Muscle Blood Flow in Diabetes Mellitus

Evidence of Abnormality After Exercise

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OBJECTIVE — To determine whether muscle blood flow before and after exercise is abnormal in patients with diabetes mellitus.

RESEARCH DESIGN AND METHODS — Muscle blood flow (MBF) was measured with the ^{133}Xe clearance technique in 15 nondiabetic subjects, 10 patients with insulin-dependent diabetes mellitus (IDDM), and 11 patients with non–insulin-dependent diabetes (NIDDM) at rest and after exercise. None of the patients had neuropathy.

RESULTS — The median resting MBF was similar in all three groups. The median postexercise MBF was significantly greater in nondiabetic subjects (40.1 ml · min^{-1} · 100 g^{-1} of tissue) than in patients with IDDM (25.7 ml · min^{-1} · 100 g^{-1} of tissue; $P < 0.01$) or NIDDM (14 ml · min^{-1} · 100 g^{-1} of tissue; $P < 0.01$). The difference between IDDM and NIDDM was not significant.

CONCLUSIONS — Diabetic patients have abnormalities of MBF in response to exercise. This abnormality occurs in the absence of clinical diabetic neuropathy.

We previously demonstrated that the response of cerebral blood flow (CBF) to CO_2 in patients with diabetes mellitus is abnormal (1,2). CO_2 challenge does not induce an appropriate increase in cerebral blood flow; indeed, in some diabetic patients, CO_2 may cause a fall in CBF (1,2). Abnormalities in CBF and vascular reactivity were confirmed by others (3), and similar abnormalities were found in blood flow to subcutaneous tissue as well (4,5). More recently, we showed that the regulation of transcutaneous O_2 tension ($tcPO_2$) is altered in the feet of diabetic people, especially those with neuropathy (6).

This finding stimulated us to investigate blood flow patterns in the skeletal muscle of diabetic patients before and after exercise. Although one previous study described abnormalities in the response of calf muscle blood flow (MBF) to elevation of legs in recumbent diabetic patients with microangiopathy, it did not provide actual values of muscle blood flow (7). This study described observations made in seven patients with diabetic retinopathy and nephropathy but did not mention whether these patients had concomitant neuropathy.

RESEARCH DESIGN AND METHODS

— Twenty-one male patients with diabetes mellitus were included in the study. Their ages were between 23 and 69 yr (median 41 yr) and the duration of diabetes between 1 and 10 yr (median 5 yr). Ten patients had insulin-dependent diabetes mellitus (IDDM; age range 23–40 yr; duration 1–10 yr). Two IDDM patients had a body weight >10% of the ideal. Eleven patients had non–insulin-dependent diabetes (NIDDM; age range 35–50 yr; duration 2–10 yr). Four NIDDM patients had a body weight >10% of the ideal. The diagnosis of IDDM was established by the presence of ketosis and presentation of diabetes at <35 yr of age and that of NIDDM was established by the consistent absence of ketosis in diabetic patients >30 yr of age at presentation who were controlled by oral hypoglycemia drugs.

None of the patients had symptoms of somatic polyneuropathy or absent ankle reflexes. None of the patients had diminished sensation to pin prick or vibration. None had postural hypotension, complained of sexual impotence, or had postgustatory sweating. Four patients with IDDM of >5 yr duration and three patients with NIDDM of >5 yr duration showed no electromyographic evidence of neuropathy. Two patients with NIDDM of 8 and 10 yr duration had

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RECEIVED FOR PUBLICATION 1 JULY 1988 AND ACCEPTED IN REVISED FORM 6 SEPTEMBER 1991.

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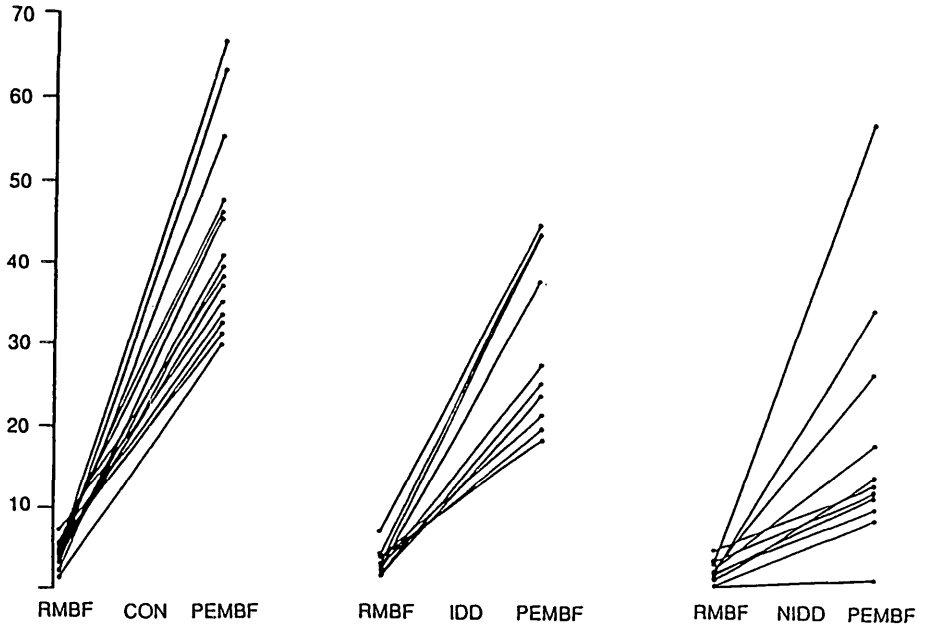

Figure 1—*Resting muscle blood flow (RMBF) and postexercise MBF (PEMBF) in control subjects (CON), insulin-dependent diabetic subjects (IDD), and non–insulin-dependent diabetic subjects (NIDD). Results are milliliter per 100 g muscle tissue per minute. RMBF in 3 groups was similar. PEMBF was significantly greater ($P < 0.01$) in control subjects than in IDD or NIDD patients. PEMBF in NIDD and IDD patients was not significantly different.*

background retinopathy. None of the patients had significant proteinuria or plasma creatinine concn >120 μM. The ankle–brachial pressure index was normal in all patients (>0.9), the dorsalis pedis and posterior tibial pulses were normally palpable in all patients, and there was no clinical evidence of ischemic changes in the feet of any of the patients. Their HbA_1 values were between 7 and 12% (mean 9.5 ± 1.2%, normal range 5.8–8.5%). None of the patients with IDDM smoked, and two patients with NIDDM smoked 15–20 cigarettes daily. None of the patients were hypertensive.

The 15 male control subjects were between 23 and 60 yr old. None had a fasting blood glucose >5 mM or postprandial blood glucose >5.5 mM. None had a body weight >10% above the ideal. MBF was measured by a method adapted from Faris et al. (8) and Lassen et al. (9) based on the clearance of Xenon 133, as described previously (10). The MBF partition for Xe was assumed to be 0.7 (8,9). The coefficient of variation (c.v.) for this technique in our hands was <10%. This method, established in 1964, yields results comparable to those obtained by venous occlusion plethysmography both at rest and after exercise (9). The effect of repeated plantar and dorsiflexion on MBF was also assessed. The subjects were asked to flex their foot up and down 80 times in 150 s. The maximum flow increase was calculated over the 1-min period immediately after completion of the exercise. The c.v. of postexercise MBF (PEMBF) after this exercise in our laboratory was <15% and is therefore reproducible. Our data on MBF have not been corrected for possible changes in capillary permeability, which may possibly affect these measurements.

Because the data on MBF were nonparametrically distributed, statistical comparisons were carried out with the Wilcoxon test for unpaired data.

RESULTS— The median resting MBF (RMBF) in normal subjects was 3.7 ml · min^{-1} · 100 g^{-1} of tissue, which increased to a median of 40.1 ml · min^{-1} · 100 g^{-1} after exercise (Fig. 1). There was no change in RMBF or PEMBF with age.

The median RMBF in patients with IDDM was 3.4 ml · min^{-1} · 100 g^{-1}, which increased to a median of 25.7 ml · min^{-1} · g^{-1} (Fig. 1). This was significantly smaller than the increase in PEMBF in nondiabetic subjects ($P < 0.01$).

The median RMBF in patients with NIDDM was 1.99 ml · min^{-1} · 100 g^{-1}. After exercise, it increased to a median of 14.1 ml · min^{-1} · 100 g^{-1} (Fig. 1). Both the postexercise MBF and the increase of postexercise over RMBF were significantly lower ($P < 0.01$) than in nondiabetic subjects. The difference in PEMBF between IDDM and NIDDM patients was not significant. There was no correlation between PEMBF or an increment in MBF after exercise and the duration of diabetes, HbA_1, retinopathy, or smoking.

CONCLUSIONS— Our data demonstrate that although there was no significant difference between RMBF in diabetic and control subjects, the increase in MBF after exercise was not as great in subjects with IDDM or NIDDM as in control subjects. The magnitude of the increase over RMBF was also significantly lower than that in nondiabetic subjects. These differences were observed in diabetic patients without overt clinical neuropathy, regardless of age or duration of diabetes. Although an exact estimate of the work carried out by each patient during exercise was not made, all patients performed the same exercise regime. Regular exercise and physical conditioning reduce MBF while increasing the extraction of O_2 from blood.

A previous study on MBF demonstrated a fall of 20% on elevation of the leg to 40 cm (7); however, this study was carried out on patients with nephropathy and retinopathy who might

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also have had neuropathy. Unfortunately, the authors did not comment on the presence or absence of these factors in their patients, although neuropathy may alter the autonomic responses necessary for the autoregulation of MBF.

The diabetic patient's inability to increase MBF adequately in response to exercise may not be reflected in clinical symptoms because MBF reserve is large. The limitation in increasing MBF may become important in diabetic patients who undertake strenuous physical exercise or have structural vascular disease. Their muscles may be predisposed to anaerobic metabolism, which may lead to lactic acid production during exercise (11).

The mechanism underlying the diminished increase in MBF after exercise in diabetic patients is not clear. The possible factors involved may be a diminution in vascular prostacyclin (PGI_2) (12–14), platelet hyperaggregability and increased thromboxane A_2 release (15), and an increase in plasma serotonin concentration (16).

In conclusion, diabetic patients have subnormal increases in calf MBF after exercise. This abnormality is similar to that previously described in CBF and skin blood flow of diabetic patients and exists even in the absence of overt clinical peripheral neuropathy. It may contribute to the pathogenesis of muscle ischemia and synergize the effects of peripheral vascular disease.

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