Hyperglycemia After Intense Exercise in IDDM Subjects During Continuous Subcutaneous Insulin Infusion

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Exercise is conventionally considered a modality for improvement of glycemia in diabetes. We have found that a short period of intense exercise (80% $\dot{V}O_{2\,max}$) in normal lean subjects produces sustained postexercise hyperglycemia 20% above basal with a corresponding 100% increase in plasma insulin. In people with insulin-dependent diabetes mellitus (IDDM) incapable of this insulin response, it was predicted that postexercise hyperglycemia would be of greater magnitude and/or duration. To investigate this possibility, the effects of the same intense exercise (80% $\dot{V}O_{2\,max}$) were studied in 8 IDDM subjects (2 on 2 occasions) in the postabsorptive state with continuous subcutaneous (abdominal) insulin infusion (CSII). When the preexercise plasma glucose was normal (n = 6, 86 ± 4 mg/dl), there ensued a postexercise hyperglycemia to 127 ± 7 mg/dl ($P < .001$) sustained for 2 h postexhaustion. Plasma free immunoreactive insulin (IRI) was 1.43 ± 0.12 ng/ml before exercise and did not change postexercise. When mean preexercise plasma glucose was 149 ± 9 mg/dl (n = 4), it rose progressively throughout the 2 h of recovery to 229 ± 28 mg/dl ($P < .025$). A small but statistically significant decrease in free IRI occurred during the last 80 min of recovery. Hyperglycemia in the diabetic subjects was not explained by abnormal or differing responses of glucagon or catecholamines. Thus, with intense exercise, diabetic control deteriorates rather than improves. Therefore, different therapeutic strategies may be required for intense compared with moderate exercise in IDDM patients. *Diabetes Care* 11:311–17, 1988

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The conventional wisdom is that physical exercise lessens hyperglycemia and diminishes insulin requirements in patients with diabetes mellitus. The glycemia-lowering effect of exercise in diabetic subjects receiving subcutaneous insulin was recognized as early as 1926 (1). Studies in humans have shown that exercise after subcutaneous insulin administration may result in hyperinsulinemia with an impaired increment in glucose production that is insufficient to match the increased glucose utilization, and thus a decline in glycemia results (2–4). The hyperinsulinemia occurs because of increased absorption from the subcutaneous site during exercise (2–4). The effect may also be due to insulin already present before exercise (5). Exercise performed during hyperglycemia due to insulin deficiency or withdrawal is associated with both impaired glucose utilization and increase in hepatic glucose production (3,6). The increase in liver glucose production exceeding peripheral glucose uptake causes exacerbation of hyperglycemia (6–8). Thus, depending largely on the state of insulinization, physical activity in insulin-dependent diabetic (IDDM) patients may lead to deterioration or improvement of metabolic control. Most exercise studies have employed moderate (50% $\dot{V}O_{2\,max}$) exercise of 45–60 min duration.

We have found that periods of intense exercise (80% $\dot{V}O_{2\,max}$) in normal subjects produce sustained postexercise hyperglycemia 20% above basal with a 100% increase in plasma insulin (9). In people with IDDM incapable of generating this rise in insulin by increased secretion, it was predicted that such postexercise hyperglycemia would be greater and/or sustained longer. Thus, in the recovery period after intense exercise, glycemia may be raised rather than improved, contrary to the usual rationale for exercise in clinical diabetes management. In this study, we examine the response to in-

TABLE 1
Subject data

	n	Age (yr)	Sex (F/M)	Weight (kg)	Duration of diabetes (yr)	Ideal body weight* (%)	Basal insulin/24 h (U)	Preexercise plasma glucose (mg/dl)	$\dot{V}O_{2\,max}$ (ml/min)
Group 1	6	31 ± 2	4/2	69 ± 5	15 ± 2	109 ± 4	20.3 ± 1.1	86 ± 3.6	2328 ± 382
Group 2	4	27 ± 2	1/3	73 ± 6	13 ± 2	109 ± 6	21 ± 1.3	149 ± 9	2865 ± 315
Control group	8	30 ± 2	4/4	65 ± 5		106 ± 4		87 ± 4	2669 ± 281

Values are means ± SE, except for sex distribution of subjects. Group 1 diabetic subjects, preexercise plasma glucose 70–120 mg/dl; group 2, 130–180 mg/dl.
*Based on Metropolitan Life Insurance Company tables, 1959.

tense exercise (80% $\dot{V}O_{2\,max}$) in IDDM subjects receiving continuous subcutaneous insulin infusion (CSII).

MATERIALS AND METHODS

Ten lean diabetic subjects were studied in the Respiratory Research Laboratories of the Royal Victoria Hospital, Montreal, Canada, and eight normal control subjects were studied at the Toronto General Hospital, Toronto, Canada. The lean control subjects also acted as control subjects for another study comparing their responses with those of obese nondiabetic subjects (9). After careful explanation of the nature, purpose, and possible risks involved in the study, consent was obtained as prescribed by the institutional human ethics committees. Each subject was screened to exclude conditions contraindicating inclusion in the study, e.g., cardiovascular, renal, or significant retinal complications or other major intercurrent illness. The designation *IDDM* was clinical, based on the patient's age at onset in the teens, with classic presentation including episodes of ketoacidosis in most. Mean duration of diabetes was 14 ± 2 yr. Usual total daily insulin doses were in the range of 40–66 U. The subjects were all on CSII therapy, which was controlled to result in HbA_{1c} levels of 6.4–9.0% at the time of study. Their glycemic control was directed by one of us (T.H.M.) by multiple daily telephone contacts with the subjects for several days before each study, including overnight the night before study. Subjects came to the hospital on the morning of the prearranged study day only if capillary glucose measurements self-monitored at 0200 and 0500 h were within the ranges required by the study and no hypoglycemia was experienced either subjectively or objectively. No medications were taken other than insulin.

Preliminary studies in the postabsorptive state with CSII established $\dot{V}O_{2\,max}$ for each subject; these tests were "ramp" studies in which the work load on the cycle ergometer was increased by 100 kilopond-meters (KPM; 100 KPM = 16.3 W) per minute every minute until the subject was exhausted. The diabetic subjects were subdivided prospectively into two groups according to their capillary glucose measurements during 5 h up to and including the plasma glucose before the test. Plasma levels of 70–120 and 130–180 mg/dl were labeled groups 1 and 2, respectively. The division was designed to determine whether prior hyperglycemia would exacerbate the postexercise increment. Anthropomorphic and exercise-load data are shown in Table 1. Two subjects were studied in both glycemic conditions and form part of the two groups. On the day of testing, each diabetic subject received insulin at his/her basal 24-h infusion rate before, during, and after exercise. The basal insulin infusion rate in some subjects had been decreased or increased during the previous 72 h to achieve the desired glucose level before testing.

Tests were begun between 0800 and 0900 h in the postabsorptive state. Each subject pedaled a calibrated electronically braked cycle ergometer at 50–60 rpm at a resistance equivalent to 80% of $\dot{V}O_{2\,max}$ until exhaustion. The subjects breathed through a Hans-Rudolph low-resistance breathing valve with a dead space of 95 ml. Breath-by-breath gas analyses were performed with a Medical Graphics Corporation (St. Paul, MN) cardiopulmonary exercise system or by Beckman O_2 and CO_2 analyzers (Fullerton, CA) as detailed previously (3). The heart rate was displayed electrographically and recorded at 1- to 3-min intervals, and systolic blood pressure was recorded at 5-min intervals with a sphygmomanometer and standard auscultatory technique. A 20-gauge Cathlon intravenous cannula (Critikon Canada, Markham, Ontario, Canada) was inserted retrogradely into a superficial vein on the dorsum of the hand 30 min before the commencement of sampling and exercise. The hand was placed in a Perspex box heated to 60°C to arterialize the blood. The box was designed to be installed on the handlebar of the bicycle to allow it to be grasped by the cannulated hand while exercising. Arterialized venous blood samples were taken while subjects were seated at rest, at −10 min and time 0, at 5-min intervals during exercise, at exhaustion, and then at 5-min and subsequently 20-min intervals up to 2 h of recovery (normal control subjects were studied up to 60 min of recovery). When the study was terminated, the diabetic subjects received their usual bolus insulin injections via the pump, followed by their usual breakfasts.

Plasma glucose was measured by a glucose oxidase

method with the Beckman Glucose Analyzer II. Plasma insulin was estimated by radioimmunoassay with anti-beef insulin antibody (P. Wright), human insulin standard (27.3 μU/ng), and ^{125}I-labeled pork insulin tracer (Novo, Copenhagen) as detailed previously (10). The plasma of the diabetic subjects was extracted with polyethylene glycol to remove insulin antibodies to determine free-insulin concentrations (11). Immunoreactive glucagon (IRG) was measured in aprotinin-containing plasma by use of Unger 30K antiserum, dextran-coated charcoal separation, and pork glucagon standard and ^{125}I-labeled glucagon (Novo) (10). For plasma catecholamine assay, heparinized blood was added to tubes containing 10 μl of a solution of 100 mg EGTA and 2.5 mg of reduced glutathione per milliliter of added blood. Samples were kept on ice and then centrifuged at 2800 rpm at 4°C. The plasma was immediately deproteinized with chilled 2 N perchloric acid and frozen at −70°C until assay. Each sample was assayed in duplicate for plasma norepinephrine and epinephrine concentrations by the radioenzymatic technique of Sole and Hussain (12). Whole-blood lactate, pyruvate, and 3-hydroxybutyrate concentrations were assayed by automated enzymatic microfluorometric methods on supernatants of blood immediately deproteinized in cold 10% (wt/vol) perchloric acid (13). The foregoing assays were performed under the direction of one of us (E.B.M.) at the two different hospitals, with identical methods that were quality controlled to ensure that comparisons were justified. Arterialized venous blood was analyzed for pH, P_{CO_2}, and P_{O_2} with a Corning 175 Automatic pH/blood gas system (Medfield, MA). Results are expressed as means ± SE.

Standard statistical methods were employed, with repeated measures analysis of variance and Student's paired *t* test to examine the significance of changes during exercise and recovery compared with rest. The unpaired *t* test with the Bonferroni correction for three comparisons was used to compare diabetic with control responses; $P < .0167$ was considered significant for these determinations.

RESULTS

Mean maximal heart rate and systolic blood pressure were 168 ± 7 beats/min and 160 ± 5 mmHg, respectively, for groups 1 and 2 combined. The mean maximal heart rate (170 ± 3 beats/min) and systolic blood pressure (157 ± 11 mmHg) in the control subjects were comparable to those of the diabetic subjects. The duration of exercise at 80% $\dot{V}O_{2\,max}$ of group 1 was 10 ± 2 min, not significantly different from the 7 ± 2 min in the control subjects. For group 2, the duration of exercise was 13 ± 3 min, not significantly different from group 1. P_{O_2} of arterialized venous blood for groups 1 and 2 combined ranged from 60 ± 3 mmHg at rest to 70 ± 4 mmHg at exhaustion. At rest the hydrogen ion and bicarbonate concentrations were 39 ± 1 nM and 26 ± 1 meq/L, respectively, whereas at exhaustion they were 50 ± 2 nM and 19 ± 1 meq/L, respectively ($P <$ .01). Similar acid-base responses were observed in the control subjects.

Figure 1 shows the glycemic responses of control subjects (baseline glycemia 87 ± 4 mg/dl) compared to

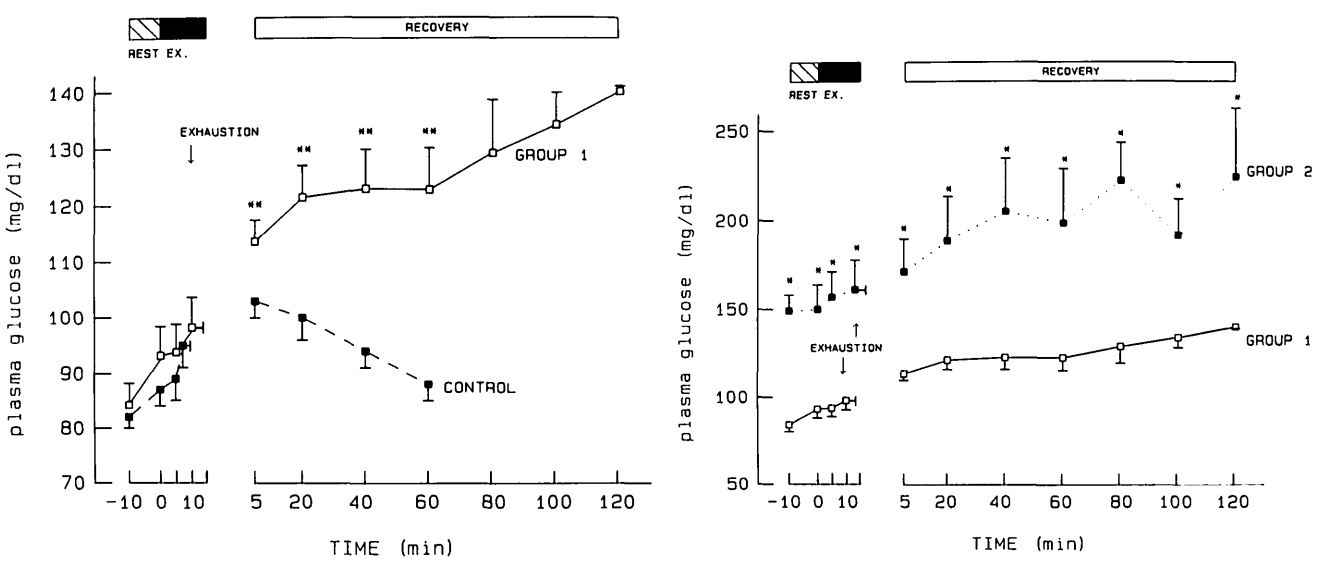

FIG. 1. Plasma glucose concentrations during intense exercise in control and diabetic subjects. Values are shown for 10-min rest period before exercise, exercise period at 80% $\dot{V}O_{2\,max}$, and 2 h of recovery. *Vertical arrows* are mean time of exhaustion. Data are means ± SE for control (■) vs. group 1 diabetic (□) subjects (*left panel*), and group 1 (□) vs. group 2 (■) diabetic subjects (*right panel*). Significant changes from rest values are detailed in text. *Values significantly different from group 1 and control group ($P < .05$). **Group 1 values different from control values ($P < .01$).

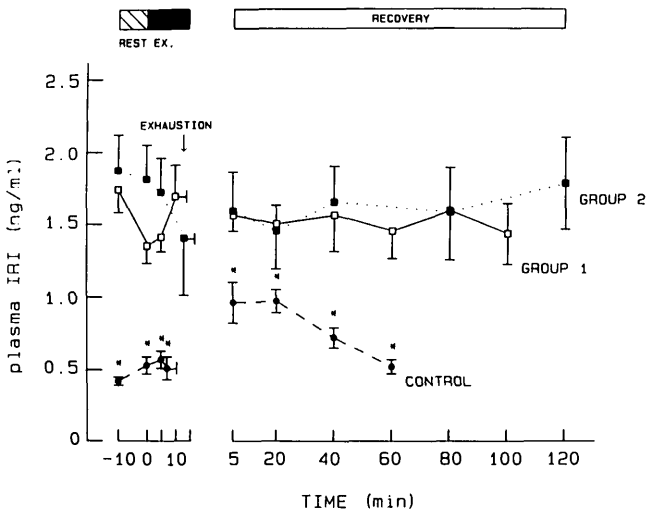

FIG. 2. Plasma insulin and free-insulin responses during intense exercise in control group and diabetic groups 1 and 2. Data are presented as means ± SE for control (●), group 1 (□), and group 2 (■). IRI, immunoreactive insulin. *Control values significantly different from groups 1 and 2 ($P < .05$).

group 1 subjects (baseline glycemia 86 ± 4 mg/dl) and group 1 versus group 2 diabetic subjects (baseline glycemia 149 ± 9 mg/dl). Control subjects' plasma glucose concentrations increased transiently but significantly ($P < .01$) at 5, 20, and 40 min of recovery and returned to resting values at 60 min. However, the hyperglycemia in group 1 diabetic subjects was greater and remained significantly ($P < .001$) elevated relative to resting values at all time points from 5 to 120 min of recovery. In group 2 there was an elevation of plasma glucose during exercise and recovery that tended to worsen progressively with time, being significantly above preexercise values at 40–120 min of recovery ($P < .025$). The glycemias in group 1 were greater than those of the control subjects throughout recovery ($P < .05$). Glycemias of group 2 were greater than those of both control and group 1 subjects throughout the experiment ($P < .01$).

In the control group, there was significant ($P < .01$) transient elevation of insulin at 5, 20, and 40 min, peaking at approximately twofold resting values. In contrast, the free insulin in group 1 subjects remained constant and not significantly different from resting values. In group 2 subjects, the free immunoreactive insulin (IRI) values showed a slight (11%) but significant ($P < .005$) decrease at 20 min that persisted until 120 min. Free-IRI values at rest were typically elevated in the diabetic subjects compared with the IRI values in the control subjects, ($P < .05$ for both groups at all points; Fig. 2).

The resting concentrations of plasma IRG were comparable in groups 1 (218 ± 14 pg/ml) and 2 (223 ± 23 pg/ml), and there was no systematic change in either group during or after exercise (Fig. 3). The results in control subjects were similar (258 ± 19 pg/ml) and also did not change. With respect to other measured energy substrates, resting and exercise concentrations were comparable in the control group and in groups 1 and 2 for lactate, pyruvate, 3-hydroxybutyrate, and free fatty acids (FFAs) except at exhaustion and 40 min of recovery for FFAs, where the plasma levels of groups 1 and 2 were significantly higher than control levels ($P < .05$; Table 2). As a reflection of the intensity of the exercise, lactate and pyruvate values rose significantly ($P < .001$) to peaks at exhaustion and 5 min of recovery, respectively. Plasma catecholamines showed marked increases ($P < .001$) by exhaustion to values indistinguishable among the three groups, and the rates of return to baseline values postexercise were not different among the groups (Table 3). The trend for higher preexercise epinephrine values in group 1 was not significant.

DISCUSSION

The results of this study show a deterioration of diabetic control in IDDM patients on CSII after intense exercise at 80% $\dot{V}O_{2\,max}$. This contrasts with the general notion that exercise improves diabetic control (14). The importance of exercise in promoting physical and mental health and improving the quality of life has recently been reemphasized (15). With the increased emphasis that sports are receiving, it is surprising how little is known of the effects of intense exercise in IDDM patients, who probably undertake this type of exercise with greater frequency than in the past.

Our studies of intense exercise at 80% $\dot{V}O_{2\,max}$ in normal lean subjects have shown a significant increase in glycemia with exercise that was sustained until 40 min

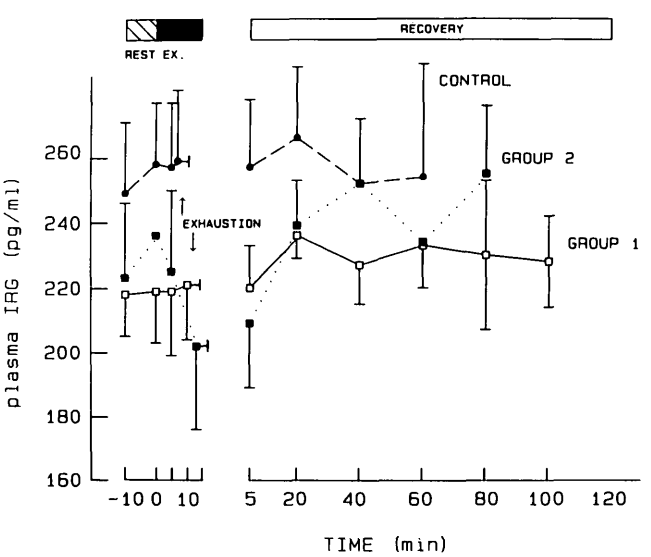

FIG. 3. Plasma glucagon responses during exercise in control group (●) and diabetic groups 1 (□) and 2 (■). Data (means ± SE) are shown for 10-min rest period before exercise, exercise period at 80% $\dot{V}O_{2\,max}$ to exhaustion, and 2 h of recovery. IRG, immunoreactive glucagon.

TABLE 2
Metabolic substrates at selected time intervals

	Preexercise	Midexercise	Exhaustion	Recovery	
				5 min	40 min
Lactate (mM)					
Group 1	0.7 ± 0.1	3.1 ± 1.0*	6.2 ± 1.0†	4.7 ± 1.1*	1.4 ± 0.4
Group 2	0.95 ± 0.2	2.6 ± 0.5*	7.7 ± 1.8*	7.1 ± 1.2*	1.5 ± 0.2
Control	0.67 ± 0.08	2.55 ± 0.3†	6.05 ± 0.5†	7.5 ± 0.59†	2.6 ± 0.3
Pyruvate (mM)					
Group 1	75 ± 11	108 ± 10*	140 ± 9†	215 ± 38	100 ± 19
Group 2	93 ± 9	123 ± 11	155 ± 20†	206 ± 54	109 ± 12
Control	60 ± 5	91 ± 13†	167 ± 15†	291 ± 21†	136 ± 22
3-Hydroxybutyrate (μM)					
Group 1	272 ± 98	165 ± 62	118 ± 48	177 ± 59	260 ± 107
Group 2	87 ± 48	66 ± 34	52 ± 19	75 ± 19	114 ± 26
Control	122 ± 26	109 ± 26	89 ± 19	87 ± 16	54 ± 6
Free fatty acid (μM)					
Group 1	864 ± 162	642 ± 66	832 ± 129	977 ± 141‡	865 ± 128‡
Group 2	695 ± 183	496 ± 93	671 ± 213	1034 ± 165‡	1004 ± 159‡
Control	819 ± 63	604 ± 40	489 ± 29*	609 ± 34	522 ± 37

Values are means ± SE. Group 1 diabetic subjects, preexercise plasma glucose 70–120 mg/dl; group 2, 130–180 mg/dl. Repeated measures analysis of variance via General Linear Models procedure revealed significant time effect for lactate ($P < .005$), pyruvate ($P < .005$), 3-hydroxybutyrate ($P < .025$), and free fatty acid ($P < .005$) but no time-group effect except for free fatty acid.
*$P < .05$ and †$P < .001$, significant difference compared with preexercise values.
‡$P < .05$, significant difference for groups 1 and 2 compared with control group.

of recovery. The hyperglycemia seen in our control subjects, which peaked at 5 min of recovery, is similar to that observed by Hermansen et al. (16), with peak values within an average of 7 min after the end of exercise, and Calles et al. (17), at 5 min of recovery. Similar but more sustained increases occur in nondiabetic obese subjects (9).

There was a twofold increase in insulin concentration in our normal control subjects, the peak occurring at 5 min of recovery. Hermansen et al. (16) reported a threefold increase in plasma IRI, with a peak 17 min after the end of a work bout, compared with the preexercise level, which was similar to the 100% increase of plasma insulin during 5 min of recovery in the subjects of Calles et al. (17); both results are consistent with our findings. With constant exogenous infusion as the sole source of insulin in our diabetic subjects, it was expected that hyperglycemia after similar intense exercise would perhaps be greater and more sustained. Notwithstanding the fact that each diabetic subject was receiving CSII at or near his/her usual 24-h basal rate, exercise in the postabsorptive state with normal basal glycemia was accompanied by significant hyperglycemia relative to baseline that was sustained for at least 2 h postexhaustion. The higher the glucose in the rest period, the greater the magnitude of glucose elevation sustained during recovery; however, in this case, it was accompanied by a depression from baseline of plasma free insulin, although significant only at one time point. The decrease of plasma insulin suggests increased tissue delivery and uptake in the face of presumed constant delivery to the circulation from the infusion site. The increased levels of free IRI relative to endogenous IRI in the control subjects are typical for CSII and continuous intravenous insulin infusion in euglycemic IDDM (3), which is presumably related to the necessity to produce portal IRI concentrations via the systemic circulation to regulate hepatic glucose production. The failure to show differences in free IRI between groups 1 and 2 probably relates to the large interindividual variability in free IRI and to a degree of imprecision of the method measuring the actual levels of unbound insulin available at its sites of binding to tissue receptors. Unfortunately, plasma C-peptide levels were not measured in this study to help discern the relative roles of altered secretion versus altered clearance.

Although we have not addressed the mechanism of the hyperglycemia, we assume that hepatic glucose output is increased to a greater extent than muscle glucose uptake. This does occur in normal subjects (17), and Wahren et al. (18) have shown that glucose uptake by exercising muscle (at 55–60% $\dot{V}O_{2\,max}$) in hyperglycemic subjects was not different from control subjects, whereas hepatic glucose output was increased. However, mechanisms underlying the hyperglycemia in recovery from intense exercise may be quite different in our diabetic subjects and remain to be elucidated by more direct measurement of glucose kinetics. The hyperglycemia is probably not related to glucagon, unless the peripheral hyperinsulinemia is not equivalent to portal insulin levels in the control subjects such that the same glucagon levels would be acting on a relatively

TABLE 3
Circulating catecholamine levels at selected time intervals

	Preexercise	Exhaustion	Recovery	
			5 min	40 min
Norepinephrine (pg/ml)				
Group 1	414 ± 49	1758 ± 234*	657 ± 68	334 ± 28
Group 2	308 ± 36	2038 ± 513*	657 ± 97	347 ± 35
Control	479 ± 64	2308 ± 214*	810 ± 238	443 ± 64
Epinephrine (pg/ml)				
Group 1	105 ± 21	411 ± 114*	97 ± 15	59 ± 12
Group 2	75 ± 11	328 ± 72*	96 ± 12	86 ± 12
Control	41 ± 7	368 ± 52*	97 ± 35	25 ± 3
Dopamine (pg/ml)				
Group 1	29 ± 5	60 ± 15†	51 ± 13	28 ± 3
Group 2	54 ± 8	75 ± 10	66 ± 8	50 ± 6
Control	30 ± 7	51 ± 11	44 ± 7	25 ± 3

Values are means ± SE. Group 1 diabetic subjects, preexercise plasma glucose 70–120 mg/dl; group 2, 130–180 mg/dl. Repeated measures analysis of variance via the General Linear Model procedures revealed significant time effect for norepinephrine ($P < .005$), epinephrine ($P < .005$), and dopamine ($P < .025$) but no time-group effect.
*$P < .001$ and †$P < .005$, exhaustion vs. preexercise values.

less "insulinized" liver. Similarly, the differences in response could not be attributed to catecholamine differences. In the absence of parallel control studies without exercise in the diabetic subjects, it is conceivable that at least part of the hyperglycemia might not be due only to the exercise, because in some subjects, glycemia might have increased somewhat in the face of constant insulin infusion.

At the onset of exercise, the plasma FFA level drops due to increased removal of FFAs from plasma (19), followed by a continuous rise above the basal level in the diabetic subjects related to failure of plasma insulin to increase, or it may even decline slightly, during exercise and recovery. The FFA level remained depressed throughout the study in the control subjects, in agreement with the rapid and sustained suppression of plasma FFA levels in the study by Jones et al. (20), who ascribed it to increased sensitivity to insulin. This difference could partly account for the greater and more sustained hyperglycemia in the diabetic subjects, acting via the glucose–fatty acid cycle of Randle et al. (21). This seems an unlikely regulator in the control subjects, in whom FFA levels decreased with exercise and tended to be lower than before exercise during the hyperinsulinemia of recovery.

The type of sport that most closely resembles exercise of the intensity used in this study would involve sprints or repeated short bouts of exercise, such as in hockey or basketball. Whereas the diabetic person who indulges in moderate exercise may forestall postexercise hypoglycemia by preceding the exercise with rapidly assimilated carbohydrate (8,22,23) or a decrease in insulin dosage (24), different therapeutic strategies may be required during intense exercise. Thus, the hockey player who enters the game with plasma glucose above normal may need to increase his/her basal pump rate or give himself/herself a small bolus of insulin injection to prevent postexercise hyperglycemia. In the case of the player who enters a game euglycemic and possibly raises glycemia stepwise with each shift on the ice, smaller insulin adjustments may be necessary but in the opposite direction as for exercise of lesser intensity. Other sports in which these considerations might apply would be those involving repeated bouts of intense exercise, such as basketball. However, we emphasize that detailed studies of these types of sports have not yet been performed, and we do not propose that such treatments be given until results of direct testing confirm that they are indicated. The prudent approach remains the systematic self-monitoring of blood glucose before, during (if possible), and certainly after intense exercise. Insulin and carbohydrate administration can be tailored to the individual. The principal problem with the use of exercise to improve metabolic control is that the blood glucose–lowering effect of exercise is not predictable in IDDM patients because of the influence of several factors including state of nutrition, metabolic control, duration and intensity of exercise, and the type, dose, and site of insulin injection.

We conclude that intense postabsorptive exercise in the diabetic person on CSII raises rather than lowers glucose levels; depending on preexercise glycemia, the magnitude of the rise can be considerable. Thus, different therapeutic strategies may be required for intense versus moderate exercise.

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