Microvascular and C-fibre function in Diabetic Charcot Neuro-arthropathy and Diabetic Peripheral Neuropathy

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Abstract

Objective
Sympathetic denervation and hyperaemia are implicated in the pathogenesis of Charcot neuro-arthropathy (CN) but also features of diabetic peripheral neuropathy (DPN). Differences in these physiological parameters were sought by determining C-fibre function (LDI flare) and maximum microvascular hyperaemia (MMH) in 13 subjects with diabetic CN (DCN), 10 diabetic neuropaths (DPN) and 10 healthy controls (HC). Additionally, unaffected limbs of the 9 DCN with unilateral charcot (UCN) were studied to determine whether any observed differences precede CN.

Results
The LDI flare was reduced in DPN (1.41 ± 0.51, cm²±SD) and DCN groups (1.42 ± 0.37) compared to HC (5.24 ± 1.33), p<0.0001. MMH was higher in DCN (432 ± 88 PU±SD) than DPN (262 ± 71), p=0.001, though lower than HC (564 ± 112) p < 0.01.

Conclusion
C-fibre function is equally impaired in neuropathic patients with and without CN, however a higher MMH distinguishes those with CN. Unaffected and affected limbs of those with unilateral CN have the same neuro-vascular abnormalities suggesting these precede rather than result from CN.
Introduction

Peripheral sensory neuropathy and autonomic dysfunction are accepted prerequisites for the development of Charcot neuro-arthropathy (CN) but are also features of diabetic peripheral neuropathy (DPN) (1,2). CN is rare compared to DPN, suggesting additional factors are involved in its pathogenesis. Small fibre neuropathy, measured with quantitative sensory testing has been implicated in its development (3,4). Moreover a relatively higher maximum microvascular hyperaemia (MMH) has been reported (5,6); however, whether this is a result of CN or pre-existing is unknown. This study examines these features in greater detail. Small fibre neuropathy was assessed using the LDIflare technique (7), a more sensitive test of small fibre function than quantitative sensory testing. MMH was assessed using the LDImax technique (8). The unaffected foot in those with CN was also studied to determine whether any defects in these measures are pre-existing and therefore aetiological, or consequential of CN.

Research Design and Methods

Four matched groups were studied: Group DPN – 10 subjects with Type 2 diabetes (T2DM) and neuropathy (age 67.2 ±7.1yr; duration 19 ±8.1yr; VPT 30.3 ±6.0volts), Group DCN – 13 with T2DM and quiescent CN (65.5 ±8.7yr; 20 ±11.3yr; 36.1 ±9.7volts) [4 with bilateral and 9 with unilateral CN], Group UCN – the 9 subjects with unilateral CN from group DCN in whom the unaffected limb was studied (64.7 ±10.2yr; 21 ±10.2yr; 33.5 ±8.1volts) and Group HC – 10 healthy subjects (61.4 ±9.7yr; 8.0 ±2.1volts).

Neuropathy was present if 2 or more of 4 sites on the plantar foot were insensitive to 10g monofilaments and if the Vibration Perception threshold (VPT) at the hallux was > 24 volts (Neurothesiometer™ Horwell Scientific, Nottingham, UK). CN was determined by clinical and radiological examination. All affected joints had been quiescent (<2°C difference between limbs) and ulcer free for more than 18 months.

The LDIflare and LDImax were assessed using a Laser Doppler Imager (LDI) (Moor instruments, Devon U.K) These methods have been validated and are described in detail elsewhere (9). Briefly, after acclimatisation, a baseline scan was performed on a 7.5x4cm area on the dorsum of the foot using the LDI. The skin was then heated to 44°C for 20 minutes using a 0.64cm² circular skin heater and then rescanned immediately after its removal. Heating indues MMH (LDImax) underneath the heater but also hyperaemia in the surrounding skin due to axon-reflex mediated vasodilatation (LDIflare). From the computer-generated flux images, the LDIflare area (cm²) and the LDImax (perfusion units [PU]) are derived. The coefficient of variations for the LDIflare and LDImax were 6.8% and 6.4% respectively.

Variables from the groups were compared using one-way ANOVA and Tukey tests.

Results

All subjects were matched for age and sex, and those with diabetes for duration and HbA1c.

LDIflares were markedly reduced in all diabetic groups compared to the HC group (p<0.0001 for each group) [Figure 1]. In the UCN patients, there was no difference in the LDIflare...
area \( \text{cm}^2 \pm \text{SD} \) between the unaffected \((1.14 \pm 0.51)\) and affected limbs \((1.42 \pm 0.37)\). LDImax (PU \pm \text{SD}) was also markedly impaired in the DPN group \((262 \pm 71)\) compared with the HC group \((594 \pm 94, \ p<0.0001)\) [Figure 1]. In contrast to the LDIflare findings, LDImax in the DCN group \((432 \pm 88)\) and UCN group \((417 \pm 110)\) was significantly greater compared to the DPN group \([262 \pm 71] \ p<0.001\) and \(p<0.01\) respectively] although lower than the HC group \((594\pm 110, \ \text{both} \ p<0.01)\). Finally, there was no difference in the LDImax between the unaffected \((417 \pm 110)\) and affected limbs \((432 \pm 88)\) in the UCN group.

**Conclusion**

The principal findings were 1) C-fibre function assessed by the LDIflare technique is severely impaired in CN and indistinguishable from those with DPN alone; 2) MMH is relatively preserved in CN and significantly higher than those with neuropathy alone, and 3) affected and unaffected limbs of patients with CN have similar C-fibre dysfunction and MMH.

The reduced MMH in the DPN group is not unexpected, having been described in a variety of diabetic states including IGT (10-12). What is surprising is the relative preservation of MMH in the DCN groups as this would be expected to be worse, or similar to, but not significantly better than, the relatively less complicated DPN group. The latter findings are supported by other studies (13,14).

As first suggested by Charcot (17,18), bone resorption as a result of increased bone perfusion secondary to the sympathetic denervation may be implicated in the development of CN (19). Preservation of the MMH in CN is consistent with hyperaemia being involved. In contrast in those with DPN without CN the observed lower hyperaemic responses may be protective.

Bone dissolution, which is the hallmark of the condition, is dependent on osteoclastic activatisation by a system of cytokines, the RANKL-NFKB system (20-22). This system is activated in diabetes (23-25) and inhibited by neuropeptides (26); an imbalance of these in CN has been suggested to activate the RANKL-NFKB system resulting in protracted inflammation (27).

Heat-induced vasodilatation is thought to be proportional to the expression of nitric oxide synthase (NOS) (28,29). The production of inducible NOS is increased by the activation of RANKL-NFKB (30), consequently increased MMH may be expected if the RANKL-NFKB were activated.

Protracted inflammation in combination with the absence of modifying sympathetic tone and neuropeptides may lead to unrestrained and prolonged hyperaemic bone perfusion, contributing to the bone dissolution in CN. The relatively high MMH seen in the skin of those with CN would support the latter suggestion of hyperaemic bone blood flow.

The finding of a high MMH in affected and unaffected limbs of those with CN suggests that this abnormality is pre-existing. A high MMH may thus be implicated in development of CN, rather than be secondary to changes in the local
microcirculation as a consequence of CN.

This study supports the suggestion that preserved MMH is a pre-requisite for the development of CN (31,32). Understanding why vascular reactivity is retained may be important in discovering the cause and identifying treatments for CN.
Reference List


Figure 1