A Human Model of Intraoral Pain and Heat Hyperalgesia

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Aim: *To examine, in a double-blind and placebo-controlled crossover manner, the effect of topical application of capsaicin on the alveolar mucosa with a battery of intraoral quantitative sensory testings (QST) in 16 healthy volunteers.* ***Methods:*** *Thirty μL of 5 mg/mL capsaicin or vehicle (control) was applied to a 3 × 3-mm paper disk and applied to the alveolar mucosa under an oral bandage. The subjects rated the perceived pain intensity on a 0 to 10 electronic visual analog scale (VAS) for 15 minutes. Quantitative sensory testings were performed before and immediately after the 15-minute application and consisted of assessments of cold detection threshold, warmth detection threshold (WDT), cold pain threshold, heat pain threshold (HPT), mechanical sensitivity to single and repeated punctate mechanical stimulation with von Frey filaments and to single and repeated brush stimulation with a cotton swab, and detection and pain thresholds to electrical stimulation of the alveolar mucosa and maxillary first premolar tooth. Analysis of variance was used to test the data.* ***Results:*** *Application of capsaicin caused moderate levels of pain (VAS_{peak} scores 5.0 ± 1.9) whereas the vehicle was practically painless (VAS_{peak} 0.9 ± 2.4). No significant effects of vehicle on QST could be detected ($P > .143$). In contrast, capsaicin application was associated with significant decreases in WDT and HPT ($P < .001$). No other significant changes in QST were observed for capsaicin application.* ***Conclusion:*** *The intraoral capsaicin pain model is associated with signs of heat hyperalgesia, but not mechanical hyperalgesia. Since the somatosensory sensitivity is not well characterized in most orofacial pain conditions, mainly due to lack of tradition and techniques, intraoral QST may provide a better description of the somatosensory sensitivity and underlying mechanisms in orofacial pain conditions.* J OROFAC PAIN 2003;17:333–340.

Key words: capsaicin, hyperalgesia, orofacial pain, pain measurement

Orofacial pain complaints are frequently encountered in the population,[1,2] but the underlying pathophysiology of several conditions, such as atypical odontalgia (AO), atypical facial pain (AFP), and burning mouth syndrome (BMS), remains enigmatic. It has been proposed that AO, AFP, and BMS represent neuropathic pain conditions[3–5]; this claim is still being discussed.[6,7] A frequent characteristic of neuropathic pain conditions is changes in somatosensory sensitivity, eg, hypo- or hyperesthesia, hypo- or hyperalgesia, windup-like pain, or aftersensations.[8] Quantitative sensory testings (QST) have been developed and described mainly for cutaneous applications,[9,10] and relatively few

techniques have been adapted to the intraoral mucosa.[5,11,12] Recently, a new pain model with intraoral application of capsaicin on the tongue mucosa was introduced and showed good reliability and sensitivity to pharmacologic modulation.[13] Topical application of capsaicin is a well-described model of cutaneous pain and has been shown to produce thermal hyperalgesia within the injured zone (primary hyperalgesic area) and various forms of mechanical hyperalgesia in the noninjured surrounding zone (secondary hyperalgesic area).[14–17] We decided to modify the intraoral capsaicin model to be used on the alveolar mucosa because patients with AO and AFP often complain about pain and sensory abnormalities from this area. The aim of this study was therefore to characterize changes in somatosensory sensitivity following topical application of capsaicin on the alveolar mucosa in a double-blind and placebo-controlled manner.

Materials and Methods

Subjects

A total of 16 healthy volunteers (2 men and 14 women) with a mean age of 27.6 ± 6.4 years were recruited among students and staff at the Dental School at the University of Aarhus. None of the subjects reported orofacial pain complaints or had taken analgesics within 48 hours of the investigation. The local Ethics Committee approved the experiments and informed consent was obtained from all participants. The study was conducted in accordance with the Declaration of Helsinki.

Study Design

The study was performed in a randomized, double-blind, placebo-controlled crossover manner. The sequence of capsaicin or vehicle (control) application was randomized as well as application on the right or left side. Sixteen cards were made and marked with treatment A or B and left or right side (4 × 4 combinations). The subject took one of these cards, and the first examiner prepared the capsaicin or vehicle on an oral bandage. A second examiner performed the QST. The first examiner then applied the oral bandage on the buccal aspect of the alveolar mucosa of the maxillary first premolar tooth on one side and the subject started to score the perceived intensity of pain on a 0 to 10 electronic visual analog scale (VAS). After 15 minutes, the second examiner performed the QST again. Then the same procedure was followed on the opposite side, again on the buccal aspect of the alveolar mucosa. Both the subject and the second examiner were blinded with respect to the topical applications. The entire session lasted about 2 hours. The study was performed in a quiet room at 22°C.

Topical Application

Capsaicin was prepared by the pharmacy at Aarhus University Hospital in 5 mg/mL concentration and diluted in Tween-80 dissolved in isotonic saline.[18] A volume of 30 mL of either the capsaicin solution or vehicle was applied on a 3 × 3-mm paper disk, which was placed on an oral bandage (Urihesive, ConvaTec).[19] The bandage is made of carboxymethylcellulose and sticks to the moist oral mucosa. The bandage with capsaicin or vehicle was then carefully applied and fitted to the alveolar mucosa above the first maxillary premolar tooth. In this way it was possible to prevent the capsaicin/vehicle from spreading into the entire oral cavity.

Subjective Sensations

Subjects used an electronic VAS to score their perceived pain intensity after the capsaicin and vehicle application. The VAS signal was sampled and stored in a computer in 1-second intervals. The area under the VAS curve (VAS_{auc}), the maximum pain (VAS_{peak}), and onset and offset of pain were calculated from the VAS signal. A Danish version of the McGill Pain Questionnaire (MPQ) was used to obtain a qualitative impression of the evoked sensations. The words used consistently (> 30%) by the subjects were noted.

Quantitative Sensory Testings

Quantitative sensory testing consisted of an assessment of thermal, mechanical, and electrical sensitivity at the region of topical application. The maxillary first premolar tooth also was tested with electrical stimulation. Quantitative sensory testing was started immediately after removal of the oral bandage with ongoing pain and always in the same sequence: *(1)* thermal sensitivity, *(2)* mechanical sensitivity, and *(3)* electrical sensitivity. Because of the anatomy and physiology of the tested area, and the limited space available, no study of signs of secondary hyperalgesia was attempted.

Thermal Sensitivity. A thermal stimulator (Medoc TSA II Neurosensory Analyzer) equipped with a dedicated intraoral probe was used to deter-

mine the cold detection threshold (CDT), warmth detection threshold (WDT), cold pain threshold (CPT), and heat pain threshold (HPT). The baseline temperature of the 6-mm-diameter thermode was set at 30°C. The methods of limits with 3 ascending or descending trials were used. The temperature increment was 1°C/s. A 50°C cutoff limit was used to avoid excessive stimulation. When the subjects first noticed a difference from the baseline temperature, they pushed a button and the temperature reverted back to baseline (30°C/s). The CPT and HPT were defined as the first temperature which was perceived as painful. The thermode was held gently in contact with the oral mucosa to avoid an uncomfortable pressure sensation. In between trials, the thermode was removed from the mucosa. At least 10 seconds elapsed between the repeated trials. The mean of the 3 repeated trials was used for further analysis.

Mechanical Sensitivity. Punctate mechanical stimuli were applied with the use of calibrated von Frey nylon filaments (Stoelting). The 4.93 (= 5.16 g) and the 6.10 (= 84.96 g) filaments were chosen based on previous experiences to provide both a clear nonpainful sensation and a painful sensation. The subjects were stimulated with the filament on the alveolar mucosa and scored the perceived pain intensity on a 0 to 100 numerical rating scale (NRS). Zero was defined as "no sensation at all" and the other extreme, 100, was defined as "worst pain imaginable." Fifty was defined as the pain threshold "just barely painful," ie, the scale accommodates both nonpainful sensations of an increasing magnitude (up to 50) and painful sensations (from 50 and above). Similar NRSs have been described previously.[20] In addition to the NRS scores of single 4.93 and 6.10 filaments, NRS scores of 5 repeated (1 Hz) stimulations were also obtained as a measure of temporal summation.[21] Finally, a cotton swab was used to provide single and repeated (5 stimulations, 1 Hz) brush stimulations, which evoked sensations that also were scored on the NRS.

Electrical Sensitivity. An electronic pulp-tester (Model 2001, Analytic Technology) was used to test the electrical detection threshold (EDT) and electrical pain threshold (EPT) on the alveolar mucosa. The electrode consisted of a 2-mm-diameter anode held in gentle contact with the mucosa. The subject responded when the slightest sensation (tingling, pricking sensation) was noticed (EDT). The anode was instantly removed from the surface and the value read on the digital display. The EPT was defined as the current needed for the subject to report a painful sensation. The EDT and EPT assessments were each repeated 3 times, and the mean was used for further analysis. With the same method, the tooth-pulp pain threshold was determined in triplicates on the air-dried facial surface of the maxillary first premolar.

Statistical Analyses

The results are presented as mean ± standard deviations. Analysis of variance (ANOVA) for repeated measures was used to test the QST data. The factors were treatment (2 levels: capsaicin and vehicle) and time (before and after application). Post-hoc tests were performed with Tukey tests to compensate for multiple comparisons. VAS pain scores for capsaicin and vehicle were compared with paired *t* tests. The level of significance was set at $P < .05$.

Results

Subjective Description

All subjects completed the study and no major side effects were noted, although 2 subjects reported a small aphthous lesion on both sides 1 to 2 days after the test. Application of capsaicin was described on the MPQ as producing a "searing" (12/16), "burning" (10/16), "pricking" (8/16), "sharp" (8/16), "annoying" (7/16), "throbbing" (7/16), "cool" (6/16), "hurting" (6/16), and "spreading" (5/16) sensation, whereas there were no consistent words to describe sensation produced by the vehicle.

The capsaicin application caused moderate levels of pain, which slowly declined after the 15-minute period (Fig 1). In contrast, vehicle application was only infrequently associated with very low levels of pain and only during the first 3 to 4 minutes (Fig 1). Thus, the VAS_{auc} for capsaicin (2551 ± 1430) was significantly greater than for the vehicle (37 ± 64; $P < .001$), and the same was true for the VAS_{peak} for capsaicin (5.0 ±1.9) compared with vehicle (0.9 ± 2.4; $P < .001$). The VAS_{peak} scores ranged from 2.2 to 8.5 for the capsaicin-evoked pain. The capsaicin-evoked pain started after 25 ± 22 seconds and for most subjects (11/16) lasted throughout the 15-minute application period; however, the mean offset of the pain was 799 ± 188 seconds.

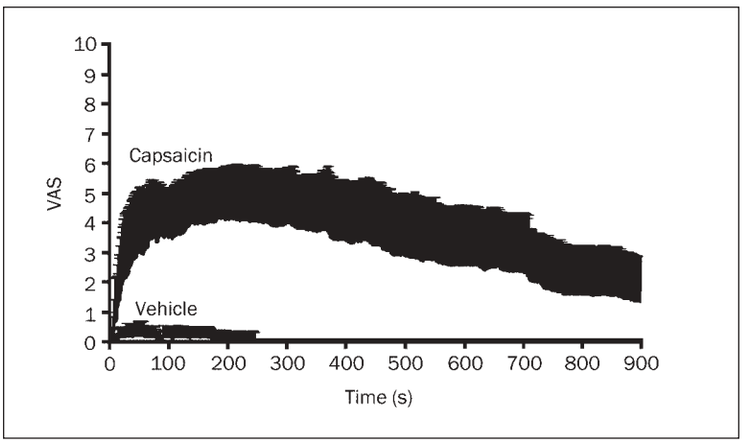

Fig 1 Subject-reported visual analog scale (VAS) scores of topical application of capsaicin and vehicle on the alveolar mucosa. Mean values + standard deviations (n = 16) during the 900-second recording period. Note the slow decline in VAS scores for the capsaicin and the very low VAS scores for the vehicle.

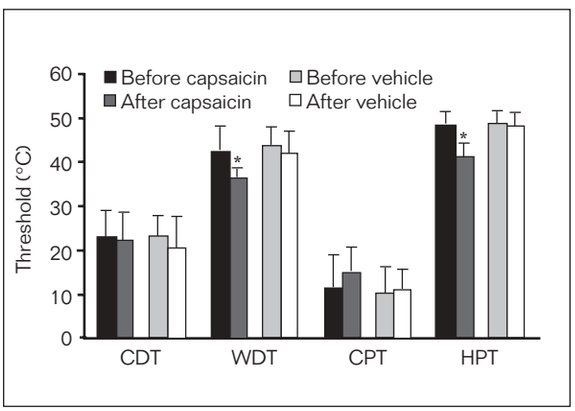

Fig 2 The cold detection threshold (CDT), warm detection threshold (WDT), cold pain threshold (CPT), and heat pain threshold (HPT) were assessed on the alveolar mucosa before and after 15-minute applications of capsaicin and vehicle in 16 subjects (mean values + standard deviations). *Indicates significant difference between before and after values ($P < .05$).

Thermal Sensitivity

There were no significant effects of treatment (ANOVA: F = 1.587; $P = .227$) or time (F = 4.042; $P = .063$) on CDT measured on the alveolar mucosa (Fig 2). The WDT was significantly influenced by both treatment (F = 22.856; $P < .001$) and time (F = 27.820; $P < .001$) with a significant interaction between the factors. Post-hoc tests demonstrated significantly lower WDT following application of capsaicin (Tukey: $P < .001$) but not vehicle ($P = .143$; Fig 2). Cold pain threshold was also influenced by treatment (F = 5.115; $P = .039$), but there were no significant time effects (F = 2.168; $P = .162$) or interactions (F = 1.040; $P = .324$). However, there was a clear trend that the CPT was increased following capsaicin application ($P = .085$). Analysis of the HPT revealed significant effects of treatment (F = 31.153; $P < .001$) and time (F = 38.296; $P < .001$) with a significant interaction between factors (F = 25.229; $P < .001$). Thus, the HPT was significantly lower following application of capsaicin (Tukey: $P < .001$), but not following application of the vehicle (Tukey: $P = .662$) (Fig 2). Additional ANOVA tests of just the female data (n = 14) did not change the statistical results for CDT, WDT, CPT, or HPT.

Mechanical Sensitivity

None of the NRS scores of the single or repeated brush stimulation were significantly influenced by treatment ($F < 0.945$; $P > .346$) or time ($F < 0.960$; $P > .343$) (Fig 3). Similarly, there were no significant effects of treatment ($F < 1.660$; $P > .217$) or time ($F < 3.578$; $P > .078$) on NRS scores of single or repeated punctate stimulations with the 4.93 and 6.10 von Frey filament (Fig 3). This was also true for ANOVA tests of just the female data (n = 14). However, repeated stimulations were consistently scored higher on the NRS for both brush and the 2 punctate von Frey filaments ($F > 5.864$; $P < .017$) (Fig 3). Analysis of the percentage increases in NRS scores from single to repeated stimulation did not indicate significant effects of treatment or time for either von Frey filament or for cotton swab brush stimulations ($F < 2.849$; $P > .112$).

Electrical Sensitivity

Analysis of the tooth-pulp pain threshold, EDT, and EPT could not demonstrate any effects of

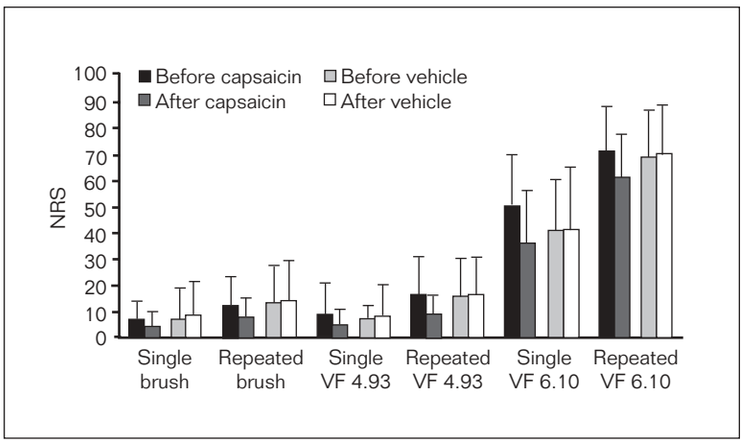

Fig 3 Subjects rated the intensity of single and repeated (5 stimulations at 1 Hz) brush and punctate von Frey (VF) filament 4.93 and 6.10 on a numerical rating scales (0 to 100 with 50 labeled as "just barely painful"). The mechanical sensitivity was tested before and after 15-minute application of capsaicin and vehicle in 16 subjects (mean values + standard deviations). There were no differences between treatment or time.

treatment ($F < 0.487$; $P > .496$) or time ($F < 2.684$; $P > .122$) (Fig 4). Similarly, ANOVA tests of just the female data (n = 14) did not indicate any significant effects of treatment or time.

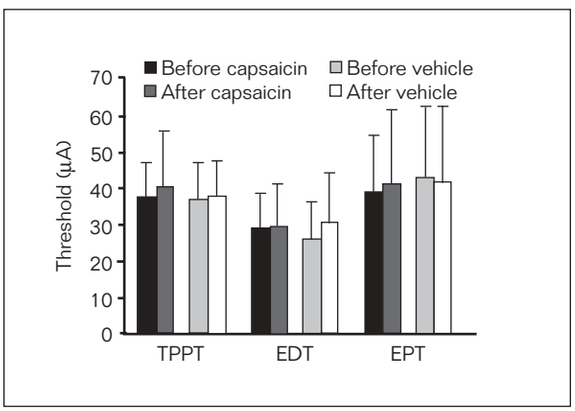

Fig 4 The tooth-pulp pain threshold (TPPT), electrical detection threshold (EDT), and electrical pain threshold (EPT) were determined on the alveolar mucosa in 16 subjects. The electrical sensitivity was tested before and after 15-minute applications of capsaicin and vehicle (mean values + standard deviations). There were no differences between treatment or time.

Discussion

The main finding in this study was the robust increases in thermal sensitivity following application of capsaicin on the alveolar mucosa, whereas the mechanical and electrical sensitivity remained unchanged. In addition, the battery of QST provided reliable information on the intraoral sensitivity. No significant side-to-side differences were detected.

Oral Pain Model

Capsaicin is widely used either intradermally or by topical application to the skin, and by comparison only a few studies have attempted to apply capsaicin to the oral mucosa.[13,22] Intraoral capsaicin application is not trivial and in our opinion there was a need to develop an intraoral pain model in which capsaicin could be protected from saliva and movements and be prevented from spreading in the oral cavity. The use of an oral bandage secured the precise location of the capsaicin, and it was indeed possible to avoid stimulation of other areas of the oral mucosa.

In the present study, only the sensory-discriminative components of pain, ie, pain intensity, were assessed with the use of a VAS. In future studies, the unpleasant dimension of pain also could be assessed[23] in order to obtain a more complete description of the capsaicin-evoked sensation in the oral cavity. However, we recorded the quality of pain with the use of the MPQ and found that the subjects used different words to describe their sensations. The most commonly used words were: searing, burning, pricking, sharp, annoying, and throbbing, and 6 subjects also reported a cool sensation. This paradoxical cool sensation can probably be explained by a cross-reaction between capsaicin and menthol at the level of the vanilloid receptor.[24] Menthol is known to produce a sensation of coolness[25] and this does not appear to be reported following skin application of capsaicin, where a burning pain is very often reported.[15,18,26,27] Studies have shown cross-desensitization of menthol by capsaicin and cross-sensitization of capsaicin by menthol on the oral

mucosa.[24] It has been suggested that menthol produces some of its sensory irritation via capsaicin-sensitive pathways, but that the mechanisms of excitation and/or desensitization are different from those of capsaicin.[24] Overall, these findings suggest that there might be differences in the cross-reactions depending on tissue and location.

The topical application of capsaicin on the alveolar mucosa caused moderate levels of pain in all subjects. It can be considered an effective, easy, and safe way to elicit oral pain without tissue injury and may complement the recent model of capsaicin application on the tongue.[13] Other ways of administering capsaicin and other algesic substances to the oral mucosa are still available, eg, submucosal injection or the use of perfusion chambers. The choice of a pain model will depend on the specific purpose of the study, for example, testing the pharmacologic efficacy of a drug or as a pain-provocation test in different pain conditions.[28–30] In this study we wished to obtain moderate levels of pain lasting for about 15 minutes, which may allow for triangulation procedures, QST, or electrophysiologic data to be recorded during ongoing pain. It will also be possible to use intraoral capsaicin as a pain provocation test in different intraoral pain conditions as it has been used on the skin of patients suffering from postherpetic neuralgia[30] and rheumatoid arthritis.[29] Higher levels of pain of a shorter duration can be obtained with the use of a submucosal injection of the capsaicin. This pain intensity and duration corresponds to the intradermal type of capsaicin application.[18] Intramuscular injection of capsaicin produces a similar pattern of evoked pain to the topical applications on skin and oral mucosa.[18,27] The type of tissue and type of capsaicin application (topical vs submucosal/intradermal) seem to be significant determinants for the intensity and duration of pain obtained in the different models.

Quantitative Sensory Testing

Two zones of abnormal pain sensitivity have been characterized following application of capsaicin to the skin[16]: *(1)* the primary zone directly affected by the capsaicin in which altered sensations are termed primary hyperalgesia, and *(2)* the secondary zone of unaffected tissue surrounding the area of capsaicin application in which the altered sensations are termed secondary hyperalgesia. In this study on the oral mucosa, QST was only performed within the primary zone of capsaicin application. Due to the anatomy of the test area and the limited space available, no attempts were made to map the extent (spatial dimension) of changes in somatosensory sensitivity. For the same reasons it was not possible to detect a clinical flare reaction, but future studies may be able to detect this phenomenon with the use of laser-doppler flowmetry.

Increased responsiveness to thermal stimuli applied to the primary zone of capsaicin application was a consistent finding in this study and is most likely explained by a peripheral sensitization of primary nociceptive afferent fibers.[14,16,17] The oral mucosa is innervated both by A-delta and C fibers,[31] and since the mechano-heat sensitive part of the C and A-delta fibers is sensitive to capsaicin,[32] it is possible that they are responsible for the present decrease in WDT and HPT. The menstrual cycle was not taken into consideration in this study. However, the capsaicin and control applications were performed on the same day, and the menstrual cycle is therefore not likely to explain the differences in thermal responses to capsaicin and control.

Hyperalgesia to mechanical stimuli in the primary zone of capsaicin application was not found in this study. These findings on the oral mucosa appear to be different from findings in hairy skin after topical application of capsaicin, where C fibers may mediate thermal hyperalgesia and A-delta fibers mediate brush hyperalgesia.[16] The lack of mechanical allodynia and hyperalgesia following oral capsaicin application was to some extent surprising but corresponds with the cutaneous capsaicin pain models, where mechanical hyperalgesia is observed mainly in the secondary zone (secondary hyperalgesia). In fact, the present data on mechanical sensitivity in the primary zone rather suggested hypoalgesia and hypoesthesia following topical capsaicin application. Hypoalgesia is also seen after injection of capsaicin into the skin. The injection induces a small analgesic bleb at the site of injection.[33] Furthermore, repeated topical applications of capsaicin can desensitize skin and oral mucosa.[22,34] It has been shown that desensitization of the tongue by multiple topical applications of capsaicin is clearly present after 15 minutes, but similar application patterns to the facial skin showed a slower increase of irritation and longer persistence of sensation. This finding has been attributed to the barrier and reservoir properties of the cornified hairy skin.[22] The time course (temporal dimension) of hyperalgesia and desensitization was not possible to determine in the present experimental protocol because the duration of the single capsaicin application was preset to 15 minutes. Further studies with other application times (eg, 5 or 10 minutes) will be needed to determine the

temporal characteristics of allodynia and hyperalgesia to mechanical stimuli. Thus, both spatial and temporal factors and desensitization may explain the lack of mechanical allodynia and hyperalgesia on the alveolar mucosa.

There were no significant changes in the electrical sensitivity of the tested area in the present study. The electrical stimulus is not selective, since it may stimulate all nerve endings and bypass the receptors. Both the alveolar mucosa and the maxillary first premolar tooth were tested in the present study, because preliminary data had shown that some subjects might describe pain sensations in the tooth when the capsaicin-evoked pain was at its peak. If there had been an increased electrical sensitivity of the tooth following capsaicin application, it might have indicated some degree of central sensitization,[7,35] but this was not observed in this study.

Interestingly, we were able with simple techniques to elicit windup-like sensations and pain by repeated mechanical stimuli applied to the oral mucosa. Also, nonpainful brush and punctate stimuli demonstrated a similar windup (ie, temporal summation) of afferent input. However, application of capsaicin did not potentiate the temporal summation.

In conclusion, further refinement of intraoral QST may be needed, but a battery of thermal, mechanical, and electrical tests are currently available and can be used in an attempt to provide a better description of the somatosensory sensitivity in the so-called idiopathic orofacial pain conditions.

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