



Tactile allodynia in patients with postherpetic neuralgia: Lack of change in skin blood flow upon dynamic stimulation

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Abstract

Tactile allodynia is a common, troublesome feature of neuropathic pain. Allodynia has been proposed to involve abnormal A β -afferent coupling in the dorsal horn resulting in C-fibre activation and increased skin blood flow (SBF). Thus, changes in SBF could provide an objective measure of allodynia. We searched for this mechanism in patients with postherpetic neuralgia (PHN) with varying degrees of cutaneous sensory loss. We mapped the allodynic area in PHN patients using cotton buds and von Frey hairs. Quantitative thermal testing was performed to assess small fibre function in the affected and mirror-image areas. At a subsequent visit the area of allodynia was remapped. Then the SBF in the affected and control areas was quantified before and after allodynic stimulation using laser Doppler imaging and subsequent single point continuous monitoring to detect rapid changes. We enrolled 10 PHN patients (medians: age 77 yrs, duration 20 months, ongoing pain 5). The allodynic area (range 11–546 cm²) was stable across the sessions. Thermal testing showed similar ($n=5$) or reduced ($n=5$) warmth and pain sensation in the affected versus control area. Following allodynic stimulation (median evoked pain-5) we saw no changes in SBF using either imaging (repeated measures ANOVA, $P=0.73$) or single point monitoring. This was the case for all patients regardless of the degree of sensory impairment in the affected dermatome. In conclusion, in a representative population of PHN patients we found no evidence of changes in SBF in response to allodynic stimulation. Hence, SBF measurements are not suitable for assessing allodynia.

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1. Introduction

Neuropathic pains result from damage to the nervous system and constitute a heterogeneous group of syndromes. A significant proportion of patients are left with distressing and disabling symptoms because current treatments often bring only partial pain relief (Sindrup and Jensen, 1999). Despite continued efforts, most novel analgesic compounds fail in clinical development due to lack of efficacy (e.g.

substance P antagonists (Hill, 2000)). It has been argued that more progress could be achieved if pain were classified and treated according to the underlying mechanisms (Woolf, 2004; Woolf et al., 1998); however, the pathophysiology of neuropathic pain remains poorly understood. Another limitation in the development of new analgesics is lack of robust, objective measures of pain, as standard clinical endpoints rely on subjective assessments.

Allodynia, the perception of innocuous stimuli as painful, is often associated with neuropathic pains. It causes significant discomfort in patients, but the mechanistic and diagnostic implications of its presence and characteristics are unclear. There is evidence that experimentally-evoked tactile allodynia in humans is triggered by activation of A β low

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threshold mechanoreceptors (Koltzenburg et al., 1992; Torebjörk et al., 1992). Both central and peripheral changes in neuronal excitability and connectivity have been implicated in the generation of allodynia (e.g. (Coderre et al., 1993; Fields et al., 1998; Woolf and Doubell, 1994). Although there is much support from animal studies for these hypotheses, it is difficult to test for their presence in humans.

In this respect it is interesting that one proposed mechanism of allodynia, implicating abnormal presynaptic coupling between A β and C-fibre afferents (Cervero and Laird, 1996a,b), should be testable in patients with neuropathic pain. According to this hypothesis, abnormally high levels of C-fibre input (e.g. following nerve injury) can shift the balance of sensory gating between A β - and C-afferents. This is mediated by spinal cord interneurons (via primary afferent depolarisation, PAD) such that A β -fibre-mediated tactile input activates nociceptive C-fibres. Whilst the anterograde conduction of such excitation leads to pain (allodynia), retrograde firing of C-fibres should evoke the release of vasoactive substances in the skin causing vasodilatation. Such abnormal afferent coupling has been demonstrated in animal and human experimental models of allodynia (Cervero and Laird, 1996a) although this has been controversial (Wasner et al., 1999). To date there is no evidence for the involvement of this mechanism in neuropathic pain in humans.

We have looked for this mechanism in patients with postherpetic neuralgia (PHN). This pain syndrome follows reactivation of latent herpes zoster in dorsal root ganglia and subsequent neural damage (Watson et al., 1991). Clinically, the condition presents with a mixture of spontaneous pain and hypersensitivity to noxious (hyperalgesia) and/or non-noxious (allodynia) stimuli (Nurmikko and Bowsher, 1990). The painful area is often stable over time and well-defined, being unilaterally limited to contiguous dermatomes, which facilitates quantitative sensory testing. Therefore, we looked for skin blood flow changes following tactile stimulation in PHN patients, in an effort to understand the significance of afferent coupling and, if present, describe it as a peripheral marker of allodynia.

2. Materials and methods

2.1. Study population

Patients were recruited from our pain clinic or from the community after referral by their general practitioner. We sought patients with at least a 3 month history of pain following resolution of their shingles rash, symptoms suggestive of allodynia and moderate or severe daily pain. Patients were given verbal and written study information before being invited to attend for the study visits. The study was approved by our hospital ethics committee and was conducted in accordance with the Declaration of Helsinki.

Patients attended clinic for an initial enrolment visit and then subsequently for a testing visit. On the enrolment visit, a clinical history was obtained followed by a physical examination to confirm that the patient had PHN with allodynia. Subjects were excluded if they had an area of allodynia that was facial or genital, if they were unable to cooperate with or tolerate the testing or were currently using a topical treatment (i.e. capsaicin cream or lidocaine patches). Once the patient had been determined as suitable for the study then written informed consent was obtained. Subjects continued on their current medication during the testing sessions (Table 1).

2.2. Testing procedures

Quantitative sensory testing (QST) was performed according to the following protocol. The subject acclimatised for at least 15 min in a temperature-controlled room (22 ± 1 °C). The approximate boundaries of the area of allodynia were determined with a cotton bud. Then a regular grid (2 cm intervals) was marked on the skin using perforated bubble wrap and a washable felt tip pen (see Fig. 1A). A cotton wool bud was used to lightly stroke the skin (2–3 cm/s) and the subject was asked to report if the sensation was normal or unpleasant and/or painful. The area of dynamic allodynia was mapped by applying the stimulus sequentially at points on the grid from a distant site into the affected dermatome. Once a complete boundary had been defined the area was transcribed onto clear film. The process was repeated to identify the area of tactile hypersensitivity using a von Frey hair (260 mN, normally felt as a slight pinprick).

We determined the thermal sensory thresholds for the affected dermatome and a contralateral mirror site using a 3×3 cm

Table 1
Patient characteristics

Patient	Sex	Age (years)	Dermatome	Area of allodynia (cm ²)	Duration (months)	Pain score (NRS 0–10)	Current treatment
1	F	74	T5 right	200	24	7	P, C
2	M	66	T11–12 left	98	6	3	None
3	M	81	T3 right	456	84	4	MST
4	F	89	T5–T6 left	307	180	6	G, Cl, T
5	M	79	T3 left	339	84	7	G, M, Ser
6	M	79	L2–3 left	533	15	5	G, AA
7	F	77	C2–3 left	157	48	5	G, P
8	F	57	T3 left	11	3	5	C, P
9	F	72	T4–5 right	186	9	8	G, O
10	F	77	T4–5 left	57	9	10	G, P

NRS: numerical rating scale; P: paracetamol; C: codeine; MST: slow release morphine; G: gabapentin; Cl: clonazepam; T: TENS machine; M: methadone; Ser: sertraline; AA: aspirin and acetone solution; O: oxycodone.

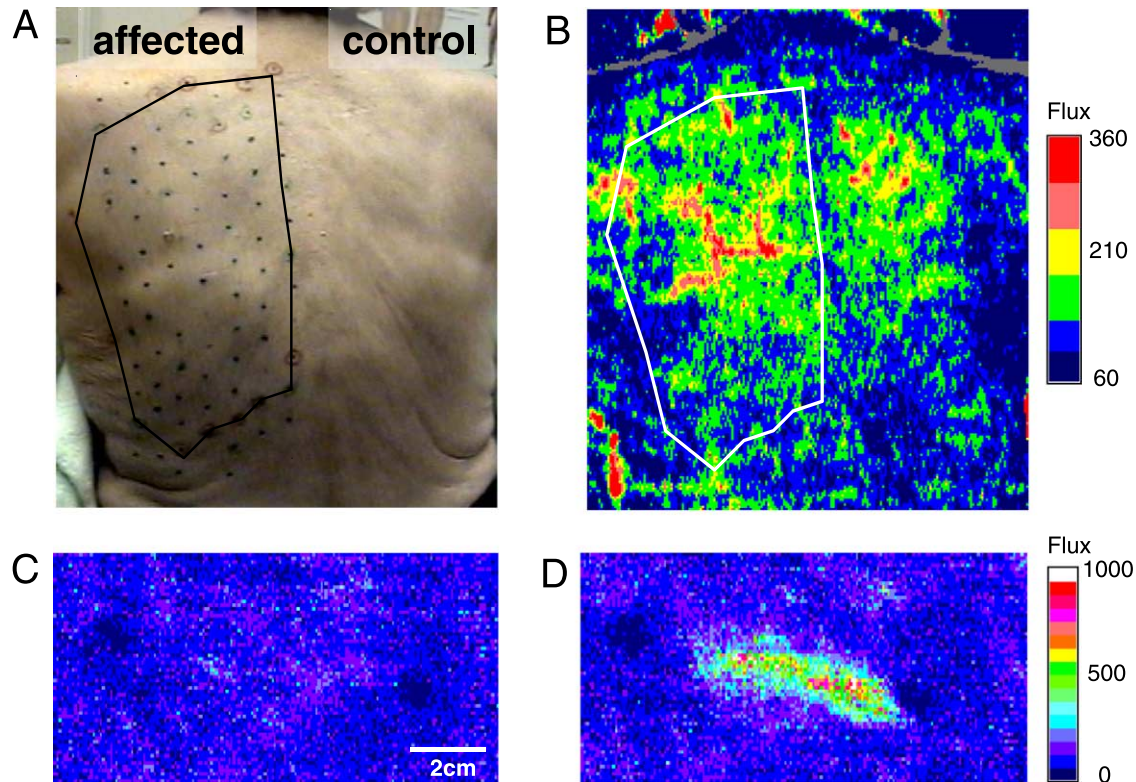


Fig. 1. (A) Subject had shingles affecting the T4 dermatome some 16 years earlier. A grid has been marked with points at 2 cm intervals covering the painful area. The boundaries of the area of allodynia were defined (outlined) using a cotton bud to stroke the skin over each marked point. Stimuli were applied sequentially starting from a normal area and working into the affected zone. (B) Image of the baseline cutaneous blood flow over the subject's back using a laser Doppler imaging device (Moor LDI II). The skin blood flow is non-homogenous over the back with an increased flow in the affected area. (C) Skin blood flow image of an 11.6×4 cm area before and 1 min after (D) a gentle scratch with an orange stick showing a dramatic localised increase in flow associated with the flare response. Dark areas show location of skin markers.

thermode (TSA-II Neurosensory analyser, Medoc, Israel). We identified a site within the area of allodynia, in which the contact of the thermode with the skin was considered tolerable. The thermode surface had a baseline temperature of 32°C and was cooled and heated within a range of 0 – 50°C . Cold and warm detection thresholds (CDT, WDT, 1°C/s) and then cold pain and heat pain thresholds (CPT, HPT, 1.5°C/s) were assessed using the method of limits. Three (CPT, HPT) or four (CDT, WDT) tests were performed for each modality and the average value recorded. The thresholds were determined first in a control area (mirror-image site) and then on the affected side.

At the end of the session, we obtained a baseline skin blood flow (SBF) image in the affected and in the control area. This was done to introduce the subject to the Laser Doppler imaging (LDI) equipment (LDI Mark 2, Moor Instruments, UK). The technique utilises the Doppler principle whereby light from a monochromatic stable laser (wavelength = 690 nm , power = 2.5 mW) incident on the skin is scattered by moving red blood cells and as a consequence the frequency is broadened. The reflected light is detected and the resulting photocurrent processed to provide a blood flow measurement. In the LDI, the laser beam is scanned across the skin surface in a raster fashion using a moving mirror. The blood flow is mapped and colour coded images of the blood flow are displayed (Fig. 1B).

The testing session started with a baseline SBF scan, followed by sensory mapping of areas of dynamic allodynia and pin-prick hyperalgesia, and then by another SBF scan to detect

any changes caused by the mapping process. Within the area of dynamic allodynia, a region was identified in which brushing with a cotton wool bud evoked the maximum pain that the patient could tolerate. We then marked the ends of a 10 cm line across this area with sticky dots applied to the skin. The LDI was set to image an area of 11.6 by 4.2 cm resolved into pixels of 0.67 mm^2 . Each scan took 80 s. Using a cotton bud we stroked along this line at 2 – 3 cm/s . We applied stimuli every 6 s over a 1-min period ($n=10$). The patients were asked to concurrently rate their pain using an 11-point numeric rating scale (NRS, 0=no pain, 10=maximum pain imaginable). The SBF was imaged before and at 1, 3, 5, 10 and 15 min after the stimulation (six images). The same protocol was repeated in the contralateral mirror area. To ensure that we did not miss any fast events because of the limited time resolution of SBF imaging we repeated the stimulation on the affected side using single point continuous SBF monitoring, collecting data for 1 min before (baseline), during and for 2 min after the allodynic stimulation. At the end of the testing session, the area of tactile allodynia was re-mapped. In each session care was taken to perform the sensory mapping and allodynic stimulation in a uniform way (by a single operator M.B.).

2.3. Statistical analysis

Differences in thermal sensory thresholds between affected and control areas were calculated as differences between the respective

median values. The areas of allodynia were quantified in cm^2 . The changes in the area of dynamic allodynia and of tactile hypersensitivity over the testing sessions were assessed using paired, two tailed *t*-test. Prior to this, the Gaussian nature of the distribution of the data was confirmed using the Kolmogorov–Smirnov test. The relationship between the area of allodynia and the pain rating scores was examined using linear regression. The LDI data were taken from a 10 pixel width profile along the line of stimulation (Fig. 2) and presented as relative flux units. Comparisons were made using repeated measures ANOVA comparing the mean flux value at each of the time points. The level of significance was set at $P < 0.05$.

3. Results

Ten PHN patients (six women, four men) with a median age of 77 years (range 57–89) were included in the study after written informed consent. The median duration of pain since rash resolution was 20 months (range 3–180 months). Patient characteristics are shown in Table 1. All of the subjects had a clearly defined unilateral area of tactile allodynia that was amenable to sensory mapping. The area of tactile allodynia and pinprick hyperalgesia remained relatively stable across the two testing sessions (Pearson

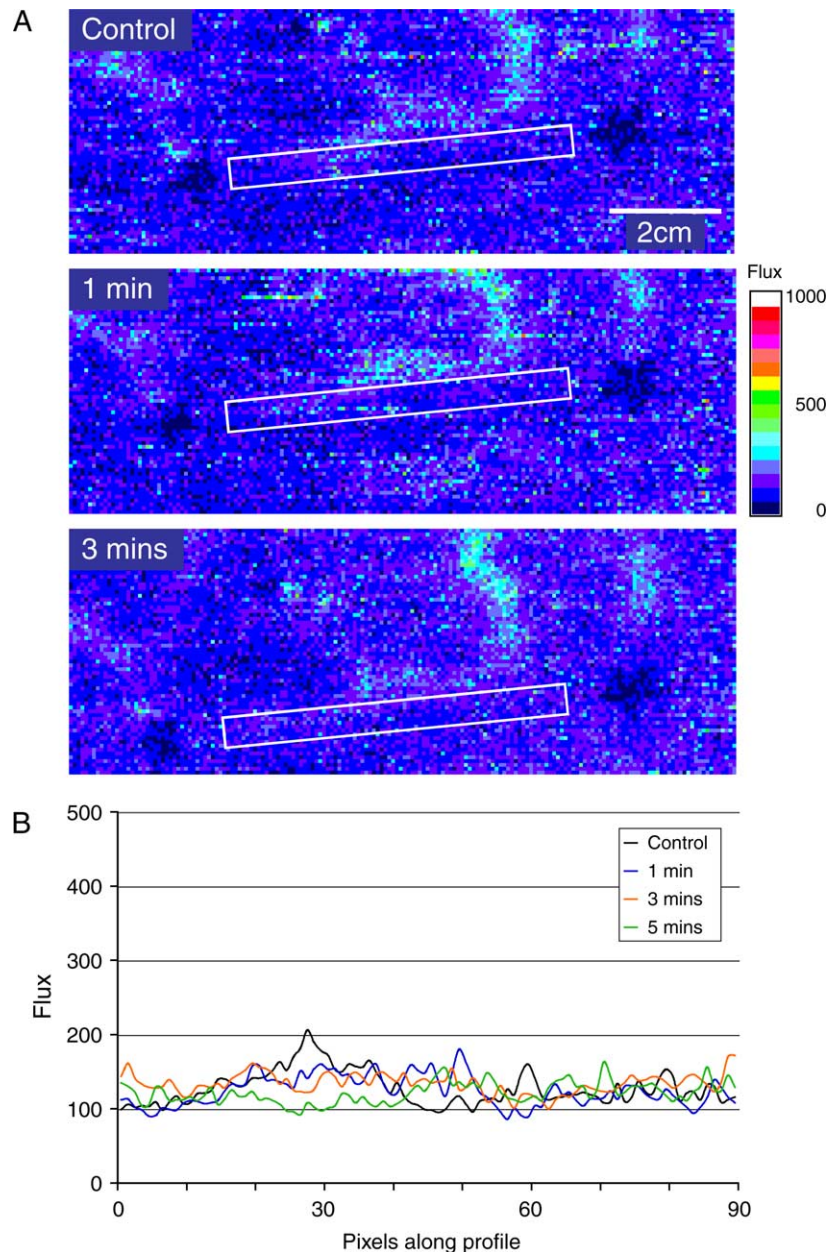


Fig. 2. Sequential skin blood flow images taken before and after allodynic stimulation. The skin was stroked with a cotton bud (2–3 cm/s) along a line connecting two markers (dark stars). No clear change in skin blood flow was observed. (A) This data was quantified by taking a blood flow profile along the line connecting the skin markers (shown by white box in A). These flux profiles are shown before, and 1, 3 and 5 min after the stimulus. No significant change was observed in the skin blood flow following cotton bud stimulation.

correlation r values 0.88 and 0.7 and P values of 0.002 and 0.05, respectively). Thus, the average area of allodynia was $234 \pm 54 \text{ cm}^2$ (mean \pm SE) in the first session and $195 \pm 56 \text{ cm}^2$ in the second ($P=0.17$, paired t -test); for hyperalgesia these values were 162 ± 36 and $223 \pm 64 \text{ cm}^2$ ($P=0.24$). There was a significant correlation between the area of tactile allodynia and pinprick hyperalgesia (allodynic area = $0.82 \times$ hyperalgesic area + 85, $R^2=0.58$, $P < 0.001$). There was no significant correlation between the area of allodynia or hyperalgesia and the baseline pain score ($R^2=0.11$ and 0.05, respectively) in agreement with previous reports (Petersen et al., 2000). None of our subjects had a demonstrable area of hypoaesthesia.

The thermal perception and pain thresholds were compared between the affected and control sides (Table 2). There was a broad range of differences in thermal perception thresholds seen across the subjects with some demonstrating little or no loss of function ($n=5$) and others demonstrating moderate or severe thermal hypoaesthesia ($n=5$).

The LDI data are based on the results from eight subjects. One subject dropped out after the first testing session. A second subject with a short history of PHN and a small area (11 cm^2) of allodynia, reported no allodynia on repeat testing some two weeks later. Baseline LDI showed the expected non-homogenous blood flow across both the affected and the control dermatomes. In several of the subjects we observed a higher baseline SBF in the affected dermatome when compared to the control dermatome (see Fig. 1B) as has been reported previously for PHN patients using thermography (Rowbotham et al., 1998). No change in SBF was observed in response to mapping the allodynic area.

Repeated brushing of the affected dermatome with a cotton bud (10 strokes over 1 min) evoked allodynia in all subjects (median of 5 on NRS, range 1–9). Visual inspection of consecutive images of the affected area before and after the application of this stimulus showed no change in the SBF. Detailed analysis of the blood flow profile along the line of stimulation also failed to show any change following

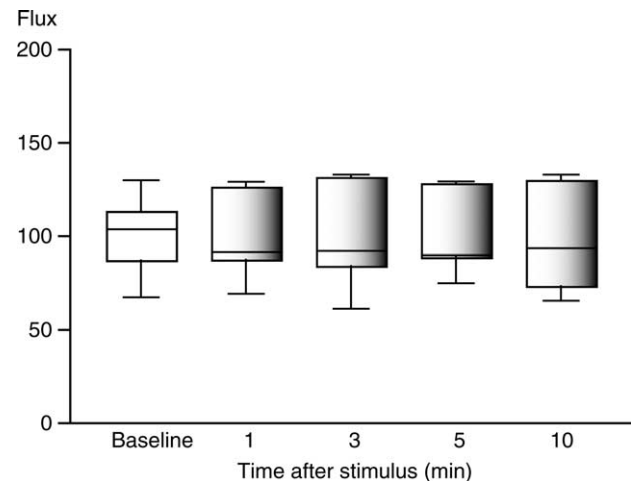


Fig. 3. Laser Doppler images of blood flow were taken before and at intervals after repeated allodynic stimulation. The flux profile between the skin markers was measured and the pooled data are presented from all subjects (5th, 25th, 50th, 75th and 95th centiles). There was no significant change in the flux at any time point after allodynic stimulation (repeated measures ANOVA, $P=0.73$).

stimulation of either the control or affected areas (see Figs. 2 and 3, repeated measures ANOVA, $P=0.73$).

Because of the delay between the application of the stimulus and the completion of acquisition of the first SBF image (80 s), we could not exclude that rapid, brief changes in SBF had been evoked by allodynic stimuli but overlooked by the imaging method. Therefore, we repeated the allodynic stimulation and monitored for blood flow changes in real time using a single point measurement on the line of stimulation. This showed very brief apparent alterations in the SBF signal associated with each cotton bud stroke that never outlasted the duration of the stimulus by more than a few seconds (Fig. 4). These brief changes in SBF during the allodynic stimulation were seen in both affected and control areas and were similar in subjects with and without pronounced thermal hypoaesthesia.

4. Discussion

One of the objectives of the present work was to investigate the role of abnormal afferent coupling as a potential mechanism of allodynia, which could lead to the development of an objective marker of afferent dysfunction in neuropathic pain. The original hypothesis implies that PAD of nociceptive fibres by spinal interneurons responding to tactile input, which normally serves as a sensory gating mechanism, can lead to generation of action potentials (dorsal root reflex) spreading along the nociceptive pathways (allodynic pain) and, retrogradely, into peripheral nerve terminals (Cervero and Laird, 1996a,b). This theory is based on data from human and animal experimental models of allodynia, where changes in SBF could be observed following tactile stimulation (reviewed in

Table 2
Thermal sensory testing

Patient	Δ Warm detection threshold	Δ Heat pain threshold
1	6.0	10.5
2	-1.2	3.4
3	5.7	9.0
4	1.7	-0.7
5	8.7	4.3
6	-2.6	-1.6
7	7.4	6.3
8	3.5	5.0
9	1.5	-1.3
10	0.9	-0.7

Values from control side are subtracted from values on affected side to give a delta value ($^{\circ}\text{C}$). Positive numbers indicate a higher threshold on the affected side.

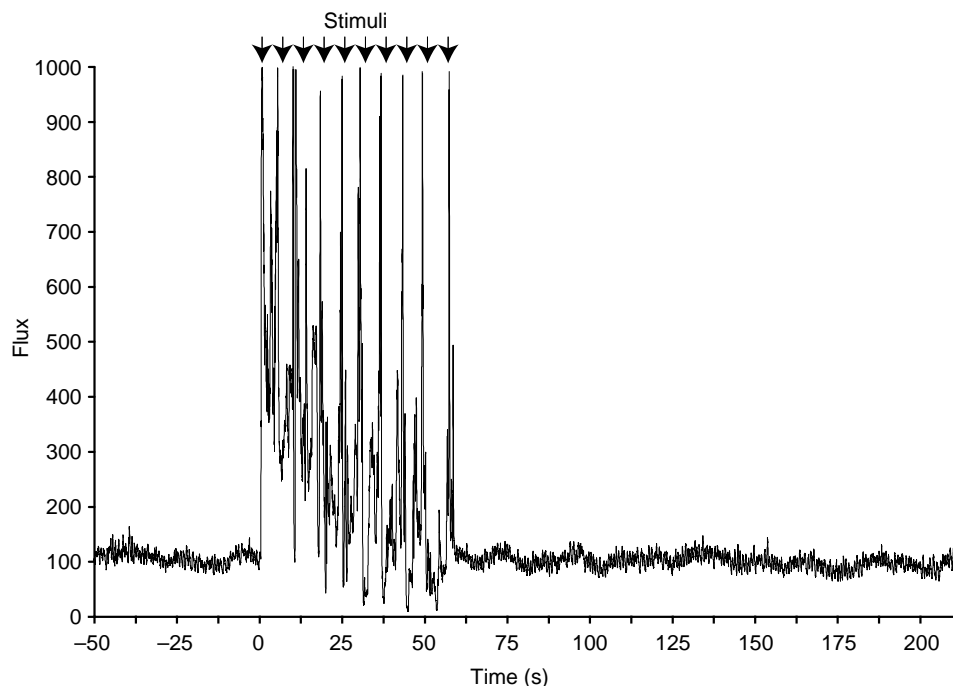


Fig. 4. Skin blood flow monitored at a single point before, during and after repeated allodynic stimulation (arrows). The baseline blood flow shows a pulse related and a slower respiratory related oscillation. During the stimulation there are a series of artefacts as the cotton bud strokes the skin. Immediately after the stimulation the pattern of blood flow is unchanged with no shift in the level of skin perfusion.

(Cervero et al., 2003), but note (Wasner et al., 1999)). We have investigated this mechanism in PHN patients.

In designing this study we were mindful of the heterogeneity of symptoms in PHN, and indeed of the differences in the degree of sensory loss in the affected dermatome(s) (Rowbotham and Fields, 1989, 1996). Although spontaneous pain and allodynia may be present in all subgroups, patients with a profound sensory loss are characterised by a relative predominance of spontaneous pain, whereas those with minimal sensory impairment typically present with pronounced allodynia (Fields et al., 1998; Rowbotham and Fields, 1989). The degree of impairment of unmyelinated (C) or thinly myelinated (A δ) fibre function in PHN can be gauged by quantifying thermal detection and pain thresholds (Nurmikko and Bowsher, 1990). Indeed in PHN patients with intact thermal sensory thresholds the density of skin innervation appears normal whereas in those with impaired thermal sensation it is decreased (Fields et al., 1998; Rowbotham et al., 1996). Furthermore, PHN patients with preserved thermal sensation have normal C-fibre vasoactive function (axon reflex flare), as recently demonstrated by direct histamine iontophoresis to the skin (Wasner et al., 2005). It has been argued that because allodynia is also found in some PHN patients with impaired C-fibre function, these fibres are unlikely to be involved in the aetiology of allodynia (Baron and Saguer, 1993). Nevertheless, it seems that it is the group of PHN patients with preserved small fibre innervation of the skin that is most suitable for investigating the role of afferent coupling in the pathogenesis of allodynia. It should

be possible in these patients to detect C-fibre activation by assessing axon reflex flare in the skin.

In the present work, we have found no evidence of changes in SBF in response to dynamic tactile stimulation in PHN patients with allodynia, regardless of the degree of sensory impairment. In considering our negative finding, several issues need to be discussed.

We used repeated stroking of the skin in the affected area to evoke allodynia. The subjects rated the evoked pain as having a median value of 5 on the 11-point NRS. This subjective pain intensity is higher than that reported previously using experimental models of allodynia in humans (Cervero and Laird, 1996b; Wasner et al., 1999). We are therefore satisfied that the stimulation produced adequate levels of allodynia. We are also confident that the duration of allodynic stimulation was sufficient to be able to detect axon reflex vasodilatation in the skin. In healthy human subjects, electrical stimulation of the skin at C-fibre intensity over 1 min was sufficient to markedly increase SBF, the onset of this axon reflex response was 15–20 s and the duration 5 min (Wasner et al., 1999). Single hair extraction in healthy volunteers triggered a flare response lasting between 5 and 60 min (Wallin et al., 2001). In PHN patients, activation of C-fibres by iontophoretic application of histamine to control areas over 20 s triggered SBF responses with a similar time-course (Baron and Saguer, 1993).

To assess SBF we used laser Doppler imaging which uses the same technology as the single point laser blood flow monitors employed in previous human studies (Cervero

and Laird, 1996a,b; Wasner et al., 1999), but has the advantage of imaging an area of skin and hence detecting regional variations. It also requires no skin contact for measurements so the area being stimulated can be directly examined. As a compromise between spatial coverage and the scan time, we imaged an area of approximately 49 cm², which completely surrounded the line of tactile stimulation and generously covered the territory in which changes in SBF have been reported to occur (Cervero and Laird, 1996a,b). The most likely site for axon reflex activation would be in this region around the stimulation site; however, we cannot completely exclude that changes in SBF occurred outside the imaging window.

The imaging process is discontinuous as it takes 80 s for the laser to raster scan over the skin. However, based on the known time-course of axon reflex flare in healthy human skin as described above, we had no reason to believe that any changes in SBF related to C-fibre activation had been overlooked because of the LDI temporal resolution (indeed we imaged responses to mechanical scratch in our subjects, Fig. 1). Nevertheless, in an attempt to detect more rapid changes in SBF we employed single point continuous monitoring that was analogous to that used by the previous studies. We only observed very transient oscillations in the SBF signal associated with each cotton bud stroke that did not outlast the duration of the stimulus by more than a few seconds. Importantly, these brief changes in SBF during the allodynic stimulation were present in all patients (in both control and affected areas) regardless of the degree of preservation of sensory function, including those with pronounced thermal hypesthesia and hypoalgesia who are likely to have substantially reduced density of sensory innervation of the skin (Rowbotham et al., 1996). We therefore conclude that these transients were artefacts of mechanical stimulation of the skin (as previously noted by Wasner et al., 1999).

Based on these observations, it does not appear likely that C-fibre mediated dorsal root reflexes contribute substantially to the pathogenesis of allodynia in PHN. Nonetheless, it is still possible that abnormal coupling between nociceptive and non-nociceptive afferents exists but has been undetectable by the methodology used in this and previous studies. Analysis of skin flare reaction can only detect activation of fibres containing vasoactive neuropeptides (substance P, calcitonin gene-related peptide). If non-peptidergic nociceptive fibres were implicated, their activation by allodynic stimuli would have remained undetected by our methods. Another remaining possibility is that, although the level of C-fibre PAD evoked by tactile input in PHN patients may be insufficient for generation of action potentials that can be conducted retrogradely into the skin, there may exist a 'subthreshold coupling' between A β - and C-fibres facilitating spontaneous (ectopic) C-fibre discharge. Again, this afferent cross-talk may not be detectable by SBF measurements. These hypotheses could potentially be tested by other techniques, e.g. by assessment

of neuronal activation in human sensory ganglia using functional magnetic resonance imaging (Borsook et al., 2004). Nevertheless, monitoring SBF changes in skin does not appear a useful tool for assessing allodynia in neuropathic pain patients.

Another objective of the present study was to evaluate various other characteristics of skin sensitisation in PHN patients as potential endpoints for future efficacy trials with novel analgesics. The size of the area of allodynia or hyperalgesia has been used extensively as a semi-objective endpoint in human experimental pain models and in patients with neuropathic pain. It is believed to reflect the level of central sensitisation maintained by peripheral input (Fields et al., 1998; Petersen et al., 2000). We assessed the areas of sensitisation to dynamic tactile and pinprick stimuli and correlated them with levels of spontaneous pain. Consistent with previous findings in neuropathic pain patients (Rowbotham and Fields, 1989, 1996), areas of dynamic touch allodynia and pinprick hyperalgesia were well-defined and relatively stable upon repeated testing. Although no correlation was observed between baseline levels of spontaneous pain and the size of allodynic area within the studied group, this analysis may require larger numbers of observations. Furthermore, it may be more appropriate to observe patients with allodynia longitudinally and investigate if changes in areas of cutaneous sensitisation correlate with the intensity of ongoing pain, e.g. by varying their medication. Although some clinical reports indicate that the sensitisation endpoints may be more sensitive to analgesic treatments, there is a considerable variability in a mixed population requiring large numbers of observations (Sjölund et al., 2001). The chronicity and relative stability of allodynia in PHN make this population suitable for this kind of studies.

In conclusion, in a representative population of PHN patients we found no evidence of changes in SBF in response to allodynic stimulation. Thus, SBF measurements are not suitable for assessing allodynia. Quantifying the size of areas of touch allodynia or pin-prick hyperalgesia may serve as a tool for characterising sensitisation in PHN.

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