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Functional Microcirculatory Impairment: A Possible Source of Reduced Skin Oxygen Tension in Human Diabetes Mellitus

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Lower extremity transcutaneous oxygen tension (TcPO2) is used as a diagnostic and prognostic indicator of tissue perfusion and is reduced in diabetes mellitus. Since cardiac output, leg blood flow and microvascular perfusion each can singly or jointly effect tissue oxygenation, the relative importance of macro- vs microvascular factors has not been resolved. To clarify this issue we compared TcPO2 levels in diabetic and nondiabetic subjects in whom cardiac output, leg pulsatile blood flow, and microcirculatory perfusion parameters were noninvasively measured. In 60 diabetic and 60 nondiabetic subjects the following measurements were done on both legs during a single session evaluation: foot dorsum TcPO2 at 45°, skin microvascular perfusion reserve (MVR) in response to local thermal provocation from 35 to 45° using laser-Doppler, ankle-brachial index using Doppler ultrasound (ABI), and pulsatile leg blood flow using magnetic resonance flowmetry; cardiac output was determined using transthoracic bioimpedance. The diabetic and nondiabetic groups were determined to have nonsignificant differences (mean ± SEM, DM vs NODM) with respect to age (63.3 ± 1.1 vs 60.1 ± 1.5 years), cardiac output (5.5 ± 0.2 vs 5.5 ± 0.2 l/min), leg blood flow (1.6 ± 0.05 vs 1.7 ± 0.06 ml/min/100 cc) and ABI. Although macrocirculatory values were equivalent, microvascular function indicators were significantly reduced in the diabetic group: TcPO2 (51.9 ± 1.4 vs 62.9 ± 1.3 mmHg); MVR (76.7 ± 1.5 vs 84.9 ± 0.9%) and were correlated only in diabetics ($r^2 = 0.48$, $P < 0.001$). The findings suggest a primary linkage between the diabetic TcPO2 deficit and the microcirculatory submaximal vasodilatory response, with little if any role of macrocirculatory factors.

INTRODUCTION

Transcutaneous oxygen tension (TcPO2) measured on the lower extremity of patients with or without diabetes mellitus (DM) has been used to provide diagnostic and prognostic information in several clinically important areas (Oh *et al.,* 1987; Rooke and Osmundson, 1990; Fronek, 1991; Bacharach *et al.,* 1992; Scheffler and Rieger, 1992; Mayrovitz, 1994). However, in patients with DM, reduced levels of TcPO2 have been reported to be present even in young individuals thought to be free of other hemodynamically compromising factors (Breuer *et al.,* 1988; Railton *et al.,* 1983; Uccioli *et al.,* 1994) but the source of the diabetes associated TcPO2 deficit has been illusive to pin down. Since TcPO2 measurements at least in part reflect local microvascular perfusion status, reductions might be explainable on the basis of one or more of the microvascular abnormalities present in some patients with DM (Flynn

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and Tooke, 1990). However, the presence and impact of possible undetected macrocirculatory impairments complicates interpretation. Two potential confounding hemodynamic factors which need to be considered but are rarely done when comparing DM with NODM patients in this regard are possible differences in lower extremity blood flow and cardiac output. Since either or both of these could impact on the primary variable being studied, inadequate attention to these aspects may be among the reasons that the dominant source of the reported TcPO2 deficit in DM has remained ambiguous and therefore unclarified. The purpose of the present study was to evaluate both of these macrocirculatory aspects as well as limb microcirculatory functional parameters in the same patient using noninvasive, quantitative methods to thereby contrast the relative impact of micro- vs macrovascular parameter values on TcPO2 in patients with and without DM.

METHODS

Cardiovascular Parameters

A total of 120 subjects was evaluated after signing an Institutional Review Board (IRB)-approved informed consent. Prior to measuring leg blood flow using the method of magnetic resonance flowmetry (described subsequently) and immediately after the leg flow measurements, cardiac stroke volume (SV) assessments were done on each subject using the method of transthoracic bioimpedance cardiography (Kubicek *et al.,* 1966; Mayrovitz and Larsen, 1996) using band electrodes in the tetrapolar configuration (Kubicek *et al.,* 1974) with the subject supine (Patterson and Raza, 1991); the average of the values of SV (Minnesota Impedance Cardiograph, model 304) obtained before and after leg flow measurements were used to characterize resting systemic parameters. Mean blood pressure (MBP) was obtained with an oscillographic automated system (DYNAMAP). SV multiplied by measured heart rate (HR) yielded cardiac output (CO) and SV and CO were also expressed as the body surface indices SVI and CI by dividing by body surface area. Total systemic vascular resistance (TSR) was approximated as the ratio of MBP to CO. The length parameter used in the stroke volume calculation was the mean of the anterior and posterior distance between sensing band electrodes (Kubicek *et al.,* 1974). There is an extensive literature showing the correlation of bioimpedance values with a variety of other methods for cardiac output monitoring (Patterson and Raza, 1991; Fuller, 1992).

Leg Blood Flow Measurement

Both legs were evaluated with noninvasive tests to characterize several leg macrocirculatory features. The test sequence was standardized for all subjects as follows. Following a 15-min supine acclimation interval in a room with independent temperature control set at 74°F, pulsatile leg blood flow (Q, ml/min) was measured bilaterally at five below knee sites using the method of magnetic resonance flowmetry (Metriflow AFM100, Milwaukee). Principles of operation, validation studies and applications of this method have been reported (Battocletti, 1986; Kerr *et al.,* 1991; Mayrovitz and Larsen, 1994). The flow measuring sites were standardized for all subjects by first measuring the distance (L) between the lateral malleolus and the tibial tubercle. Five leg sites between the malleolus and knee were marked at locations equal to 10, 25,

50, 75, and 90% of the malleolus-tubercle distance with the zero reference point at the malleolus. Thus flow measured at the 90% site (e.g., Q90) represents the approximate pulsatile flow perfusing the lower limb. The raw pulsatile blood flow data at each site was recorded for 30 beats and ensemble averaged to yield an average flow value (ml/min) for each site. Leg circumference measurements at each site were used together with an algorithm incorporated in the AFM100 system to calculate blood perfusion (Q′) expressed as ml/min/100 cc of distal tissue volume. For each site, a derived quantity known as arterial status index (ASI) was calculated as the ratio of the perfusion pulse 50% amplitude divided by the corresponding pulse width normalized to the cardiac period. Since the ASI value is sensitive to both the amplitude and relative width of the flow pulse, it has been reported to better discriminate between patients with and without lower extremity arterial disease than perfusion values alone with threshold values for peripheral arterial disease of <4.5 useful for detecting arterial disease in patients with calcified vessels (Bendick *et al.*, 1992). The leg average of all measured sites was used to characterize the ASI of each leg. Brachial and ankle systolic blood pressures were measured at the end of the leg blood flow determinations using Doppler ultrasound from which the ankle/brachial index (ABI) was calculated.

Microvascular Evaluations

With the subject remaining supine, TcPO2 at a standardized site on the foot dorsum was measured using a probe temperature setting of 45° (Novametrix, model 811). The probe was left in place for a duration of 20 min and the steady state value obtained at the end of this interval was recorded. At a dorsum site adjacent to the TcPO2 probe, skin microvascular blood perfusion was measured using the method of laser-Doppler, (Vasamedics, Model BPM2). The laser-Doppler probe was inserted in the center-hole of a 19-mm diameter cylindrical thermal control module and the combined probe-heater secured to the skin with double-sided tape. The initial temperature setting was 35° thereby providing a standardized baseline local environment. After securing to the skin, a 4-min delay in data acquisition was observed to allow for transient effects associated with probe placement. Continuous laser-Doppler data was obtained at the 35° baseline interval for 4 min after which the temperature setting was rapidly increased to 45° while continuously monitoring the thermal response. All laser-Doppler data was displayed on a chart recorder and simultaneously acquired by a computer for postprocessing procedures. This laser-Doppler thermal provocation and measurement cycle was also done on a skin site on the anterior leg, 2 cm distal to the tibial tubercle. Skin temperature of the dorsum was measured at three standardized sites prior to thermal heating and the average of these used to characterize dorsum skin temperature.

Subjects

The total study population consisted of 120 subjects; 60 with DM (40 insulin dependent, 42 male) and 60 free of diabetes (NODM, 37 male). All DM subjects had DM >5 years with a mean $\pm$ SEM duration of 14.9 ± 1.2 years. Ages of DM and NODM were 63.3 ± 1.1 and 60.1 ± 1.5 and did not significantly differ. Of the DM subjects, 36 had peripheral neuropathy (DMPN+, 26 male) as judged by history and neurosensory testing which included both vibration thresholds and standard fiber testing, 24 subjects had no detectible symptoms or signs of neuropathy (DMPN−, 16 male). No difference in age was present between DMPN+ and DMPN− (62.9 vs

63.9), but duration of diabetes was significantly greater in DMPN+ (17.4 vs 11.0 years, $P < 0.001$). Presence of peripheral arterial disease (PAD) was judged on the basis of history, symptoms, and on noninvasive diagnostic test results. Thirty-five DM subjects (70 legs) and 34 NODM subjects (68 legs) were judged not to have PAD.

ANALYSIS

Parameters

Quantitative parameters used to compare limb macrocirculatory differences were ABI, below-knee blood perfusion (Q′), and limb average ASI. The primary parameters used to compare microcirculatory differences were foot dorsum TcPO2 and the laser-Doppler perfusion response to thermal provocation. One of the most functionally useful is termed microvascular reserve (MVR); a computed quantity which is an index of the relative microcirculatory perfusion reserve (Mayrovitz, 1994). It is calculated using the ratio of the average baseline perfusion (q35) to the perfusion achievable at 45° (q45) according to the equation $MVR(\%) = [1 - (q35/q45)] * 100$. MVR lies between 0 and 100%, with smaller values indicating less reserve.

Group Comparisons

To determine overall differences, DM vs NODM subjects were compared with respect to cardiovascular, limb macrovascular, and limb microvascular parameters. Subsets of the limb groupings were then used: to determine the impact of PAD on the micro–macro differences, subjects free of PAD (DM vs NODM) were compared; to determine the impact of neuropathy on the microvascular differences within DM subjects, DMPN+ vs DMPN− comparisons were used. In all cases statistical testing was based on the nonparametric Mann–Whitney procedure with a level of $P < 0.05$ taken as significant.

RESULTS

Patients with and without Diabetes

Systemic parameters. Table 1 summarizes and compares pertinent cardiovascular parameters for all DM and NODM subjects. With respect to cardiac output and cardiac index, the DM group as compared with NODM are observed to be similar with no significant differences between groups. The near identical cardiac outputs of the two groups is however associated with oppositely directed differences in heart rate (higher in DM) and stroke volume (lower in DM). The DM group also had significantly higher systolic and mean blood pressures.

Leg macrovascular parameters. Overall comparisons of key limb macrovascular and microvascular parameters are shown in Table 2. With respect to ABI and leg blood perfusion, no significant differences between DM and NODM subjects were detected. However, these group comparisons revealed that the DM subjects had a lower mean ASI value (5.29 ± 0.23 vs 6.78 ± 0.28, $P < 0.001$) suggestive of a significant macrovascular differential. Because of the unknown impact of this differential on the microcirculatory parameters, a subset of NODM patients in whom ASI values were restricted ($ASI \leqslant 9.0$) was included, results of which are shown in the

TABLE 1
Systemic Cardiovascular Parameters

Parameters	Subject group		*P*-value
	NODM	DM	
N	60	60	
SV (ml)	90.2 (4.6)	77.1 (3.2)	0.022
SVI (ml/m^2)	49.0 (2.4)	39.8 (1.7)	0.003
CO (1/min)	5.5 (0.2)	5.5 (0.2)	NS
CI (l/min/m^2)	3.0 (0.1)	2.9 (0.1)	NS
HR (min^{-1})	62.5 (1.3)	73.2 (1.5)	0.001
SBP (mmHg)	134.4 (2.9)	152.3 (3.1)	0.001
DBP (mmHg)	76.4 (1.9)	80.8 (1.3)	NS
MBP (mmHg)	96.2 (2.0)	105.3 (1.7)	0.001

Note. Values are mean and SEM. SV and SVI are cardiac stroke volume and index; CO and CI are cardiac output and index; HR is heart rate; SBP, DBP, and MBP are systolic, diastolic, and mean blood pressure. *N*, number of subjects; NS, no significant difference, NODM vs DM.

far right column of Table 2. This restriction eliminated 30 legs from the total NODM group and resulted in a NODM group which was matched in all measured macrovascular parameters with the DM group with one exception. The blood flow at the midcalf (Q50) was actually now greater in the DM group.

Microvascular parameters. Corresponding microcirculatory contrasts between DM and NODM groups reveal significant differences in each microvascular parameter whether or not comparisons are made with the full NODM group or the restricted NODM subset. Full-group comparisons show each DM parameter value to be signifi-

TABLE 2
Limb Macrocirculatory and Microcirculatory Parameters

Parameters	All subjects			NODM (ASI $\leqslant$ 9.0)	
	NODM	P1	DM	P2	NODM
n (Legs)	120		120		90
Pank (mmHg)	132.5 (5.3)	NS	134.5 (4.5)	NS	128.4 (5.9)
ABI (mmHg/mmHg)	0.99 (0.02)	NS	0.93 (0.02)	NS	0.93 (0.03)
ASI (ml/min/100cc)	6.78 (0.28)	0.001	5.29 (0.23)	NS	5.42 (0.23)
Q_{50} (ml/min)	33.4 (1.4)	NS	34.4 (1.3)	0.001	28.2 (1.2)
Q′ (ml/min/100cc)	1.70 (0.06)	NS	1.60 (0.05)	NS	1.49 (0.05)
q35 (a.u.)	3.7 (0.2)	0.01	4.6 (0.2)	0.03	3.8 (0.3)
q45 (a.u.)	30.0 (2.0)	0.02	24.5 (1.2)	0.03	29.8 (2.4)
Temp (°C)	28.2 (0.1)	0.001	29.7 (0.2)	0.001	27.9 (0.1)
MVR (%)	84.9 (0.9)	0.001	76.7 (1.5)	0.001	83.8 (1.1)
TcPO2 (mmHg)	62.9 (1.3)	0.001	51.9 (1.4)	0.001	60.4 (1.5)

Note. Values are mean and SEM. P1, *P* value, DM vs NODM all subjects; P2, *P* value DM vs NODM restricted to ASI $\leqslant$ 9.0; NS, not significant. Microcirculatory parameters measured on foot dorsum. Pank, systolic ankle pressure.

cantly lower: TcPO2 (51.9 ± 1.4 vs 62.9 ± 1.3 mmHg, $P < 0.001$; Dorsum MVR, 76.7 ± 1.5 vs 84.9 ± 0.9%, $P < 0.001$; Knee MVR, 80.7 ± 1.3 vs 84.7 ± 0.9%, $P < 0.01$). Interestingly, baseline resting laser-Doppler perfusion levels (in arbitrary units, a.u.) were slightly but significantly higher in the DM subjects at the dorsum (4.6 ± 0.2 vs 3.7 ± 0.2, $P < 0.01$ but not at the knee (5.0 ± 0.3 vs 5.4 ± 0.4). Contrastingly, perfusion values at 45° were significantly less at the dorsum (24.5 ± 1.2 vs 30.0 ± 2.0, $P < 0.01$) and knee (28.8 ± 1.3 vs 38.3 ± 2.0, $P < 0.001$). Similar differences are seen with the completely matched groupings. These seemingly parallel reductions in both microcirculatory parameters prompted a test for possible correlations between dorsum TcPO2 and MVR and correlation analyses were carried out separately for DM and NODM groups. A significant correlation was indeed found for DM subjects ($r^2 = 0.48$, $P < 0.001$) which remained even when jointly controlling for both subject age and leg arterial status ($r = 0.46$, $P < 0.001$); the corresponding correlation in NODM subjects was not significant ($r^2 = 0.11$, $P = 0.23$).

Patients free of PAD. Exclusion from analysis of subjects with PAD allows for comparisons between DM and NODM groups in which possible confounding effects of superimposed macrovascular factors are largely eliminated. Macrovascular and microvascular results for these subsets are respectively shown in Figs. 1A and 1B. As shown in Fig. 1A, ABI and leg averaged blood flow values are similar between groups but as shown in Fig. 1B, TcPO2 levels for DM subjects compared with NODM (55.7 ± 1.6 vs 62.2 ± 1.7 mmHg) and MVR (80.9 ± 1.2 vs 86.8 ± 1.1%) are significantly reduced.

Patients with and without neuropathy. No significant impact of neuropathy on any macro- or microparameter was detected as assessed by comparisons of DMPN+ vs DMPN− as shown in Fig. 2.

Insulin dependent vs noninsulin dependent. With the exception of duration of diabetes being greater in the IDDM group (16.8 ± 1.0 vs 11.6 ± 1.5 years) no other significant difference in any macro- or microparameter was detected (data not shown).

Patients with and without PAD. As expected, subjects with PAD (whether DM or NODM) are shown to have significantly reduced ABI and leg perfusion values as compared with subjects free of PAD (Fig. 3). However, as shown by the microcirculatory assessment results (Fig. 3), it is only in the DM subjects that the superimposed PAD results in a TcPO2 level significantly less than in subjects free of PAD.

DISCUSSION

Reduced TcPO2 as a Feature of Diabetes Mellitus

Reduced levels of transcutaneous oxygen in patients with diabetes mellitus have been reported by a number of investigators. Early evidence was given by Railton and coworkers (Railton *et al.*, 1983) who describe a reduced foot dorsum TcPO2 in young type-I diabetic patients (mean age 28 years) who were apparently free of clinical signs of peripheral arterial disease and neuropathy. Breuer and coworkers (Breuer *et al.*, 1988) also focusing on young type I diabetic patients (mean age, 24 years) without apparent clinical signs of peripheral arterial disease, found TcPO2 values measured at the supramalleolar area to be significantly less than in nondiabetic controls; the mean level reported for diabetics was 55.8 mmHg which is the same as the value

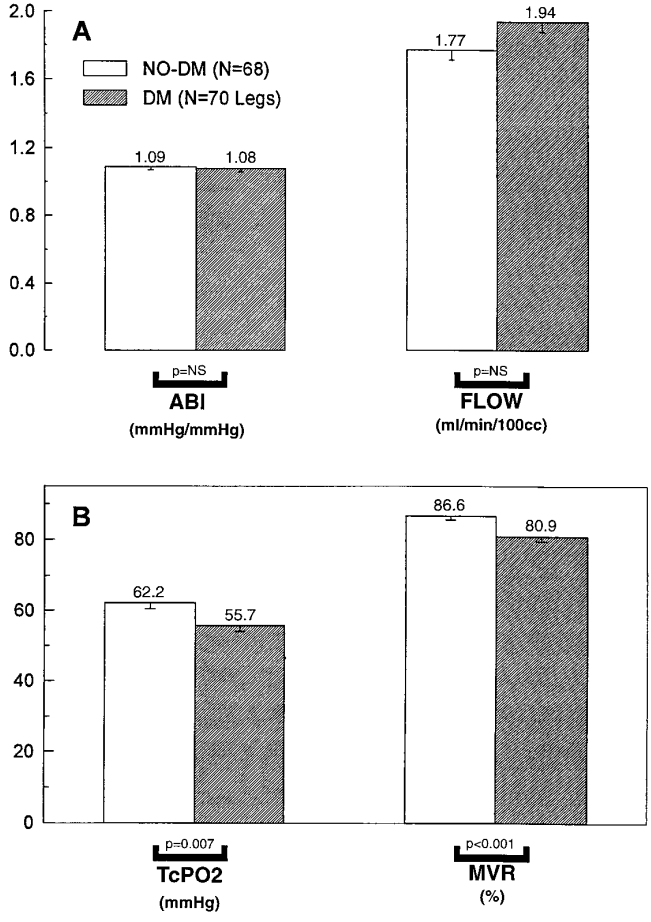

FIG. 1. Leg macrovascular and microvascular comparisons for subjects free of peripheral arterial disease. Although no leg macrovascular differences are present (A) there are significant decreases in the microvascular parameters of the DM (diabetic) group as shown in (B).

herein obtained at the dorsum for limbs free of PAD. However, the present age distribution was considerably older, not restricted to only Type I diabetes with control TcPO2 values from our nondiabetic group less (62.2 mmHg) than they reported (66.3 mmHg). This (slightly) lower value may reflect the age difference in the two nondiabetic subject groups and/or differences attributable to the TcPO2 instrumentation used. Uccioli and coworkers (Uccioli *et al.*, 1994) selected for study noninsulin diabetic patients in whom ankle/brachial pressures were confined to a range of 0.9 to 1.1, thereby largely excluding patients with overt peripheral arterial disease. Comparisons among these middle-age (51–56 years) nondiabetic controls and NIDDM patients with and without autonomic neuropathy showed a reduced dorsum TcPO2 in diabetic patients but no influence of the neuropathy. These, other reports, and the present results clearly demonstrate the presence of TcPO2 reduction associated with both Types I and II diabetes mellitus.

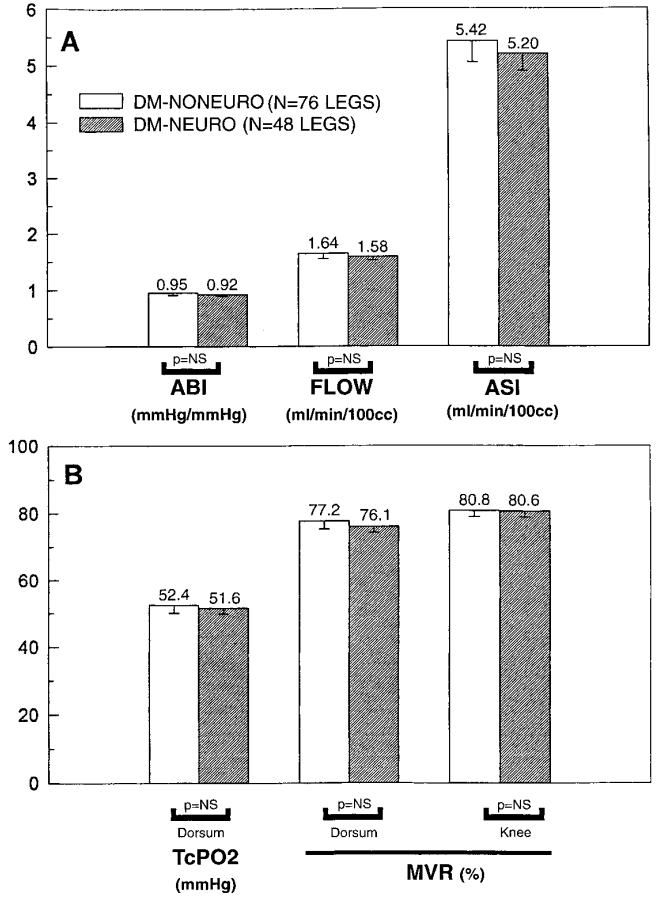

FIG. 2. Absence of effect of peripheral neuropathy on macrovascular and microvascular parameters. In diabetic patients without neuropathy (DM-NONEURO) or with (DM-NEURO) no significant differences in macrovascular or microvascular parameters was present.

Macro vs Microcirculatory Potential Sources of TcPO2 Deficit

The central issue of the present study was to clarify the relative roles of limb macro- and microcirculatory parameters as possible sources of the TcPO2 deficit. Comparisons between diabetic and nondiabetic patients having equivalent objectively measured cardiac outputs and limb macrocirculatory parameters reveal that the diabetic patient has TcPO2 values which, even under these ''matched'' conditions, are significantly less than those individuals free of diabetes. The fact that a TcPO2 deficit is present in the total unselected diabetic grouping and in diabetic subjects free of peripheral arterial disease suggests that the predominant source of the TcPO2 reduction is not macrocirculatory in origin. This suggestion is reinforced by the observation that among patients with peripheral arterial disease, it is only the diabetic patients in whom a significant decrease in TcPO2 is uncovered.

The findings with regard to the laser-Doppler derived differences in microvascular

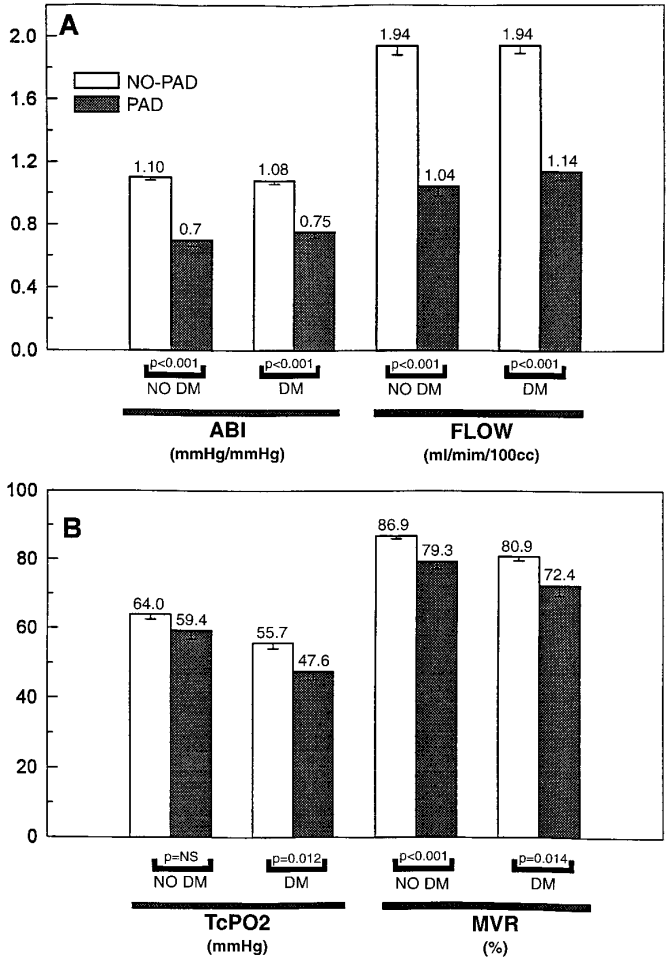

FIG. 3. Macrovascular and microvascular comparisons between patients with and without peripheral arterial disease. Presence of peripheral arterial disease (PAD) was associated with significantly reduced macrovascular parameters in patients without diabetes (NO DM) and with diabetes (DM) as shown in part (A). Both microvascular parameters were significantly reduced only in patients with DM as shown in part (B).

reserve subsequent to local thermal provocation are consistent with a linkage between the TcPO2 and microcirculatory perfusion–response deficits. The significant correlation between these two microcirculatory functional indices in subjects with diabetes, independent of age or arterial status, tends to support this linkage concept. The absence of microcirculatory differences between diabetic subjects with and without peripheral neuropathy suggests that neuropathy per se is not a dominant factor with regard to the overall TcPO2 and MVR reduction in the diabetic group. This conclusion is consistent with the results obtained in diabetic patients with autonomic neuropathy (Uccioli *et al.*, 1994) in whom the reported TcPO2 deficit did not differ from a matched group of diabetic patients without neuropathy.

The findings with regard to combined diabetes and peripheral arterial disease show

an associated greater decrease in TcPO2 than in PAD patients free of diabetes; even though both groups had similar leg macrocirculatory indices. Further, as compared with subjects without PAD, a lower mean TcPO2 was noted in the diabetes-free group, but only in patients with diabetes was a significant reduction detected. Contrastingly, MVR was significantly reduced in both diabetic and nondiabetic PAD patients. The TcPO2 and MVR measurements thus appear to provide somewhat different information as to microcirculatory function.

Comparison of Microcirculatory Indicators

The MVR parameter is primarily an index of local microvascular relative vasodilatory capacity. Low values of MVR could occur if baseline blood perfusion was elevated or if maximal thermally induced blood perfusion was diminished. In the present instance the primary factor was a decreased maximal response in DM subjects. This is consistent with results from young IDDM in whom impairment of lower extremity skin hyperemic responses both with long duration heating (Rayman *et al.,* 1986) and shorter duration (Rendell *et al.,* 1989) thermal provocations have been reported. These previous findings, based on the maximum laser-Doppler value (a.u.), are thus confirmed and extended in several ways. Using a bounded (0–100%), nondimensional functional parameter, it is shown that the diabetes-related deficit is not restricted to IDDM, is less in diabetic limbs as compared with nondiabetic limbs with equivalent (normal) limb macrovascular parameters, is further reduced by the presence of PAD whether diabetic or nondiabetic, and in diabetics is not influenced by the presence of peripheral neuropathy. The corresponding TcPO2 features, with the exception of the nonsignificant decrease in the NODM PAD subjects, is in every other respect similar.

Possible TcPO2-MVR Linkage

The present findings clearly suggest that the DM-NODM TcPO2 differential at least in part may be a reflection of the diminished microvascular reserve capacity (MVR) related to the inability of the DM hyperemic flow to reach levels equivalent to those reached in NODM subjects. Since in the present design both TcPO2 and laser-Doppler probes were set to the same temperature we have at least the possibility of making some inferences on this issue. Regarding the temperature per se, it is well established that measured values of TcPO2 are strongly dependent on the heating temperature—decreasing with lower temperatures. The TcPO2-temperature dependence is in part due to (reversible) skin changes which increase the skin oxygen diffusion which, at a temperature of about 42°, increases by almost a factor of 10 above unheated skin. Under these conditions the measured TcPO2 depends on several factors including the intravascular oxygen tension in the microvascular compartment, the net blood perfusion in the vicinity of the oxygen measuring electrode, and skin oxygen consumption. It has previously been shown (Wyss *et al.,* 1981) that the TcPO2–blood perfusion relationship is nonlinear resulting in a reduction in measured TcPO2 that is increasingly steep with decreasing arteriovenous perfusion pressure. Similar results were shown using laser-Doppler measurements. The important question is how much would the maximal blood perfusion need to be reduced to account for the observed TcPO2 reduction in the present study? There is at present insufficient data to fully answer, but one may provide an estimate based on a conservative assumption of linearity between perfusion and TcPO2. The overall ratio of mean hyperemic perfusion in

diabetics vs nondiabetics (DM/NODM) herein determined was 24.5/30.0 = 0.82; multiplying this ratio by the measured NODM mean TcPO2 (62.9 mmHg) yields 51.4 mmHg, a value which is remarkably close to the measured mean TcPO2 in the diabetic subject group (51.9 mmHg). Though the result of this computation may simply be fortuitous it is not inconsistent with the notion that the TcPO2 deficit is a direct effect of a diabetes associated impairment in microvascular perfusion reserve capacity. Though this hypothesis remains to be prospectively tested, the present overall findings clearly demonstrate that the dominant source of the diabetes TcPO2 deficit is not macrocirculatory in origin and strongly suggests an important microcirculatory perfusion linkage.

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