



Editorial comment

Reliability of pressure pain threshold testing (PPT) in healthy pain free young adults



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Quantitative sensory assessments of musculoskeletal pain using pressure algometry require, as for assessing neuropathic pain, two different disciplines where the first is standardised stimulation of deep-tissue nociceptors, and the second is standardised quantification of the evoked pain sensation. Both of those disciplines can introduce variability and hence hamper the reliability of the method.

1. Reliability, specificity, and sensitivity of quantitative sensory testing (QST)

Quantitative sensory testing (QST) is being applied more and more frequently in clinical studies for profiling pain patients or for profiling the mode-of-action of new/existing analgesics. Advanced QST profiling can provide a better understanding of the mechanisms involved in pain transduction, transmission, and perception under normal and pathophysiological conditions and provide the basis for mechanism-based diagnosis, prevention, and management of pain. Before such tests can be applied in clinical trials, the reliability, specificity, and sensitivity have to be known. Furthermore, QST techniques by nature rely on subjective responses from the person being tested which is introducing uncertainties and variation. However, some of the techniques, e.g. hand held pressure algometry, also rely on how the experimenter/rater is doing the tests.

2. Documenting variability caused by the person doing pressure pain measurements

Validating such variability, although important, is often not prioritised as it takes a lot of time and is not the most exciting to do from a scientific point of view. The study by Waller et al. in this issue of the *Scandinavian Journal of Pain* [1] focuses on the inter- and intra-individual rater variability of pressure pain thresholds (PPT) when assessed from different locations. The inter-rater variability is of particular importance when large multi-centre trials are planned. The stimulus-dependent assessment methods, such

as PPT, are based on adjustment of the pressure stimulus intensity until a pre-defined response, typically a threshold, is reached (e.g., pain, or tolerance). Hand held pressure algometry has previously been validated and clinically applied [2–6], but the recent study by Waller et al. [1] included detailed information about sample size calculations for PPTs assessed from different locations and calculated for both crossover and parallel study designs.

3. Equipment related variability in PPT-measurements

There are factors related to the equipment that may influence the PPT measurements. Some systems allow the *pressure increase rate*, when applied perpendicularly to the skin, to be controlled and in most studies a 30 kPa/s rate is used. Also the probe diameter and design influence the results, and in most studies a 1 cm² flat probe covered with rubber is used. As the pressure increase rate can be difficult to maintain at a constant level by a handheld algometer, and as the PPT may be very high (e.g. 500 kPa) for some locations, attempts have been made to develop automated, computer controlled pressure algometers [7] in order to minimise variability. However, they are not yet available for clinical use.

4. Novel, advanced automated equipment for PPT-measurements

An automated system provides the additional advantage that repeated pulses can be delivered (e.g. 10 pulses with 2 s intervals), and *temporal summation* can be evaluated. It is known that central integration is a highly important and potent mechanism in the pain system and strongly facilitated in patients with chronic musculoskeletal pain due to generalised sensitisation [7,8].

The application of pressure pain algometry has recently been further refined in order to construct *pressure pain sensitivity maps* based on many PPT assessments over a localised region [7]. Such topographical pain sensitivity mapping technique has been applied to, e.g. the knee [7], neck (e.g. mapping sensitivity changes in tension type headache), spine (e.g. mapping chronic low back pain), arm (e.g. mapping tendinopathies), or skull (e.g. mapping pericranial muscles in headache). This provides the opportunity to study in detail specific areas or *deep tissue hyperalgesia* and thereby provide a better understanding of the origin of the clinical pain problem. By changing the geometry of the pressure probe,

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different musculoskeletal structures can be activated, and recent studies have shown specific pain reactions from the muscles, fascia, aponeuroses, and periost. The more advanced techniques have so far not been validated for clinical use.

5. QST-protocols for neuropathic pain differ from protocols for deep musculoskeletal pain

Different QST protocols have been suggested for profiling patients, and the QST battery developed by the German Research Network on Neuropathic Pain has been applied in many studies [2–4]. Briefly, the protocol assesses the function of small (*thermal thresholds*) and large (*tactile and vibration thresholds*) nerve fibre pathways and increased/decreased pain sensitivity (*hyperalgesia, allodynia, hyperpathia, wind-up like pain*). The battery consists predominantly of cutaneous stimulus modalities and is, therefore, not adequate for profiling musculoskeletal or visceral pain conditions. The stimulus modality applied, which activates also deeper somatic structures, is pressure algometry as this modality is more applicable for patients with musculoskeletal pain as compared to those with neuropathic pain. As musculoskeletal pain in quantity is a much bigger clinical problem compared with neuropathic pain, the QST techniques used in profiling patients with musculoskeletal pain also have a big potential and hence need detailed validation.

6. Localised and generalised, spreading hyperalgesia

Pressure pain stimulation is often assessed from different locations in order to assess some fundamental mechanisms of sensitisation such as *localised deep tissue hyperalgesia* (PPT at the site of a given pathology) and *generalised spreading hyperalgesia* (PPT assessed extra-segmentally to the site of a given pathology). An example of this is when PPTs are used for profiling patients with painful knee osteoarthritis where the PPTs assessed around the knee show specific knee regions with pressure hyperalgesia, but at the same time patients have different degrees of spreading sensitisation as assessed by PPT hyperalgesia assessed from remote locations such as the arm [7].

7. Pressure-pain-measurements in analgesic drug development

PPT is also widely used in profiling studies of new analgesic compounds where a multi-modal and multi-tissue approach is applied [9], and the effect of a given compound on evoked musculoskeletal pain can be assessed and compared with the effect on pain provoked experimentally from the skin or viscera.

Translation of the analgesic efficacy from pre-clinical pain models into clinical trial phases is associated with a high risk of failure. Application of QST in early stages of clinical trials can provide new and important information to be used in the later development phases.

One of the major limiting factors for the successful development of new analgesics is the lack of efficient translation between animal and human findings in manifestation of pathologies and in drug effect [10]. In general, this lack of efficacy contributes to 51% of phase II trial failures. Thus, it is important to find new and efficient ways of optimising the analgesic drug development process. QST is found to act as a bridge between animal and clinical research and potentially enhance the rate of successful translation, which would eventually reduce both length and costs of drug development after the pre-clinical stage. For this purpose, there has been substantial focus on which QST techniques may translate from animals into humans. Pressure stimulation is used in as well animals and humans where the readouts in animals are vocalisation

or withdrawal. As most new drugs developed in the area of pain are supposed to interact with peripheral and central mechanisms such as sensitisation, it is important to investigate which aspects are being modulated. The PPT may be used to differentiate the effect on localised and on generalised sensitisation by assessing the PPT from different locations. If in addition repeated pressure stimuli can be applied, readout of the effect on temporal summation can also be evaluated.

As PPT is used across many different applications, detailed information on reliability between experimenters and between sessions are important in order to plan studies and estimate sample sizes for different study designs.

8. Conclusion and implications

Previous inter-rater reliability studies for PPT using algometry have been conducted. These have varied with respect to sites assessed, number of raters examined, reliability statistics reported, and the degree of standardisation of algometry. In the study of Waller et al. [1], some aspects of PPT reliability have been addressed in a clinical setting with non-specialised experimenters. The study established the reliability of PPT measurement using handheld algometry by multiple experimenters assessing the PPT from multiple body sites. The sample size calculations presented will help determine the sample sizes, which account for measurement error for interventions using PPT as an outcome measure. This may be applied in powering clinical trials on patient profiling or for parallel or cross-over drug studies.

Conflicts of interest

None has been declared.

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