Microvascular and C-Fiber Function in Diabetic Charcot Neuroarthropathy and Diabetic Peripheral Neuropathy

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OBJECTIVE — Sympathetic denervation and hyperemia are implicated in the pathogenesis of Charcot neuroarthropathy (CN) but are also features of diabetic peripheral neuropathy (DPN). Differences in these physiological parameters were sought by determining C-fiber function (laser Doppler imager [LDI]flare technique) and maximum microvascular hyperemia (MMH) in 13 subjects with diabetic CN (DCN), 10 subjects with DPN, and 10 healthy control subjects. Additionally, unaffected limbs of the nine DCN subjects with unilateral CN (UCN) were studied to determine whether any observed differences precede CN.

RESULTS — LDIflare area was reduced in DPN (mean ± SD 1.41 ± 0.51 cm^2) and DCN (1.42 ± 0.37) groups compared with the healthy control group (5.24 ± 1.33; $P < 0.0001$). MMH was higher in DCN (432 ± 88 PU [perfusion units]) than in DPN (262 ± 71; $P = 0.001$) subjects but lower than in the control group (564 ± 112; $P < 0.01$). LDIflare area and MMH were similar in the UCN and DCN groups.

CONCLUSIONS — C-fiber 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 neurovascular abnormalities, suggesting that these abnormalities precede CN and are not a result of CN.

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Peripheral sensory neuropathy and autonomic dysfunction are accepted prerequisites for the development of Charcot neuroarthropathy (CN) but are also features of diabetic peripheral neuropathy (DPN) (1,2). CN is rare in comparison with DPN, suggesting that additional factors are involved in its pathogenesis. Small-fiber neuropathy, measured with quantitative sensory testing, has been implicated in its development (3,4). Moreover, a relatively higher maximum microvascular hyperemia (MMH) has been reported (3,4); however, whether this is a result of CN or preexisting is unknown. This study examines these features in greater detail. Small-fiber neuropathy was assessed using the laser Doppler imager (LDI)flare technique (5), a more sensitive test of small-fiber function than quantitative sensory testing. MMH was assessed using the LDImax technique (5). The unaffected foot in those with CN was also studied to determine whether any defects in these measures were preexisting, and therefore etiological, or consequential of CN.

RESEARCH DESIGN AND METHODS

— Four matched groups were studied: the DPN group, 10 subjects with type 2 diabetes and neuropathy (aged 67.2 ± 7.1 years, diabetes duration 19 ± 8.1 years, vibration perception threshold [VPT] 30.3 ± 6.0 V); the DCN group, 13 subjects with type 2 diabetes and quiescent CN (aged 65.5 ± 8.7 years, diabetes duration 20 ± 11.3 years, VPT 36.1 ± 9.7 V) (4 with bilateral and 9 with unilateral CN); the unilateral CN (UCN) group, 9 subjects with UCN from the DCN group in whom the unaffected limb was studied (aged 64.7 ± 10.2 years, diabetes duration 21 ± 10.2 years, and VPT 33.5 ± 8.1 V); and the control group, 10 healthy subjects (aged 61.4 ± 9.7 years, VPT 8.0 ± 2.1 V).

Neuropathy was present if two or more of four sites on the plantar foot were insensate to 10-g monofilaments and if the VPT at the hallux was >24 V (Neurothesiometer; Horwell Scientific, Nottingham, U.K.).

CN was determined by clinical and radiological examination. All affected joints had been quiescent (<2°C difference between limbs) and ulcer free for over 18 months.

The LDIflare and LDImax were assessed using an LDI from Moor Instruments (Devon, U.K.). These methods have been validated and are described in detail elsewhere (5). Briefly, after acclimatization, a baseline scan was performed on a 7.5 × 4 cm area on the dorsum of the foot using the LDI. The skin was then heated to 44°C for 20 min using a 0.64-cm^2 circular skin heater and then rescanned immediately after its removal. Heating induces MMH (LDImax) underneath the heater but also hyperemia in the surrounding skin due to axon-reflex–mediated vasodilatation (LDIflare). From the computer-generated flux images, the LDIflare area (centimeters squared) and the LDImax (PU [perfusion units]) are derived. The coefficients of variation for the LDIflare and LDlmax 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 A1C.

LDIflares were markedly reduced in all diabetic groups compared with the control group ($P < 0.0001$ for each

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Abbreviations: CN, Charcot neuroarthropathy; DCN, diabetic CN; DPN, diabetic peripheral neuropathy; LDI, laser Doppler imager; MMH, maximum microvascular hyperemia; NF-κB, nuclear factor-κB; RANKL, receptor activator of the NF-κB ligand; UCN, unilateral CN; VPT, vibration perception threshold.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

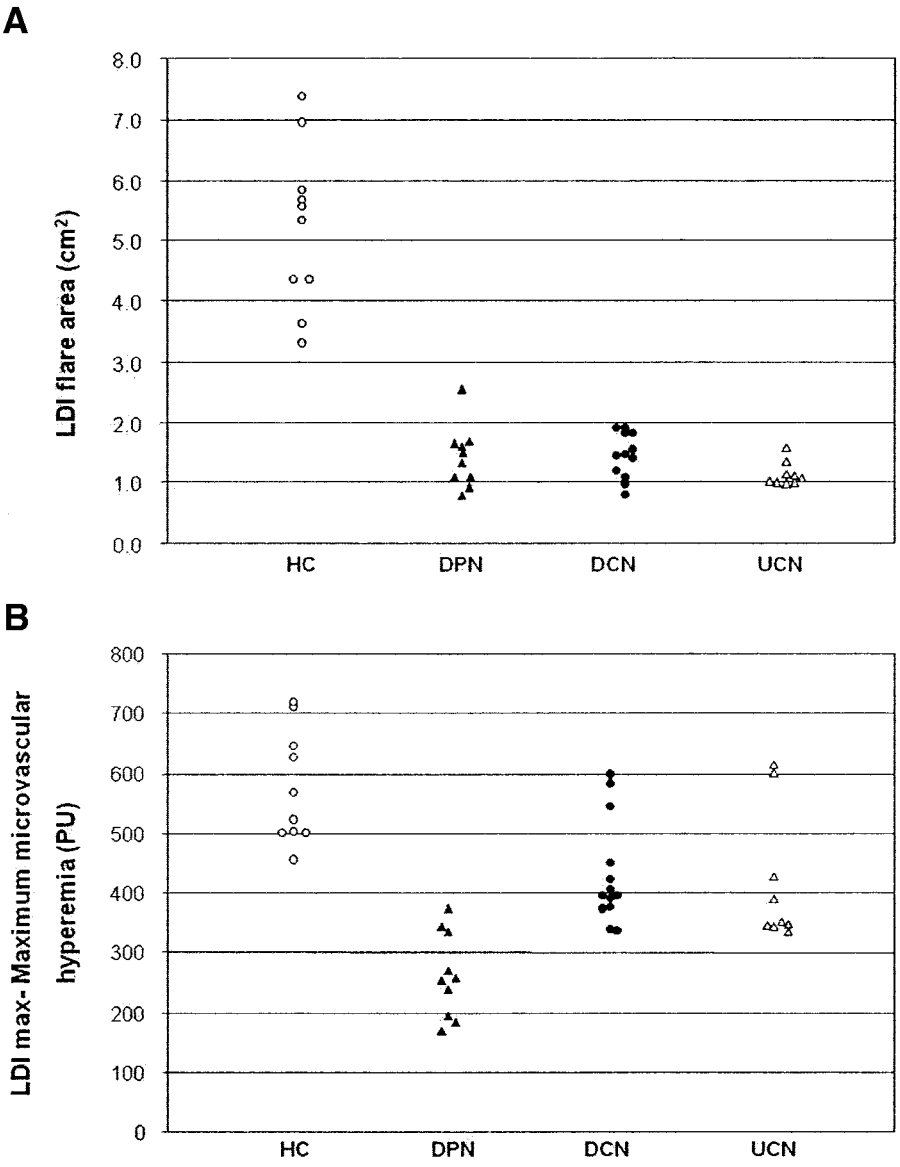

Figure 1—*A: C-fiber function measured by the LDIflare technique. B: Maximum microvascular hyperemic response measured using LDImax technique. HC, healthy control group.*

group) (Fig. 1). In the UCN patients, there was no difference in LDIflare area between the unaffected (1.14 ± 0.51 cm^2) and the affected (1.42 ± 0.37 cm^2) limbs. LDImax was also markedly impaired in the DPN group (262 ± 71 PU) compared with the control group (594 ± 94, $P < 0.0001$) (Fig. 1). In contrast to the LDIflare findings, LDImax in the DCN (432 ± 88) and UCN (417 ± 110) groups was significantly greater than in the DPN group (262 ± 71; $P < 0.001$ and $P < 0.01$, respectively) but lower than in the control group (594 ± 110, both $P < 0.01$). Finally, there was no difference in the LDImax between the unaffected (417 ± 110) and affected (432 ± 88) limbs in the UCN group.

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

The reduced MMH in the DPN group is not unexpected, having been described in a variety of diabetic states including impaired glucose tolerance (6–8). 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 (9,10), bone resorption as a result of increased bone perfusion secondary to the sympathetic denervation may be implicated in the development of CN (11). Preservation of the MMH in CN is consistent with hyperemia being involved. In contrast, in those with DPN without CN, the observed lower hyperemic responses may be protective.

Bone dissolution, which is the hallmark of the condition, is dependent upon osteoclastic activativation by a system of cytokines, the receptor activator of the nuclear factor-κB (NF-κB) ligand (RANKL)–NF-κB system (RANKL–NF-κB) (10,12,13). This system is activated in diabetes (14–16) and inhibited by neuropeptides (13). Thus, diabetic neuropathy may favor RANKL–NF-κB system activation and may lead to protracted inflammation in CN (10).

Heat-induced vasodilatation is thought to be proportional to the expression of NO synthase (4,17), and RANKL–NF-κB activation increases the production of inducible NO synthase (18).

Protracted inflammation in combination with the absence of modifying sympathetic tone and neuropeptides may lead to unrestrained and prolonged hyperemic 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 hyperemic bone blood flow.

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

This study supports the suggestion that preserved MMH is a prerequisite for the development of CN (3,4). Understanding why vascular reactivity is retained may be important in discovering the cause and identifying treatments for CN.

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