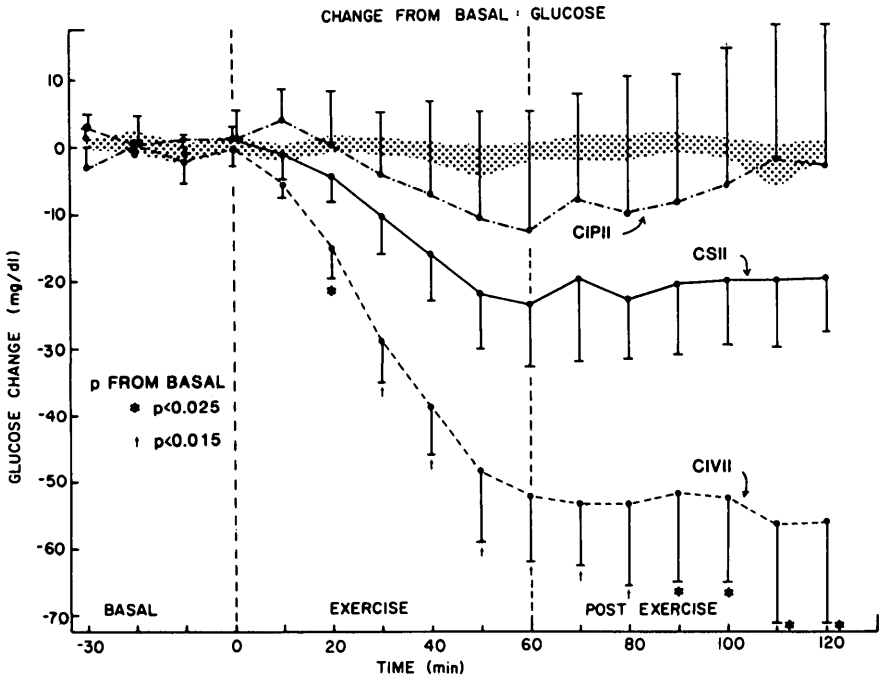

FIG. 2. Comparison of the glucose change (mean ± SEM) during and after exercise. The normal mean ± SEM is represented by the shaded area.

Glucagon (Table 2)

Mean basal glucagon in the diabetic subjects was higher than normals. No significant changes were observed during or after exercise.

Catecholamines (Table 3)

Epinephrine (E) values were similar for all subjects during the basal, end-exercise, and recovery periods. As expected, E rose with exercise for each protocol. These returned to basal values in the recovery period, except for CIVII where they remained elevated, most probably due to prevailing lower plasma glucose. Basal norepinephrine (NE) values were slightly higher in the diabetic subjects as compared with controls, with CIPII significantly so ($P < 0.04$). By the end of exercise, NE increased 30–50% in each group, but returned to basal levels in the recovery period.

TABLE 2
Glucagon (pg/ml)

	Basal	End exercise (60 min)	End recovery (120 min)
CSII	104 ± 25	104 ± 28	107 ± 29
CIVII	169 ± 47	180 ± 22	165 ± 30
CIPII	159 ± 40	170 ± 54	176 ± 45
Normal	73 ± 10	74 ± 11	75 ± 13

TABLE 3
Catecholamines (pg/ml)

	Basal		End exercise (60 min)		End recovery (120 min)	
	E	N	E	N	E	N
CSII	56 ± 7	308 ± 60	178 ± 83	467 ± 27	56 ± 12	252 ± 30
CIVII	41 ± 7	360 ± 83	123 ± 45	497 ± 107	78 ± 36	345 ± 101
CIPII	41 ± 6	407 ± 71*	88 ± 17	683 ± 148	39 ± 12	419 ± 102
Normal	51 ± 6	217 ± 37	98 ± 28	397 ± 66	23 ± 4	210 ± 33

*$P < 0.04$ compared with normals.
E = Epinephrine; N = norepinephrine.

Metabolites

Lactate (*Figure 3*). Whole blood lactate values were quite variable in each group, but significant differences from normal were only observed in the basal period for the CIVII group ($P < 0.05$). In all protocols, lactate concentrations rose in response to exercise and returned to basal levels in the recovery period.

Ketone bodies (*Figure 3*). Basal blood ketone levels in the normals (27 ± 11 μmol/L) were significantly lower ($P < 0.05$) than in diabetic subjects (CSII = 169 ± 42, CIVII = 137 ± 41, CIPII = 266 ± 78 μmol/L) and persisted through exercise.

FFA (*Figure 3*). Within each protocol, significant variations were observed in plasma FFA levels. There was, however, a tendency for the CIVII group to exhibit levels comparable to normals and lower than with CSII or CIPII protocols.

Glycerol (*Figure 3*). Blood glycerol levels were not significantly different among the groups during any of the study periods. There was a trend, however, for the CIPII route to produce the highest values while CIVII resulted in the lowest and closest levels to normal. Exercise resulted in a progressive rise in blood glycerol in all protocols, which rapidly declined to basal levels by the end of the recovery period.

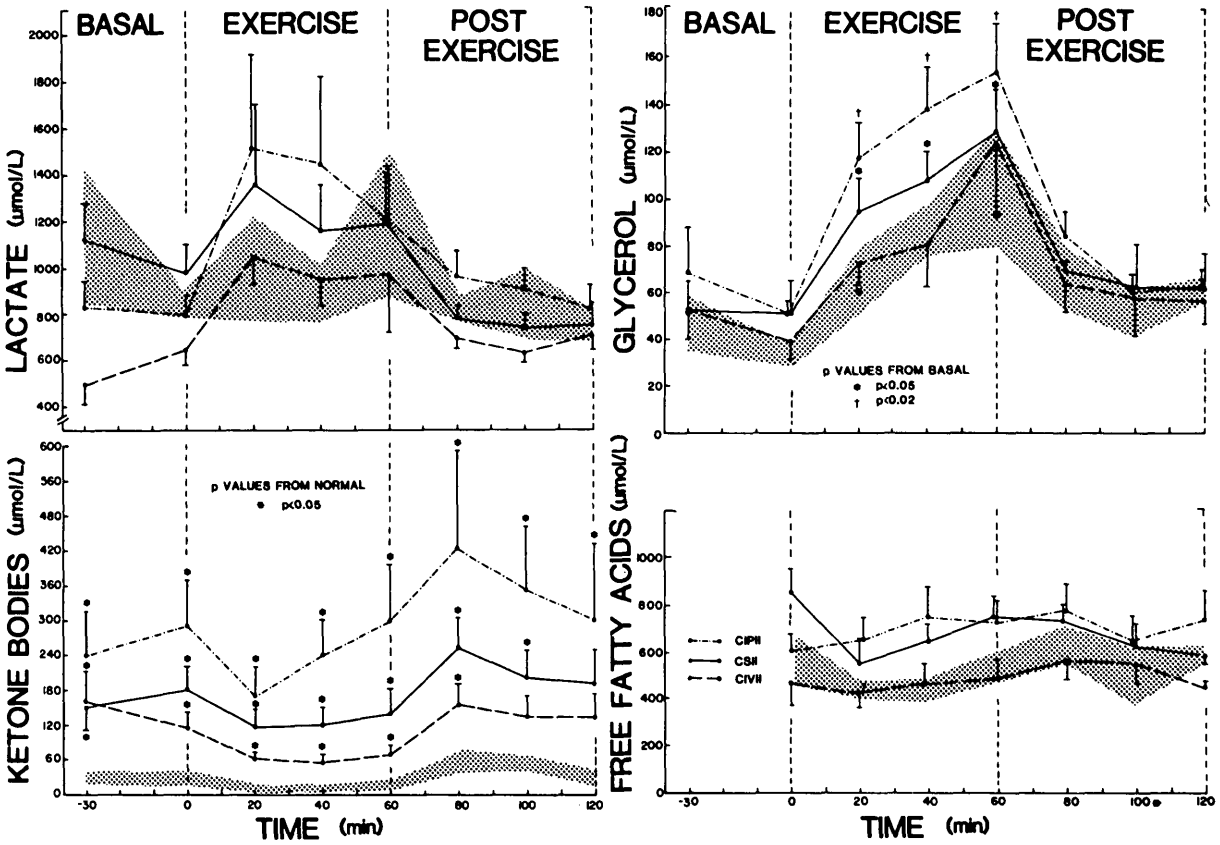

FIG. 3. Whole blood lactate, ketone bodies, glycerol, and plasma free fatty acid concentrations (mean ± SEM). The normal values (mean ± SEM) are represented by the shaded areas.

DISCUSSION

Our study was aimed at controlling plasma glucose in diabetic subjects with CSII. Using the basal rate necessary to accomplish this in an exercise protocol, we then compared subcutaneous, intravenous, and intraperitoneal insulin delivery. Diabetic subjects were well controlled with CSII, with a mild reduction of their glucose during 60 min of exercise, confirming what Champion et al.[6] and Koivisto et al.[15] found in shorter exercise periods. These also support data by Dupre et al.,[16] who reported no significant changes in plasma glucose or glucose turnover when comparing diabetic subjects treated with CSII with normals during moderate exercise. All these studies would suggest that CSII approximates physiologic basal insulin delivery, and is also appropriate during exercise. This is supported by the fact that insulin levels remained unchanged in all study periods, demonstrating that insulin absorption during exercise was not substantially altered while using CSII, and therefore the hypoglycemic effect was reduced. Since our subjects used the thigh or hip for their daily (pre-study) depot injections, the expected rapid absorption of insulin from these sites[3,17] would have predisposed them to sudden fluctuations in plasma glucose and possible hypoglycemia.

The intraperitoneal route (CIPII) provided significantly reduced peripheral basal insulin levels and the highest glucose levels, but this route had the most stable glycemia for the study period. During and after exercise, insulin levels were unchanged. Plasma glucose declined minimally during exercise, then rose slightly in the recovery period. Peritoneal absorption of insulin probably occurs through the portal venous system thereby allowing increased delivery to, and subsequently increased clearance of insulin by the liver accounting for the reduced peripheral concentrations. Our results confirm the reduced peripheral insulin levels but vary with respect to the glucose control found by Schade et al.[9] These authors reported similar glycemic control with the same dose of insulin subcutaneously or intraperitoneally, but with half the peripheral insulin values by the latter route. It is thus possible that the peritoneum may accelerate insulin degradation without a glycemic effect, resulting in a blunted suppression of hepatic glucose production. More likely, however, the elevated glucose with this route may reflect diminished peripheral glucose utilization as a result of lower peripheral insulin levels. This explanation is in accord with that of Vranic et al.,[18] who found that peripheral insulin levels of 12 μU/ml were necessary to increase peripheral uptake in the dog.

The most dramatic decline in plasma glucose was with

CIVII. Intravenous insulin immediately and directly bathes the peripheral tissues, thereby stimulating greater glucose utilization than is obtained with CSII or CIPII. Peripheral insulin levels with CIVII were not different than those with CSII suggesting the intravenous insulin has a greater biologic effect. Alternatively, the subcutaneous route may alter insulin's biologic activity without reducing its immunoreactivity although we have no direct evidence for this. Schade et al.[9] found similar results when comparing subcutaneous, intravenous, and intraperitoneal insulin during meals. In their study, the subcutaneous and intravenous insulin integrated areas were not different, yet glucose values were significantly lower with the intravenous group suggesting a more potent insulin effect with this route than with the other two.

The findings of intermediary metabolite parallel those of insulin and glucose. Large interindividual variations in blood lactate, β-hydroxybutyrate, glycerol, and plasma FFA were observed in all protocols. CIVII, however, produced the lowest mean values, and unlike the glucose changes, these were closest to normal. The explanation for this is not clear. Plasma glucagon and epinephrine were similar in all protocols and therefore should not be considered as a cause. Plasma norepinephrine, however, was higher in all diabetic protocols as compared with normals with the highest values in the CIPII group. This would partially account for the elevated ketones, particularly in the CIPII protocol. Steiner, Alberti, and Cherrington have found that selective elevation in norepinephrine levels in the overnight (16–18 h) fasted dog, comparable to those seen in this study, resulted in 15% increase in hepatic ketone production (personal communication). The diminished peripheral insulin levels seen with CIPII were associated with higher FFA concentrations thereby allowing a greater substrate supply for ketogenesis.[19] Interestingly, FFA levels were higher with CSII than with CIVII or normal controls, again reflecting diminished peripheral insulin effect with the subcutaneous route. The pattern of the metabolite responses are similar to those reported previously for CIVII in diabetic man during exercise[20] by Murray et al. In this study, CSII resulted in stable plasma glucose comparable to normal controls; interestingly, the basal metabolite levels tended to be higher than normal before, during, or after exercise. Other authors have found that normalization of plasma glucose with a glucose-controlled insulin infusion system does not normalize ketone body metabolism despite normalization of blood lactate, glycerol, and alanine.[20] Hence, we could speculate that during moderate exercise intermediary metabolites of IDD may be normalized with an insulin infusion that is inappropriately high for plasma glucose.

One important observation from this study is that in the basal state CSII may have a special place in the management of diabetic patients engaged in strenuous activity. It produced a minimal hypoglycemic effect during reasonably vigorous exercise and allowed other metabolic processes to proceed in a near-normal manner. We did not address the issue of postprandial exercise and therefore our results only pertain to the basal postabsorptive fasting state. Further studies will be needed to determine optimal postprandial insulin delivery during exercise in diabetic patients using continuous insulin infusion.

In summary, the results of this study emphasize several important points: (1) Continuous insulin infusion produces a less dramatic hypoglycemic effect during exercise than that reported for depot subcutaneous injection. Additionally, peripheral plasma insulin levels remain stable before, during, and after exercise of moderate intensity. (2) Exercise has a glucose-lowering effect independent of insulin as evident by stable insulin, but declining glucose levels. In contrast, in the normal subjects, peripheral insulin levels declined during exercise while plasma glucose remained constant. (3) Peripheral concentrations of intermediary metabolites (lactate, βOHB, glycerol, and FFA) and of the counterregulatory hormones (glucagon and the catecholamines) in diabetics treated with CII approached normal levels during moderate exercise. (4) Of the continuous infusion methods, CSII is an adequate, simple, and effective method of achieving glycemic and metabolic control before, during, and after exercise.

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