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Quantifying Allodynia in Patients Suffering From Unilateral Neuropathic Pain Using Von Frey Monofilaments

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Objectives: The aim of this study is to investigate whether quantitative sensory testing with Von Frey monofilaments (VFMs) can be used for the quantification of allodynia in patients with chronic neuropathic pain, and how the pain threshold of affected skin differs from healthy skin.

Methods: Using VFMs, we aimed to determine the pain threshold in 22 patients suffering from allodynia as a consequence of a chronic unilateral neuropathic pain syndrome. We performed quantitative sensory testing according to the Method of Limits protocol. We used the patient's own contralateral side and 5 healthy control participants to obtain reference values.

Results: On the affected side, we found in 20 out of 22 patients that the pain threshold could be determined with the monofilaments. On average, these 20 patients indicated pain upon the application of monofilament with logarithmic nr. 4.56, whereas no pain threshold could be determined on the contralateral, unaffected side, and in the healthy control participants for any monofilament.

Discussion: We showed that although etiology and pathophysiology of allodynia vary individually, with VFMs the clinical symptom allodynia can be quantified in a simple and practical fashion in almost all patients.

Key Words: allodynia, neuropathic pain, Von Frey monofilament, threshold

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About 1% to 1.5% of the population in western countries suffers from some form of neuropathic pain.¹ Neuropathic pain is a common symptom of various conditions, ranging from diabetic polyneuropathy to the nerve entrapment by tumors. The pathophysiology of

neuropathic pain is extremely complex and differs amongst various pain syndromes.

Stimulus-evoked pain is a phenomenon that can be frequently observed in patients with neuropathic pain and includes allodynia and hyperalgesia.^{2–5} The International Association for the Study of Pain (IASP) defines allodynia as pain due to a stimulus, which does not normally provoke pain, and hyperalgesia as an increased response to a stimulus, which is normally painful.⁶ Allodynia may well be one of the most disabling physical symptoms in neuropathic pain.^{7,8} Allodynia is manifested in pain resulting for example from contact between clothing and skin, or between water and skin when taking a shower.

The clinical symptoms allodynia and hyperalgesia can be used to evaluate the effect of therapy aimed to reduce neuropathic pain. Neuropathic pain is notoriously difficult to alleviate, especially when compared with nociceptive pain.^{9,10} In general, evaluation of the effect of therapeutic interventions is complicated by the fact that the variable, that is pain, is subjective in nature. Whereas subjective pain scores can be obtained by means of the Visual Analog Scale (VAS) or the Numeric Rating Scale (NRS), more objective information concerning the severity of neuropathic pain can be obtained with quantitative sensory testing (QST) of allodynia or hyperalgesia.

Von Frey monofilaments (VFMs) are frequently used as a means of QST to assess perception thresholds of sensory function at specific body sites, for example, for quantifying hypoesthesia in diabetic polyneuropathy.^{11,12} In pain research, VFMs can be used to administer painful stimuli on hypersensitive skin in human experimental pain conditions or to determine the size of the hypersensitive skin area.^{13–15} In rodents the withdrawal responses of painful hindpaws can be determined with VFMs.^{16,17}

When used in a standardized fashion, application of VFMs provides the clinical investigator with practical, reproducible, and reliable test results.^{18,19} The most important condition is that measurement with VFMs should occur according to a uniform and standardized protocol.²⁰ In the presence of stimulus-evoked pain of the skin, apart from the perception threshold, a pain threshold can be determined as well.

The aim of this study was to investigate whether QST with VFMs can be used to quantify stimulus-evoked pain in patients with chronic neuropathic pain, and how these thresholds differ from the healthy skin. QST with

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VFM) can be used for measuring stimulus-evoked pain irrespective of the underlying pathophysiologic mechanisms. Whereas thin VFMs stimulate low threshold A β -fibers, thick VFMs also recruit A δ -fiber nociceptors or even C-fiber nociceptors.^{5,21–24} The extent in which the different nerve fibers are involved in the—subjective—sensation that is perceived by the participant cannot be ascertained.

We present the mean value of pain thresholds, as determined with VFMs using the Method of Limits,^{25,26} in 20 patients suffering from stimulus-evoked pain as a consequence of a unilateral neuropathic pain syndrome. We will argue that this stimulus-evoked pain is in accordance with the IASP definition of *allodynia*. The pain threshold is defined as the logarithmic number of a VFM, which expresses the force exerted by this VFM that is reported as painful by the participant. QST on the patient's own contralateral, unaffected side was performed to acquire appropriate reference values.²⁰ Furthermore, to exclude the possibility that a relative hypalgesia might occur on the unaffected skin, we also performed QST in 5 healthy participants. To our best knowledge, a mean pain threshold of allodynia in patients with chronic neuropathic pain has not been published. In this study, we demonstrate that the symptom of allodynia, irrespective of the underlying pathophysiologic mechanisms, is quantifiable in a simple and practical way with the use of VFMs.

MATERIALS AND METHODS

Patients and Control Participants

Twenty-two patients suffering from unilateral neuropathic pain and stimulus-evoked pain participated in this study after giving their informed consent. The study was approved by the Medical Ethics Committee of the University Hospital in Groningen. In these patients, history and physical examination revealed the presence of allodynia, which was regarded to be present when a normally nonpainful stimulus of any kind was considered painful by the patient. At the time of the inclusion, no distinction was made in type of stimulus-evoked pain or in medical diagnosis as a result of which the pain syndrome had arisen or in duration of the pain syndrome.

Patients with polyneuropathy and or diabetes mellitus were excluded, as those conditions may influence the outcome of QST. Drug addiction or psychiatric diseases were also considered exclusion factors. Participants continued their (analgesic) medication.

Five control participants, who did not suffer from pain of any kind and did not use any medication, were also included after they signed an informed consent. Originally, we intended to include 10 healthy participants, however, after the study had been performed in 5 participants, there was no variation of the results, therefore we decided to include no more participants.

Experimental Setting

All patients underwent the experiment in a quiet room with a constant temperature of 20°C to 22°C. Each of the examinations was carried out by the same investigator (D.K.). To acclimatize, the patients were present in the room for 10 to 15 minutes before the actual QST procedures. During this time, they were informed about the procedure and the monofilaments were demonstrated to familiarize the patients with the procedure. Subsequently, the patients underwent the experiment lying on an examination table. The patient was asked to point out the skin area where the stimulus-evoked pain was perceived as the most intense. The punctum maximum was marked by a small square (± 1 cm²) drawn on the skin. The corresponding spot on the contralateral side of the body was marked similarly.

QST of the control participants was performed on the dorsum of the hand above the first interosseus muscle on the left or right hand; allocated at random. Again, measurements took place within a square drawn on the skin, in the same manner as the patients.

QST With VFMs

A set consisting of 20 nylon VFMs with constant length and increasing diameter of the firm Touch Test (North Coast Medical, Inc; Morgan Hill) was used. When applied, these VFMs exert a constant force onto the tested skin. The bending of the VFM reduces measurement outcome artifacts resulting from movement or trembling of the examiner's hand.¹⁸ The VFMs are calibrated in a logarithmic scale from 0.008 to 300 g (0.08 to 2943 mN), within a 5% standard deviation. Numbers on each monofilament ranging from 1.65 to 6.65, represent the common logarithm of 10 times the force in milligrams.²⁷

The VFMs were applied in increasing thickness on the affected and nonaffected side successively—in a randomized sequence—until a pain threshold was detected. This method is called the “Method of Limits.”^{25,26} The patient was asked to give a clear verbal signal when the stimulus was perceived as painful. We asked the patients to pay specific attention to the pricking sensations evoked by stimulation with the monofilaments; would they consider this sensation to be painful or not? Each VFM was applied 3 times, with approximately 10 seconds between 2 successive stimuli, to avoid temporal summation.^{23,28,29} Subsequently, the procedure was repeated on the contralateral side.

The VFM was applied perpendicularly to the skin surface for approximately 2 seconds, until a bending of 3 to 5 mm of the VFM was produced. Patients kept their eyes closed during the investigation to avoid visual feedback concerning the stimuli.

The pain threshold was defined as the logarithmic number on the VFM in which at least 2 out of 3 applications on the affected side resulted in the perception, and subsequent reporting of pain, the so-called “appearance”-threshold.^{20,25,30} Once a pain threshold was

reached, we asked the patients to rate the amount of pain that was induced by the stimulus on a NRS. Next, QST was stopped. To exclude interference of learning effects, the side on which the examination began was randomized.

Data Analysis

The mean value of the pain threshold, as measured with VFMs was determined, and the standard deviation. The pain threshold is expressed as the number of the logarithmic scale mentioned earlier.

RESULTS

The group of included patients consisted of 6 men and 16 women, with a mean age of 49.2 years (range 24 to 78 y). The duration of their underlying pain syndromes varied from only a few months to several decades. The neuropathic pain was either the result of trauma, surgery, or herpes zoster, or was due to chronic complex regional pain syndrome type 1 (Table 1). The group of 5 control participants consisted of 2 men and 3 women, with a mean age of 40.0 years (range 25 to 50 y).

At the time of inclusion, 6 patients did not use any medication, 11 used a tricyclic antidepressant and/or an antiepileptic drug, sometimes in combination with analgesics. None of the control participants were under the influence of medication at the time of inclusion. In the case of the patients, the procedure of QST took approximately 5 to 10 minutes, which was about twice as long compared to the control participants.

In 2 of the 22 patients, a pain threshold could not be measured using VFMs. Although the presence of stimulus-evoked pain had been demonstrated during the examination of the affected skin area, no pain threshold was reached with the application of any VFM.

Figure 1 illustrates the various pain thresholds as determined in the remaining 20 patients. All pain thresholds were above VFM log nr. 4.08 (9.8 mN) and under VFM log nr. 4.93 (78.5 mN). A pain threshold could neither be determined on the nonaffected side for any VFM, nor in any of the control participants. The patients indicated that the transition from nonpainful sensation to painful sensation was clearly noticeable; the NRS scores of the stimulus-evoked pain averaged 6.8 (range 4 to 9).

TABLE 1. Characteristics of Participating Patients

Patient nr.	Age	Sex	Location of Pain	Neuropathic Pain Due to	Duration of Pain (mo)	Severity (NRS)	Medication
1	41	M	Lower abdomen	Appendectomy	300	4	None
2	59	F	Left ankle	Bimalleolar fracture	65	6	Naproxen, tramadol
3	34	F	Right flank (side)	Nephrectomy	55	5	Amitriptyline
4	69	F	Right Th4 dermatome	Herpes zoster	4	6	Amitriptyline
5	37	F	Dorsal right upper arm	Excision melanoma	5	7	None
6	27	F	Left dorsal foot	Excision neurofibroma	100	7	Ibuprophen
7	54	M	C2 dermatome right	Excision fibroma	72	4	Gabapentin
8	39	M	Left leg	CRPS type 1	44	7	Diclofenac, acetaminophen
9	57	F	Right area of infraorbital nerve	Orbital fracture	38	8	Tramadol, oxycodone, amitriptyline, gabapentin, oxazepam
10	56	M	Right C6 dermatome	Spontaneous	22	8	None
11	58	M	Left leg	CRPS type 1	30	9	None
12	24	F	Right leg	CRPS type 1	115	6	None
13	56	F	Right upper thorax and upper arm	Amputation right mamma	54	9	Amitriptyline
14	40	F	Left arm	CRPS type 1	6	7	Amitriptyline, tramadol, acetaminophen
15	48	F	Area of lateral cutaneous nerve	Surgery in right groin	30	7	Gabapentin
16	72	F	Left armpit	Excision lymph node	7	5	Acetaminophen, ibuprophen, amitriptyline, temazepam
17	26	F	Right wrist	CRPS type 1	18	7	Diclofenac, acetaminophen, ibuprophen
18	72	F	Right Th8 dermatome	Herpes zoster	16	8	Acetaminophen, tramadol, gabapentin, oxazepam
19	28	F	Left leg	CRPS type 1	1	8	Tramadol, amitriptyline, gabapentin
20	78	F	Right L3 Dermatome	Herpes zoster	8	8	Gabapentin
21	54	M	Left lateral heel	Fracture both calcanei	43	8	Amitriptyline, clomipramine,
22	53	F	Right shoulder and upper arm	Amputation right mamma	115	7	Amitriptyline

In the last 2 patients (nr. 21 and 22), no pain threshold could be measured with VFMs.

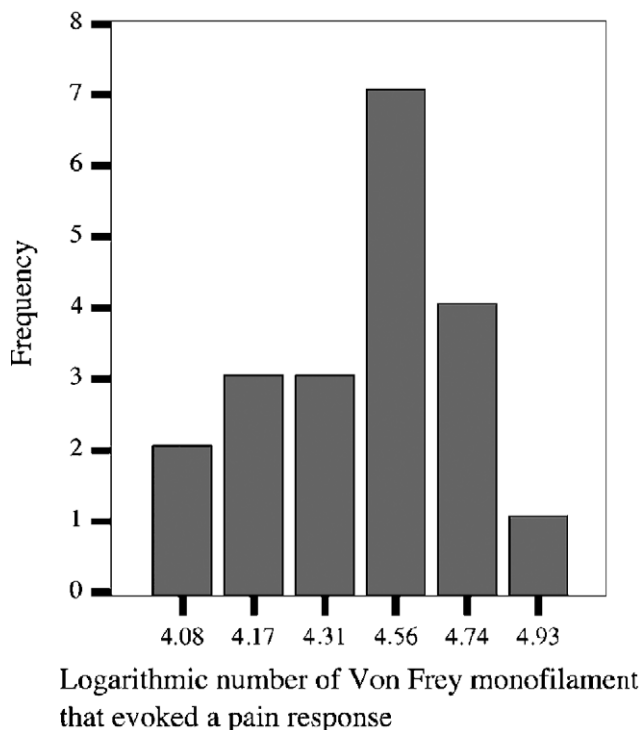


FIGURE 1. Exerted force for each Von Frey monofilament and corresponding number of patients that considered the application of the VFM as painful.

In this study, we found a mean pain threshold corresponding with the logarithmic number 4.47, (SD = 0.25) on the affected skin, which signifies that the patients suffering from stimulus-evoked pain will on average experience VFM with log nr. 4.56 (39.2 mN) as painful (Fig. 1). The standard deviation of 0.25 corresponds with 2 VFMs thinner or thicker than the VFM with log nr. 4.56.

DISCUSSION

Despite the heterogeneous character of the patients and their neuropathic pain syndromes, we showed that stimulus-evoked pain is quantifiable using VFMs—within a narrow range of deviation—in 20 of 22 patients. On average, these 20 patients indicated pain upon the application of VFM with log nr. 4.56, whereas no pain threshold could be determined on the contralateral, unaffected side for any VFM or in any of the control participants. Several aspects of this method of QST need further consideration.

Although thick VFMs evoke a pricking sensation on unaffected skin, none of the patients or control participants described this pricking sensation as pain. Therefore, we decided to call the patient's stimulus-evoked pain "allodynia" in stead of (pinprick or punctate) "hyperalgesia." The IASP definition of pain also explicitly states that "experiences which resemble

pain but are not unpleasant, for example pricking, should not be called pain."⁶

Despite the presence of allodynia, which had been established during history taking and physical examination, a pain threshold could not be determined in 2 of the 22 patients. Several explanations may account for this finding. First, a primarily psychogenic cause of allodynia or insufficient cooperation may frustrate the outcome of QST by inconsistent reporting.²⁵ Second, it is not exactly known to what extent the different subtypes of afferent nerve fibers—A β , A δ , or C fibers—are stimulated by the various VFMs.^{5,21–24} Because the involvement of one of these subtypes of afferent nerve fibers may predominate in a patient's clinical symptom of allodynia, it is possible that the dominant subtype of afferent fiber is not activated sufficiently with VFMs to reach a pain threshold. To elucidate the extent in which the different types of afferent fiber are involved in the perception of the different VFMs, future studies using differential nerve blocks would be needed.

We believe that wind-up-like pain or temporal summation did not influence the outcome of our measurements, because of the intervals of over 10 seconds between stimuli with the successive stimuli (0.1 Hz). Wind-up-like pain, lowering of the pain threshold, has shown to be evoked when stimuli are applied at a frequency of 0.3 Hz or higher.^{23,28,29} We assumed that no significant loss of attention occurred during the brief period when QST was performed.

Apart from QST, VFMs have also been deployed for investigating the *qualitative* aspects of sensory function that is to determine the presence of hyposensitivity or hypersensitivity. In patients with diabetic polyneuropathy, VFMs can be used to assess whether nerve function is compromised, as is described by Olaleye et al¹¹ and Perkins et al.¹² In these 2 studies, the hallux of each foot was stimulated with one specific VFM, while the patient was asked to respond if the stimulus was perceived. This screening method enables clinicians to rapidly assess the presence of impaired sensory function. However, no information is obtained concerning the severity of the sensory impairment.

The severity of sensory dysfunction can be determined in various manners. The first method is to measure or "map" the area of altered sensibility, by changing the location where the VFM is applied on the skin. A change in the size of the skin area where the stimulus-evoked pain is located, can aid in evaluating the effect of therapeutic interventions.^{28,31–33}

An alternative method to quantify the severity of stimulus-evoked pain, is to apply a stimulus following which the patient is asked to rate the severity of pain on a VAS or NRS.^{31,34,35} The major disadvantage of this method of QST, however, is that VAS and NRS scores are highly subjective.

Finally, the smallest stimulus intensity needed to evoke a response can be determined. For example, Voerman et al²⁷ measured sensory detection thresholds in patients with chronic cervicobrachialgia, by applying

VFM of increasing thickness on the skin according to the Method of Limits protocol, after these patients had undergone a diagnostic dorsal root blockade. The patients were asked to respond as soon as the stimulus was felt. The detection threshold was expressed as the physical force exerted by the smallest monofilament that evoked the patient's response. Similarly, Wallace et al³¹ measured both sensory detection thresholds and pain thresholds with VFMs after infusion of analgesics in healthy participants in whom pain had been induced with intradermal capsaicin injections. Although we used a comparable design in our study, several differences in methodology warrant further discussion. Wallace and coworkers used VFMs to measure both sensory detection thresholds and pain thresholds; we only measured pain thresholds. They selected the monofilaments at random, whereas we applied always the same ascending order of monofilaments. In both studies, the pain threshold was expressed as the smallest force needed to evoke a response from the participant, however, Wallace and coworkers measured sensory thresholds with a methodology that seems to be more complex than the Method of Limits. Finally, Wallace and coworkers³¹ asked their participants to report "discomfort," rather than "pain" as we did.

A mean pain threshold measurement with VFMs according to the Method of Limits protocol, in patients with allodynia as a consequence of a neuropathic pain syndrome, has not been published before. In this study, we showed that, although the etiology and pathophysiology of allodynia vary, quantification of this symptom with VFMs using the Method of Limits is simple and practical in almost all the patients with allodynia (20 of 22). Future studies are needed to evaluate the response of these pain thresholds to therapeutic interventions, in order to demonstrate that this method of QST can also measure a change in (hyper) sensibility after the treatment.

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