Oxygen Transport and Peripheral Microcirculation in Long-Term Diabetes (43164)

JEFFREY L. YOUNG, DAVID R. PENDERGAST,[1] AND JEHUDA STEINBACH

Departments of Physiology and Nuclear Medicine, State University of New York at Buffalo School of Medicine, and Veterans Administration Medical Center, Buffalo, New York 14214

Abstract. **The purpose of this investigation was to evaluate the impact of long-term diabetes on muscle blood flow (MBF) and oxygen transport ($\dot{V}O_2$) during exercise. Twelve male patients (58 ± 8 years, mean ± SD), with at least a 10-year history of diabetes controlled by insulin, and seven age-matched controls (56 ± 5 years, mean ± SD) participated in this study. No patient had been clinically diagnosed as having peripheral vascular disease, and on the average resting ankle/arm systolic blood pressure ratios were normal. Following a baseline period, 5 min of cycle ergometer exercises at 75 W were performed in the upright position and, after 1-hr recovery, in the supine position. Continuous $\dot{V}O_2$ was determined via breath-by-breath analysis. MBF was measured in the vastus lateralis (VL) and tibialis anterior (TA) by ^{133}Xe clearance. In the erect position, the diabetic group (compared with the control group, respectively) exhibited significantly ($P < 0.05$) lower exercise MBF [ml·(100 g·min)$^{-1}$] in both VL (19 ± 2.5 vs 30.9 ± 2) and TA (13.7 ± 2 vs 22.0 ± 4), a lower steady-state $\dot{V}O_2$ (1.3 ± 0.3 vs 1.7 ± 0.2 liters·min^{-1}) during exercise including the values in the last 15 sec of exercise, and greater accumulation of blood lactate (35 ± 2 vs 22.0 ± 2 mg/100 ml). The same trends in the data were observed during supine exercise; however, the blood pressure of the diabetics was significantly elevated during exercise when compared with that of controls. The reduced exercise MBF in the TA and VL demonstrated that impaired microvascular flow, without clinically overt peripheral vascular disease, in long-term diabetics leads to reduced oxygen delivery and exercise tolerance.** [P.S.E.B.M. 1991, Vol 196]

Among the many secondary sequelae associated with prolonged diabetes mellitus is the decrease in exercise tolerance and earlier onset of lactic acid (La) accumulation during submaximal work when compared with age-matched nondiabetics (1–4). The decreased exercise tolerance has been suggested to be a result of decreased supply of oxygen to exercising muscles due to reduced blood flow (5, 6). In addition, peripheral vascular disease (PVD) occurs five to six times more frequently in diabetics than in the general population (7). Given a population of long-term diabetics, whose circulation to peripheral muscle beds is compromised and who have potentially decreased O_2 carrying capacity of the blood, one anticipates altered $\dot{V}O_2$ kinetics (prolonged $\dot{V}O_2$-on) and greater La accumulation during the transition from rest to exercise while trying to establish the appropriate $\dot{V}O_2$ steady-state ($\dot{V}O_2$ss).

The Doppler ultrasonic technique is commonly used in the clinical setting to screen for PVD (7, 8). This type of measurement estimates large vessel flow; however, it may fail to detect microvascular pathology (9). Estimation of muscle blood flow (MBF) via radioisotopic xenon washout was introduced by Lassen *et al.* (10) in 1964. Numerous subsequent investigators successfully utilized this method to evaluate hyperemic or exercise MBF in individuals exhibiting occlusive vascular disease (11, 12), in sedentary adults (10, 13–15), and in endurance-trained athletes (16). Cerretelli *et al.* (17) have shown that MBF values as estimated by this ^{133}Xe washout technique correlate well with measurements from both the microsphere injection technique ($r = 0.80$) and direct venous outflow method ($r = 0.86$) in exercising dogs (18).

The primary purpose of this study was to compare the heart rate (HR), blood pressure (BP), MBF, kinetics of readjustment of $\dot{V}O_2$, and blood La during rest,

[1] To whom requests for reprints should be addressed at Department of Physiology, 124 Sherman Hall, State University of New York at Buffalo, Buffalo, NY 14214.

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exercise, and recovery of diabetics when compared with age-matched control subjects. In addition, the possible alterations in total plasma catecholamines were investigated.

Methods

Twelve adult diabetic males (mean age ± SD, 58 ± 8.0 years) from the Veterans Administration Hospital of Buffalo, NY, and seven age-matched control subjects (mean age ± SD, 56 ± 5 years) participated in this study. All patients had at least a 10-year history of diabetes mellitus controlled by insulin. Eight of the 12 diabetic and 5 of the 7 control subjects smoked one to two packs of cigarettes per day for 20 to 30 years. There were no statistical differences in the MBF data (all muscles) between smokers and nonsmokers (diabetics and controls together by analysis of variance, $n = 13$ and 6 for smokers and nonsmokers, respectively). The data for smokers and nonsmokers were considered together based on the small number of nonsmokers and the absence of significant differences between the two groups.

The diabetics were given a clinical examination, and upper and lower extremity BP measurements were performed to screen for large vessel disease (7, 8) (Doppler probe, Life Sciences PVR). Systolic BP were determined at the level of the brachial, femoral, popliteal, posteriortibial, and dorsalis pedis arteries. Measurements were performed twice at each site on both limbs with the average of the four recordings being used. The ratio of the lower limb to upper limb extremity systolic BP was calculated and used as a criterion for the presence of large vessel disease (ratio <1.0) (7, 8). The subjects used as controls were assumed to have a normal cardiovascular system at baseline and during exercise.

The protocol for testing was as follows. Subjects sat erect at rest for 10 min on an electrically braked cycle ergometer (Collins). Baseline measurements of MBF, $\dot{V}O_2$, La, and total plasma catecholamines were taken over the next 5 min. Square-wave exercise at 75 W was then initiated and subjects pedaled at 60 rpm for 5 min. Work was then stopped and recovery measurements were made over the next 60 min. Subjects were then placed in a supine position on an electrically braked cycle ergometer (Collins). The center of the pedal shaft was positioned approximately 30 cm from the board that the subject was lying on. The same resting, exercise, and recovery procedures utilized in the erect posture were followed in the supine posture. In the event that any subject could not exercise for a full 5 min, recovery measurements were initiated immediately upon cessation of work.

An electrocardiogram was recorded continuously and HR calculated during the steady state of each condition. BP was taken by auscultation during the steady state of each condition.

To measure MBF, a 50- to 70-μCi bolus of ^{133}Xe in saline was injected intramuscularly with a 27-gauge needle. Because vascular diseases are more prevalent in the legs than arm, and more pronounced peripherally, we studied a proximal and a distal muscle that are used during leg ergometry. Due to technical and safety considerations, only four simultaneous measurements could be made, so we elected to only study two muscles: the tibialis anterior (TA) and vastus lateralis (VL). This allowed us to average measurements from muscles of the right and left legs, the right and left TA and VL muscles. ^{133}Xe clearance was measured at rest, during exercise, and for the first 6 min of recovery in the erect and supine positions (16). MBF was calculated by the formula (16, 19):

$$\text{MBF}\ [\text{ml}\cdot(100\ \text{g}\cdot\text{min})^{-1}] = \frac{\text{a constant (0.69)}\cdot\text{the tissue blood partition coefficient (0.693 }\mu\text{Ci/g muscle/}\mu\text{Ci/ml blood)}}{\text{halftime clearance of }^{133}\text{Xe clearance (ml}\cdot\text{g}^{-1}\cdot\text{min}^{-1})}$$

Blood samples were withdrawn from an antecubital vein at rest, during peak exercise, and at 6, 10, 15, and 20 min of recovery for La determination (enzymatic, CalBiochem). Total catecholamines were assayed (radioenzymatic, Cat-A-Kit) from the blood samples at rest, during peak exercise, and at 6 min of recovery.

To determine $t_{1/2}\dot{V}O_2$-on, subjects breathed through a mouthpiece and a one-way valve system into a linear displacement spirometer (Ohio 823 spirometer) connected to a Grass Polygraph Recorder. The sample probe of a mass spectrometer (Perkin Elmer 1100) was attached to the outflow portion of the spirometer to obtain O_2 and CO_2 fractions. The operator, guided by the visual signal triggered at the mouth of the subject, emptied the spirometer after each breath. A computer (DEC PDP 11) was utilized to determine and plot $\dot{V}O_2$ on a breath-by-breath basis. A $\dot{V}O_2$-on response curve was obtained directly or extrapolated from measured data utilizing previously validated models (20–22) (diabetic group) from which the halftime (sec) was determined. $\dot{V}O_2$ss values were determined from the last 30 to 60 sec of exercise.

Statistical comparisons were made via a two-way analysis of variance followed up by Scheffe post hoc analysis to separate significantly different findings ($P < 0.05$).

Results

The mean values (±SE and range) for the ratios of lower extremity/upper extremity systolic BP are presented in Table I. Ratios of BP at the level of the femoral and popliteal vessels were significantly greater than 1.0 and were ~20 to 30% higher than at the level of the brachial artery. The more distal average BP ratios

Table I. Arterial Pressure Ratios (Leg, Arm) for the Diabetic Subjects[a]

	Femoral	Popliteal	Posterior tibial	Dorsalis pedis
Mean	1.28	1.18	0.96	0.91
± SD	0.16	0.19	0.08	0.07
Range	1.0–1.4	0.95–1.4	0.9–1.1	0.8–1.0
#0.95	0	1	6	8

[a] Femoral, popliteal, posterior tibial, and dorsalis pedis artery BP were compared with the bracheal artery BP. A ratio of ≥1.0 is considered normal.

(posteriortibial and dorsalis pedis) were not significantly less than the normal value of 1.0. It would appear that the diabetic subjects, as a group, did not have a significant degree of large vessel peripheral vascular disease, in the upper leg (VL), whereas in the lower limb (TA) this may have been a factor.

Total exercise time differed significantly between the two groups. Surprisingly, even at this modest exercise level, the diabetics were able to exercise for only 3.56 ± 1.17 and 3.50 ± 1.21 min in the upright and supine positions, respectively. Premature termination of exercise was uniformly associated with leg fatigue or cramping.

The electrocardiogram was monitored continuously and integrated with a cardiotachometer, whereas BP was determined at 3 and 5 min of exercise. No significant changes in HR or BP were observed between the third and fifth min measurements of either HR or BP. The mean and SE for HR and BP responses of the diabetic and control subjects in both the erect and supine positions are shown in Table II. The resting BP of the diabetics were not significantly elevated in either the erect (systolic BP 126 ± 122, diastolic BP 8 vs 83 mm Hg, respectively) or supine position (systolic BP 130 vs 1222, diastolic BP 83 vs 81 mm Hg, respectively) when compared with age-matched controls. The resting HR of the diabetics were significantly greater than those of the controls in both the erect and supine positions (~88 vs 72 and 89 vs 61 beats·min^{-1}, respectively). HR in the supine position was lower than in the erect position in the control group (61 vs 72 beats·min^{-1}, respectively); however, these values were not significantly different in the diabetics (89 vs 88 beats·min^{-1}, respectively). During exercise, the HR in the erect (113 and 119 beats·min^{-1}) and supine (97 and 115 beats·min^{-1}) position, was less than ~75% of the age-predicted maximum HR in both groups (23). In the erect position, the HR (113 and 199 beats·min^{-1}) and BP (151 and 162, and 90 and 84 mm Hg) reached the same steady-state levels in the diabetic group that they did for the control group. In the supine position, the HR (115 and 97 beats·min^{-1}) and BP (181 vs 152 mm Hg) were greater in the diabetic than in the control group.

Results of the MBF measurements during erect and supine conditions are shown in Figure 1. In the erect position, resting flow rates for both muscles were similar in the two groups [~2.5 ml·(100 g·min)$^{-1}$]. Diabetics exhibited significantly lower MBF during exercise; their values were only 63% (VL) and 62% (TA) of the flows observed in the control group. At 6 min into recovery, MBF in both the VL (MBF_{VL}) and TA (MBF_{TA}) in the controls and MBF_{TA} in the diabetics had returned to preexercise levels [~3ml·(100 g·min)$^{-1}$]. MBF_{VL} remained significantly elevated when compared with pre-exercise levels in the diabetic group [~10 vs 3 ml·(100 g·min)$^{-1}$] (see Fig. 1).

Under supine conditions, MBF were, again, not significantly different in the two groups at rest [~5 ml·(100 g·min)$^{-1}$] but were significantly greater than those observed before erect exercise in both groups [~2.5 ml·(100 g·min)$^{-1}$]. MBF rose significantly with exercise (~3-fold) but, with the exception of MBF_{TA} in the diabetics, were significantly lower than corresponding values observed during erect work (~10-fold). The diabetic group exhibited a lower exercise MBF than the

Table II. Steady-State Cardiovascular Parameters for Control and Diabetic Subjects[a]

	Rest			Exercise		
	HR (beats·min^{-1})	SBP[b] (mm Hg)	DBP (mm Hg)	HR (beats·min^{-1})	SBP (mm Hg)	DBP (mm Hg)
Erect	72	122	83	113	151	90
Control	(6)	(14)	(5)	(20)	(9)	(5)
Diabetic	88[c]	126	83	119	162	84
	(11)	(13)	(9)	(20)	(20)	(14)
Supine	61	122	81	97	152	88
Control	(5)	(7)	(6)	(15)	(5)	(6)
Diabetic	89[c]	130	83	115[c]	181[c]	87
	(12)	(14)	(8)	(14)	(25)	(9)

[a] Values are mean ± SD.
[b] SBP, systolic BP; DBP, diastolic BP.
[c] Significantly different from control ($P < 0.05$).

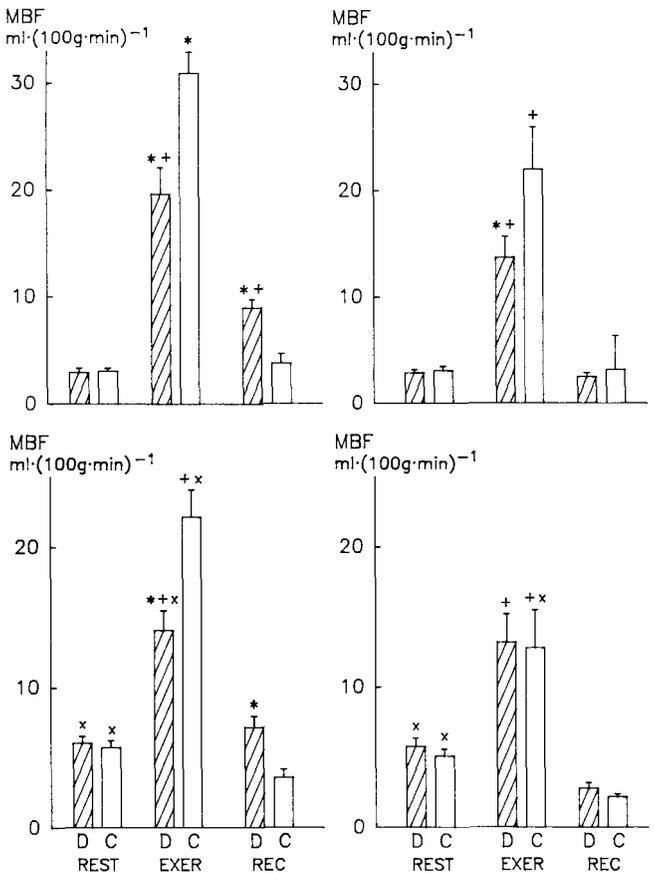

Figure 1. Average ±SD values for muscle blood flow during rest, exercise (EXER), and recovery (REC) in diabetic (D) and control (C) subjects. Data for the VL are in the two left plates, for the TA in the two right plates, and erect and supine posture in the two upper and lower plates, respectively. *Significantly different from controls; +, from resting; ×, from erect values.

controls in the VL only (64% control value). During the 6 min after the exercise recovery period, only MBF_{VL} [7 vs 2.5 ml·(100 g·min)$^{-1}$] in the diabetic group failed to return to resting levels. After the 60 min of recovery, the MBF in the resting supine position was not significantly elevated in the diabetics when compared with controls [2.5 ml·(100 g·min)$^{-1}$].

Oxygen uptake values appear in Table III. Resting $\dot{V}O_2$ values were not statistically different between the two groups and were independent of posture (0.32–0.401·min^{-1}). Peak O_2 uptake during exercise was unaffected by posture, but was significantly lower in the diabetics under both conditions (~22–25%). A true $\dot{V}O_2$ss was not achieved by the diabetic group. This was related to the diabetic group's inability to exercise for the full 5 min, and their markedly delayed kinetics of O_2 uptake (Fig. 2). Their $t_{1/2}$ $\dot{V}O_2$-on were significantly slower on the average with values of (109 ± 20 sec for erect and 118 ± 21 sec for supine) as compared with control values of 33 ± 10 and 44 ± 5 sec, respectively. After 1, 2, and 3.5 min of exercise, the $\dot{V}O_2$ of the diabetics was 40, 40, and 22% lower than that of the control subjects.

The diabetics exhibited significantly greater concentrations of La while cycling (20 vs 35 mg/100 ml, respectively) and were unable to clear La as effectively from the circulation during recovery (Fig. 3). At 20 min after erect exercise, the patients still exhibited significantly elevated lactate levels (33.0 ± 3.9 mg/100 ml), whereas control values had fallen to near resting levels (15.0 ± 4.1 mg/100 ml). At the beginning of supine exercise (1 hr after erect exercise), the average diabetic La concentration (15.4 ± 1.9 mg/100 ml) was significantly different from that of the controls (10.2 ± 1.3 mg/100 ml). Lactate levels during peak supine exercise and at 6 min into recovery were, again, higher in the diabetic group (~2 fold) (see Fig. 3).

Total plasma catecholamine levels are shown in Table III. Catecholamines increased significantly in response to supine exercise in both groups (~2- to 3-fold). Recovery values did not differ from rest or exercise levels in either group. No significant differences between the two groups were observed in the erect position, although the mean values for the diabetics were considerably higher (729·511) before, during (1358·856), and after (929·658 pg·ml^{-1}, respectively) exercise. All average catecholamine levels in the supine position were lower than their corresponding upright values in both groups (~10–40%). However, only resting and recovery values in the control group were found to be statistically different from the upright value (303 vs 511 pg·ml^{-1}, respectively). Mean catecholamine levels were significantly greater during supine exercise in the diabetic group when compared with the values for the control group (~60%). No other significant differences in catecholamine levels between diabetics and controls were observed.

Discussion

Five min of cycling at 75 W was chosen because the energy requirement was similar to a brisk walk and it was believed that all subjects could perform the task. The diabetics, who were reportedly asymptomatic, were unable to complete a brief period of moderate exercise. More than likely, the patients' $\dot{V}O_2$ss values represent the $\dot{V}O_2$ peak of these subjects, which was 23 (ml·kg·min)$^{-1}$, a value similar to those reported for patients with cardiac or PVD (24). The resting MBF values were within the accepted normal range of blood flow in resting skeletal muscle in both controls and diabetics (3, 13, 14, 25, 26). In both groups (VL and TA observed), lower resting MBF in the erect posture than in the supine position are in agreement with previously reported values and are probably related to the reflex vasoconstriction of resistance vessels after the increase in transmural pressure associated with orthostasis (13, 26–28).

Table III. Physiologic Characteristics of the Diabetic and Control Groups during Erect and Supine Exercise[a]

	Group	Rest	Exercise	Recovery
$E\dot{V}O_2$ (liters·min^{-1})	D	0.40 ± 0.09	1.30 ± 0.29[b,c]	
$S\dot{V}O_2$ (liters·min^{-1})	C	0.36 ± 0.05	1.66 ± 0.17[c]	
	D	0.36 ± 0.14	1.14 ± 0.40[b,c]	
	C	0.32 ± 0.04	1.50 ± 0.25[c]	
E catecholamines (pg·ml^{-1})	D	729 ± 175	1358 ± 325	929 ± 235
S catecholamines (pg·ml^{-1})	C	511 ± 46	856 ± 153	658 ± 94
	D	467 ± 136	1222 ± 257[b,c]	544 ± 127
	C	303 ± 39[d]	527 ± 100[c]	389 ± 42

[a] Values are mean ± SD.
[b] Significantly different from controls ($P < 0.05$).
[c] Significantly different from resting value ($P < 0.05$).
[d] Significantly different from erect ($P < 0.05$).

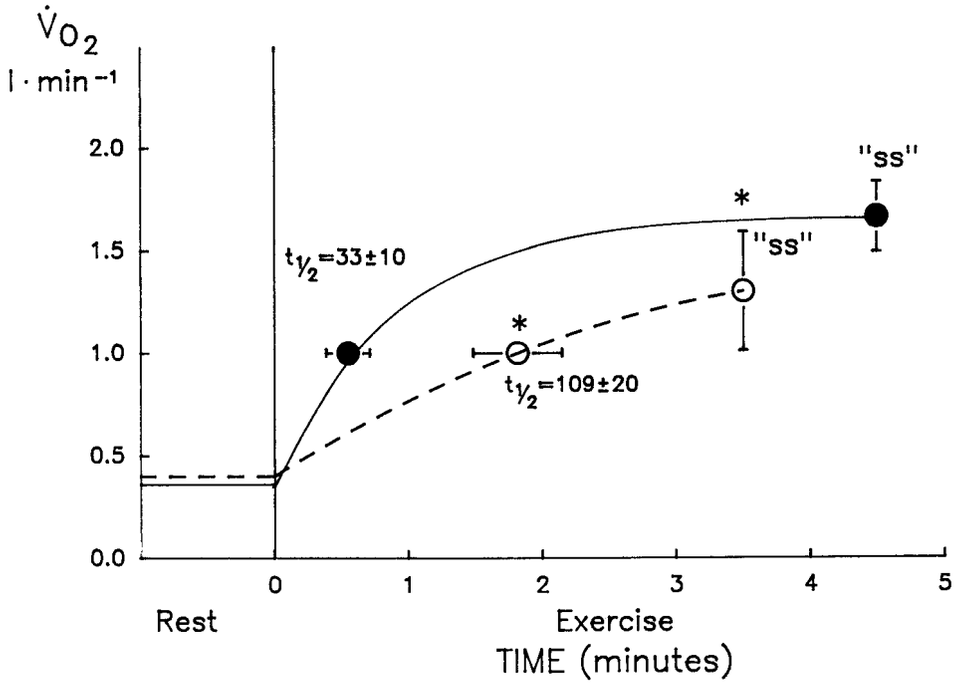

Figure 2. Oxygen uptake during upright exercise plotted as a function of time for controls and diabetics. The average ±SD of the time to reach half steady state ($t_{½}$ in sec) and steady-state oxygen uptake ("SS") are indicated. *Significant difference ($P < 0.05$) from control.

The rise in MBF_{VL} during upright exercise was approximately 10-fold in the control group, consistent with what was expected for this amount of metabolic demand (14). The significantly lower flow in the TA as compared with the VL [22 ± 4 vs 31 ± 2 (ml·100 g·min)$^{-1}$] may be explained by its lesser importance in bicycle exercise. The lower flows in both the TA and VL muscles of normal subjects during supine exercise may be a postural effect that persists during exercise or a function of other muscle groups (e.g., hip flexors) assuming a greater role in the exercise, rather than a true decrease in perfusion in the exercising limb. On the other hand, the lower MBF in the diabetics for both muscles during erect exercise and VL during supine exercise clearly indicate a deficit in perfusion. This is supported by the "hyperemic" pattern of MBF_{VL} during recovery, analogous to what is normally observed following isometric exercise. Exercise flows in the TA were low and unaffected by postural change in the diabetic group and were almost identical to MBF in the control group's TA during supine cycling. This suggests that under both conditions the diabetic group's MBF_{TA} was at its maximum, and that there was no "reserve" in the upright position. Recovery MBF_{TA} was not elevated. Since maximal reactive hyperemia following occlusion normally sets in rapidly (10, 14, 24), it would appear that this clearly represented the MBF_{max}.

The femoral, popliteal, posterior tibial, and dorsalis pedis systolic BP at rest were not significantly below normal, on the average. It should be noted, however, that some of the subjects in the diabetic group (1, 6, and 8 of the 12 subjects for the popliteal, posterior

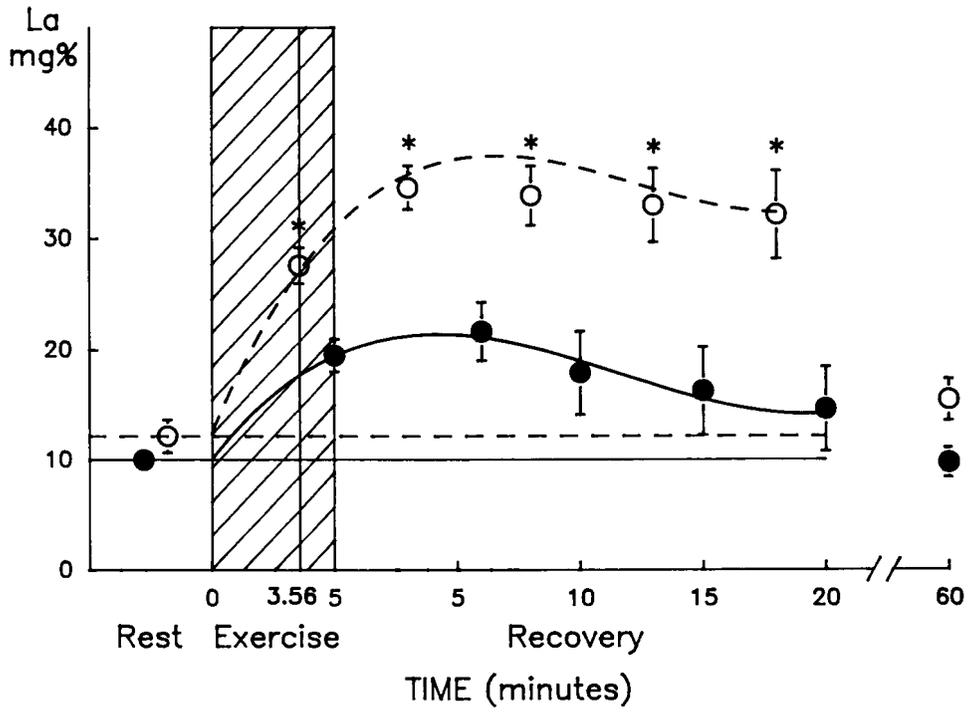

Figure 3. Average ±SD for venous blood lactic acid plotted as a function of rest, exercise, and recovery from upright exercise at 75 W. *Significant difference ($P < 0.05$) from control.

tibial, and dorsalis pedis, respectively) did have reduced BP ratios. The femoral and popliteal systolic BP ratios in all subjects were above 1.0, indicating that large vessel resting blood flow to the quadriceps muscle group was normal. These values were high enough that it is unlikely that these ratios would drop below normal during the modest level of exercise utilized in this study. Despite the absence of reduced pressure ratios to this muscle, the blood flow in the muscle during exercise was reduced ~50%, and oxidative metabolism was reduced.

The reduced BP ratios in the lower limb would suggest the presence of large vessel disease; however, in the upper leg this cannot be concluded from the present data. It has been recently reported (29) that diabetics can have normal systolic BP ratios even though they have medical calcification, as collateral blood flow to the muscle (particularly to the quadriceps in this study) could be increased. In the present study, the upper limb pressure ratios were normal while the blood flow was reduced. It appears that there is a generalized reduction in the microcirculation throughout the body that could be independent (quadriceps) or additive (tibialis anterior) with a decrease in large vessel blood flow.

The diabetic group's reduced MBF may be attributed to maladjustment of the peripheral circulation. Thickening of the intimal layer of arterioles, often seen in long-term diabetics, could limit the ability of the affected vessels to dilate (3, 28).

To the extent that higher total catecholamines are indicative of enhanced sympathetic tone, the diabetic group's higher levels raise the possibility of increased vascular resistance limiting MBF (2). The possibility of enhanced sympathetic tone is also supported by the observation that BP was elevated in the diabetic group when compared with the control group, especially in the supine position, which has previously been shown for epinephrine infusion (30). The elevated catecholamines may have also contributed to the greater La levels observed in the diabetics. It has been demonstrated that when epinephrine is infused into contracting skeletal muscle, both arterial and venous La concentrations rise (30). Given the amount of time necessary to reoxidize La in our study population (Fig. 3), it is understandable that many patients with PVD have to rest for long periods of time between exercises (20–22).

Both peripheral and automatic neuropathic changes often accompany the vascular degeneration in diabetics. The higher catecholamine concentrations in the diabetics were unanticipated, inasmuch as most studies of long-term diabetics indicate decreased catecholamine levels when compared with nondiabetics (2, 31, 35). However, the subjects' exercise load was considerably more stressful for the diabetic group. Catecholamines have been shown to rise more sharply during "heavy" exercise than during mild or moderate exercise (34, 36), and the elevated BP would suggest greater vasoconstriction even during exercise. This po-

tential role of vasoconstriction was particularly evident in the supine position.

Finally, MBF may have been reduced secondary to the greater amount of relative effort this work may have represented for the diabetics. MBF increases linearly with exertion until 40 to 70% $\dot{V}O_2$max (14). Thereafter, the force of muscular contraction itself results in vessel occlusion, which results in decreased flow (14, 20). Although the diabetics apparently achieved their peak $\dot{V}O_2$, the observed HR was well below maximal and less than 20 beats higher than that for the normals group. This would not support any difference between diabetics and controls being related to physical fitness or relative workload and suggests a local microcirculatory limitation to $\dot{V}O_2$ and exercise.

Significant delivery and utilization of oxygen at the tissue level is essential to exercise performance. The control group's $t_{1/2}$ $\dot{V}O_2$-on and $\dot{V}O_2$ss values are consistent with previously reported values for this work intensity (20–22). The 33% longer $t_{1/2}$ $\dot{V}O_2$-on during supine exercise is also in agreement with data in the literature (20–22). The diabetics' lower $\dot{V}O_2$ at all exercise times when combined with increased blood La indicate inadequacies of their oxygen transport system. As anticipated, longer half-times were accompanied by greater O_2 deficits and higher transient La. Lower submaximal $\dot{V}O_2$ss values have been previously reported in long-term diabetics, but this was in patients with autonomic neuropathy (2). If the muscle La levels of the diabetics were not elevated and they could have continued to exercise, they would have reached the same $\dot{V}O_2$ss levels as the control subjects in ~6 to 7 min of exercise.

It would be convenient to ascribe the diabetic group's altered O_2 kinetics to decreased availability resulting from their abnormal MBF. However, other factors must also be considered: (i) elevated Hb_{A1C} levels could compromise O_2 unloading (3, 37); (ii) poorly controlled diabetics exhibit decreased red blood cell deformability and increased blood viscosity (29, 37); (iii) lower capillary/muscle fiber ratios could affect diffusion of O_2 (38, 39); and/or (iv) finally, there could be a decrease in slow twitch muscle fibers or the loss of their oxidative potential (40).

Clinical Observations

None of the subjects in the present study has been diagnosed as having PVD, and only one of the subjects studied had diminished femoral and popliteal pulses. The subjects exhibited varying degrees of secondary complications of diabetes mellitus (e.g., decreased vibratory sense perception, background retinopathy, mild hypertension), but none had been diagnosed as having neuropathy, proliferative retinopathy, myopathy, or autonomic nervous system dysfunction. None of the subjects was reported by the hospital's diabetes clinic as having cardiac or peripheral vascular disease. Clinically, the diabetics were classified as mildly hypertensive; however their BP values at rest in both the erect and supine positions were not significantly different from those of age-matched control subjects. None of the subjects in the control group was taking any medications. Only three of the diabetics were on chronic medications other than for diabetes, and this was limited to a diuretic. It is alarming that the diabetic subjects in the present study have extensive degeneration of the peripheral circulation without clinical detection or the presence of reported symptoms. Due to the presence of smoking and the potential for risk factors in our subjects that could influence our data, we cannot attribute the reduced MBF to diabetes per se. Furthermore, we cannot rule out asymptomatic vascular disease.

Conclusions

Reduction in MBF in the diabetic group resulted in compromised O_2 delivery, increased oxygen extraction and greater contribution of anaerobic energy metabolism during exercise, and diminished ability to remove lactate during recovery. The reduced exercise MBF in the TA is a consequence of impaired microvascular and large vessel flow. The compromised MBF in the VL, a larger, more central muscle without reduced large vessel blood flow, is of even greater significance. There is no doubt that there is widespread microvascular disease in this type of patient. The present study clearly indicates that selected patients or muscle groups in individual patients can have reduced exercise microvascular flow without reduced large vessel flow (at least at rest) and emphasizes the potential importance of microvascular flow in diabetes.

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