Skin microcirculation of the foot in diabetic neuropathy

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1. In the feet of patients with diabetic neuropathy, total skin blood flow is increased due to an increased shunt flow. The question is, does this increased anastomotic shunt flow lead to either under- or overperfused nutritive capillaries.
2. To solve this question, skin microcirculation tests of the left big toe were performed in 20 healthy control subjects and in 40 insulin-dependent diabetic patients without macroangiopathy, 20 without and 20 with neuropathy. Skin temperature measurements and laser Doppler fluxmetry were performed to record mainly shunt flow and capillaroscopy to study nailfold capillary blood flow.
3. The insulin-dependent diabetic patients with neuropathy had a higher baseline skin temperature (mean ± SEM; 30.0 ± 0.6°C) and laser Doppler fluxmetry [26.2 ± 2.2 perfusion units (pu)] than patients without neuropathy (27.2 ± 0.8°C, $P < 0.01$; 16.1 ± 2.0 pu, $P < 0.01$) and healthy control subjects (27.9 ± 0.7°C, $P < 0.05$; 18.6 ± 2.8 pu, $P < 0.05$). Sympathetic stimulation (inspiratory gasp) resulted in a smaller laser Doppler fluxmetry decrease in the neuropathic patients (31.4 ± 4.6%) compared with non-neuropathic patients (48.2 ± 5.1%, $P < 0.05$) and control subjects (49.0 ± 3.8%, $P < 0.05$), while no difference between the three groups was seen in the laser Doppler fluxmetry decrease during a postural vasoconstriction test. The number of visible capillaries was highest in the neuropathic patients (10.2 ± 0.6/0.5 mm²), when compared with non-neuropathic patients (8.7 ± 1.2/0.5 mm², $P < 0.05$) and control subjects (8.3 ± 0.3/0.5 mm², $P < 0.001$). Capillary blood-cell velocity was significantly higher in the neuropathic patients (0.32 ± 0.05 mm/s) compared with non-neuropathic patients (0.23 ± 0.03 mm/s, $P < 0.05$) and control subjects (0.23 ± 0.02 mm/s, $P < 0.01$).
4. We conclude that there is an overperfused nutritive capillary circulation in the feet of patients with diabetic neuropathy. This is in contradiction to the capillary steal phenomenon and favours the hyperdynamic hypothesis to explain the decreased healing potential in diabetic neuropathic foot ulceration.

INTRODUCTION

One of the most serious long-term sequelae of diabetes mellitus is the diabetic foot complicated by trophic skin lesions [1]. These may develop in spite of an increased total skin blood flow [2–4]. This increase in flow is supposed to be related to peripheral sympathetic denervation, resulting in an increased flow through the arteriovenous anastomoses (AVA) [5, 6]. These AVA are essential for body temperature homoeostasis. Exposure to cold results in selective vasoconstriction [7]. At room temperature, 80–90% of total skin blood flow passes through the AVA and so bypasses the more superficial localized nutritional capillaries [7]. The massive increase in AVA skin blood flow in patients with peripheral autonomic neuropathy due to diabetes may compromise the nutritive circulation, a hypothesis known as the capillary steal phenomenon [8]. Using an open-tipped platinum electrode in the skin of the lower extremities of normal subjects, it was found that preganglionic sympathetic denervation resulted in a decrease in skin oxygen tension. In the presence of an increased total skin blood flow, this suggests a decrease in capillary blood flow after denervation [9]. However, in a previous experimental study in healthy volunteers, using capillary microscopy, we found an increase in capillary blood-cell velocity (CBV) of the fifth finger after temporary ulnar nerve blockade [10]. In the one and only clinical study by Flynn et al. [11], no change in the CBV of the toe nailfolds was found in patients with diabetic neuropathy. There was, however, an increase in the estimated 'capillary volume flow' in these diabetic patients, because of the increase in erythrocyte column width [11]. The results of this clinical study argue against capillary underperfusion distal to high anastomotic shunt flow.

In patients with diabetic neuropathy, red skin of the foot and venous distension are visible especially in the dependent position [12], as a result of a diminished venoarteriolar reflex [13, 14]. It has been postulated that this is caused by sympathetic neuropathy [13]. In contrast, we have found no difference in postural vasoconstrictor response of the blocked fifth finger after ulnar nerve blockade

Key words: diabetic foot, neuropathy, skin microcirculation.
Abbreviations: AVA, arteriovenous anastomoses; CBV, capillary blood-cell velocity; LDF, laser Doppler fluxmetry; PRH, postocclusive hyperaemia test; pu, perfusion units.
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[10]. Further evidence suggests that this vasoconstriction is mediated by a local sympathetic axon reflex, only partially supplemented by a central component [11, 15, 16]. Finally, the fall in blood flow may also be explained by myogenic autoregulation at the precapillary level [17].

In the present study we carefully selected diabetic patients with and without neuropathy, but without signs of macroangiopathy. Neuropathy was scored and microcirculation tests of the big toe were performed under standardized conditions, to elucidate the influence of diabetic neuropathy on nutritive capillary skin blood flow.

METHODS

Subjects

Using a database of 1054 diabetic patients controlled at the outpatient clinic of the University Hospital Nijmegen, 40 patients (20–65 years of age) with insulin-dependent diabetes of 10 or more years duration were selected. All were without clinical signs of macroangiopathy, none had hypertension (blood pressure below 160/90 mmHg), nor used any medication except for insulin or oral contraceptives. The HbA_{1c} level had to be below 10% (normal level $<6.4\%$).

Of these 40 patients, 20 showed absence of vibration sense in two or more of the four standard places (dorsal aspect of the big toes and ankles) tested on both feet and absence of tendon reflexes of both knees and/or both ankles. The other 20 selected patients had no signs of neuropathy. Furthermore, 20 healthy, age- and sex-matched volunteers were selected as control subjects, by a newspaper announcement. None smoked or consumed more than two alcoholic drinks a day. All had a normal ECG and normal renal function (creatinine <110 μmol/l for men and <90 μmol/l for women), and the total cholesterol level was below 6.5 mmol/l. To exclude macroangiopathy of the lower legs the ankle/brachial index should be ≥ 0.9 and toe systolic blood pressure >100 mmHg [18]. The subjects were asked to refrain from caffeine- or alcohol-containing beverages for 24 h and from meals 1 h before the tests. None had foot ulcers at the time the tests were performed. All subjects gave their informed consent to the protocol, which was approved by the local ethics committee.

Study protocol

All subjects were studied in an environmentally controlled room maintained at a temperature of 24.0 ± 0.4°C (mean ± SD) and a relative humidity of $55.0 \pm 2.2\%$. Five cardiovascular autonomic reflex tests were performed with an automated computer program using a Finapres device [19]. Cardiovascular autonomic neuropathy was considered to be present if two or more of the five test parameters were below the fifth percentile of the normal value. The five test parameters were: (i) The mean difference between the highest heart rate during inspiration and the lowest during expiration for six consecutive forced breathings: inspiration–expiration difference. (ii) The difference between the maximum heart rate after standing up and the control heart rate before: ΔHR_{max}, and the quotient of maximum heart rate after the manoeuvre and the minimal heart thereafter: tachycardia/bradycardia ratio. (iii) Difference between mean diastolic blood pressure 50 to 80 s after standing up and during the supine position: ΔBP_{dias}. (iv) Highest heart rate divided by the lowest heart rate after the Valsalva manoeuvre: Valsalva ratio. (v) Highest increase in average diastolic blood pressure over 5 s during 3 min of sustained handgrip: ΔBP_{dias} [19].

Thereafter, peripheral neuropathy was assessed by a neurological disability score, and by measurements of both current perception threshold in mA (Neurometer®; Minimed Technologies, Sylmar, CA, U.S.A.) and by vibratory perception threshold in μm (Vibrameter IV®; Somedic, Stockholm, Sweden) [20]. The neurological disability score is based on testing lower leg reflexes and gnostic (tuning fork and fine touch) and vital (pricking pain) sensitivity. The maximal score is 48 points [20]. The current perception threshold of both big toes was obtained, for the three frequencies (5, 250 and 2000 Hz). Vibratory perception was tested at the metatarsal phalangeal joint of the big toes and at the lateral ankle of both feet.

Subsequently the subjects were placed in a comfortable supine position. Laser Doppler fluxmetry (LDF) (Periflux Pf1d; Perimed, Linköping, Sweden) was used to measure capillary and arteriovenous blood flow [21]. The Periflux was adjusted to an upper frequency limit of 12 kHz and the output circuit time constant and gain were, respectively, 0.2s and 3×. LDF was measured in perfusion units (pu) [22]. The LDF probe was attached to the plantar surface of the left big toe by double-sided adhesive tape. Skin temperature of the toe was measured using a thermocouple (Ellab Instruments, Copenhagen, Denmark).

During 10 min both instruments measured baseline LDF and skin temperature. Thereafter the feet were warmed with an electric blanket, if skin temperature was below 28°C, before the microcirculation tests were performed in an attempt to standardize cutaneous thermoregulatory mechanisms which exert powerful modulatory effects on skin vasomotor reflexes [23].

After 2 min registration with a skin temperature above 28°C the first inspiratory gasp test was performed. The subjects were asked to take a deep breath as quickly as possible and hold it for 10 s. Outflow to sympathetic skin nerves is increased by an inspiratory gasp [24], resulting in a decrease in skin blood flow [25]. After 2 min baseline registra-

tion, a second inspiratory gasp test was performed. The parameters during these tests were mean LDF during the last minute of the preceding baseline registration, and the absolute and percentage decrease.

After the inspiratory gasp test, the postural vasoconstrictor response was tested. After 5 min baseline registration, the subjects were tilted head-up with an automated tilt table to an angle of 90° to horizontal. Five minutes later the table was turned back to the horizontal position. During this test LDF was averaged for each minute of, respectively, the 5 min baseline registration, the 5 min postural challenge and the 2 min thereafter.

Before the postocclusive hyperaemia test (PRH test) baseline LDF was again recorded for 5 min. A toe cuff was inflated to a suprasystolic pressure to arrest the circulation for 5 min, followed by a sudden deflation. During the last minute of circulatory arrest a biological zero was determined and subtracted from all previous LDF measurements [26]. Absolute and percentage LDF increase during the hyperaemic phase were calculated. Approximately 20 min after this PRH test, the LDF and temperature probe were removed.

To measure capillary nutritive flow, capillaroscopy of the nailfold of the left big toe was performed, while the subjects were half-sitting in a stable dentist chair, with the feet at the same level as the pelvis. The foot was fixed to a support with an angle of 45° to horizontal.

During 1 min video recordings were made (magnification ×140) to count the number of capillaries per 0.5 mm^2. On the television screen a rectangle (1 mm by 0.5 mm) was placed parallel to the nailfold and all visible capillaries were counted.

To measure CBV, a computerized video-photometric system, based on the dual-window cross-correlation technique (CapiFlow AB, Kista, Sweden), was used [27]. The microscope–television system enables video recording of capillary dynamics. Thereafter the video signal passes through a photometric analyser that generates two windows onto the television screen over a capillary loop. These windows are sensitive to variation in light intensity within the window. Passage of erythrocytes, leucocytes and plasma gaps through the investigated capillary loop causes variation in optical density, which are quantified by the windows and converted to electronic equivalents. By determining the time interval by which the distal signal of the second window has to be delayed to achieve maximum cross-correlation with the proximal first window signal, the CBV is calculated. The filter time constant was 1.0 s and the cross-correlation limit was above 0.5. Five-minute video recordings with a ×560 magnification of two or three capillary loops were used to measure CBV. The video recordings were mixed to blind the investigator. The measured CBV during 2 min with the lowest (at least less than 15%) artefact percentage was chosen as CBV (artefact excluded). The CBV of each capillary was calculated twice on different occasions and averaged (coefficient of variation in five normal subjects was 4.2%). The coefficient of variation of CBV measurements of two video recordings of the same capillary in succession in five normal subjects was 21.7%.

Statistics

The results are expressed as means ± SEM, unless stated otherwise. Statistical analysis was performed by Wilcoxon signed-rank test and Student's *t*-test for paired samples when appropriate. A two-sided *P*-value below 0.05 was regarded as statistically significant.

RESULTS

Subjects

The characteristics of the study population are shown in Table 1. The duration of diabetes was significantly longer for the diabetic patients with neuropathy. In this group the supine systolic blood pressure was higher compared with the others, while diastolic blood pressure was only higher compared with the diabetic patients without neuropathy. Baseline heart rate in the neuropathic group was significantly increased compared with the control group, but there was no difference between the patients with and without neuropathy. Microvascular diabetic complications such as retinopathy and incipient nephropathy were more often present among patients with neuropathy.

Neuropathy (Table 2)

The diabetic patients with neuropathy obviously had the highest neurological disability score. The thresholds of current and vibratory perception were significantly worse in the neuropathic group, while there was no difference between normal subjects and diabetic patients without neuropathy. Cardiovascular autonomic neuropathy tests were more often disturbed in the patients with neuropathy, especially the tests based on heart rate variability. Only one of the patients without neuropathy had two abnormal autonomic function test results (heart rate response during forced breathing and Valsalva manoeuvre), while two or more abnormal test results were found in 19 of the patients in the neuropathic group.

Baseline skin temperature and LDF (Table 3)

Baseline skin temperature and LDF before warming up were significantly higher in the group with neuropathy than in the healthy volunteers and diabetic patients without neuropathy.

Table 1. Characteristics of the study population. Values are means ± SD. Statistical significance: *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$.

		Diabetic patients	
	Control subjects	With neuropathy	Without neuropathy
Age (years)	46.4 ± 10.6	47.9 ± 9.3	43.3 ± 9.9
Sex (M/F)	8/12	9/11	8/12
Duration of diabetes (years)		31.5 ± 11.6†	17.8 ± 5.7
Total daily insulin dose (i.u.)		43.0 ± 15.4	54.1 ± 18.4
Supine blood pressure (mmHg)			
Systolic	119.3 ± 13.6†	141.6 ± 13.9‡	118.2 ± 10.1
Diastolic	71.9 ± 7.2	76.5 ± 6.5	69.8 ± 8.2
Baseline heart rate (beats/min)	64.5 ± 11.4*	74.8 ± 13.2*	69.0 ± 12.3
Ankle/brachial index	1.1 ± 0.1	1.1 ± 0.1	1.2 ± 0.1
Blood pressure, left toe (mmHg)	132.9 ± 22.6	136.4 ± 19.3	127.8 ± 20.0
Retinopathy		13	2
HbA_{1c} (%)	5.2 ± 0.3	8.9 ± 1.0	8.4 ± 1.1
Glucose (mmol/l)	5.2 ± 0.6	10.4 ± 4.6	9.3 ± 5.1
Cholesterol (mmol/l)	5.3 ± 1.0	5.6 ± 0.9	5.3 ± 1.0
Creatinine (μmol/l)	76.6 ± 7.3†	84.3 ± 9.5†	75.6 ± 8.7
Microalbuminuria (albumin excretion rate 20–200 μg/min)		7	2

Table 2. Results of the peripheral nerve function tests and a number of abnormal cardiovascular reflex tests. Values are means ± SEM. Statistical significance: †$P < 0.01$, ‡$P < 0.001$, §$P < 0.0001$.

		Diabetic patients	
	Control subjects	With neuropathy	Without neuropathy
Neurological disability score	0.8 ± 0.3	24.6 ± 1.9	1.1 ± 0.3
Current perception threshold (mA)			
2000 Hz	372.7 ± 19.5§	763.0 ± 54.8§	352.6 ± 15.8
250 Hz	175.3 ± 12.0‡	450.0 ± 62.8‡	179.0 ± 11.9
5 Hz	108.6 ± 10.8†	317.6 ± 57.9†	126.8 ± 10.0
Vibratory perception threshold (μm)			
Metatarsal	1.8 ± 0.4‡	48.2 ± 11.2‡	1.4 ± 0.3
Malleolus	0.9 ± 0.1‡	21.3 ± 7.0‡	0.7 ± 0.1
Cardiovascular reflex tests			
More than 2 abnormal test results	0	19	1
Forced breathing	3	17	5
Standing up			
Heart rate response	0	12	0
Blood pressure response	0	5	0
Valsalva manoeuvre	1	17	1
Sustained handgrip	0	4	0

Inspiratory gasp (Fig. 1 and Table 3)

Because baseline skin temperature was below 28°C in 12 normal subjects, four neuropathic patients and 11 non-neuropathic patients, the foot skin was warmed up before a duplicate inspiratory gasp test. Median (minimum–maximum) percentage LDF decrease was significantly lower in the group of patients with neuropathy [27.8 (0.0–66.5)%] compared with patients without neuropathy [47.8 (13.0–82.5)%; $P < 0.05$] and healthy volunteers [51.3 (11.0–77.5)%; $P < 0.05$]. The individual results of the patients with neuropathy showed a somewhat bipartite distribution. Five of the neuropathic patients had a percentage LDF decrease of more than 60%, while in all the others it was less than 40%.

Postural vasoconstrictor response test (Fig. 2 and Table 3)

No difference was seen in LDF response during postural changes between the groups. Percentage LDF decrease in the diabetic patients with and

Table 3. Results of microcirculation tests. Values are means ± SEM. Statistical significance: *$P < 0.05$, †$P < 0.01$.

		Diabetic patients	
	Control subjects	With neuropathy	Without neuropathy
Skin temperature (°C)	27.9 ± 0.7*	30.0 ± 0.6†	27.2 ± 0.8
LDF			
Baseline LDF (pu)	18.6 ± 2.8*	26.2 ± 2.2†	16.1 ± 2.0
LDF decrease during inspiratory gasp			
Percentage (%)	49.0 ± 3.8*	31.4 ± 4.6*	48.2 ± 5.1
Absolute (pu)	10.1 ± 1.4	7.9 ± 1.2	9.4 ± 1.3
LDF decrease during tilt test			
Percentage (%)	16.0 ± 14.6	17.8 ± 10.4	−0.8 ± 14.2
Absolute (pu)	7.1 ± 2.9	4.4 ± 3.6	1.0 ± 3.2

without neuropathy and control subjects were, respectively, [median (minimum–maximum)] 41.1 (−166.7–80.0)%, 28.0 (−117.5–77.5)% and 14.7 (−138.5–73.7)%.

PRH test

Percentage LDF increase was lowest in the diabetic patients with neuropathy (174.7 ± 29.1%). Patients without neuropathy had an LDF increase of 287.8 ± 40.7% ($P < 0.05$), and in the control group the increase was 384.3 ± 65.1% ($P < 0.001$). Absolute LDF increase in the diabetic patients without neuropathy (50.3 ± 4.5 pu) was significantly lower ($P < 0.05$) than in the control group (62.3 ± 3.7 pu).

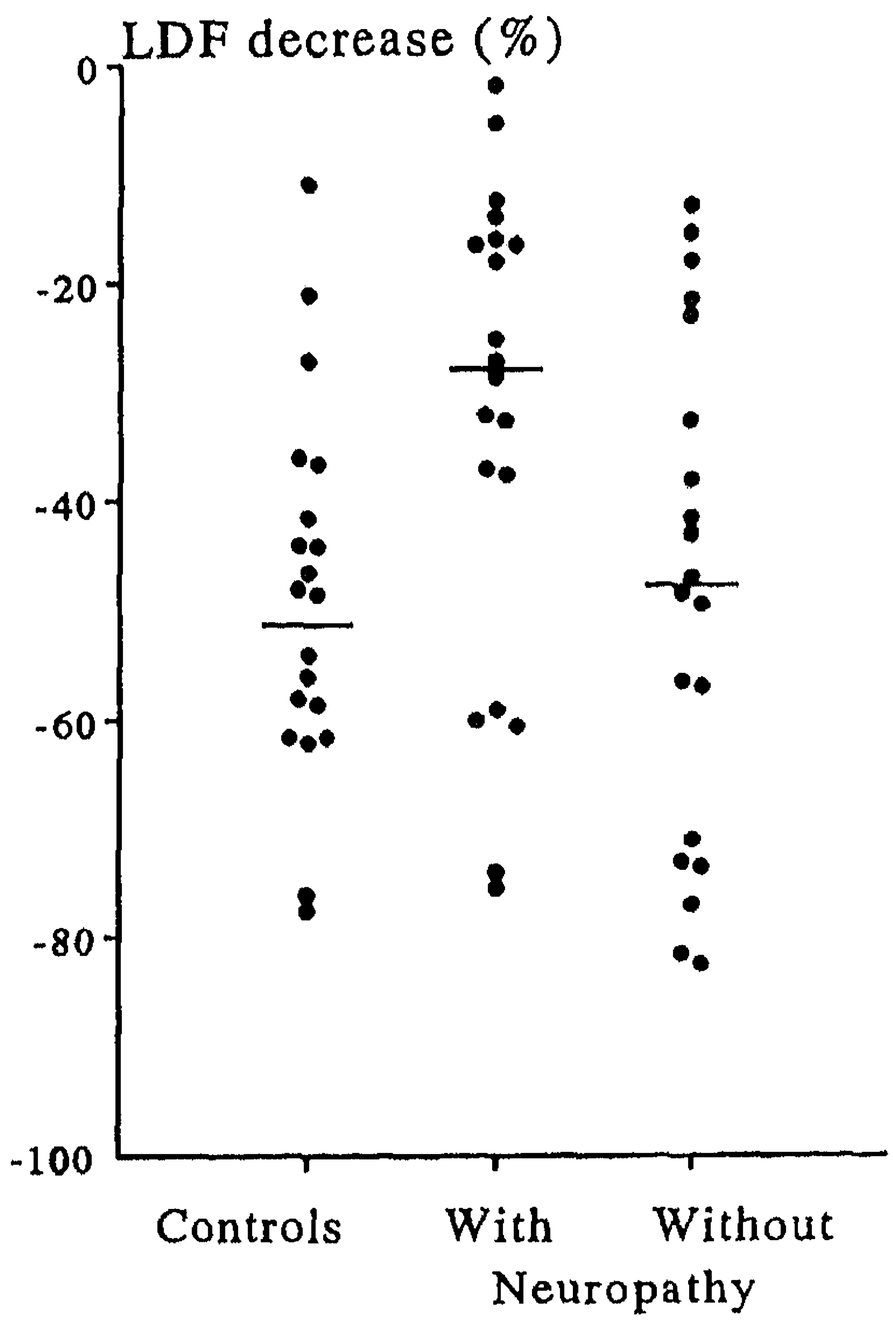

Fig. 1. Mean percentage LDF decrease during two inspiratory gasp tests (individual test results, median and minimum–maximum). The mean percentage LDF decrease was significantly lower in the diabetic patients with neuropathy.

Capillary microscopy (Table 4)

The number of visible nailfold capillaries and CBV were significantly higher in the diabetic patients with neuropathy. The capillaries of the neuropathic patients were visible over a smaller distance than those of the other groups. No difference was found in the diameter of the arterial or venular limb.

DISCUSSION

This study shows that in insulin-dependent diabetic patients with clinical signs of neuropathy, both baseline arteriovenous shunt flow as well as nutritive capillary blood flow in the foot are

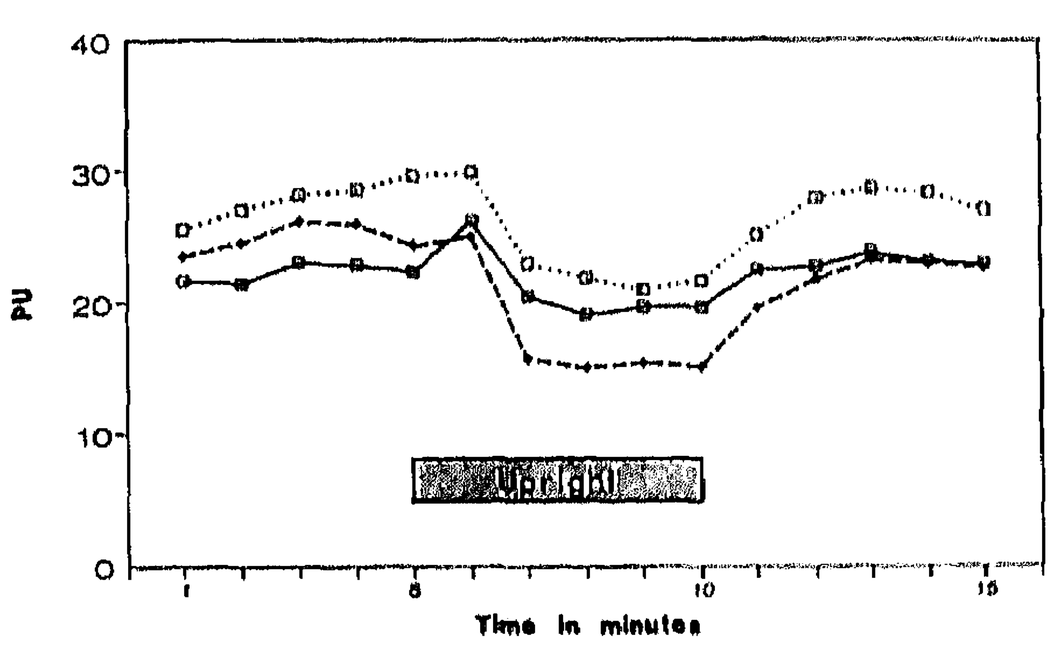

Fig. 2. LDF (mean of each minute registration in PU) during a postural vasoconstriction test in control subjects (--◆--), and diabetic patients with (··□··) and without neuropathy (—□—).

Table 4. Results of capillaroscopy of the nailfold of the first left toe. Statistical significance: *$P < 0.05$, †$P < 0.01$, ‡$P < 0.001$.

		Diabetic patients	
	Control subjects	With neuropathy	Without neuropathy
Number of visible capillaries (n/0.5 mm^2)	8.3 ± 0.3 ‡	10.2 ± 0.6*	8.7 ± 1.2
Length (μm)	137.0 ± 6.9*	110.6 ± 8.6*	145.2 ± 10.2
Diameter of the capillaries (μm)			
Arterial limb	8.0 ± 0.8	8.1 ± 0.6	7.5 ± 0.5
Venular limb	10.5 ± 1.1	9.8 ± 0.8	9.6 ± 0.5
CBV (mm/s)	0.23 ± 0.02†	0.32 ± 0.05*	0.23 ± 0.03

increased, opposing the steal hypothesis and supporting the haemodynamic hypothesis. The decrease in skin blood flow normally seen during sympathetic stimulation was smaller in the neuropathic patients. The reaction to postural changes was not different between diabetic patients with and without neuropathy, suggesting a more local reflex.

The patients were carefully selected from a database of 1054 patients of the outpatient department of a university hospital, for the presence or absence of (autonomic) neuropathy. Since we wanted to be as sure as possible that neuropathy was completely absent, we had to accept some incomplete matching. Consequently, patients with neuropathy had a longer duration of diabetes, a higher systolic blood pressure and a higher incidence of microvascular complications. Thus the difference in microvascular skin blood flow found in this study cannot be definitely ascribed to sympathetic dysfunction alone.

The diabetic patients were selected on the basis of absence of vibration sense and lower leg reflexes. In the neuropathic disability score these two conditions are also involved, which explains the higher score in the neuropathic group. Furthermore, differences were found in the current perception threshold and vibratory threshold, and cardiovascular autonomic test results. Because of the lack of a clear definition of diabetic neuropathy and absence of a simple, universally accepted test procedure, all the tests were performed in order to define and to quantify the severity of diabetic neuropathy as carefully as possible [28].

As was found by others, baseline skin temperature and LDF were higher in the diabetic patients with neuropathy [13, 29], which is explained by sympathetic hypofunction resulting in opening of the AVA [5, 6] and consequently arteriovenous shunting. In agreement with this is the attenuated vasoconstrictor response of the AVA in the neuropathic patients during sympathetic stimulation by an inspiratory gasp [30].

It has been hypothesized that the increase in shunt flow in diabetic patients with neuropathy may compromise capillary nutritive blood flow [8]. This capillary steal phenomenon could explain the disturbed healing potential of a diabetic foot ulcer. Our results are in contradiction with this hypothesis. Flynn et al. [11] found no difference in CBV of the toe nailfold between diabetic patients with or without neuropathy, nor did they find an increase in the number of visible capillaries. To detect an increased 'volume flow' Flynn et al. [11] measured erythrocyte column width and calculated the product of CBV and erythrocyte column width. In the present study a clear increase in nailfold capillary blood flow was found due to a significantly higher number of functioning capillaries and an increased CBV. In contrast to Flynn et al. [11], we have not found an increase in capillary diameter.

There are a number of differences between the study of Flynn et al. [11] and our study. The diabetic patients with and without neuropathy in the study of Flynn et al. [11] did not differ in their duration of diabetes. Non-insulin-dependent diabetic patients were involved too and none of the diabetic control group had clinical signs of microangiopathy such as retinopathy and nephropathy. Flynn et al. [11] used the frame-to-frame technique to measure CBV at 5-min intervals, while in this study the cross-correlation dual-window technique was used, which is a more continuous method of measuring capillary blood flow [27].

The significance of our findings is that long-standing raised capillary hyperperfusion could induce late structural changes, with the ultimate loss of microvascular function and consequently relative underperfusion: the haemodynamic hypothesis [31, 32].

However, some limitations should be applied to our study results. Skin temperature in the neuropathic group was significantly increased. CBV is positively correlated to skin temperature [10]. It is therefore unclear if the capillary flow is increased appropriately for the increase in skin temperature. Furthermore, in diabetic patients, impaired vascular reactivity and limitation of skin microcirculation hyperaemia is found [33]. Jörneskog et al. [34] found a significant decrease in the ratio between capillary and total (LDF) microcirculation in the foot skin of diabetic patients, but in their patient groups no increase in baseline LDF was found. In our study the percentage LDF increase after suprasystolic toe pressure was lower in both groups of diabetic patients compared with the healthy control subjects.

No significant difference in postural vasoconstriction response was found between the groups under study. There was an obvious variation in response, as can be seen from the minimum and maximum values. A marked overlap in postural vasoconstriction between normal subjects and patients with diabetic and other neuropathies was also reported by Moy et al. [14]. In a previous study we showed that postural vasoconstriction still occurred in the fifth finger after blocking the ulnar nerve [10]. Our results once more suggest that this response is mainly mediated by local neurogenic and/or myogenic mechanisms, only partially supplemented by a central component [17].

In conclusion, in insulin-dependent diabetic patients with neuropathy an increase in anastomotic shunt flow as well as nutritive skin blood flow was found. This contradicts the capillary steal phenomenon and supports the haemodynamic hypothesis. However, the increase in capillary blood flow may be insufficient to meet the increase in oxygen demand as a result of the higher skin temperature found in patients with diabetic neuropathy.

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