The influence of diabetes and lower limb arterial disease on cutaneous foot perfusion

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Objective: **Peripheral arterial occlusive disease and peripheral neuropathy are major risk factors in diabetic foot disease. We evaluated the relative influences of noncritical lower limb arterial disease and peripheral neuropathy on cutaneous foot perfusion in diabetes.**

Method: **Toe-brachial pressure indices, transcutaneous oxygen, and carbon dioxide tensions at foot and chest sites were measured in individuals with diabetes, with or without detectable peripheral neuropathy and with or without significant arterial disease on color duplex imaging. Subjects without diabetes, with and without arterial disease, were used as controls.**

Results: **A total of 130 limbs were studied during an 8-month period. Toe-brachial pressure indices reflected the presence of arterial disease in all groups. Foot transcutaneous oxygen values were reduced in diabetes and correlated with chest transcutaneous oxygen values. Low foot transcutaneous oxygen with elevated transcutaneous carbon dioxide values were only demonstrated in individuals with diabetes, arterial disease, and peripheral neuropathy. Toe-brachial pressure indices demonstrated a positive correlation with foot transcutaneous oxygen values, but values >1.2 demonstrated a negative correlation.**

Conclusions: **We demonstrated two influences on cutaneous foot perfusion in diabetes: (1) a global microcirculatory dysfunction, reflected in low chest and foot transcutaneous oxygen values, and (2) macrovascular disease as indicated by reduced toe-brachial pressure indices and foot transcutaneous oxygen values. Further, the results demonstrated that in diabetic individuals without critical limb ischemia, impaired foot perfusion secondary to arterial disease is amplified significantly by coexisting microcirculatory disease. (J Vasc Surg 2006;44:770-5.)**

Patients with diabetes are prone to foot ulceration and frequently fail to respond to treatments despite optimization of the healing environment. Microvascular dysfunction has been identified in diabetes, but its influence on cutaneous perfusion in the presence of clinically detectable peripheral neuropathy and peripheral arterial occlusive disease (PAOD) is unclear.[1] We evaluated changes in foot perfusion associated with diabetes, detectable peripheral neuropathy, and PAOD. The presence or absence of PAOD was established by color duplex imaging, not by clinical assessment. Most individuals with PAOD had claudication, but several had limited mobility owing to other factors.

No toe pressures were <30 mm Hg. Foot perfusion was analyzed in individuals with and without diabetes using toe-brachial pressure indices (TBI), transcutaneous oxygen tension ($TcPO_2$) and transcutaneous carbon dioxide ($TcPCO_2$). TBI is a method widely used for detecting lower limb PAOD, particularly in individuals with diabetes, whilst $TcPO_2$ and $TcPCO_2$ are established as indicators of local cutaneous perfusion.[2,3] Individuals with symptoms or signs of critical ischemia or active foot disease were excluded to facilitate analysis of the relative influences of microvascular and macrovascular disease on cutaneous perfusion.

Exposure of the tests to a representative population required that subjects with both diabetes types 1 and 2 and subjects without diabetes be recruited from outpatient clinics and the community. The study was given ethical approval by the local ethics committee, and all individuals included in this study gave informed written consent. Financial support for this project was provided by departmental funds.

PATIENTS AND METHODS

No individuals had active foot disease, rest pain, or signs suggestive of lower limb critical ischemia. Individuals without diabetes and with and without peripheral vascular disease were the controls. Based on pragmatic factors related to feasibility of recruitment, study duration, and participant burden, we estimated that an analysis of 120 limbs would be required to facilitate valid comparisons of the effects of diabetes and PAOD on foot perfusion. Subjects with diabetes were selected consecutively, and control subjects were selected to match for age and body mass index (BMI).

Patients with diabetes mellitus were confirmed as having diabetes from their medical records. Patients with types 1 and 2 diabetes were included. Subjects were stratified according to the presence or absence of diabetes, peripheral vascular disease on color duplex imaging, and peripheral neuropathy. The nondiabetic control limbs were divided into those with (V) and without (C) arterial disease. The diabetes groups were divided into groups based on the presence (DN) or absence (D) of peripheral neuropathy.

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These two groups were then subdivided based on the presence of arterial disease (DNV, DV).

Neuropathy was tested with a 10-gram monofilament, vibration using a 128-Hz tuning fork, and proprioception at the first metatarsophalangeal joint, according to the International Consensus on the Diabetic Foot guidelines. Loss of sensation of any modality was indicative of peripheral neuropathy.

The study was performed during a period of 8 months. All tests were performed at one visit. All subjects had arterial color duplex imaging performed at the end of each attendance. Capillary blood sugar measurements were taken from all individuals at commencement, including control individuals to exclude diabetes. The duration of each subject attendance, together with unreliability of ankle pressure and laser Doppler in our hands precluded their use as markers of foot perfusion in this study.

Subject exclusion criteria included: age <40 years; cigarette smokers ≤3 months of the study date to avoid the vasoactive effects of nicotine and reduce the likelihood of coughing; those with other causes of peripheral neuropathy, including spinal conditions, history of alcohol dependence, pernicious anemia, and thyroid disease; a history of reconstructive vascular surgery, other causes of peripheral vascular disease, including Buerger's disease, vasculitis; those currently involved in vascular interventions; the presence of pyrexia or foot infection; and significant cardiorespiratory or renal disease determined by medication, blood tests, and clinical assessment.

All hemoglobin values were no lower than 11g/dL. Levels of serum creatinine in all patients were <0.2 mmol/L, with two exceptions whose levels were about 0.3 mmol/L.

On the morning of the study, all antihypertensive and oral hypoglycemic medication was omitted, and the insulin administered was reduced by 50% to reduce the potential vasoactive effects of these agents. The laboratory room temperature was maintained between 24°C and 25°C. Individuals were rested reclining at approximately 20° to the horizontal and acclimatized for a minimum of 20 minutes before commencing the study. Foot skin temperatures were measured until a steady state was achieved.

Toe pressures were measured with the photoplethysmographic (PPG) method, by using an infrared sensor placed on the hallux, (Dopplex assist, Huntleigh Healthcare, Cardiff, UK). Toe pressures were taken at 5-minute intervals on three occasions and a mean calculated.

The $TcPO_2$ and $TcPCO_2$ levels were measured using a MicroGas 7650 rapid (Kontron Instruments, Milton Keynes, UK). The sensor used for measuring P_{CO_2} and P_{CO_2} was a Combi·M Sensor 82 (Linde Medical Sensors AG, Basel, Switzerland) containing a pH/Clarke silver electrode housed with a heating element, with the temperature set at 44°C.

Three machines were used, each with a single sensor, allowing three simultaneous measurements. Each foot electrode was placed on the dorsum between the first and second metatarsal heads, just proximal to the web space and not over a visible vein. A third reference probe was placed on the anterior chest wall (midclavicular line, infraclavicular fossa). Measurement was taken after 15 minutes. Quality checks were performed every 3 months to ensure intrameasurement and intermeasurement agreement between the three probes.

Table I. Criteria used for identification of significant lower limb arterial disease using color duplex imaging

Arterial ultrasound finding	*Change in peak flow velocity*	*Distal waveform analysis*
Occlusion	No flow	Loss of reverse flow
Single or multiple stenoses	≥×2 increase	Loss of reverse flow
Diffuse stenotic disease	<×2 increase	Loss of reverse flow

Color duplex imaging was performed at the end of each visit using a Toshiba SSH-140A (Toshiba Medical Systems, Crawley, UK) with two probes, a 5-MHz linear array probe (PLF-503NT) and 3.75-MHz curvilinear probe (PVF-375MT). All individuals were scanned from the common femoral artery to the distal third of the tibial and peroneal arteries. The criteria used for identifying significant arterial disease in the femoropopliteal segments are listed in Table I. Occlusions of any of the three arteries below the knee were also regarded as significant.

Heavy calcification frequently prevented flow analysis over large segments of the lower limb arteries. However, distal Doppler analysis was possible in all limbs. Where heavy calcification prevented flow analysis of segments of below knee vessels, a damped waveform distally was deemed to signify occlusive disease was present and maintenance of waveform profile its absence. Quality control was assured by acquiring a second color duplex imaging on 10 individuals with and without arterial disease ≤1 month of the original scan. The repeat scan was performed by medical physicists at the local teaching hospital who were blinded to the authors' color duplex imaging findings.

Statistical analysis. Analysis was performed using SPSS 11 software (SPSS Inc, Chicago, Ill). Group variables were compared using one-way analysis of variance (ANOVA) with post hoc multiple comparisons assuming homogenous variance. Significance was set at $P = .05$. Comparisons between transcutaneous measurements and TBI employed Pearson correlation coefficients with two-tailed significance set at $P = .05$.

RESULTS

Demographics. A total of 130 limbs were studied on 68 volunteer subjects (Table II). All subjects were white, and predominantly male (74%) in the diabetes groups. The groups were matched for age and BMI (Table II). Generally there were more type 2 diabetes patients (85% of total) evenly distributed, except in group five (arterial disease, no neuropathy), the group with the lowest number of recruits, which had only type 2 diabetes patients.

Table II. Group distribution and characteristics

Group no.	*Abbreviation*	*Limbs (n)*	*Age**	*BMI†*
1	V	14	68.89 ± 8.82	26.68 ± 5.39
2	D	25	64.40 ± 8.78	28.59 ± 3.48
3	DN	41	64.75 ± 9.49	30.28 ± 5.38
4	C	27	63.13 ± 12.66	26.07 ± 3.58
5	DV	7	66.17 ± 8.28	29.58 ± 4.58
6	DNV	16	69.45 ± 10.35	28.18 ± 3.40
Total		130		

BMI, Body mass index; *V,* controls with arterial disease; *D,* diabetes; *DN,* diabetes with neuropathy; *C,* controls; *DV,* diabetes with arterial disease; *DNV,* diabetes with neuropathy arterial disease.
*Mean ± SD; analysis of variance $F_{5,74} = 0.783$ $P = .565$
†Mean ± SD; analysis of variance $F_{5,74} = 2.04$ $P = .083$

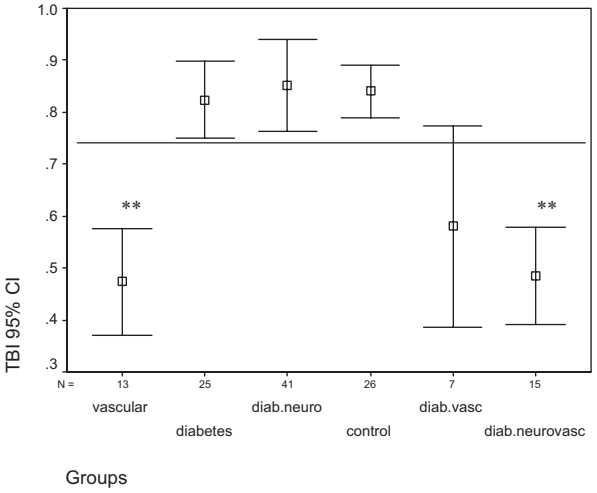
Table III. Classification of arterial disease identified in the three vascular groups

Arterial disease	*Groups*		
	DNV	*DV*	*V*
Occlusion	2	2	5*
Stenosis	6	2	7
Diffuse disease	7	1	0
Distal vessel occlusion only	1	2	2
Total	16	7	14

DNV, Diabetes with neuropathy; *DV,* diabetes without neuropathy; *V* controls.
*Includes one limb with femoral and distal vessel occlusion

Color duplex imaging. Comparison with quality control scans demonstrated complete agreement on the presence or absence of significant arterial disease. There was close agreement on the severity of disease detected, four limbs in complete agreement, and two with 50% stenoses identified by the author and 50% to 70% by a second color duplex imaging. The character of arterial disease identified in each group is summarized in Table III. More occlusions were identified in the control group, but stenoses and single distal vessel disease were evenly distributed. Diffuse femoropopliteal disease was only identified in individuals with diabetes. Severe arterial calcification, affecting color duplex imaging in >50% of the arteries visualized, was encountered in 76% of subjects with diabetes vs 17% in control groups (Mann-Whitney *U* test, two-tail, $P < .001$).

Toe-brachial pressure index. There was close agreement between significant arterial disease detected on color duplex imaging, toe pressures, and TBI values. All groups with identified arterial disease had lower values compared with the remaining groups with no arterial disease (Fig 1). Statistical analysis, excluding abnormally high TBI values influenced by digital artery calcification (>1.2), identified the control vascular and diabetic neurovascular groups to have low mean values (F5, 115=14.361, $P < .001$) (Table IV). However, using TBI values <0.75 as indicating significant PAOD (based on control group values), several low values (<0.75) were also identified in groups with no significant arterial disease on color duplex imaging, These were almost exclusively found in groups with diabetes and particularly in those with peripheral neuropathy, which in addition, was the only group identified as having TBI values >1.2. Further analysis of TBI values in the diabetes groups with no arterial disease demonstrated that a greater degree of arterial calcification was associated with lower mean values compared with those limbs with lesser degrees of calcification on color duplex imaging, 0.81 vs. 0.94, respectively ($t = 1.997$, $P = .050$).



ANOVA $F_{5, 115} = 14.63$, $P < .001$ ** Significance @ 0.01 level
(Analysis excluding TBI values >1.2 in non-vascular groups)

Fig 1. Toe brachial pressure indices *(TBI)* in all groups. *Horizontal line* represents TBI value of 0.75. Whiskers represent 95% confidence intervals *(CI)*. ANOVA F5,115=14.63, $P < .001$ **Significance at $P = 0.01$. Analysis excluding TBI values >1.2 in non-vascular groups.

Table IV. Toe-brachial pressure index (TBI)

Group	*Mean*	P
Control vascular	0.47	<.001*
Diabetes no neuropathy	0.82	.965
Diabetes neuropathy	0.85	1.0
Control	0.84	1.0
Diabetes vascular	0.58	.061
Diabetes neurovascular	0.48	<.001*

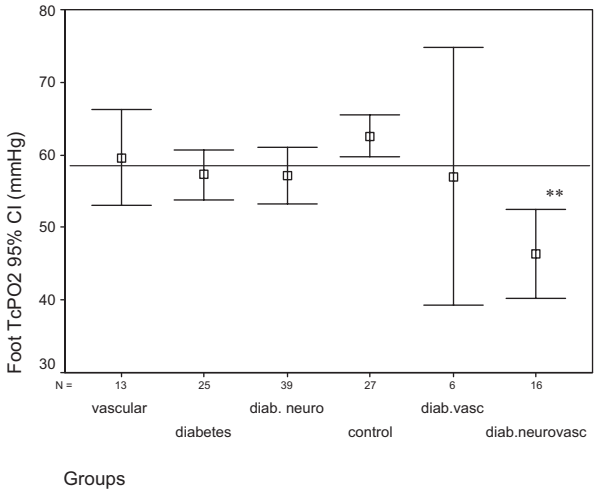
Analysis of variance, F5, 115=14.63, $P < .001$
Analysis excluding TBI values > 1.2 in nonvascular groups
*Significance $P = 0.01$.

Transcutaneous oxygen tension. There were only modest reductions in the mean $TcPO_2$ values of the diabetes groups with no arterial disease and the control group with arterial disease compared with the control group (Table V and Fig 2). However, the group with diabetes, arterial disease, and peripheral neuropathy demonstrated a mean value that was lower than the control, control vascular, and diabetes with neuropathy groups (Table V).[4] The reference chest $TcPO_2$

Table V. Foot transcutaneous oxygen values

Group	*Mean (mm Hg)*	P
Control vascular	59.60	0.982
Diabetes no neuropathy	57.24	0.642
Diabetes neuropathy	57.15	0.511
Control	62.58	1
Diabetes vascular	57.00	0.924
Diabetes neurovascular	46.41	<0.001*

Analysis of variance, F5,120=4.972, $P < .001$
*Significance $P = 0.01$



ANOVA $F_{5,120}$=4.972, P<.001 ** Significance @ 0.01 level.

Fig 2. Foot transcutaneous oxygen tension *($TcPO_2$)* for all groups. Horizontal line represents approximate normal value of 60 mm Hg. Whiskers represent 95% confidence intervals *(CI)*. ANOVA F5,120=4.972, $P < .001$ **Significance at $P = 0.01$ level.

values were lower across all the groups with diabetes compared with the control group (ANOVA $F_{5,121} = 12.132$, $P < .001$) (Fig 3). There were no differences between the values in the diabetes groups; however, mean chest $TcPO_2$ values generally reflected changes in foot $TcPO_2$ values across all groups ($r = 0.346$, $P < .001$) (Fig 3).

Transcutaneous carbon dioxide tension. Mean foot $TcPCO_2$ measurements were higher in the diabetes group with peripheral neuropathy and arterial disease vs all other groups except the group with diabetes alone (ANOVA $F_{5,120} = 6.358$, $P < .001$). For all limbs, high foot $TcPCO_2$ values correlated with low $TcPO_2$ ($r = -0.317$, $P < .001$) (Fig 4). Chest values mirrored foot values with a close correlation between the two sites ($r = 0.619$, $P < .001$).

Toe-brachial pressure index and transcutaneous oxygen tension. Despite TBI values reflecting the presence of arterial disease identified on color duplex imaging, there

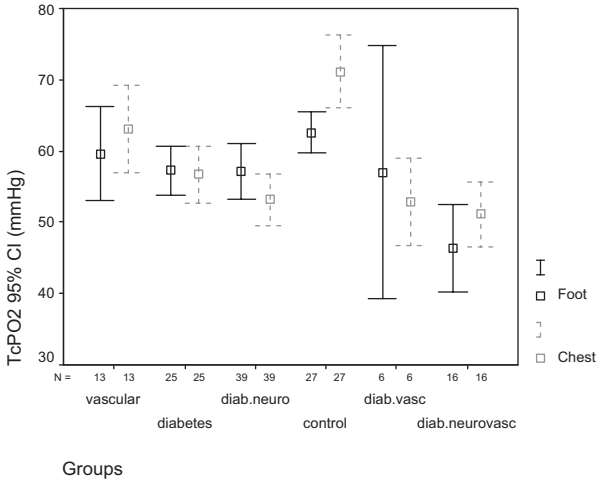
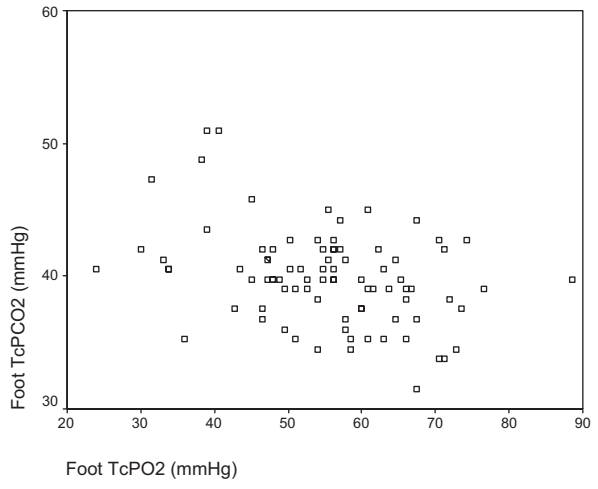


Fig 3. Foot *(black, solid line)* and chest *(gray, dashed line)* transcutaneous oxygen tension *($TcPO_2$)* for all groups. Whiskers represent 95% confidence intervals *(CI)*.



Pearson correlation r=-0.317, P<.001

Fig 4. Foot transcutaneous oxygen tension *($TcPO_2$)* vs carbon dioxide tension *(TcPCO2)* in all diabetes groups. Pearson correlation $r = -0.317$, $P < .001$.

were a wide range of TBI values demonstrated in the diabetes groups, particularly in those with demonstrable peripheral neuropathy and no significant arterial disease. To further analyze this, foot $TcPO_2$ values were correlated with TBI results for all groups with diabetes.

The correlations performed demonstrated an interesting relationship between the two parameters. In the groups with arterial disease, increases in foot $TcPO_2$ values correlated closely with increasing TBI ($r = 0.642$, $P = .002$) (Fig 5, *A*). In the diabetes groups with no arterial disease on color duplex imaging, low TBI values were associated with low $TcPO_2$ values. However, there was also a strong association between abnormally high TBI values and low

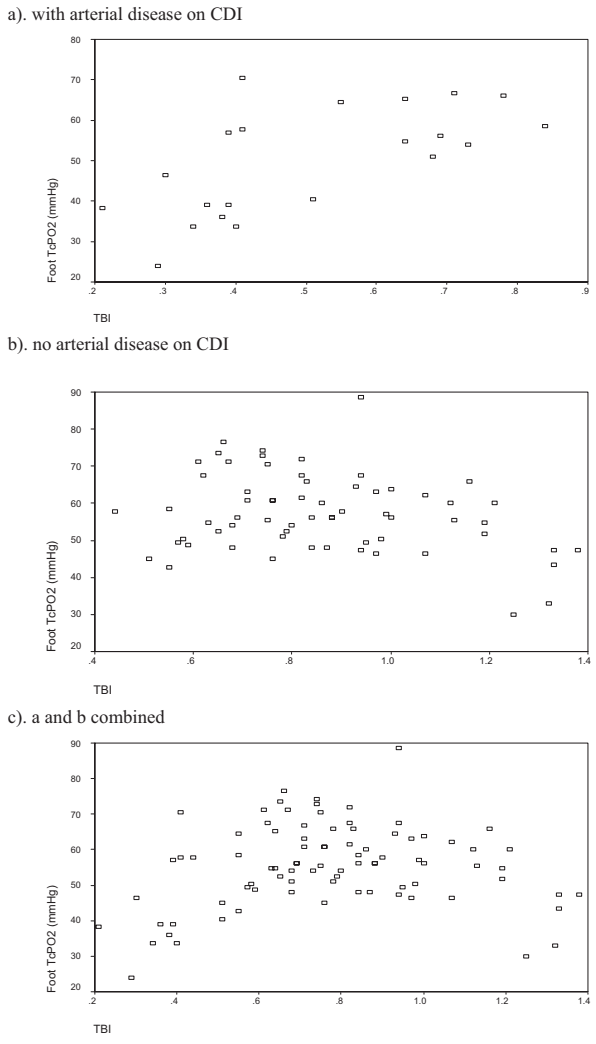


Fig 5. Foot transcutaneous oxygen tension *($TcPO_2$)* vs toe-brachial pressure index *(TBI)* for the diabetes groups. **A,** Subjects with arterial disease on color duplex imaging. **B,** Patients with no arterial disease on color duplex imaging. **C,** Subjects **(A, B)** combined.

$TcPO_2$ values, resulting in a negative correlation between TBI and foot $TcPO_2$ ($r = -0.270$, $P = .034$) (Fig 5, *B*). The relationship between the two modalities is graphically demonstrated when all data for the diabetes groups is combined (Fig 5, *C*).

DISCUSSION

The pathophysiology of diabetic foot disease is intimately related to tissue perfusion. Lower limb PAOD can have profound effects on foot perfusion. Microvascular disease in diabetes influences the cutaneous response to injury, but its influence on perfusion in the presence of detectable peripheral neuropathy and PAOD is unclear. This study endeavored to determine the influence of these two variables on cutaneous foot perfusion in diabetes.

The selection of subjects with no active foot disease avoided the potentially confounding influences of sepsis and ulceration on test interpretation. Group sizes were not uniform. Recruitment of nonsmokers with arterial disease but no active foot disease was difficult. The small number of subjects in the group with diabetes, arterial disease but no detectable peripheral neuropathy, was a consequence of the strong association between peripheral neuropathy and PAOD. Invasive arterial assessment could not be justified in this study population; however, the accurate detection of PAOD was critical to the validity of results.

Color duplex imaging. Color duplex imaging was used as our gold standard in detecting and excluding PAOD, as the symptoms and signs of noncritical lower limb PAOD are unreliable, particularly in diabetes.[5,6] Color duplex imaging has been demonstrated to accurately detect PAOD and is the gold standard in noninvasive testing for macrovascular disease.[7,8]

As expected in individuals without critical ischemia, most of the limbs with PAOD had disease of one segment only, and individuals with diabetes had more diffuse disease (Table III). Diffuse stenotic disease was a pattern of atherosclerosis identified only in subjects with diabetes. Varying degrees of arterial collateralization may, of course, influence distal perfusion despite similar degrees of main vessel disease.

It was not surprising that many limbs with PAOD had normal $TcPO_2$ and TBI values, as none had critical ischemia. In agreement with other research, TBI values in this study generally reflected the presence of significant arterial disease in all groups with and without diabetes.[9] TBI also correlated closely with foot $TcPO_2$ values. A wide range of TBI values was demonstrated in the groups with no PAOD on color duplex imaging, particularly in those groups with diabetes and peripheral neuropathy. High TBI values, particularly those >1.2, likely reflected the presence of heavily calcified digital arteries.

The finding of low TBI values in the absence of color duplex imaging-detected arterial disease, particularly in those limbs with demonstrable peripheral neuropathy, was probably partly due to more diffuse arterial disease hidden by tibioperoneal calcification or disease distal to the area scanned, or both, a limitation of color duplex imaging in this study.[10] A low TBI appears therefore to be a better indicator of PAOD than color duplex imaging in this study. A surprising finding was that TBI values >1.2 were associated with low $TcPO_2$. Severe digital arterial calcification may therefore be associated with occult arterial occlusive disease or a more dysfunctional cutaneous circulation.

Our study, in common with other work, demonstrated that individuals with diabetes had mild falls in $TcPO_2$ (Table V).[11] The group with diabetes and arterial disease but no peripheral neuropathy demonstrated only mild falls in $TcPO_2$ and no change in foot $TcPCO_2$, although mean TBI values were higher than the other vascular groups. However, abnormally low foot $TcPO_2$ values were demonstrated in the group with diabetes, arterial disease, and detectable peripheral neuropathy. In comparison, the con-

trol group with arterial disease demonstrated normal $TcPO_2$ and no change in $TcPCO_2$, despite similar TBI values. This suggests that despite similar degrees of arterial disease, individuals with diabetes demonstrate greater reductions in cutaneous foot perfusion, particularly in the presence of detectable peripheral neuropathy.

The lower chest $TcPO_2$ values in the groups with diabetes, in agreement with other work, suggests that there was a global reduction in $TcPO_2$ values.[12] However, our results demonstrated that these effects were independent of detectable peripheral neuropathy. Foot $TcPCO_2$ values were highest in the group with diabetes, peripheral neuropathy, and arterial disease, and again correlated closely with chest measurements. Elevations in $TcPCO_2$ values showed a negative correlation with $TcPO_2$ across all groups, probably reflecting altered tissue perfusion, with increasing tissue perfusion facilitating increased oxygen delivery and more rapid removal of carbon dioxide.

$TcPO_2$ and $TcPCO_2$ results demonstrated that the group of subjects with diabetes, detectable peripheral neuropathy, and significant arterial disease was the only group with a reduced cutaneous perfusion. Accepting that the group with arterial disease and no detectable peripheral neuropathy was small and interpretation of these results guarded, the presence of detectable peripheral neuropathy in diabetes appears to be associated with the greatest disruption of cutaneous perfusion.

CONCLUSIONS

We can deduce from this study that there were two influences on cutaneous foot perfusion in subjects with diabetes and arterial disease: (1) a global microcirculatory change, as reflected by the close correlation between chest and foot $TcPO_2$ values, and (2) macrovascular disease affecting limb perfusion, as limbs identified as having PAOD had reduced TBI values that correlated with decreased $TcPO_2$ values. The minimal effects of noncritical arterial disease on the cutaneous perfusion of nondiabetic individuals appears to be exaggerated in diabetes by the presence of microcirculatory dysfunction to significantly reduce cutaneous perfusion.

The data suggest that diabetic individuals who have degrees of noncritical PAOD similar to nondiabetic individuals are potentially more vulnerable to the detrimental effects of tissue edema and sepsis on tissue perfusion. These individuals may therefore not only be more susceptible to injury but may also be predisposed to delayed healing after injuries have occurred. This further emphasizes the importance of an accurate assessment and optimization of perfusion in diabetic foot disease.

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AUTHOR CONTRIBUTIONS

Conception and design: DTW, PP, KGH
Analysis and interpretation: DTW, PP
Data collection: DTW, KGH
Writing the article: DTW, PP, KGH
Critical revision of the article: DTW, PP, KGH
Final approval of the article: DTW, PP, KGH
Statistical analysis: PP, DTW
Obtained funding: KGH
Overall responsibility: DTW

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