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NEW TECHNOLOGIES FOR QUANTITATIVE ASSESSMENT OF PAIN: EXPERIMENTAL AND CLINICAL APPLICATIONS

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Abstract: This paper deals with new technologies today used to assess pain in patients with chronic pain. The author describes the state of art concerning the current scenario of pain assessment issue. Attention is focused on Quantitative Sensory Testing (QST) technology used to stimulate pain in order to evaluate the patient sensation and score the perceived pain level. In detail, QST can provide an understanding of the mechanisms involved in pain transduction, transmission, and perception under normal and pathophysiological conditions and provide mechanism-based diagnosis, prevention, and management of pain.

A discussion on clinical applications of the above mentioned assessment technique is reported.

Keywords: pain, quantitative sensory testing, pain stimulation, pain assessment.

1. INTRODUCTION

Chronic pain is a major medical and societal problem in the Western world and there is an ample body of research identifying the limited impact of current standard therapeutic approaches.

Chronic pain is common and causes suffering, disability, and high social costs. Over the last four decades the number of research papers on nociception and pain has increased enormously, leading to impressive advances in the fundamental understanding of pain. Studies in animals or healthy volunteers have been highly successful in providing mechanistic knowledge leading to a better understanding of the clinical signs and symptoms and thus to a more rational use of available treatments. Although part of this knowledge has been translated into the benefit of patients, the treatment of chronic pain is still generally unsatisfactory due to the lack of adequate diagnostic tools and drugs which provide the opportunity for developing individualized treatment regimes.

Application of quantitative sensory testing (QST) technologies in pain research involves a large variety of painful stimulus modalities (thermal, mechanical, chemical, electrical), assessment methods (psychophysics, electrophysiology, imaging, microdialysis), and structures (skin, musculoskeletal, and viscera). QST can provide an understanding of the mechanisms involved in pain transduction, transmission, and perception under normal and

pathophysiological conditions and provide mechanism-based diagnosis, prevention, and management of pain.

QST involve two separate topics:

- standardized activation of the nociceptive system and particular mechanisms;
- quantitative assessment of the evoked responses.

The response can be assessed by psychophysical methods (thresholds, stimulus-response functions) or electrophysiological responses. Quantification of verbal responses to painful stimuli is also denoted as psychophysical pain research. The electrophysiological methods (EEG, evoked potentials, reflexes), imaging techniques (PET, fMRI) or biochemical methods (microdialysis) are to assess to provoked response.

The modern concept of advanced QST for experimental pain assessment is a multi-modality, multi-tissue approach where different pain modalities (thermal, mechanical, electrical, chemical) are applied to different tissues (skin, muscles and viscera) Many new advanced technologies have been developed to evoked standardized painful reactions. Assessing pain has become a question of solving a multi-input, multi-output problem which provides the possibility to tease out which pain pathways and mechanisms are involved, impaired or affected.

Many Different QST protocols, consisting of different technologies, have been suggested for profiling patients, and different QST batteries have been developed.

Most protocols assesses the function of small (thermal thresholds) and large (tactile and vibration thresholds) nerve fiber pathways and increased/decreased pain sensitivity (hyperalgesia, allodynia, hyperpathia, wind-up like pain). Most QST batteries consist predominantly of cutaneous stimulus modalities and is not adequate for profiling musculoskeletal or visceral pain conditions. However the two later areas have in recent years developed significantly, [1], [2].

In addition to standard QST the battery should include assessment techniques related to e.g., pain modulation and pain integration. The challenges for the future are to develop QST platforms adequate for children or elderly possible demented patients.

2. TECHNIQUES FOR PAIN STIMULATION

Selectivity is a major problem for experimental pain stimuli. Most studies have used electrical stimulation, but

this technique is non-selective and by-pass the receptors by depolarising the afferent nerve fibre. Many attempts have been made to refine electrodes and stimulation paradigms to activate selectively the pain fibres, but so far without success.

The most selective heat stimulator is probably a laser that can emit concentrated light or heat radiation. Many types have been applied to the skin (argon (488-515 nm), copper vapour lasers (510-577 nm), semi-conductor lasers (e.g., 980 nm), Nd-YAG (1064 nm), Thulium-YAG (1800 nm), and CO₂ (10600 nm). The advantage is that the laser light can be applied without touching the skin and hence does not contaminate the stimulation by mechanosensitive input, [3].

The stimuli can be short (e.g., 50 ms) and be used for both psychophysical and electrophysiological (evoked potentials, reflexes) evaluations. The Peltier contact thermode, which can either warm or cool depending on the direction of the current, is easy to use and is often used in the clinic, see Fig. 1 for reference.

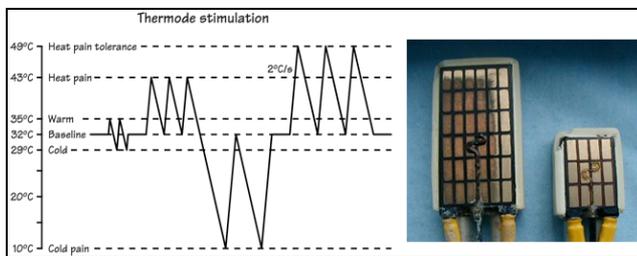


Fig. 1. The use of Peltier contact thermode to provoke the different thermal thresholds (warmth, cold, heat pain, cold pain, heat pain tolerance).

Pressure stimulation is widely used to induce pain from deep structures has been extensively used and validated; computer-controlled stimulation may reduce the variability, which also allows accurate construction of the stimulus-response function related to the somatosensory sensitivity. A topographical mapping technique has recently been developed where pain sensitivity maps of e.g. the knee, neck, spine, head or muscles can be obtained by recording pain responses from many different sites providing the possibility in more details to explore localised hyper-sensitive spots in given musculoskeletal structures. Pressure algometry assesses a relatively small volume of tissue. Instead, a larger volume can be assessed by computer-controlled cuff-algometry technique, see Fig. 2.

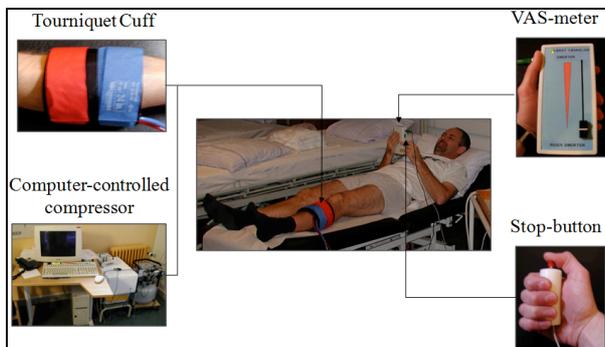


Fig.2. The use of cuff algometry to provoke pain from deep structures. The cuff is inflated by a computer controlled pneumatic system and the pain threshold and the pain ratings can be measured.

The pain intensity related to inflation of a tourniquet applied around an extremity is used to establish stimulus-response curves, and by this the deep-tissue sensitivity can be assessed. The cuff-algometry is also less influenced by local variations in the pain sensitivity. The cuff algometry has the advantage that the same technique provides the opportunity to measure a pain threshold, stimulus-response function, temporal summation of pain (repeated stimulation), spatial summation of pain (inflation of one or two cuffs), and descending conditioning pain modulation.

For more tonic cold stimulation the so-called cold pressor test (immerse the hand into ice water) has been used. During this test the person continuously score the pain intensity/unpleasantness. Depending on the duration, for which the person can endure the pain, they are classified as pain tolerant or pain sensitive. Depending on the condition, mechanical stimuli can activate all fibres – ranging from Aβ-fibres (brushing/stroking used to assess allodynia, tactile (von Frey hair) to assess hyper-, hypo- or dysaesthesia), via activation of both Aβ- and Aδ-fibre (pin prick, often used to assess hyper- or hypoalgesia) to full activation of Aβ-, Aδ- and C-fibres (pressure or pinch). For visceral stimulation different distension techniques have been used where the most advanced methods also include the assessment of the cross sectional area, which can be used to calculate the actual strain applied to the wall of a hollow organ.

Chemical stimuli are of nature tonic and difficult to repeat over time as some of them induce peripheral and central sensitisation (e.g., capsaicin). Stimulation of muscle tissue has in particular utilised chemical stimulation as e.g., intramuscular hypertonic saline is useful to generate local and referred pain phenomena in healthy volunteers or in patients. An adequate chemical method to elicit pain from the nasal mucosa is using an air stream with high CO₂ concentration. Somatic pain differs from visceral pain in many aspects and in recent years various techniques have been developed for stimulating the hollow organs. Visceral stimulation is generally problematic to apply due the localisation of the organs. Furthermore visceral pain is diffuse in nature and confounded by autonomic responses, which complicates precise evaluation of the pain by the subjects. Mechanical, thermal, electrical and chemical stimulus modalities have been used for evoking pain in visceral tissue. Mechanical stimulation is evoked in hollow organs by distension organ wall, Fig.3.

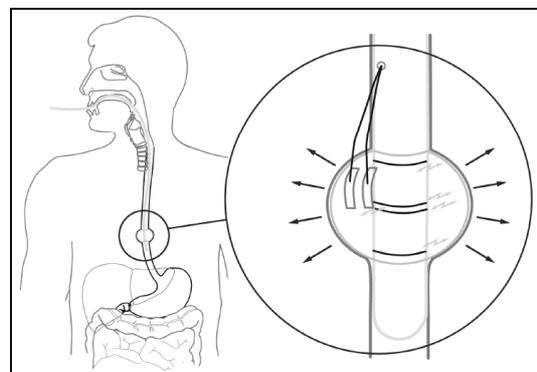


Fig.3. Stimulation of the hollow organs can be done by mechanically by balloon distension. Electrodes can be attached to the balloon and electrical stimulation can be delivered to the mucosa of e.g. the oesophagus.

It is a widely used model and new techniques allows for determination of the cross sectional area, which can be related to stress in the organ wall. This seems advantageous in determining the true stimulus intensity compared to the older methods using pressure or volume as a measure of stimulus intensity.

Thermal stimulation, which is rarely used, is evoked by recirculation of hot or cold water in a balloon placed inside a hollow organ.

3. APPLICATIONS OF TECHNOLOGIES FOR QUANTITATIVE ASSESSMENT OF PAIN

Many QST technologies are available for studying cutaneous, muscle and visceral pain and it is recommended to combine various stimulus modalities and assessment techniques to get sufficient advanced and differentiated information about the human nociceptive system under normal and pathophysiological conditions. Many different QST protocols, consisting of different technologies, have been suggested for profiling patients, and different QST test platforms have been developed.

Advanced QST can provide an understanding of the mechanisms involved in pain transduction, transmission, and perception under normal and pathophysiological conditions and provide mechanism-based diagnosis, prevention, and management of pain. Assessing pain has become a question of solving a multi-input, multi-output problem which provides the possibility to tease out which pain pathways and mechanisms are involved, impaired or affected. The entropy and amount of information obtainable in an experimental study increase as a function of QST procedures added.

Obvious psychological differences are present in the experience of a well-defined, short-lasting, controlled, experimental pain stimulus and a chronic, intractable pain condition. However, experimental techniques are the only way to bridge the gap between basic science and clinical application. Most test platforms used clinically consist predominantly of cutaneous stimulus modalities and is not adequate for profiling musculoskeletal or visceral pain conditions. However the two later areas have in recent years developed significantly. In addition to standard QST the battery should include assessment techniques related to dynamic aspects of the pain system e.g. descending pain modulation and pain integration.

Mechanistic QST assessment can be applied in experimental healthy volunteer studies, for patient assessment, and in proof-of-mechanism drug screening trials. There two major clinical applications are for pain diagnostics and for phenotyping. In pain diagnostic the sensory abnormalities can be quantified and monitored over time and it may in the future provide the basis for mechanism-based therapy. Phenotyping patients prior to e.g. surgery can provide information about which patients are vulnerable for developing post-operative chronic pain.

There is a massive unmet need for new and better analgesics in the area of pain management. The development of new pain drugs poses significant challenges, and few drugs have made it to the market in recent years.

Therefore, there is a need to refine and optimize the drug development process to ensure a higher success rate (i.e., avoiding discarding drugs that may be efficient and removing ineffective drugs from the costly development process). QST technologies can help advance development programs and can also assist in pain profiling (phenotyping) and recognizing the right patients for specific trials. The success rate in translating preclinical data to clinical outcomes may also be further facilitated using specific translational pain biomarkers.

Application of QST has therefore in recent years gained a lot of interest in profiling new analgesic compounds in early development. The pharmacological activity of a given compound can be identified in the pain pathways by using QST. Based on the preclinical profile of the tested drug and also the feasibility of assessments in humans, a platform of tests is chosen and applied, both in healthy volunteers and pain patients, prior to and after pharmacological interventions. This mechanistic approach is not limited to new drugs but can also be utilized for profiling existing analgesics with action mechanisms that are not clearly defined (and thus this may limit their applications). Because pain is a complex phenomenon with an interaction between peripheral and central mechanisms, it is important to investigate which aspects are being modulated using analgesics to select the most adequate patient population and outcome parameters for large clinical trials. These agents can be profiled by their differentiated modulation of specific QST technologies.

4. CONCLUSIONS AND FUTURE PERSPECTIVES

Basic pain research has led to enormous improvements in the understanding of the mechanisms underlying chronic pain. Human experimental pain research and mechanistic QST studies have confirmed that mechanisms described in animals can be translated into volunteers and pain patients. QST is today an important and integrated part of many basic and clinical studies and an important tool in proof-of-mechanism studies related to new analgesics under development. Translating QST-based mechanistic knowledge into the benefit of patients as better diagnosis and treatment is the future research agenda for the field. Treatment of chronic pain remains unsatisfactory as there is a lack of new and efficient drugs, which hamper the implementation of a mechanistic and individualized pain management regime based on QST diagnostics.

5. REFERENCES

- [1] Arendt-Nielsen L, Curatolo M. Mechanistic, Translational, Quantitative Pain Assessment Tools in Profiling of Pain Patients and for Development of New Analgesic Compounds. *Scand J Pain* 2013;4(4), 226-230.
- [2] Arendt-Nielsen L, Yarnitsky D. Experimental and Clinical Applications of Quantitative Sensory Testing Applied to Skin, Muscles and Viscera. *J. Pain* 2009;10(6):556-572.
- [3] Arendt-Nielsen, L. and Chen, A.C.N. (2003) Lasers and other thermal stimulators for activation of skin nociceptors in humans. *Neurophysiol. Clin.* 33, 259-268.

- [4] Drewes AM, Schipper KP, Dimcevski G et al. Multimodal assessment of pain in the esophagus: a new experimental model. *American journal of physiology. Gastrointestinal and liver physiology* 283(1), G95-103 (2002).
- [5] Konopka KH, Harbers M, Houghton A, Kortekaas R, van Vliet A, Timmerman W, den Boer JA, Struys MM, van Wijhe M. Bilateral sensory abnormalities in patients with unilateral neuropathic pain; a quantitative sensory testing (QST) study. *PLoS One* 2012;7(5):e37524.
- [6] Magerl W, Krumova EK, Baron R, Tölle T, Treede RD, Maier C. Reference data for quantitative sensory testing (QST): refined stratification for age and a novel method for statistical comparison of group data. *Pain* 2010;151(3):598-605.
- [7] Neziri AY, Scaramozzino P, Andersen OK, Dickenson AH, Arendt-Nielsen L, Curatolo M. Reference values of mechanical and thermal pain tests in a pain-free population. *Eur J Pain* 15(4), 376-383 (2011).
- [8] Polianskis R, Graven-Nielsen T, Arendt-Nielsen L. Spatial and temporal aspects of deep tissue pain assessed by cuff algometry. *Pain* 2002;100:19-26.
- [9] Rolke R, Magerl W, Campbell KA et al. Quantitative sensory testing: a comprehensive protocol for clinical trials. *European journal of pain* 10(1), 77-88 (2006).
- [10] Rolke R, Baron R, Maier C et al. Quantitative sensory testing in the German Research Network on Neuropathic Pain (DFNS): Standardized protocol and reference values. *Pain* 123(3), 231-243 (2006).
- [11] Sorensen J, Graven-Nielsen T, Henriksson KG, Bengtsson M, Arendt-Nielsen L. Hyperexcitability in fibromyalgia. *J Rheumatol* 1998;25(1):152-5.
- [12] Staahl C, Reddy H, Andersen SD, Arendt-Nielsen L, Drewes AM. Multi-modal and tissue-differentiated experimental pain assessment: reproducibility of a new concept for assessment of analgesics. *Basic Clin Pharmacol Toxicol* 98(2), 201-211 (2006).