Blood flow patterns in painful diabetic neuropathy

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Summary. Peripheral blood flow is known to be qualitatively increased in diabetic patients with neuropathy. We have measured the actual blood flow in the feet of diabetic patients with neuropathy using non-invasive mercury strain gauge plethysmography and Doppler sonogram techniques and shown that it is increased on average five times above normal at an ambient temperature of 20°–22°C. Moreover, reduction of this high flow by sympathetic arousal stimuli proved possible in those with severe painful neuropathy contrasting strongly with failure to reverse it in those with severe non-painful sensory neuropathy. Reduction of blood flow was associated with reduction in neuropathic pain. We studied 22 diabetic patients with severe sensory neuropathy and eight with painful neuropathy. High resting foot blood flows were demonstrated in both groups with neuropathy. The big toe flow in those with severe sensory neuropathy was $29.3 \pm 9.2 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$ (mean $\pm$ SD) and in the painful neuropathy group,

25.9 ± 7.5 , compared with $5.2 \pm 2.4 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$ in the non-diabetic control subjects ($p < 0.001$). High foot skin temperatures were also recorded in the groups with neuropathy, reflecting the high blood flow. The subjects with painful neuropathy retained the ability to constrict peripheral blood vessels in response to arousal stimuli, and reduce peripheral flow on average by 32% compared with the patients with sensory neuropathy who responded on average by only 10%. The demonstration of a peripheral sympathetic defect, responsible for the high blood flow and the potential reversal of such flow in painful neuropathy may be important in our further understanding of the aetiology of such pain and its treatment.

Key words: Diabetes mellitus, peripheral blood flow, sensory neuropathy, painful neuropathy, peripheral sympathetic neuropathy.

During the nineteenth century, the feet of diabetic patients with peripheral neuropathy were observed to be hot and erythematous [1] and the blood flow in such feet was considered to be increased. This increase is now thought to be due to the dilation of denervated arterio-venous shunts [2–9] normally controlled by sympathetic nerves.

Measurement of actual blood flow in diabetic neuropathic feet has only been undertaken in one previous study [10]. Blood flow was not found to be increased in neuropathic subjects probably because the studies were conducted by waterbath plethysmography at 32°C causing vasodilatation and increased flow in the control subjects.

The aim of this study was to measure the magnitude of resting foot blood flow in a group of diabetic patients with severe sensory neuropathy and to discover whether the hot, burning foot, so characteristic of distal painful neuropathy, also has a high resting flow resulting from a peripheral sympathetic defect. In addition, the sympathetic responses of both types of neuropathy were tested

to discover whether either retained the ability to reduce peripheral flow by vasoconstriction, and whether any benefits might result from this.

Subjects and methods

Subjects

Two groups of patients with neuropathy (Table 1), one group of diabetic control subjects and one group of non-diabetic control subjects, were studied. The first of these consisted of 20 Type 1 (insulin-dependent) and two Type 2 (non-insulin-dependent) diabetic patients with severe sensory neuropathy. All had grossly impaired sensation – in 14, of sufficient severity to have caused previous neuropathic ulceration, and in five, Charcot joints, and there was universal absence of ankle reflexes. Sensory impairment of the lower limbs was quantified according to the method described by Fagius [11]. In this way, a summary of touch, pin prick and temperature responses was graded as follows: slight impairment = 1; moderate impairment = 2; marked impairment = 3; absent sensation = 4. A score was then calculated for six areas; including the toes, proximal and distal half of the foot, distal, middle and proximal third of the lower leg. Thus, absent touch, pin

Table 1. Clinical details of the subjects with severe sensory neuropathy and painful neuropathy

Clinical details	Sensory neuropathy group (<i>n</i> = 22)	Painful neuropathy group (<i>n</i> = 8)
Mean age (years)	43.5 (range 20–60)	42.5 (range 21–57)
Sex (M:F)	12:10	3:5
Mean duration of diabetes (years)	21.3 (range 5–43)	13.5 (range 1–35)
Sensory loss score	46.1 ± 17.3	10.4 ± 10.0
Pain	None	Disabling
Heart rate variation with respiration [18] (normal > 10 beats/min)	4.6 ± 1.6	13.9 ± 9.2
Postural hypotension (systolic drop > 30 mmHg)	4	0
Previous foot ulceration	14	0
Charcot arthropathy	5	0
Amputation	3	0
Retinopathy (background: proliferative)	10:12	5:0
Nephropathy (persistent Albustix-positive)	6	1 ^a

Results expressed as mean ± SD. ^aNon-diabetic nephropathy

prick and temperature sensation in each area scored 12 and intact sensation scored 0. If sensation in all modalities was absent to the knee, this gave a maximum score of 72 from all six areas. All had evidence of autonomic neuropathy with abnormally low beat-to-beat scores (the difference in heart rate between maximal inspiration and expiration) of <10. In none was there any complaint of pain.

The second group consisted of five Type 1 and three Type 2 diabetic patients with profoundly painful distal symmetrical neuropathy, sometimes described as neuropathic cachexia [12] and recently described by ourselves [13]. None had been recently started on insulin. Peripheral sensory loss was minimal and ankle reflexes were present in five of the eight. In five, tests of cardiac autonomic function were also within the normal range. Characteristic neuropathic symptoms were present in all cases. These included severe burning affecting the soles of the feet and at times of exacerbation this would spread to affect the whole of both feet. Intense tingling, aching and a sensation of tightness and swelling accompanied the burning. In addition, two subjects suffered intermittent needle-like pains which originated between and beneath the toes and radiated up into the legs. These were likened to electric shocks or red hot needles pushed into the feet. Contact discomfort described as when skin is abraded with sandpaper or stung by stinging needles was present in all and provoked by socks, tights, footwear, clothing and bedclothes. It was a major cause of insomnia, although all symptoms were reported to be worse at night.

There was no evidence of peripheral vascular disease in any of the subjects. All had palpable lower limb pulses and foot pulses and none was hypertensive or currently receiving medication likely to affect peripheral blood flow. Feet were excluded from the study if there was evidence of a local cause for increased blood flow such as infection, active ulceration or Charcot arthropathy. When only one foot demonstrated any of these features the other foot was included in the study.

There were 23 diabetic control subjects with no clinical evidence or symptoms of neuropathy and the ankle jerks of all of them were intact (14 males and nine females). Their mean age was 40 years (range 21–60 years) and mean duration of diabetes 19.1 years (range 1–45 years). Nineteen non-diabetic control subjects were also examined (8 males, 11 females; mean age 38 years, range 22–60 years).

Blood glucose concentrations in the diabetic patients were between 4.0 and 14.6 mmol/l during the blood flow investigations, and none was hypoglycaemic.

Electrophysiological studies were not performed, and indeed correlate poorly with the clinical neuropathy, especially in cases of painful neuropathy [13].

All subjects gave informed consent for all aspects of the study, which had Ethical Committee approval.

Methods

Four investigations were undertaken: (1) measurement of resting foot skin temperature; (2) measurement of resting foot blood flow in the big toe and mid foot; (3) assessment of sympathetic responses of peripheral vasculature to sympathetic arousal stimuli; and (4) assessment of responses of neuropathic symptoms to reduction in foot blood flow. All measurements were made in a constant temperature environment of 20°–22 °C with the subjects supine and a light blanket covering both hands and feet.

Skin temperature: Sensors were applied to the dorsal surface of the big toe over the head of the first metatarsal. Skin temperature was read using a flat disc recorder (Light Laboratories, Brighton, UK). Skin temperatures were considered stable if the reading varied by no more than 1 °C over 30 min.

Resting blood flow: Resting flow was recorded for 5 min at two sites in the big toe at the level of the nail bed and at the mid-foot position. Recordings were made using the Periflow mercury strain gauge plethysmograph (Periflow SU4 developed by Janssen Scientific Instruments Division, Janssen Pharmaceutica, Beerse, Belgium). The mean blood flow and SD of each 5 min study period were then calculated.

Sympathetic responsiveness: Subjects were stressed with arousal stimuli, such as cough, gasp, loud noises and mental summation [14–16]. The resulting reduction in big toe blood flow following each stimulus was recorded by two methods. First, blood flow change was determined by the plethysmograph and calculated as a percentage reduction. The second method of testing sympathetic responses was by 10 MegaHertz continuous wave Doppler probe (Doppler Velocimeter, Rigel Research, Morden, Surrey, UK) to record sonograms [17] from foot arteries both at rest and following the arousal stimuli, and the pulsatility index which reflects blood flow [17] was calculated as $\frac{\text{peak to peak height}}{\text{mean area}}$. The mean index of 15 consecutive wave forms at rest and the maximum index following each stimulus were calculated.

Reduction in foot blood flow: This was performed in five of the patients with painful neuropathy. A standard sphygmomanometer cuff was placed around the leg just above the ankle joint and inflated to a pressure sufficient to reduce the big toe flow to the mean value of the non-diabetic controls. Each case kept a running commentary of symptoms before, during and after deflation. They were not told what they might expect. The resting blood flow throughout this time was measured in the big toe at the level of the bed using the Periflow.

Statistical analysis

A random numbers table was used to select one foot from each pair where both were eligible. All values are presented as mean ± SD and statistical analysis was by the Mann-Whitney U test (two-tailed).

Results

Skin temperature

The sensory and painful neuropathic groups were found to have similar high toe skin temperatures (33.5 ± 0.9 °C in the severe sensory neuropathy group

Fig. 1. Big toe skin temperature in the sensory neuropathy group, painful neuropathy group, non-neuropathy diabetic control group and non-diabetic control group. Mean of each group represented by horizontal bar

Fig. 2. Big toe blood flow at rest in the sensory neuropathy group ($29.3 \pm 9.2 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$), painful neuropathy group ($25.9 \pm 7.5 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$), non-neuropathic diabetic control group ($13.5 \pm 11.6 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$), and non-diabetic control subjects ($5.2 \pm 2.4 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$). Mean of each group represented by horizontal bar. $p < 0.002$ sensory neuropathy group versus control subjects; $p < 0.001$ diabetic control patients versus control subjects

and $33.2 \pm 1.4^\circ\text{C}$ in the painful neuropathy group; Fig. 1). These were significantly greater than either of the groups without neuropathy ($p < 0.001$) – diabetic control group had a mean temperature of $27.8 \pm 4.2^\circ\text{C}$ and the non-diabetic patients $25.8 \pm 2.2^\circ\text{C}$, which were themselves not significantly different.

Fig. 3. Mid foot blood flow at rest in the sensory neuropathy group ($6.0 \pm 2.3 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$), painful neuropathy group ($5.2 \pm 1.9 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$), non-neuropathic diabetic control group ($2.3 \pm 2.9 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$) and non-diabetic control subjects ($0.8 \pm 0.5 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1}$). Mean of each group represented by horizontal bar. $p < 0.01$ sensory neuropathy group versus control subjects; $p < 0.03$ diabetic control patients versus control subjects

Blood flow

Big toe and mid-foot skin flows were similarly raised in both neuropathic groups and were significantly greater than either group without neuropathy (Figs. 2 and 3).

The neuropathic groups were shown to have similarly low pulsatility indices at rest (i.e. high blood flow): they were 3.2 ± 1.0 in the severe sensory neuropathy group and 3.6 ± 2.0 in the painful neuropathy group. These values were significantly less than either of the control groups whose pulsatility index at rest was 17.1 ± 9.5 in the diabetic control patients and 18.3 ± 5.4 in the non-diabetic control subjects ($p < 0.001$).

Sympathetic responses

The responses of both neuropathic groups to arousal stimuli are shown in Table 2. The sensory neuropathic group failed to respond to a gasp, mental summation or loud noise but gave a response (reduction of blood flow) to coughing which reached significance ($p < 0.05$, Fig. 4). Blood flow was reduced in response to all stimuli in the painful neuropathy group and the response to coughing was particularly pronounced.

Both control groups responded well to stimulation, with reduction in blood flow following the response to a cough giving pulsatility indices on average > 25 . The percentage reductions in big toe flow following the arousal stimuli are given in Table 3. The overall mean reduction for all stimuli in the sensory neuropathy

Table 2. Pulsatility index at rest and following arousal stimuli in the neuropathic groups

Arousal stimulus	Sensory neuropathy group (n=11)	Painful neuropathy group (n=7)
At rest	3.2 ± 1.0	3.6 ± 2.0
Gasp	4.2 ± 1.7	20.6 ± 11.3 ^c
Cough	4.7 ± 1.8 ^a	19.6 ± 11.1 ^c
Mental arithmetic	3.7 ± 1.5	12.7 ± 6.3 ^b
Noise	3.3 ± 0.8	16.3 ± 8.8 ^a

Results expressed as mean ± SD. ^a $p < 0.05$; ^b $p < 0.02$; ^c $p < 0.01$

Table 3. Percentage reduction in big toe blood flow following arousal stimuli in the neuropathic and diabetic control groups

Sympathetic stimulus	Reduction in big toe blood flow (%)		
	Sensory neuropathy group (n=22)	Painful neuropathy group (n=8)	Diabetic control group (n=23)
Gasp	11.1 ± 7.2	34.3 ± 26.0 ^c	33.9 ± 16.0
Cough	11.8 ± 9.3	30.8 ± 23.6 ^b	37.1 ± 15.6
Mental	11.2 ± 8.2	29.4 ± 25.6 ^a	31.5 ± 24.9
Noise	7.1 ± 5.9	33.8 ± 30.8 ^d	35.3 ± 15.8

Results expressed as mean ± SD. ^a $p < 0.05$; ^b $p < 0.025$; ^c $p < 0.01$; ^d $p < 0.001$ (sensory neuropathy versus painful neuropathy patients)

Fig. 4. Change in pulsatility index in response to a cough in the sensory neuropathy (○, n=11) and the painful neuropathy (●, n=7) groups

group was $10 \pm 6\%$ which was considerably less than amongst the painful neuropathy group in which it was $32 \pm 25\%$ (Table 3).

Reduction in foot blood flow and neuropathic symptoms

A mean ankle cuff pressure of 72 mmHg (range 55–90 mmHg) was required to reduce big toe flow to

that of the non-diabetic control subjects ($5.2 \text{ ml} \cdot \text{min}^{-1} \cdot 100 \text{ ml}^{-1} \text{ tissue}$). In four of the patients, reduction in painful burning symptoms appeared to be associated with reduction in flow. In the fifth patient, lightning pains in the feet were diminished in frequency but not abolished by cuff inflation. The mean time from cuff inflation to a pain-free state was 3.4 min (range 1.5–6.5 min). The above assessments were made from the spontaneous commentaries given during this period and were similar amongst the patients. Occlusion produced a sensation of swelling in the foot, probably as a result of the venous engorgement. Symptoms then subsided in an orderly fashion. Diminution of pain in the toes occurred before the ball of the foot, and this was followed by reduction in the sole and dorsum of the foot. Following cuff deflation and resumption of high flow, symptoms returned, being noted in the toes initially, but with rapid spread to all areas previously affected. One case reported waxing and waning of pain. This was observed to correlate with spontaneous changes in her foot sonograms. Thus, rises in pulsatility index to 9 units (i.e. fall of blood flow) were accompanied by subjective reduction in pain. When stressed by an arousal stimulus at the height of pain, the pulsatility index increased promptly (blood flow decreased) with lessening of pain.

Discussion

Blood flow in the diabetic neuropathic foot is considerably increased, and we have now shown that it is on average five times greater than that in non-diabetic subjects. Foot skin temperatures are also high in these patients reflecting the increased circulation. Comparable high blood flow rates were demonstrated both in those with severe sensory neuropathy and in those with painful neuropathy most of whom had negligible evidence of sensory loss. The high blood flow recorded in some diabetic patients without clinical evidence of neuropathy suggests that autonomic (sympathetic) impairment is sometimes the earliest feature of neuropathy, and similar observations have been made in cardiac denervation [18]. Direct measurement of sympathetic fibre discharges by microneurography has also demonstrated sympathetic loss to be a relatively common feature of diabetic neuropathy [19].

Sympathetic stimulation causes peripheral vasoconstriction – an observation which was made as long ago as 1895 [20]. We have now shown a striking difference in the ability of different groups of patients to decrease blood flow by vasoconstriction. Thus, while those with severe sensory neuropathy failed to respond to sympathetic stimulation, the group with predominantly painful neuropathy did so with considerable reduction of blood flow. This response could be explained by recruitment of previously silent sympathetic units, and it is indeed considered that the electrophysiological de-

fects in painful neuropathy might be less severe than in other neuropathic patients [13].

Reduction of high blood flow might have important therapeutic implications. Neuropathic oedema decreases when patients are given ephedrine [21] and it is possible that nutritive blood flow, impaired by arteriovenous shunting, might be improved. Many patients and physicians know that pain can be diminished by cooling the feet [9, 22] and unsatisfactory attempts have been made in the past to reduce blood flow [23]. Evidence from the present investigation suggests that reduction of blood flow might alleviate pain. This study involved the use of a sphygmomanometer cuff to reduce blood flow, and could not of course be performed as a 'blind' procedure. Nonetheless, each of five patients spontaneously observed some relief of the burning pain, which returned after release of the cuff. One patient observed fluctuations of pain which seemed to be associated with spontaneous variations of blood flow. The explanation for this apparent association between pain relief and reduction of blood flow is not known. One may speculate that sympathetic activity to some extent regulates the rate of sensory receptor firing [24] and may thus modulate painful stimuli. However, the mechanisms which underly painful neuropathy are not well understood, and the observation that both those with and without pain have a high blood flow is not explained.

We conclude that sympathetic defects resulting in high peripheral blood flow are common in diabetic neuropathy. These abnormalities may occur as the earliest feature of neuropathy but are very striking in those with established somatic neuropathy. High blood flow from sympathetic failure is usual in those with severe sensory deficit and cannot be reduced by sympathetic stimulation. This contrasts with the situation in painful neuropathy where clinical neurological signs may be few, but blood flow is both high and responsive to sympathetic stimulation. The reduction of blood flow which results from sympathetic stimulation appears to be associated with diminution of pain. This preliminary observation and the fact the artificial flow reduction relieves pain needs further investigation.

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