Combined Effect of Exercise and Ambient Temperature on Insulin Absorption and Postprandial Glycemia in Type I Patients

Tapani Rönnemaa, MD
Veikko A. Koivisto, MD

We studied the combined effect of cool (10°C) and warm (30°C) ambient temperatures and physical exercise on insulin absorption and postprandial glycemia. Nine type I (insulin-dependent) diabetic patients were injected subcutaneously with their usual morning dose of short- and intermediate-acting human insulin and were given breakfast. Warm temperature was associated with 3- to 5-fold higher insulin absorption ($P < .01$) and significantly lower blood glucose concentration ($P < .001$) than cool temperature regardless of exercise. Exercise was associated with 28% ($P < .01$) and 22% ($P < .05$) increases in plasma insulin and maximally 5.7 mM ($P < .025$) and 7.1 mM ($P < .01$) lower blood glucose at cool and warm temperatures, respectively. Warm temperature and exercise had an additive effect in stimulating insulin absorption and in lowering blood glucose concentrations. However, there was no evidence of synergism between higher temperature and exercise in increasing free-insulin concentrations or decreasing blood glucose concentrations. To avoid postprandial hyperglycemia at cool temperature or hypoglycemia after exercise at warm temperature, appropriate adjustments in diet and insulin dose, or both, should be made. *Diabetes Care* 11:769–73, 1988

Previous studies have demonstrated that the insulin absorption rate from an injection site at rest is related to ambient temperature: whereas warm temperature accelerates absorption (1–3), exposure of the injection site to cold delays the rate of insulin absorption (3). In addition, physical exercise can markedly stimulate the insulin disappearance rate from an exercising limb (4–8). These changes in the insulin absorption rate are clinically important, because they are reflected in alterations in blood glucose concentrations. Insulin-treated diabetic patients are involved in various types of exercise in which ambient temperature varies greatly, as exemplified by skiing in winter (9) or jogging in summer. Under these conditions, both ambient temperature and physical exercise may cause changes in the insulin absorption rate. To what extent these changes can be additive (by warmth and exercise) or whether opposing changes (by cold and exercise) can overcome each other is not known. Moreover, previous studies regarding the effect of exercise on insulin absorption was performed mainly with animal insulin, and data on human insulin is scanty (7). We are not aware of any data on the influence of ambient temperature on the absorption of human insulin, which is now commonly used in clinical practice and has absorption kinetics different from animal insulin (10). Consequently, this study examined the combined effect of ambient temperature and physical exercise on the absorption of human insulin in type I (insulin-dependent) diabetic patients. As a measure of the biological efficacy of insulin, we determined simultaneous changes in blood glucose concentration.

From the Rehabilitation Research Centre of the Social Insurance Institution, Turku, and the Finnish Academy of Science and Third Department of Medicine, University of Helsinki, Helsinki, Finland.

Address correspondence and reprint requests to Tapani Rönnemaa, MD, Rehabilitation Research Centre of the Social Insurance Institution, Peltolantie 3, SF-20720 Turku, Finland.

MATERIALS AND METHODS

Patients. Nine type I men participated in the study. Mean ± SE age was 25 ± 2 yr, and duration of diabetes was 10 ± 1 yr. Mean height, weight, and body mass index were 179 ± 2 cm, 76 ± 3 kg, and 23.9 ± 0.5 kg/m^2, respectively. All had plasma C-peptide concen-

trations after breakfast <0.20 nM. Two patients had mild background retinopathy, whereas none had symptoms or signs of neuropathy or proteinuria, and all had normal serum creatinine values. None had evidence of lipodystrophy at insulin-injection sites. All patients had used human soluble and protamine insulin (Velosulin Human Insulin and Insulatard Human Insulin, Nordisk, Gentofte, Denmark) for at least 1 mo before the study. Five patients took three daily injections (morning, before dinner, and bedtime), and four had two daily injections (2 patients: morning and before dinner; 2 patients: morning and bedtime). Mean daily dose of insulin was 52 ± 5 or 0.68 ± 0.06 U/kg. Mean morning doses of intermediate- and short-acting insulins were 32 ± 3 and 5 ± 1 U, respectively. Mean glycosylated hemoglobin A_{1c} was 8.5 ± 0.7% (reference range 4.2–6.0%).

Design. Resting and exercise studies at both 10 and 30°C were performed. Each patient participated in all four studies, which were performed in a randomized fashion at 1- to 2-wk intervals. After an overnight fast, an indwelling catheter was inserted into an antecubital vein for blood sampling. The patients were injected with their normal morning dose of insulin at 0740. Insulin was injected subcutaneously into the right thigh, similarly in each experiment. The patients had breakfast (400 kcal as 50% carbohydrate, 30% fat, and 20% protein) at 0800, and exercise started at 0900. At 0955, patients had a snack (150 kcal, same composition as breakfast). Exercise was performed on a cycle ergometer in three 15-min periods with 5-min rest intervals between periods. The absolute exercise intensities were the same at warm and cool temperatures. Intensity of exercise during the 1st, 2nd, and 3rd min of each 15-min period was adjusted to 15, 30, and 45% of the maximum aerobic capacity ($VO_{2\,max}$), respectively, whereas in the last 12 min, intensity was 60% of $VO_{2\,max}$. $VO_{2\,max}$ was estimated with an incremental cycle exercise test (11) performed 2–4 wk before the absorption studies. When not exercising, patients were seated.

Experiments were performed in specially constructed cabins (area 2 × 3 m, height 2.5 m) where the temperature was adjusted to the desired level and maintained constant. Relative humidity was 40% during each study. At 30°C, patients wore shorts and sport shoes, and at 10°C, they added long stockings and a cotton shirt; thighs were left uncovered.

Measurements. Plasma free insulin and blood glucose were determined at 0 (0740), 20, 35, 50, 65, 80, 95, 115, 135, 165, and 195 min. Skin temperature was recorded at 95, 115, and 135 min, and the mean of the three measurements is given in the results. Urine was collected throughout the 195-min period for the measurement of glucose excretion. Plasma free insulin was

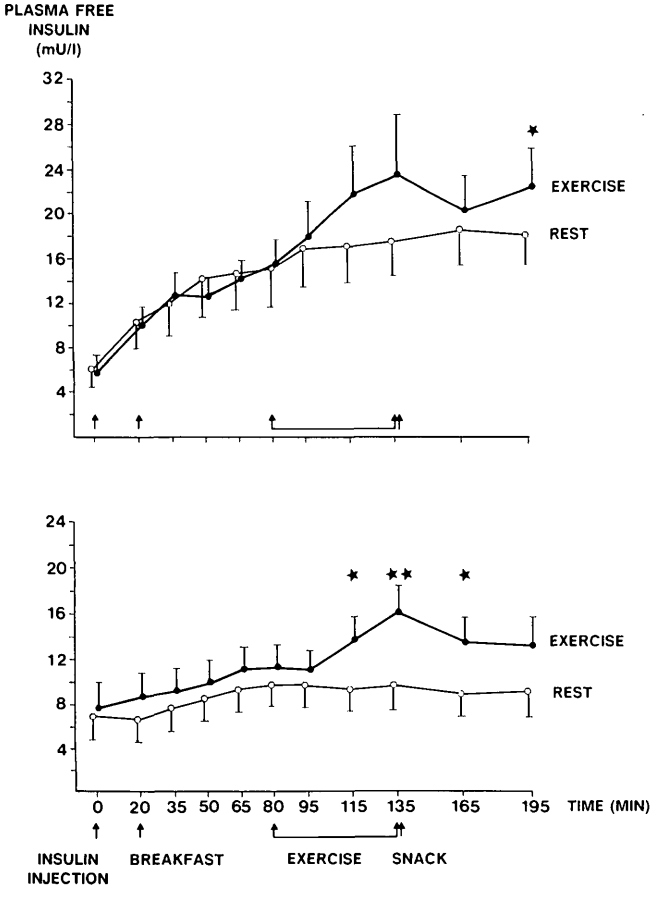

FIG. 1. Mean ± SE plasma free-insulin concentrations after subcutaneous human insulin injection at 30°C (*top*) and 10°C (*bottom*) with and without exercise. *$P < .05$, **$P < .025$ exercise vs. rest.

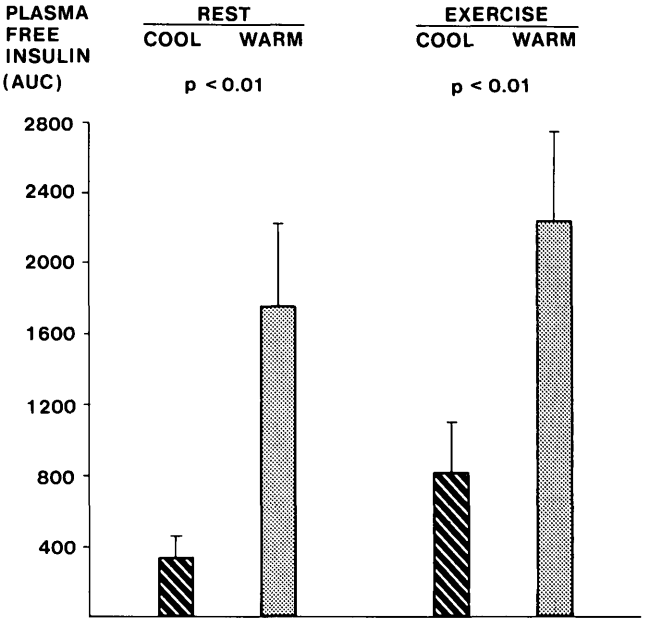

FIG. 2. Mean ± SE of areas under curve (AUC) for plasma free insulin (mU · L^{-1} · min^{-1}) after subcutaneous human insulin injection at 10 and 30°C with and without exercise. AUC was calculated with values from insulin injection to end of study.

measured by radioimmunoassay (12), and blood and urinary glucose were measured with the glucose dehydrogenase method (13). Skin temperature was recorded 5 cm distal to the injection site by a digital thermometer (DM-100, Envic OY, Turku, Finland) connected to a thermocouple probe (type A-H1, Ellab A/S, Copenhagen).

Overall comparisons of plasma free-insulin and blood glucose profiles between the four experimental conditions over different time points were first made with a three-way repeated-measures analysis of variance (ANOVA) with the SAS/GLM procedure (14). Comparisons of two experimental conditions over different time points were made with a two-way repeated-measures ANOVA. Individual time points were compared with Student's paired *t* test. Results are given as means ± SE. Correlations were calculated with the Pearson method of least squares.

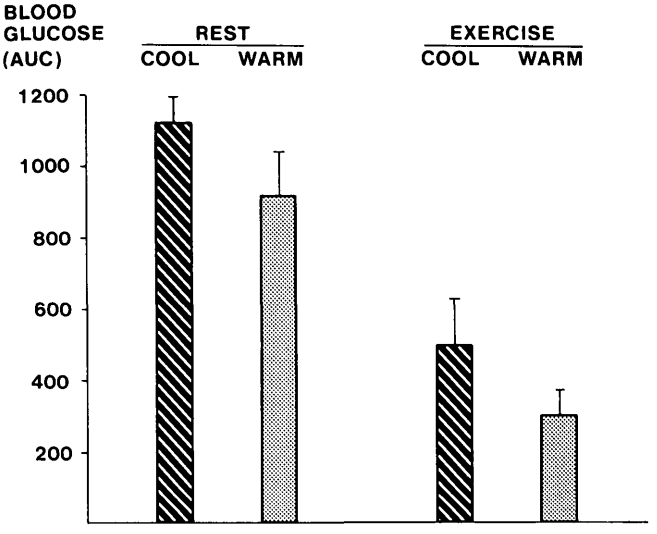

FIG. 4. Mean ± SE areas under curve (AUC) for blood glucose (mM · min) after subcutaneous human insulin injection at 10 and 30°C with and without exercise. AUC was calculated with values from insulin injection to end of study.

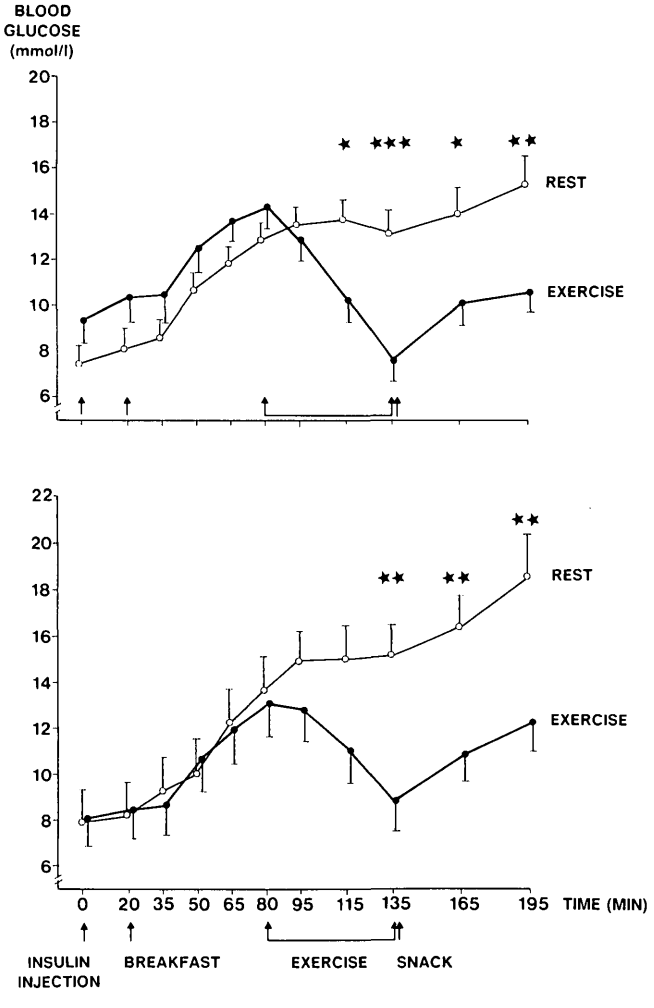

FIG. 3. Mean ± SE blood glucose concentrations after subcutaneous human insulin injection at 30°C (*top*) and 10°C (*bottom*) with and without exercise. *$P < .05$, **$P < .025$, ***$P < .01$ exercise vs. rest.

RESULTS

The effects of exercise and temperature on plasma insulin levels are shown in Fig. 1. Plasma free-insulin values rose during exercise more than during rest at both temperatures. The average difference in the changes in plasma insulin between the exercise and rest periods was 2.7 mU/L or 28% ($P < .01$, ANOVA) at cool and 3.7 mU/L or 22% ($P < .05$, ANOVA) at warm temperatures. Regarding the effect of temperature, plasma free insulin values from insulin injection to the end of the study were significantly higher at warm than cool temperatures in both the rest and exercise experiments (Fig. 1). The average difference between warm and cool temperatures (after correction for difference in baseline value) was 7.6 mU/L or 86% ($P < .001$, ANOVA) in the resting experiment and 7.4 mU/L or 63% ($P < .001$, ANOVA) in the exercise experiment. Accordingly, the area under the curve (AUC) for plasma free insulin when calculated from insulin injection to the end of the experiment was 3- to 5-fold higher ($P < .01$) at 30°C than at 10°C, regardless of exercise (Fig. 2). The differences in AUC values for plasma free insulin between experiments performed at 30 and 10°C were similar when calculated from the start of exercise to the end of the study (data not shown). Three-way repeated-measures ANOVA showed that warm temperatures and exercise had no interaction in raising plasma insulin levels ($P = .86$).

The effect of exercise on blood glucose concentrations is shown in Fig. 3. Blood glucose values from the start to the end of exercise at both temperatures were significantly lower during exercise than at rest. Mean difference in the changes in blood glucose between

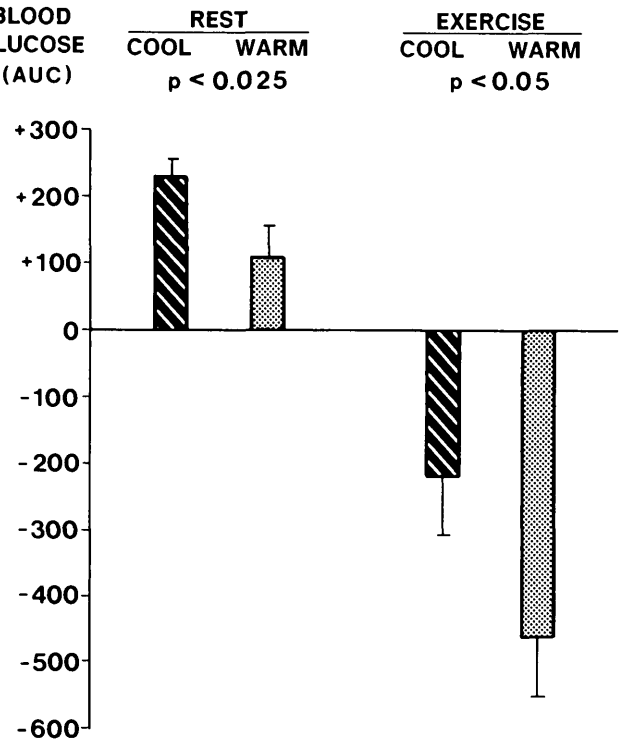

FIG. 5. Mean ± SE areas under curve (AUC) for blood glucose (mM · min) after subcutaneous human insulin injection at 10 and 30°C with and without exercise. AUC was calculated with values from start of exercise to end of study.

exercise and rest were 3.3 mM or 22% ($P < .001$, ANOVA) at cool and 4.8 mM or 36% ($P < .001$, ANOVA) at warm temperatures. Maximal hypoglycemic effect of exercise was 5.7 mM ($P < .025$) in cool and 7.1 mM ($P < .01$) in warm environments. Regarding the effect of temperature in both the rest and exercise experiments, blood glucose values from insulin injection to the end of the study were lower at warm than at cool temperatures. The average difference between warm and cool temperatures (after correction for the baseline difference) was 1.1 mM or 8% ($P < .001$, ANOVA) at rest and 0.9 mM or 8% ($P < .001$, ANOVA) during exercise. Warm temperature and exercise had no interaction ($P = .71$) in lowering blood glucose. When calculated from insulin injection to the end of the study, AUC values for blood glucose were 55–65% lower ($P < .01$) during exercise than at rest (Fig. 4). Temperature had a smaller nonsignificant effect. When calculated from the beginning of exercise to the end of the experiment, AUC values for blood glucose were negative on the exercise day at both temperatures ($P < .001$ vs. resting day; Fig. 5). Also, the effect of temperature was significant regardless of exercise (Fig. 5).

Urinary glucose excretion in the four studies varied from 6.8 ± 3.4 to 17.7 ± 5.9 g with no significant difference between the experiments.

The AUC values for plasma free insulin and blood glucose calculated from the beginning of exercise to the end of the study were inversely related both in the warm ($r = -.69$, $P < .05$) and cool ($r = -.74$, $P < .025$) environments. At rest, this correlation was seen only in the warm environment when calculated for the whole study period ($r = -.76$, $P < .025$).

Skin temperature at rest was higher in warm (35.7 ± 0.2°C) than cool (22.9 ± 0.7°C; $P < .001$) ambient temperature. During exercise, skin temperature fell in the warm environment to 34.2 ± 0.5°C ($P < .05$) but rose in the cool environment to 25.8 ± 0.7°C ($P < .025$).

DISCUSSION

Numerous studies have demonstrated a rise in insulin absorption by an increase in ambient temperature (1–3,8) or physical exercise (3–5,7,8). In contrast, exposure to a cold bath reduces insulin absorption (3). The combined effects of exercise and ambient temperature on insulin absorption are not known nor is the effect of temperature on the absorption of human insulin. Regarding exercise studies, with one exception (7), all have employed only animal insulins, most investigating short-acting insulins only (1,2,4–7). Most insulin in therapeutic use is of the human rather than animal type. To obtain results applicable to clinical practice, our patients were injected with their usual dose of short- and intermediate-acting human insulin. Experimental temperatures were chosen to reflect environmental conditions where diabetic patients may exercise.

At rest at 10°C there was only a modest rise in plasma free insulin levels, and the postprandial rise in blood glucose was substantial. Compared with cool temperature, at 30°C the increase in plasma insulin values from baseline was 3- to 5-fold greater, and postprandial glycemia was significantly reduced. When exercise was performed, it raised plasma free-insulin levels significantly both in cool and warm environments. Simultaneously, exercise induced a rapid decline in blood glucose concentrations, which at most were >7 mM lower than on the resting day at the same ambient temperature. The importance of the rise in insulin concentrations for the decline of blood glucose during exercise is emphasized by the inverse correlation between the AUC for plasma free insulin and blood glucose. Hyperinsulinemia during exercise further stimulates peripheral glucose utilization and prevents an appropriate increase in hepatic glucose production (15). Augmented glucose utilization beyond the rate of production results in a decline in blood glucose, as occurred in our patients. Note, however, that hypoglycemia during exercise may also occur in the absence of augmented insulin absorption, provided serum insulin levels are high, such as occurs after an injection of short-acting insulin (16).

Three-way repeated-measures ANOVA showed that warm temperature and exercise had no interaction in their effects on plasma insulin and blood glucose levels, indicating that warm temperature and exercise have an

additive effect in both increasing plasma insulin levels and reducing postprandial glycemia.

Because both warm temperature and exercise caused an early rise in plasma insulin concentration, this reflects an increase in the absorption rate rather than a decline in insulin clearance, although the possibility of changes in clearance are not totally excluded. Skin blood flow and temperature are correlated and depend on environmental temperature (17). The absorption of soluble insulin and insulin suspension are correlated to skin blood flow when injected subcutaneously (8,18). Therefore, in our study the greater insulin absorption rate at rest in warm compared with cool temperature is probably explained by higher skin temperature and blood flow (8). However, the greater insulin absorption rate during exercise in warm temperature compared with the resting state in the same temperature cannot be explained by the same mechanism, because skin temperature fell during exercise at 30°C. This is consistent with the previous finding that constriction of skin veins and decrease in skin blood flow occurs during exercise in warm temperature (19). A likely explanation for the enhanced insulin absorption in warm temperature during exercise is that repetitious muscle contractions result in a massage-like effect, which enhances insulin absorption from subcutaneous tissue (3). This view is further supported by the unchanged insulin absorption from the nonexercised areas during leg exercise (4) and by the fact that insulin absorption during exercise does not correlate with changes in blood flow (7).

Our results are applicable to clinical routine, where patients inject a combination of short- and intermediate-acting insulin. Further studies are needed to relate the hypoglycemic effect of exercise and high temperature to the type of insulin administered and to its time of injection.

Our study has clinical implications for type I diabetic patients. First, because an exposure to a cool environment reduced insulin absorption and augmented the postprandial rise in blood glucose at rest, this has to be taken into account in the planning of insulin dose and diet in sedentary patients exposed to cool weather. Second, the stimulatory effects of warm environment and exercise on insulin absorption are additive. Consequently, an appropriate reduction in insulin dose or an increase in carbohydrate intake, or both, should be considered for patients exercising in a warm environment.

ACKNOWLEDGMENTS

We thank Pauli Puukka, M.Pol., for help in statistical analyses.

Financial support from the Yrjö Jahnsson Foundation is gratefully acknowledged.

REFERENCES

1. Koivisto VA, Fortney S, Hendler R, Felig P: A rise in ambient temperature augments insulin absorption in diabetic patients. *Metabolism* 30:402–405, 1981
2. Koivisto VA: Sauna-induced acceleration in insulin absorption from subcutaneous injection site. *Br Med J* 280:1411–13, 1980
3. Berger M, Cüppers HJ, Hegner H, Jörgens V, Berchtold P: Absorption kinetics and biologic effects of subcutaneously injected insulin preparations. *Diabetes Care* 5:77–91, 1982
4. Koivisto VA, Felig P: Effects of leg exercise on insulin absorption in diabetic patients. *N Engl J Med* 298:79–83, 1978
5. Dandona P, Hooke D, Bell J: Exercise and insulin absorption from subcutaneous tissue. *Br Med J* 1:479–80, 1978
6. Ferrannini E, Linde B, Faber O: Effect of bicycle exercise on insulin absorption and subcutaneous blood flow in the normal subject. *Clin Physiol* 2:59–70, 1982
7. Fernqvist E, Linde B, Östman J, Gunnarsson R: Effects of physical exercise on insulin absorption in insulin-dependent diabetics: a comparison between human and porcine insulin. *Clin Physiol* 6:489–98, 1986
8. Binder C, Lauritzen T, Faber O, Pramming S: Insulin pharmacokinetics. *Diabetes Care* 7:188–99, 1984
9. Sane T, Helve E, Pelkonen R, Koivisto VA: The adjustment of diet and insulin dose during long-term endurance exercise in type I (insulin dependent) diabetic men. *Diabetologia* 31:35–40, 1988
10. Gulan M, Gottesman IS, Zinman B: Biosynthetic human insulin improves postprandial glucose excursions in type I diabetes. *Ann Intern Med* 107:506–509, 1987
11. Saltin B, Åstrand P-O: Maximal oxygen uptake in athletes. *J Appl Physiol* 23:353–58, 1967
12. Kuzuya H, Blix PM, Horwitz DL, Steiner DF, Rubinstein AH: Determination of free and total insulin and C-peptide in insulin-treated diabetics. *Diabetes* 26:22–29, 1977
13. Bergmeyer HU: *Methoden der enzymatischen Analyse*. Weinheim, FRG, Chemie, 1974
14. Freund RJ, Littell RC, Spector PC: *SAS System for Linear Models*. Cary, NC, SAS Inst., 1986
15. Zinman B, Murray FT, Wranic M, Albisser AM, Leibel BS, McClean PA, Marliss EB: Glucoregulation during moderate exercise in insulin treated diabetics. *J Clin Endocrinol Metab* 45:641–52, 1977
16. Kemmer FW, Berchtold P, Berger M, Starke A, Cüppers HJ, Gries FA, Zimmermann H: Exercise-induced fall of blood glucose in insulin-treated diabetics unrelated to alteration of insulin mobilization. *Diabetes* 28:1131–37, 1979
17. Rowell LB: Human cardiovascular adjustment to exercise and thermal stress. *Physiol Rev* 54:75–159, 1974
18. Kølendorf K, Bojsen J, Nielsen SL: Adipose tissue blood flow and insulin disappearance from subcutaneous tissue. *Clin Pharmacol Ther* 25:598–604, 1979
19. Zitnik RS, Ambrosioni E, Shepherd JT: Effect of temperature on cutaneous venomotor reflexes in man. *J Appl Physiol* 31:507–12, 1971