# Capsaicin-Induced Muscle Hyperalgesia in the Exercised and Non-Exercised Human Masseter Muscle

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**Aims:** *Strong jaw muscle exercises such as tooth grinding in sleep bruxism are frequently believed to be a predisposing factor in myogenous types of temporomandibular disorders. However, it is not known whether tooth grinding in sleep bruxism is associated with increased sensitivity to intramuscular stimuli. This study therefore compared the hyperalgesic effects of an intramuscular injection of capsaicin into the right masseter with and without a prior experimental tooth-grinding exercise.* **Methods:** *Ten healthy men participated in 2 randomized sessions (exercise, non-exercise session) separated by 1 week. In the exercise session, 0.1 mL capsaicin (100 µg/mL) was injected into the right masseter immediately after 45 minutes of experimental tooth grinding. In the non-exercise session, the exact same paradigm was used, except that the experimental tooth grinding was omitted. The perceived intensity of pain evoked by intramuscular capsaicin was scored on a 100-mm visual analog scale (VAS). Pain detection thresholds (PDTs) to pressure stimuli and maximal voluntary occlusal force (MVOF) were measured before capsaicin injection; 5, 15, and 45 minutes after the injection; and once a day for the following 3 days.* **Results:** *Injections of capsaicin into an exercised or non-exercised masseter did not cause significant differences in peak pain intensity on the VAS (57 ± 6 mm in exercised masseter vs. 53 ± 6 mm in non-exercised masseter; P = 0.464). The PDTs in the exercised masseter were significantly decreased for up to 1 day after the capsaicin injection (P ≤ 0.038), whereas PDTs in the non-exercised masseter were decreased for only 5 minutes (P = 0.017). The MVOF on the right side was decreased 5 minutes after the capsaicin injection in both sessions (P < 0.010). The MVOF on the left side was significantly reduced for up to 15 minutes after the capsaicin injection in the exercise session only (P < 0.019).* **Conclusion:** *Increased sensitivity to percutaneous pressure stimuli probably reflects a post-exercise muscle soreness following tooth grinding, whereas intramuscular sensitivity to noxious chemical stimuli immediately following exercise seems to be unchanged.*
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**Key words:** masticatory muscles, bruxism, sensory thresholds, pain threshold, pain measurement, bite force, electromyography

Sleep bruxism is defined as "a stereotyped movement disorder characterized by grinding or clenching of teeth during sleep" by the American Sleep Disorders Association.[1] It is commonly believed that sleep bruxism is involved in the etiology of pain in the masticatory muscles.[2] Clinically, many patients with temporomandibular disorders (TMD) exhibit a tendency to clench or grind their teeth.[3,4] However, a causal relationship between sleep bruxism and myogenous TMD is not clear, and strong scientific evidence for an etiologic importance of bruxism is lacking.[5,6]

Overloading or overuse of muscle may indeed cause pain, a common experience that has been verified in a large number of studies on post-exercise muscle soreness (PEMS) in limb muscles.[7–9] Eccentric contractions, ie, forced lengthening of contracting muscles, are especially effective in evoking PEMS in limb muscles.[10] Recently, it was suggested that orofacial motor activity during sleep, such as sleep bruxism, might cause PEMS in the masticatory muscles.[11]

Laskin[12] hypothesized that as soon as sleep bruxism had initiated jaw muscle pain, the condition would become self-perpetuating, with increased muscle activity reinforcing the original myospasm and pain, thus setting up a chronic, vicious cycle. Therefore, there have been large numbers of experimental trials with different types of sustained concentric or eccentric contractions, and they have all reported significant levels of jaw muscle pain and soreness as an immediate consequence of the exercise (for review see Arima et al[13]). However, as in limb muscles, it might be important to examine subjects for several days following the exercise for investigation of PEMS in jaw muscles. Relatively few studies have examined subjects in the post-exercise period. Clark et al[14] attempted to induce jaw muscle pain by a protrusive task but could not detect any significant changes in spontaneous or pressure-evoked pain in the post-exercise period. Svensson and Arendt-Nielsen[15] reported that 5 days of repeated concentric contraction at 50% of maximal voluntary occlusal force (MVOF) caused a progressive reduction in jaw muscle pain and soreness, in contrast to the prediction from the vicious cycle. Furthermore, there is reliable evidence that acute jaw muscle pain does not cause muscle hyperactivity in humans.[16–18]

Arima et al[13] recently examined pain and soreness levels evoked by standardized jaw movements at more than 50% of MVOF for 45 minutes to determine whether experimental tooth-grinding activity, which may partly imitate the nature of sleep bruxism, can produce long-lasting muscle soreness and initiate a vicious cycle. Significant but low levels of jaw muscle pain and soreness were found in the post-exercise period, suggesting that experimental tooth-grinding activity has little potential for setting up longer-lasting painful conditions in non-TMD subjects. Madeleine et al[19] showed in healthy subjects that sustained standing on a hard surface for 2 hours sensitizes the soleus muscle to an acute, deep, painful experimental input when compared to standing on a soft surface. This suggests that muscle activation may sensitize the muscle nociceptors. Recent studies have indicated that intramuscular injection of capsaicin is a suitable technique to study muscle hyperalgesia,[20,21] but so far this experimental model has not been used in the craniofacial region.

The aim of this study was therefore to investigate whether jaw muscles would be sensitized to intramuscular chemical stimuli following an experimental tooth-grinding exercise.

## Materials and Methods

### Subjects

Ten male volunteers (mean age 24.0 years, SD 2.0, range 20 to 30 years) participated in this study. All of them were in good health and, according to previously published guidelines, were without any signs or symptoms of TMD.[22] Specifically, all subjects reported that they had not noticed any particular clenching habits or tooth grinding during sleep. Furthermore, none of the subjects had participated in any other experimental tooth-grinding study. Informed consent was obtained from each subject. This study had been approved by the local ethics committee.

### Study Design

All subjects participated in 2 experimental sessions separated by 1 week. Both sessions consisted of 4 days (1 experimental day and 3 follow-up days). On the experimental days, subjects received an injection of capsaicin in their right masseter muscle. In the exercise session, capsaicin was injected immediately after a standardized exercise consisting of 45 minutes of experimental tooth grinding.[13] In the non-exercise session, capsaicin was injected without prior experimental tooth grinding. The sequences of the sessions were randomized. Thus, 5 subjects participated in the non-exercise session first, and 5 subjects participated in the exercise session first; the groups were then switched. Pain intensity and muscle function were measured during the experimental period by a 100-mm visual analog scale (VAS), the McGill Pain Questionnaire (MPQ), pain detection threshold (PDT) to pressure stimuli, and MVOF.

**Experimental Tooth Grinding.** In accordance with a previous study,[13] the subjects were instructed to move the mandible from the intercuspal position to the right side canine-canine position and back to the intercuspal position and to keep electromyographic (EMG) activity level at

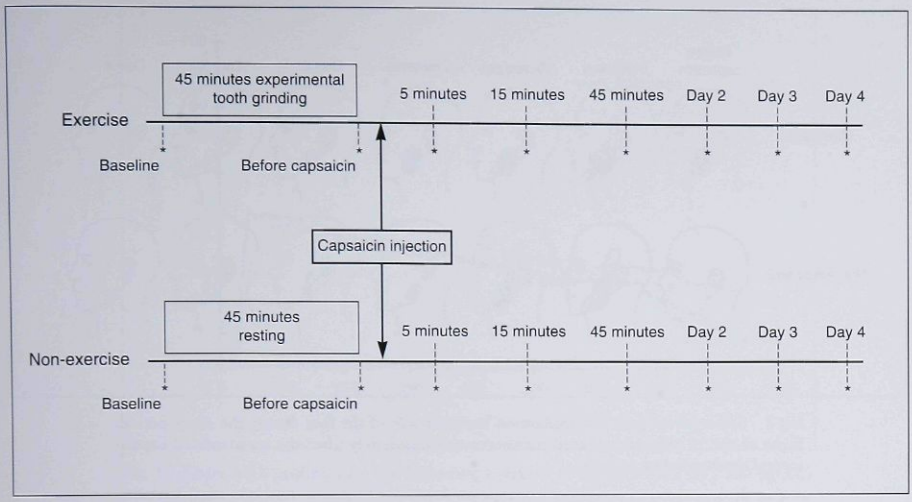



**Fig 1** Time course of the experiment. Ten volunteers participated in 2 sessions. The experimental tooth-grinding exercise was performed in only 1 session (Exercise). Visual analog scales, MPQ, PDT, and MVOF were measured during the experiment (*asterisk*, 8 examinations).

50% of MVOF. To standardize movements, only right-side grinding was performed in this study. The movement was repeated every 2 seconds (0.5 Hz) for 5 minutes (= 1 trial). The subjects were asked to perform 9 trials, with a 1-minute rest between trials. An electronic metronome and visual feedback of the EMG amplitude from the right masseter muscle helped the subjects to maintain a consistent rhythm and force of grinding.

**Capsaicin Injection.** Capsaicin injection (0.1 mL, 100 μg/mL) was used in this study to produce pain and hyperalgesia in the masseter muscle. The anteroposterior and the inferior-superior borders of the right masseter muscle were located by palpation during contraction of the muscle, and the central part of the muscle was located by intersecting lines drawn from the middle of the borders of the muscle. The needle was inserted into the central part of the muscle until the mandibular bone was reached, the needle was pulled back approximately 1 to 2 mm, and after aspiration the capsaicin solution was injected. The total duration of the manual injection was about 5 seconds.

**Outcome Measures.** All outcome measures were repeated at baseline; before capsaicin injection; 5 minutes, 15 minutes, and 45 minutes after injection of capsaicin; and on Day 2 (ie, 1 day after injection of capsaicin), Day 3, and Day 4 (Fig 1).

**Visual Analog Scale.** The subjects were asked to score pain intensity, unpleasantness, and soreness on 3 separate 100-mm VAS with the jaw at rest. The left end of the VAS was labeled as either "no pain," "no unpleasantness," or "no soreness," and the right end was either "most pain," "most unpleasantness," or "most soreness." The subjects also scored their pain intensity continuously with the use of an electronic VAS for 15 minutes after the capsaicin injection on both experimental days.

**McGill Pain Questionnaire.** A Danish version of the MPQ was used to calculate the pain rating index of the sensory, evaluative, affective, and miscellaneous components of pain.[23,24] Furthermore, the subjects were asked to draw the pain distribution on a figure showing the left and right profile of a face. The area of pain distribution was digitized (ACECAD, model D9000+ digitizer) and calculated in arbitrary units (Sigma-Scan).

**Pain Detection Threshold.** An electronic pressure algometer (Somedic AB) was used with a probe diameter of 6 mm and a constant application rate

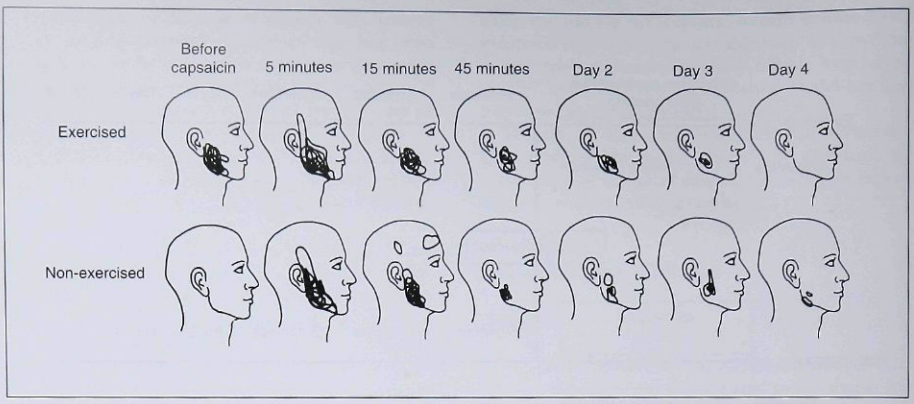



**Fig 2** Self-reported pain distribution on the right side of the face during the study period. Eight of the 10 subjects reported pain/soreness immediately after the standardized experimental tooth-grinding exercise.

of 30 kPa/sec. The measurements were performed on the central parts of the masseter muscles, which were located as previously described. To reproduce the location of the measurement sites, a pair (right and left side of the face) of clear pliable plastic templates was indexed to the inferior surface of the earlobes, the lateral angle of the mouth, and the lateral angle of the eyes. Subjects were instructed to keep their teeth slightly apart (about 1 to 2 mm) to avoid contraction of the jaw-closing muscles during pressure stimulation.[25] The PDT was defined as the pressure (in kPa) that the subjects first regarded as painful. The subject pushed a small thumb switch, which froze the pressure on a digital display when the threshold was reached. The PDT was determined in triplicate. The interval between successive pressure stimuli was about 2 minutes.

**EMG Activity and Maximal Voluntary Occlusal Force.** Bipolar disposable surface electrodes (Blue Sensor, type N-10-E, Medicotest) were placed symmetrically in the central part of the right masseter muscle, which was palpated during contraction. The inter-electrode distance was 10 mm. A saline-soaked ground electrode was placed on the neck.

A U-shaped bite force transducer (7 mm high, 1.1 × 1.1 cm area, Aalborg University) was covered with plastic tubes to protect the teeth.[15] The MVOFs were measured from both right and left sides between the first molars; subjects were instructed to clench their teeth as hard as they could for 3 to 4 seconds. Verbal encouragement was given to obtain the maximal effort.

### Statistical Analysis

Parametric statistics (mean ± standard error of the mean [SEM]) and 1- and 2-way analyses of variance (ANOVA) with repeated measures were used to describe the data. The PDT and MVOF values were normalized with respect to baseline values. The levels of significance were adjusted for multiple comparisons with the use of Student-Newman-Keuls correction (SNK). The association between pain intensity measured on the VAS and normalized PDT and MVOF values was analyzed with the use of Pearson's product moment correlation. The VAS scores of capsaicin-induced pain were compared with the use of Student's $t$ test. Significance was accepted at $P < 0.05$.

## Results

### Effects of Experimental Tooth-Grinding Exercise

Immediately after the 9 trials of the experimental tooth-grinding activity (before capsaicin), 8 of the 10 subjects experienced unilateral pain/soreness in the right masseter muscle only (Fig 2). Soreness on

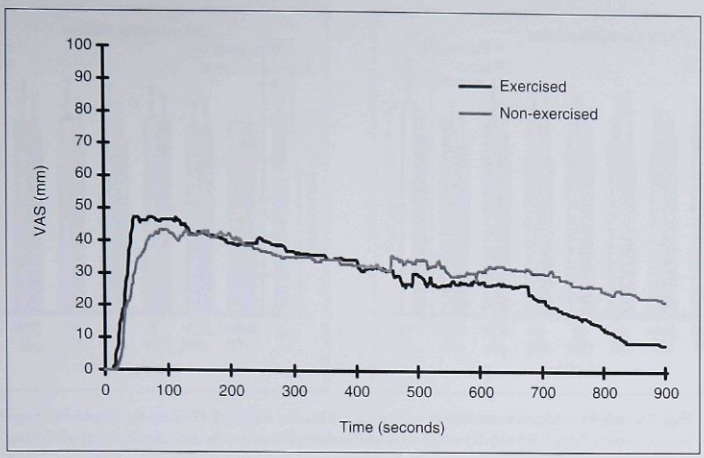



**Fig 3** Mean VAS profiles (n = 10) following injection of capsaicin (0.1 mL, 100 μg/mL) into the right masseter muscle. There were no significant differences between peak pain or pain duration.

VAS was significantly increased compared to baseline values (mean ± SEM: 13.7 ± 4.8 mm, SNK: $P = 0.041$), but not for pain (1.6 ± 0.7 mm, SNK: $P = 0.990$) or unpleasantness (6.7 ± 1.6 mm, SNK: $P = 0.505$). The most frequently chosen word in the MPQ was "tender" (50%). There were no significant differences between MVOF measured at baseline (right side: 76 ± 6 kg, left side: 71 ± 5 kg) and after the experimental tooth-grinding exercise (right side: 73 ± 5 kg, left side: 69 ± 6 kg) (SNK: $P = 0.363$ and $P = 0.398$). The PDTs in the right and left masseter muscles (256 ± 25 kPa and 261 ± 24 kPa) were not significantly influenced by the experimental tooth-grinding exercise (241 ± 25 kPa and 243 ± 19 kPa) (SNK: $P = 0.320$ and $P = 0.203$).

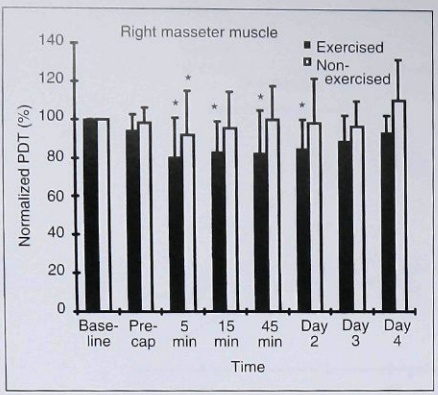
There were no differences in any outcome parameter between baseline and the before-capsaicin measurement in the without-exercise session.

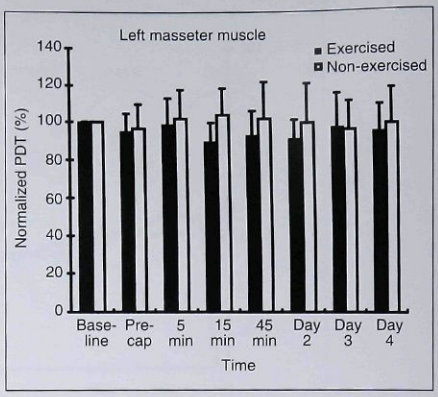
### Effects of Capsaicin

**Pain Drawings, McGill Pain Questionnaire, and Visual Analog Scale.** Immediately after the capsaicin injection, pain intensity increased progressively and reached a peak (VAS) (Fig 3) in the exercised masseter of 57.0 ± 6.4 mm and in the non-exercised masseter of 52.8 ± 6.2 mm; there was no significant difference between the 2 sessions (Student's $t$ test: $P = 0.464$). A further analysis of the capsaicin-evoked pain showed that there were no significant differences in VAS scores calculated in 9 consecutive 100-second epochs between the 2 sessions (2-way ANOVA: $F(1,72) = 0.515$, $P = 0.491$). The offset of pain intensity was not significantly different between the sessions (exercised: 795 ± 118 seconds, non-exercised: 1,004 ± 178 seconds; Student's $t$ test: $P = 0.254$).

Five minutes after the capsaicin injection, all subjects reported pain in their right masseter muscle, temporomandibular joint, and temporal regions (Fig 2). The area of pain distribution was significantly increased over the baseline measurement (2-way ANOVA: $F(7,63) = 15.858$, $P < 0.001$) and lasted for up to 15 minutes after injection, with no significant differences occurring between the exercise and non-exercise groups (2-way ANOVA: $F(1,63) = 2.038$, $P = 0.187$).

The MPQ data revealed that the capsaicin injection had a significant effect on all dimensions of pain (sensory, affective, evaluative, and miscellaneous) in both sessions (1-way ANOVA: $F(3,27) \geq 3.541$, $P \leq 0.003$). The most frequently chosen words (> 30%) from the MPQ were "hurting" (50%), "pressing" (50%), "tender" (50%), "beating" (40%), and "spreading" (40%).




**Figs 4a and 4b** Mean normalized values (n = 10) and SEM of PDT in right and left masseter muscles. *$P < 0.05$ (SNK) compared to baseline. Pre-cap = before capsaicin application.

**Pain Detection Thresholds.** The normalized PDTs in the right masseter, but not in the left masseter, were significantly influenced by the capsaicin injection in both sessions (2-way ANOVA: $F(7,63) = 3.364$, $P = 0.004$), with no significant interaction occurring between the experimental tooth-grinding task and the capsaicin injection (2-way ANOVA: $F(7,63) = 1.565$, $P = 0.163$). In the exercise session the PDT in the right masseter was significantly decreased at 5, 15, and 45 minutes and 1 day (Day 2) after the injection (SNK: $P \leq 0.038$) (Figs 4a and 4b). In the non-exercise session, the PDT in the right masseter was significantly decreased 5 minutes after the injection (SNK: $P = 0.017$) (Figs 4a and 4b).

**Maximum Voluntary Occlusal Force.** The normalized MVOF on the right side was significantly decreased by the capsaicin injection in both sessions (2-way ANOVA: $F(7,63) = 5.806$, $P < 0.001$). This lasted for 5 minutes in the exercised subjects (SNK: $P \leq 0.010$) and up to 15 minutes in the non-exercised subjects (SNK: $P \leq 0.047$) (Figs 5a and 5b). There was no significant interaction between the experimental tooth-grinding task and the capsaicin injection (2-way ANOVA: $F(7,63) = 0.458$, $P = 0.861$). The normalized MVOF on the left side was significantly decreased for up to 15 minutes in the exercised subjects (SNK: $P \leq 0.019$), with no significant changes occurring in the non-exercised subjects (SNK: $P \geq 0.056$) (Figs 5a and 5b).

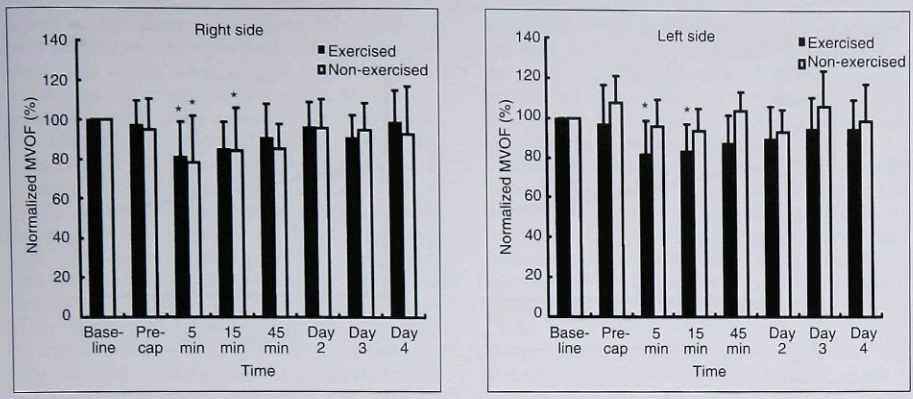
### Correlation Analysis

There was a weak but significant negative correlation between VAS scores for pain intensity evoked by capsaicin injection and the normalized PDT in the right masseter muscle during the exercise session (Pearson: $r = -0.24$, $P = 0.032$) (Fig 6), whereas there was no significant correlation in the session without exercise (Pearson: $r = -0.20$, $P = 0.076$).

There were significant negative correlations between the normalized MVOF and VAS on the right side in the session with exercise (Pearson: $r = -0.338$, $P = 0.002$) and in the session without exercise (Pearson: $r = -0.328$, $P = 0.003$). The normalized MVOF on the left side was negatively correlated to VAS only in the exercise session (Pearson: $r = -0.347$, $P = 0.001$) (Fig 7).

## Discussion

The main finding in the present study was significant decreases in PDTs to percutaneous pressure stimuli and MVOF, particularly when capsaicin was administered in a jaw muscle that had been exercised by the experimental tooth-grinding activity. The correlation analysis suggested slightly stronger relationships between pain intensity on VAS and changes in PDT and MVOF in the exercised muscle. However, there were no differences in capsaicin-evoked pain intensity between an exercised and non-exercised jaw muscle.




**Figs 5a and 5b** Mean normalized values (n = 10) and SEM of MVOF on right and left sides. *$P < 0.05$ (SNK) compared to baseline. Pre-cap = before capsaicin application.

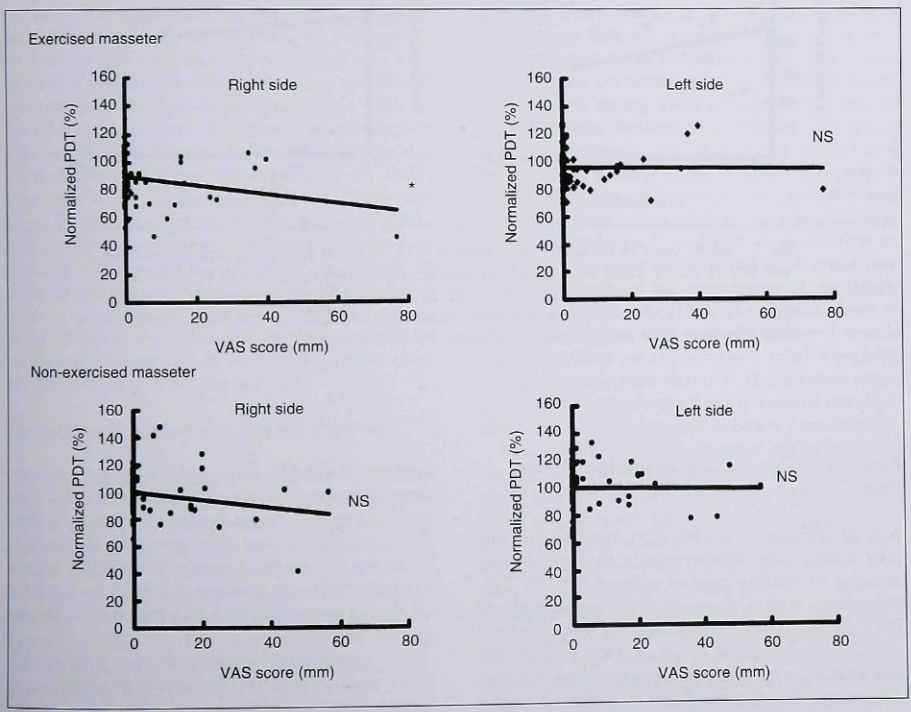



**Fig 6** Scatter plots of the correlation between VAS scores of pain (mm) and normalized PDT values of the left and right masseter muscles. Only the exercised masseter muscle showed a significant correlation ($r_s = -0.240$, n = 10, $P < 0.05$). *Significant correlation, $P < 0.05$ (Pearson), NS = no significant correlation, $P \geq 0.05$ (Pearson).

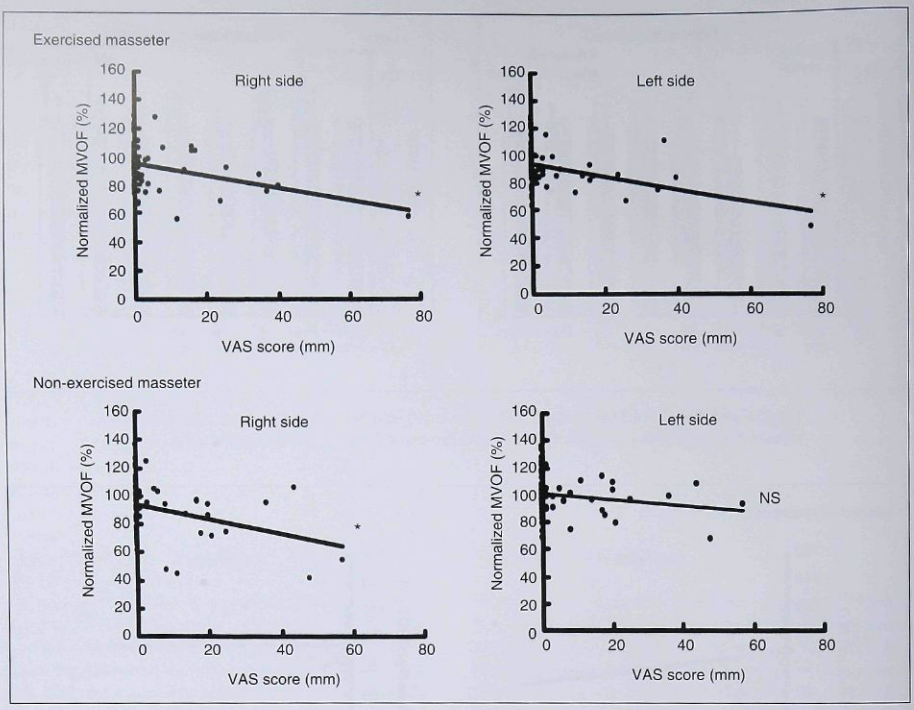



**Fig 7** Scatter plots of the correlation between VAS scores of pain (mm) and the normalized MVOF values. There were significant correlations on both the right side ($r_s = -0.338$, $P < 0.01$) and the left side ($r_s = -0.347$, $P < 0.01$) in the session with exercise and on the right side ($r_s = -0.328$, $P < 0.01$) in the session without exercise. *Significant correlation, $P < 0.05$ (Pearson); NS = no significant correlation, $P \geq 0.05$ (Pearson).

### Experimental Tooth Grinding and Jaw Muscle Pain

A large number of studies have tried to develop long-lasting pain or soreness in the jaw-closing muscles of healthy human subjects.[13–15,26–31] In accordance with a recent study,[13] the normalized PDT in the exercised masseter muscle was significantly decreased by about 15% to 20% the day after the experimental tooth-grinding exercise. Therefore, the decreased PDT on Day 2 in the present study might be a result of the experimental tooth-grinding exercise. However, VAS ratings of pain intensity, unpleasantness, and soreness were lower than those in the previous study. This discrepancy might be due to the subjects' expectations in the study, since all subjects knew that they were going to receive a capsaicin injection in their masseter muscle and that it would be painful. Thus, the low levels of pain/soreness following the experimental tooth grinding may have been related to the expectation or knowledge of a strong painful stimulus.

The experimental grinding or clenching models have generally provided good evidence that healthy jaw muscles are quite resistant to the development of pain or soreness.[14,15] This also fits with the clinical impression that subjects with hypertrophic masseter muscles and severely worn teeth often are without any symptoms. In fact,

recent studies suggest that about 54 to 56% of such subjects may have rhythmic masticatory muscle activity during sleep,[32,33] but the entire group has no signs or symptoms of bruxism. Thus, tooth grinding is most likely a normal orofacial motor behavior and, under normal circumstances, is not a significant risk factor for the development of muscle pain or soreness.

The experimental tooth-grinding and clenching models have also addressed the vicious cycle concept. The idea that muscle spasms, muscle pain, and hyperactivity could be mutually linked was originally an attractive idea,[3,4] because the cause-effect relationships seemed logical and appeared to be substantiated by clinical findings of tense and taut muscles. However, the vicious-cycle theory has never been properly validated,[34] and questions have been raised about the generalization of muscle hyperactivity leading to muscle pain and muscle pain leading to muscle hyperactivity. The experimental tooth-grinding and clenching studies have documented the fact that healthy jaw muscles are rather difficult to overload. This was also shown in the present study. However, the second part of the statement—that muscle pain leads to muscle hyperactivity—has not received support from controlled human studies of experimental induction of pain and observation of the EMG responses in the jaw-closing muscles.[16,17] Although there is some evidence that the postural EMG activity in jaw-closing muscles is increased in patients with painful muscles,[35] the magnitude of these changes is in the range of 1 to 2 μV and may have no pathophysiologic importance.[16] In summary, it seems that pain and soreness induced by tooth-grinding activity is self-limiting rather than self-perpetuating in healthy subjects.

### Neurobiologic Factors and Jaw Muscle Pain

The present study demonstrated that capsaicin injected into the masseter muscles produced hyperalgesia to percutaneous pressure stimuli, in accordance with recent findings in the brachioradialis muscle,[21] and that this hyperalgesia was slightly more pronounced and lasted longer when a tooth-grinding task had been performed immediately before the injection. However, there were no significant differences in capsaicin-evoked pain intensity between an exercised and non-exercised jaw muscle. This is in contrast to the study of Madeleine et al,[19] which demonstrated that sustained standing on a hard surface was associated with significantly more discomfort and significantly increased pain responses to injection of hypertonic saline into the leg muscles versus standing on a soft surface. Differences in types (static versus dynamic) and duration (2 hours versus 45 minutes) of the exercise, between leg and jaw-closing muscles, and between hypertonic saline and capsaicin might explain these findings.

Strong tooth-grinding activity is associated with reactive hyperemia in the post-contraction period[36–38] as well as a possible release of bradykinin, serotonin, and prostaglandins[34] and accumulation of mast cells.[39] Furthermore, histamine has recently been implicated in jaw muscle fatigue and pain.[40] Thus, thin nociceptive afferents could be sensitized by the tooth-grinding task through the release of endogenous mediators, and intramuscular capsaicin could thereby evoke a stronger and more pronounced response. However, little is known about the specific interactions between different endogenous algesic substances in natural muscle contractions associated with tooth grinding, but it has been shown in both animals and humans that, eg, serotonin sensitizes the neural responses to subsequent bradykinin injections.[41–43] An accumulation of mast cells in muscle tissue after a strong tooth-grinding task could be of importance, because these cells are known to contain serotonin but also to synthesize and release nerve growth factor (NGF).[44] Recently, it was shown that NGF injected systemically into healthy subjects caused diffuse myalgia and long-lasting hyperalgesia.[45] Stohler[46] suggested that an interaction between estrogen and NGF could play a significant role in the explanation of the female preponderance in the TMD population. Plesh et al[31] demonstrated that women developed muscle symptoms after an experimental tooth-clenching task more easily than men did. The question about gender differences in the development of jaw muscle pain needs to be studied in future experiments.

Recent findings on the neurobiology of jaw muscle pain give a new perspective on the importance of tooth grinding and clenching in the development of TMD pain. It seems clear that simple overloading of the jaw-closing muscles is insufficient to trigger more than brief and self-limiting periods of pain or soreness. Although jaw-closing muscles are not easily sensitized to intramuscular stimuli following a single episode of tooth-grinding, endogenous algesic substances may have the potential to contribute to longer-lasting changes in peripheral afferents as well as central neurons in conditions with repeated exercises. The identification of neurobiologic factors, eg, endocrine and hormonal, seems important to allow rational and individualized diagnosis and management of pain in the jaw-closing muscles.

The increased sensitivity to percutaneous pressure stimuli after the exercise session was probably a reflection of PEMS following experimental tooth grinding, whereas the intramuscular sensitivity to noxious chemical stimuli immediately following the exercise seemed to be unchanged.

## Acknowledgments

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