Circulatory and Temperature Regulatory Responses to Exercise in a Warm Environment in Insulin-Dependent Diabetics

SUZANNE M. FORTNEY, VEIKKO A. KOIVISTO, PHILIP FELIG, AND ETHAN R. NADEL

John B. Pierce Foundation Laboratory and Departments of Epidemiology and Public Health, Physiology, and Medicine, Yale University School of Medicine, New Haven, Connecticut

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Because diabetics are prone to the development of neuropathy and microvascular disease, abnormalities of cardiovascular reactivity and capillary permeability in response to acute exercise and/or an increase in environmental temperature might presage the development of clinically overt complications. In the present study insulin-dependent diabetics without evidence of microangiopathy or neuropathy and controls matched for the same level of physical fitness performed cycle ergometer exercise for 20 minutes at 65 percent VO$_{2}$max in a temperature maintained at 35°C. The rise in heart rate (82–85 beats min$^{-1}$), the fall in plasma volume (11–13 percent), and the increase in total serum proteins (13–16 percent) induced by exercise were the same in the two groups. Furthermore, comparable increments in skin blood flow (two- to threefold) and in core and skin temperatures were observed. The relationship between increases in body core temperature and increases in skin blood flow and the vasodilatory threshold (37.0°C) were also the same in the diabetics and controls.

INTRODUCTION

Exercise is often recommended to diabetic patients as an important part of the therapeutic program [1]. Since diabetics are prone to neuropathy and capillary basement membrane thickening, changes in cardiovascular reactivity and capillary permeability in response to exercise would also be expected, and might presage the development of clinically overt neuropathy and microangiopathy. However, only limited and somewhat conflicting data are available regarding such variables as heart rate and plasma volume responses to exercise in juvenile-onset, insulin-dependent diabetics.

Diabetics have been observed to have a diminished capacity to increase skin blood flow and to dissipate body heat in response to whole body heating when examined in the resting state [2,3,4,5]. Although exercise is known to cause an increase in core temperature, particularly when performed in a warm environment [6], the effects of diabetes on the peripheral circulatory and thermoregulatory responses to exercise have not been determined.

The present study was consequently undertaken to examine the heart rate, plasma
volume, peripheral circulatory, and thermoregulatory responses to acute exercise performed at the same relative as well as absolute intensity in insulin-dependent diabetics and control subjects. To place the subjects in a condition of high thermoregulatory demands, the studies were conducted in a temperature-controlled environment maintained at 35°C.

MATERIALS AND METHODS

Subjects

Four male insulin-dependent diabetics and four healthy subjects, matched for age, sex, and physical fitness, participated in the study. The clinical data on the subjects are given in Table 1. The patients were known to have had diabetes for three to thirteen years (mean 8 ± 2 years) and were receiving a total of 30 to 56 units of intermediate-acting, or short plus intermediate-acting insulin per day. There was no clinical evidence of diabetic retinopathy, nephropathy, or neuropathy in any of the patients as reflected by a normal ophthalmoscopic and neurologic examination and the absence of proteinuria. At the time of the study, all the subjects were actively employed. The subjects were informed of the nature, purpose, and possible risks of the study before their written, voluntary consent to participate was obtained.

Procedures

The maximal aerobic power (VO₂ max) of each subject was estimated by means of a standard incremental exercise test on a cycle ergometer (Monark, Sweden). Because of the possibility of eliciting a hypoglycemic reaction in our diabetic subjects following a maximal test, we chose to estimate VO₂ max from the pattern of increment in heart rate and oxygen uptake, as described by Åstrand and Rodahl[7].

Each subject was studied in the morning two hours after his regular injection of insulin and a breakfast meal of 350 to 450 kcal. An indwelling catheter was inserted in an antecubital vein for obtaining blood samples before, during, and after exercise. An esophageal thermocouple was inserted to the heart level for the recording of internal body temperature (Tₑₛ). Skin temperatures were measured by thermocouples applied at eight skin sites as previously described, and mean skin temperature (Tₛₖ) was computed from area and sensitivity weighting [8]. Forearm blood flow was deter-

| TABLE 1 |
| Anthropometric Data of Subjects |
| Age (yr) | Height (cm) | Weight (kg) | VO₂ max (ml • kg⁻¹ • min⁻¹) |
|---|---|---|---|
| †BT | Control | 21 | 178 | 65.9 | 46.9 |
| KK | Diabetic | 21 | 175 | 69.5 | 42.4 |
| DW | Control | 34 | 165 | 65.9 | 42.5 |
| MK | Diabetic | 21 | 178 | 67.3 | 42.4 |
| KB | Control | 37 | 188 | 77.6 | 45.1 |
| AM | Diabetic | 29 | 173 | 65.9 | 42.0 |
| WC | Control | 29 | 183 | 97.2 | 38.3 |
| HR | Diabetic | 27 | 185 | 77.3 | 32.7 |
| X ± SE | Controls | 30 ± 3 | 179 ± 4 | 76.7 ± 6.4 | 43.2 ± 1.6 |
| Diabetics | 25 ± 2 | 178 ± 2 | 70.0 ± 2.2 | 40.9 ± 2.5 |

†Subjects were paired for similar values of maximum aerobic power (VO₂ max).
mined by venous occlusion plethysmography, using a Whitney strain gauge on the free forearm [9]. Because changes in forearm blood flow during leg exercise and body heating are limited to the skin [10], changes in forearm blood flow can be interpreted as representatives of changes in skin flow over most of the body.

Following a 4 ml blood sample taken just prior to the onset of exercise, after at least 20 minutes of rest, subjects exercised for 20 minutes at an intensity corresponding to 65 percent of \( \dot{V}O_2 \) max. During exercise, blood flow was determined at 30-second intervals, \( T_{es} \) and \( T_{sk} \) at one-minute intervals, and heart rate at two-minute intervals. Blood samples were taken at 2, 6, 12, and 20 minutes of exercise. All test procedures were performed in an environmental chamber which maintained the ambient temperature at 35.0\(^\circ\)C ± 0.1\(^\circ\)C. The procedures were precisely the same for the control group except that no insulin was administered.

Due to the nature of the experimental design (vigorous exercise in a warm environment with an esophageal thermocouple and indwelling venous catheter), only a limited number of subjects could be tested. However, to improve the reliability of the data, each of the subjects was studied twice, and in each case the mean values from the two tests were used in all comparisons. For all subjects, the values obtained on duplicate test days were similar.

Plasma glucose was determined by the glucose oxidase procedure [11] before and after 20 minutes of exercise. Serum osmolality (freezing point depression), total protein (refractometry), protein electrophoretic fractionation with a Gelman chamber and cellulose acetate strips [12], hemoglobin (cyanomethemoglobin technique), and hematocrit (corrected for trapped plasma and for whole body hematocrit) were determined at 5- to 10-minute intervals during exercise. The resting plasma volume was calculated from the dilution of Evans Blue Dye [13], and blood and red cell volumes were then calculated from the hematocrit. Percentage changes in plasma volume during exercise were calculated using the formula described by van Beumont et al. [14].

In the statistical analysis of the data, paired \( t \)-tests were employed, using the differences between paired subjects. Each subject was studied twice; the mean value of each variable from the duplicate runs was used to represent each subject's data.

RESULTS

Table 2 shows the plasma volume and osmolality, hematocrit, hemoglobin, mean corpuscular hemoglobin concentration, and blood glucose concentration data for each subject. In each adjacent column, the absolute change in each of these values between the start and the end of each 20-minute exercise test is shown. In both groups during exercise there was a significant increase in hematocrit and hemoglobin, suggesting a significant loss of fluid from the plasma volume. The mean corpuscular hemoglobin concentration did not significantly change, indicating no alteration in red cell volume during exercise. The postprandial blood glucose concentration was significantly higher in the diabetic subjects than in the controls, and the mean blood glucose concentration decreased in both groups during exercise.

As also seen in Table 2, plasma volume significantly decreased during exercise for all subjects with a similar relative loss seen for both groups. The average PV loss was 11.3 percent for controls, and 12.6 percent for diabetic subjects. We have previously observed a comparable decrease in plasma volume in healthy subjects performing exercise in similar conditions [15]. In both diabetic and control subjects plasma osmolality rose by about 6 percent (\( p < 0.05 \)) in concert with a 11 to 12 percent increase in serum total protein concentration (\( p < 0.02 \)).
### TABLE 2
Hematological Data at Rest, and Changes after 20 Minutes of Exercise in Control and Diabetic Subjects

|                | Plasma Volume (ml) | Plasma Osmolality (mosmols × kg⁻¹) | 'Hematocrit (units) | Hemoglobin Concentration (g × dl⁻¹) | Mean Corpuscular Hemoglobin Concentration (g × dl⁻¹) | Blood Glucose (g × dl⁻¹) |
|----------------|--------------------|-------------------------------------|---------------------|-------------------------------------|----------------------------------------------------|--------------------------|
|                | Rest | Exercise Change | Rest | Exercise Change | Rest | Exercise Change | Rest | Exercise Change | Rest | Exercise Change | Rest | Exercise Change |
| BT            | Control | 3305 | -250 | 290 | +8 | 38.6 | +1.8 | 15.6 | +1.0 | 40.4 | +0.8 | 110 | -23 |
|               | Diabetic | 4040 | -710 | 278 | +13 | 38.9 | +3.9 | 15.7 | +0.8 | 40.4 | -1.8 | 320 | -38 |
| DW            | Control | 3775 | -420 | 287 | +14 | 34.4 | +2.8 | 13.3 | +1.0 | 38.7 | -0.6 | 106 | -33 |
|               | Diabetic | 4105 | -340 | 290 | +17 | 41.8 | +2.1 | 15.8 | +0.8 | 37.8 | 0.0 | 263 | -39 |
| KB            | Control | 3980 | -516 | 281 | +12 | 39.3 | +2.8 | 15.7 | +1.8 | 39.9 | -0.9 | 106 | -35 |
|               | Diabetic | 3330 | -370 | 297 | +7 | 38.5 | +2.9 | 14.0 | +1.5 | 36.4 | +1.0 | 295 | -3 |
| WC            | Control | 4600 | -580 | 285 | +14 | 39.0 | +3.3 | 15.9 | +1.6 | 40.8 | +0.6 | 93 | +12 |
|               | Diabetic | 3670 | -500 | 292 | +32 | 42.5 | +3.6 | 16.3 | +1.6 | 38.4 | +0.4 | 202 | -9 |
| **± SE**      | Controls | 3915 ± 233 | -442 ± 62 | 286 ± 2 | +12 ± 1 | 37.8 ± 1.0 | +2.7 ± 0.3 | 15.1 ± 0.5 | +1.4 ± 0.2 | 40.0 ± 0.4 | 0.0 ± 0.4 | 104 ± 3 | -20 ± 9 |
|               | Diabetics | 3786 ± 156 | -480 ± 73 | 287 ± 3 | +17 ± 5 | 40.4 ± 0.9 | +3.1 ± 0.3 | 15.5 ± 0.4 | +1.2 ± 0.2 | 38.3 ± 0.7 | -0.1 ± 0.5 | 270 ± 22 | -22 ± 8 |

*Hematocrits corrected for trapped plasma and venous sampling.*
The serum protein profile was further analyzed by determining the various protein fractions (Table 3). In the resting state, most protein concentrations tended to be higher in the diabetic subjects than in the controls; however, the differences were not significant. Exercise caused a 10 to 15 percent rise in serum albumin concentration in both groups \((p < 0.05)\); the globulin concentrations also tended to increase. No significant differences between diabetics and controls were observed in any of the protein fractions over the course of exercise.

Figure 1 depicts the exercise-induced changes in heart rate, body temperature, and forearm skin blood flow. A comparable rise in heart rate occurred in controls (85 beats \(\cdot\) \(\text{min}^{-1}\)) and diabetic subjects (82 beats \(\cdot\) \(\text{min}^{-1}\)) during exercise. In addition, the pattern of heart rate increase was similar in both groups (Fig. 1). In both groups, exercise caused a significant \((p < 0.05)\) and comparable rise in \(T_{es}\) and \(T_{sk}\) increased slightly but not significantly. Forearm skin blood flow was similar in both groups at rest and showed a comparable two- to threefold increment during exercise.

To assess the responsiveness of the skin vasculature to changes in body temperature, we plotted the forearm skin blood flow against the core temperature data, each of which was determined at 30-second intervals during exercise, and calculated the \(T_{es}\) threshold at which vasodilation occurred (where forearm blood flow was greater than 3 ml \(\cdot\) \(\text{min}^{-1}\) \(\cdot 100\ \text{ml tissue}^{-1}\)). and the slope of the \(T_{es}\) : forearm blood flow relationship (Table 4). If the cutaneous blood vessels and/or the nerves supplying such vessels were impaired in diabetic subjects, the relationship between core body temperature and forearm skin blood flow should have been different between groups. As shown in Table 4, there were no significant differences between the two groups in either the slope \((13.6 \pm 2.5\ \text{ml} \cdot \text{min}^{-1} \cdot 100\ \text{ml}^{-1} \cdot ^{\circ}\text{C}^{-1}\) for diabetics and \(15.7 \pm 5.7\ \text{ml} \cdot \text{min}^{-1} \cdot 100\ \text{ml}^{-1} \cdot ^{\circ}\text{C}^{-1}\) for controls), or in the vasodilatory threshold (37.0\(^{\circ}\)C for diabetics and controls). The highest skin blood flow attained by both groups was also virtually identical \((15.1 \pm 2.6\ \text{ml} \cdot \text{min}^{-1} \cdot 100\ \text{ml}^{-1}\) for diabetics and \(15.4 \pm 2.9\ \text{ml} \cdot \text{min}^{-1} \cdot 100\ \text{ml}^{-1}\) for controls). The results from both the diabetic and control subjects in this study are similar to values previously reported for normal subjects exercising under similar conditions [15].

**DISCUSSION AND CONCLUSIONS**

Diabetic patients are prone to the development of neuropathy which may alter cardiovascular reflexes when the autonomic nervous system is involved. In addition, diabetic patients develop morphologic changes in the micro-circulation which have been shown to correlate with an increase in capillary permeability to water and small molecules [16,17]. Previous studies have reported elevated heart rates both at rest and in response to exercise in diabetic patients as compared to healthy controls [18,19], whereas others have failed to show significant differences between diabetics and controls [20,21]. Furthermore, previous studies have suggested that the loss of plasma volume during exercise may be greater in diabetic patients than in healthy controls [18].

The diabetic subjects in the present study had a tendency toward an elevated heart rate at rest, although the difference from controls was not significant. The increase in heart rate during exercise was virtually identical in both groups. Furthermore, we found no significant exercise-induced differences between diabetic and control subjects in any of the measured indices reflecting alterations in plasma volume or protein composition, such as total blood volume, hemoglobin, hematocrit, plasma volume, osmolality, or total protein concentration or protein fractions.

Several factors may contribute to the apparent conflict between the results of our
### TABLE 3
Serum Protein Fractions (g • dl⁻¹) at Rest and the Change after 20 Minutes of Exercise in Control and Diabetic Subjects

|                  | Total Protein (g) | Albumin (g) | Alpha-1 Globulin (g) | Alpha-2 Globulin (g) | Beta Globulin (g) | Gamma Globulin (g) |
|------------------|-------------------|-------------|----------------------|----------------------|------------------|------------------|
|                  | Rest       | Exercise Change | Rest | Exercise Change | Rest | Exercise Change | Rest | Exercise Change | Rest | Exercise Change | Rest | Exercise Change |
| BT    | Control  | 7.5          | +0.4    | 4.98          | +0.32   | .31           | +0.07 | .64            | +0.06 | .94            | -0.18 | .63            | +0.24 |
| KK    | Diabetic | 6.9          | +0.8    | 4.43          | +0.75   | .25           | +0.05 | .55            | 0.00  | .65            | +0.08 | 1.02           | +0.15 |
| DW    | Control  | 6.7          | +0.7    | 4.19          | +0.57   | .17           | +0.10 | .64            | +0.14 | 1.02           | 0.00  | .65            | +0.21 |
| MK    | Diabetic | 7.9          | +0.8    | 4.48          | +0.14   | .24           | +0.06 | .85            | +0.02 | 1.01           | +0.11 | 1.34           | +0.48 |
| KB    | Control  | 7.0          | +0.9    | 4.36          | +0.94   | .20           | 0.00  | .75            | -0.07 | .70            | -0.05 | .99            | +0.04 |
| AM    | Diabetic | 7.7          | +0.8    | 4.61          | +0.49   | .29           | +0.01 | .83            | +0.08 | .86            | +0.05 | 1.12           | +0.21 |
| WC    | Control  | 7.8          | +1.0    | 4.63          | +0.58   | .23           | 0.00  | .54            | +0.20 | 1.11           | +0.03 | 1.27           | +0.21 |
| HR    | Diabetic | 8.0          | +1.1    | 5.12          | +0.66   | .30           | +0.02 | .59            | +0.28 | 1.09           | -0.05 | 0.85           | +0.26 |

± SE

|                  | Controls | Diabetics |
|------------------|----------|-----------|
| Total Protein    | 7.3±.2   | 7.6±.2    |
| Albumin          | 4.54±.15 | 4.66±.14  |
| Alpha-1 Globulin | 0.60±.11 | 0.51±.12  |
| Alpha-2 Globulin | 0.23±.03 | 0.27±.01  |
| Beta Globulin    | 0.64±.04 | 0.71±.07  |
| Gamma Globulin   | 0.04±.02 | 0.04±.01  |
|                  | 0.08±.05 | 0.10±.06  |
|                  | 0.04±.03 | 0.05±.03  |
|                  | 0.08±.08 | 0.09±.06  |
|                  | 0.06±.05 | 0.05±.03  |
|                  | 0.04±.04 | 0.08±.06  |
|                  | 0.13±.09 | 0.28±.06  |
study and those of previous studies. First, in some of the earlier studies diabetic subjects were not strictly matched with controls according to the level of physical fitness [16,18,19,21], but both groups of subjects performed exercise at the same absolute intensity. In this case, diabetics, in poorer physical condition, exercised at a greater heart rate and plasma volume response. In the present study, the diabetic and control subjects had comparable levels of physical fitness, as determined by similar maximal aerobic power in the two groups [22]. Consequently, the absolute as well as the relative exercise intensity was comparable between groups. Second, the diabetic subjects in previous studies may have been different with respect to the duration of diabetes and the presence of microvascular complications. In the present study, the mean duration of the disease was 8 ± 2 years, and none of the patients had clinical evidence of retinopathy, nephropathy, or neuropathy. In the studies by Langer et al. [18] and Viberti et al. [19] the duration of diabetes varied from one to 27 years. Since the prevalence of clinically manifest complications is proportional to the duration of diabetes [23], it is possible that patients with longer duration of diabetes also had a greater degree of microangiopathy.

In the resting state an abnormal thermoregulatory response has been reported in diabetic subjects, as indicated by a decreased cutaneous blood flow response to body heating [2,3,4,5]. This impairment has been attributed to changes in the blood vessel wall [4] and/or the nerves supplying the vessels [2]. In the present study, no impairment in the forearm skin blood flow response to body heating could be seen in the resting state or during exercise in diabetic subjects. The normal relationship between forearm skin blood flow and core temperature (Table 4) would suggest that
TABLE 4

Vasodilatory Thresholds and Regression Slopes of
the $T_{es}$: FBF Ratio for Diabetic and Control Subjects

|       | Vasodilatory Threshold $(^\circ C)$ | Regression Slope $(\text{ml} \cdot \text{min}^{-1} \cdot 100 \text{ml}^{-1} \cdot ^\circ C^{-1})$ |
|-------|-------------------------------------|------------------------------------------------|
| BT    | Control 37.3                        | 34.8                                           |
| KK    | Diabetic 37.2                        | 21.1                                           |
| DW    | Control 37.2                         | 12.5                                           |
| MK    | Diabetic 36.9                        | 14.0                                           |
| KB    | Control 36.2                         | 10.8                                           |
| AM    | Diabetic 36.8                        | 12.0                                           |
| WC    | Control 37.4                         | 4.8                                            |
| HR    | Diabetic 37.2                        | 7.4                                            |
| $\bar{X} \pm SE$ | Controls $37.0 \pm 0.24$ | $15.7 \pm 5.7$ |
|       | Diabetics $37.0 \pm 0.10$           | $13.6 \pm 2.5$ |

†Vasodilatory threshold is chosen when the forearm blood flow exceeds a value of 3 ml $\cdot$ min$^{-1} \cdot 100$ ml$^{-1}$

neither the sensitivity of the vessels nor the threshold for vasodilation was altered in these diabetic subjects.

In conclusion, the present data failed to provide sufficient evidence of a significant difference in the regulation of heart rate, plasma volume, skin blood flow, and body temperature in insulin-dependent diabetic subjects exercising in a warm environment as comparable to that of non-diabetics with equal physical fitness. Because of the small number of subjects studied, the results have to be interpreted cautiously. However, the data suggest that in the absence of clinical evidence of vasculopathy or neuropathy, circulatory and temperature regulation and muscle capillary permeability during exercise remain normal in patients with juvenile-onset diabetes. The results of the present study agree with previous findings which indicate beneficial metabolic effects of exercise in diabetes, and support the use of exercise as a therapeutic agent in insulin-dependent diabetes. Finally, whether the circulatory or thermoregulatory responses to exercise seen in non-insulin dependent diabetics are also comparable to controls remains to be established.

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