Quantitative Assessment of Mechanical Allodynia and Central Sensitization in Endodontic Patients

ABSTRACT

Introduction: Patients seeking endodontic treatment commonly present with reduced mechanical pain thresholds (ie, mechanical allodynia [MA]) in the offending teeth. In patients with moderate to severe pain, MA may manifest in the teeth contralateral to the offending teeth because of the onset of central sensitization (CS). We hypothesize that there are quantitative differences in MA and CS in patients with different pulp and periradicular diagnoses.

Methods: Patients (n = 70) receiving endodontic treatment in the graduate endodontic clinic at the University of Texas Health Science Center at San Antonio and healthy volunteers (n = 10) were included in this cross-sectional study. The mechanical pain threshold from molar teeth was measured by a digital bite force transducer on the offending tooth (ipsilateral) and the contralateral tooth. Ipsi- and contralateral MA among different endodontic diagnoses were analyzed using the Kruskal-Wallis with Dunn post hoc test and the Student t test for differences between sexes. Multivariate regression models analyzed predictors for MA and CS. Results: Periradicular diagnoses of asymptomatic apical periodontitis, symptomatic apical periodontitis, and chronic apical abscess cases were significantly associated with MA. CS, seen as contralateral MA, was only detected in pulpal diagnosis of symptomatic irreversible pulpitis (SIP) previously initiated treatment, symptomatic apical periodontitis, and chronic apical abscess. Females experienced significantly lower pain thresholds than males on both sides. MA and CS were significantly correlated in both sexes. The preoperative pain level and duration were significant predictors for MA and CS only in female patients. Lastly, age was a significant predictor for MA in females. Conclusions: The magnitude of MA and CS varied with different endodontic diagnoses, with CS being correlated with increases in MA. Only in female patients were age, preoperative pain duration, and intensity significant predictors for the development of MA and CS. (J Endod 2020;46:1841–1848.)

KEY WORDS

Apical periodontitis; bite force; central sensitization; diagnosis; mechanical allodynia; pain

Mechanical allodynia (MA) has been defined as a reduced mechanical pain threshold to a nonnoxious stimulus (ie, biting). It is seen clinically as tenderness to biting or percussion, both innocuous stimuli under normal conditions. Given the subjective and nonquantitative nature of these tests, a method was developed to quantify MA in patients using a modified digital bite force transducer that accurately measures the intensity of mechanical forces that produce pain when biting. Khan et al demonstrated that healthy teeth have similar mechanical thresholds to their healthy contralateral counterparts. In contrast, teeth diagnosed with symptomatic irreversible pulpitis (SIP) have significantly lower mechanical pain thresholds compared with their contralateral counterparts. Importantly, contralateral teeth in patients with SIP displayed lower mechanical pain thresholds compared with healthy subjects. This was the first demonstration that pulpal inflammation produced measurable changes in pain thresholds not only in the offending teeth but also in contralateral teeth because of central sensitization (CS).

Reduction of the mechanical pain threshold (ie, MA) is the result of the peripheral sensitization of pulpal and periradicular nociceptors and possibly CS resulting in loss of function for an affected tooth. Although many key inflammatory mediators involved in peripheral sensitization underlining endodontic pain have been identified, far less is known about the generation and maintenance of CS in odontogenic conditions.
pain. Intense activation of pulpal nociceptors has been shown to evoke changes in wide dynamic range second-order neurons in the trigeminal complex in the medullary dorsal horn. The process of CS often underlies persistent pain states because it has been shown to be present long after the removal of the primary afferent input (i.e., etiology)\(^1\). Also, it has been shown to result in contralateral changes in the trigeminal system\(^2\). Therefore, this understudied pain state is likely present in most patients requiring endodontic treatment, having a key role in a heightened state of nociception that may involve other sites such as contralateral teeth and muscles of mastication. Hence, the identification of predictors of CS and its quantification allow clinicians to establish a more accurate diagnosis for odontogenic and nonodontogenic pain.

Regardless of the complex interplay between peripheral sensitization and CS, patients undergoing either nonsurgical or surgical endodontic treatment often report the alleviation of symptoms and increased quality of life\(^3\). Unfortunately, despite the high success rates of the alleviation of symptoms after endodontic therapy, there are approximately 5% of patients who present with persistent pain despite adequate treatment\(^4\). Indeed, the factors related to the resolution of MA after endodontic therapy are not fully understood. One of the main challenges with the assessment of treatment effectiveness of restoring normal function (i.e., bite force) has been the lack of objective measurement of the clinical symptoms. This challenge can be overcome with the use of the bite force transducer as an objective diagnostic tool. Notably, several studies have identified predictors for postoperative endodontic pain, including intensity and duration of the preoperative pain and patient age\(^5\). Although these are strong predictors for postoperative pain, and possibly its transition into chronic odontogenic pain, far little is known about their association with the magnitude of MA, a chief complaint in persistent endodontic pain\(^6\). Knowledge on how MA is present in different clinical presentations can provide invaluable information for clinicians to formulate individualized pharmacologic management of intra- and postoperative pain while better informing patients of expected outcomes.

In the present cross-sectional study, we investigated whether quantitative differences exist in MA and CS in patients with different pulp and periradicular diagnoses in molar teeth. We further investigated predictors for the development of MA and CS.

**MATERIALS AND METHODS**

**Patients and Data Collection**

This study was approved by the Institutional Review Board of the University of Texas Health San Antonio (UTHSA). Patients (n = 70) who attended the Department of Endodontics at UTHSA were invited to participate in the study. Another group of healthy volunteers (n = 10) was included as a control. The enrolled patients had a mean age of 43 ± 17 years and were composed of 62.5% women and 37.5% men. A total of 53% of molars were present in the maxillary arch, whereas 47% were in the mandibular arch.

The inclusion criteria were as follows:

1. Patients referred for a diagnosis or treatment of a molar tooth with suspected endodontic disease
2. American Society of Anesthesiologists classification 1 or 2
3. Minimum age of 18 years old and maximum age of 89 years old

The exclusion criteria were the following:

1. American Society of Anesthesiologists classification 3 to 5
2. Periodontal probing >6 mm
3. Pain medication usage of >7 days
4. Patients who have taken pain medications within the last 6 hours
5. Absence of a contralateral tooth
6. Sensitivity to percussion or spontaneous pain on a contralateral tooth
7. Symptoms in a nonmolar tooth (i.e., anterior or premolar)

**MA and Pain Measurement Using the Digital Bite Force Transducer**

Informed consent was obtained from every participant who fit the inclusion and exclusion criteria and agreed to participate in the study. All patients were seen by endodontic residents at UTHSA who determined and recorded the pulp and periradicular diagnosis based on the American Association of Endodontists consensus for diagnostic terms\(^7\) before formulating a treatment plan. In brief, for pulp diagnosis, normal pulp (control) was defined by the lack of spontaneous pain and positive nonlingering responses to the cold sensitivity test or a positive response to the electric pulp test. Asymptomatic irreversible pulpitis was defined as an asymptomatic tooth with normal pulp responses to sensitivity tests but with gross caries requiring endodontic therapy. SIP was defined by an exaggerated and lingering response to the cold sensitivity test with or without absence of spontaneous pain. Pulp necrosis was defined as the absence of a response to both cold and electric pulp tests.

For periradicular diagnosis, asymptomatic apical periodontitis (AAP) was defined by the absence of biting, percussion, or palpation sensitivity on a tooth presenting with apical radiolucency. Symptomatic apical periodontitis was defined by the presence of biting, percussion, or palpation tenderness, whereas chronic apical abscesses (CAA) was defined as the presence of a sinus tract. During the patient recruitment phase, patients with a pulpal diagnosis of reversible pulpitis or a periradicular diagnosis of acute apical abscess who met the inclusion criteria were not identified.

The providers further recorded the preoperative pain intensity level reported by the patient via the 11-point numeric rating scale, tooth pain duration, and demographic data, namely, age, sex, and ethnicity. Next, mechanical pain withdrawal force in newtons was measured from molar teeth twice from the offending ipsilateral and contralateral teeth using a digital bite force transducer. The measurements were recorded and averaged. The endodontic provider read the following instructions before recording the mechanical pain threshold:

“I am going to place this bite force measuring device between your upper and lower teeth to measure how hard you are able to bite. I will place the bite fork against your upper tooth and then I would like you to close and gently rest your teeth together on the device. When I signal you, increase biting pressure slowly until you are exerting as much force as possible and release immediately when you feel discomfort or pain. Other patients have described the feeling they have on maximal biting as a pinch, tingle, or strong pressure feeling. The bite force measurement from the time I signal you to start until you open should take approximately five seconds."

**Data Analysis**

Mechanical pain thresholds of groups of different pulpal and periradicular diagnoses were analyzed with the Kruskal-Wallis with Dunn post hoc test, whereas differences between men and women were analyzed by the Student t test using Prism 7 software (GraphPad, La Jolla, CA). In addition, Pearson correlation coefficients were used to analyze bivariate associations in men and women and between mechanical pain thresholds and age, pain intensity, and duration followed by multivariate analysis using stepwise linear regression using JMP software (SAS Institute, Cary, NC). All statistical analyses were tested at P < .05. To account for multiple testing in regression analyses, P values were adjusted according to the false discovery rate.
RESULTS

A total number of 80 molars (first molar or second molar) from 80 patients (30 [37.5%] men and 50 [72.5%] women) were included in this study. The age of individuals participating in this study was 18–77 years old with a mean age of 43 years. The distribution of pulpal and periradicular status of the offending teeth in the study are summarized in Tables 1 and 2, respectively.

Pulpal and Periradicular Diagnosis and MA

There was marked ipsilateral MA for all pulpal diagnoses with the exception of normal pulp (control teeth in pain-free volunteers) and previous endodontic treatment (Fig. 1A). Previously initiated treatment teeth showed the greatest reduction (64%) in the mechanical pain threshold followed by asymptomatic irreversible pulpitis (60%), SIP (55%), and pulp necrosis (42.5%). Interestingly, only the diagnoses of SIP and previously initiated therapy were associated with the development of contralateral MA or CS (P < .05) (Fig. 1B).

The periodical status of the treated teeth had a significant impact on the bite force threshold on treated teeth with all diagnoses evaluated displaying marked MA and a reduction in the mechanical pain threshold. Teeth with CAA and SAP had the greatest reduction of the mechanical pain threshold (56% and 55%, respectively) followed by AAP (28%) (Fig. 1C). Furthermore, contralateral MA was only detected in patients with offending teeth diagnosed with SAP and CAA (P < .05) (Fig. 1D).

Predictor Variables for MA and CS

Sex was a significant predictor for MA and CS, as measured by mechanical pain threshold levels, with women associated with significantly lower thresholds than men on both sides (P < .05). In further detail, female patients had a reduction of the mechanical pain threshold of 48% compared with 23% in men (Fig. 2A). This sex difference was also observed in contralateral measurements, with women showing a 19% reduction in the threshold and men showing no reduction of the mechanical pain threshold compared with the control group (Fig. 2B). Notably, ipsi- and contralateral mechanical pain thresholds were significantly correlated in both men and women (r = 0.72 and r = 0.75, respectively; Pearson correlation coefficient, P < .05; Fig. 3).

Furthermore, multivariate regression analysis revealed that, only in female patients, the reduction in the mechanical pain threshold was associated with pain intensity and duration for ipsilateral teeth and age, pain intensity, and duration for contralateral teeth (Fig. 3A). This association was not noted in male patients (Fig. 3B). Lastly, ethnicity was not a significant predictor in any group.

DISCUSSION

Clinicians rely on subjective percussion or biting tests for the diagnosis of apical periodontitis and the assessment of its resolution. A previous study showed that a digital bite force transducer can be used to quantitatively detect MA with good inter- and intraobserver reliability. The present study used this bite force transducer device to detect the presence of MA in patients referred for endodontic diagnosis and treatment. In addition, the mechanical pain threshold was measured and recorded in healthy volunteers, which resulted in an average bite pain threshold of approximately 525 N. This threshold was found to be dramatically decreased in patients with self-reported moderate to severe pain and pulpal and periradicular diagnoses requiring initial endodontic therapy. The use of this device was found to be sensitive enough to detect the differences in bite pain withdrawal forces among many of the evaluated factors.

The use of both thermal and electric pulp tests provides clinicians with subjective methods to determine pulp status and establish a clinical diagnosis with acceptable accuracy and reliability. A previous study showed that the mechanical pain threshold of teeth with SIP and symptomatic periradicular periodontitis reduced by 77% compared with contralateral teeth. The current study expanded the findings of the original study by evaluating the presence of MA in teeth with other pulpal and periapical diagnoses. A significant decrease in the mechanical pain threshold (ie, MA) was found in teeth diagnosed with asymptomatic irreversible pulpitis, SIP, pulp necrosis, and previously initiated therapy in comparison with the control group. Actually, the result shows that SIP and previously initiated therapy had greater allogdynia than other groups in comparison with the control and previously treated groups. These findings suggest that inflammation in either pulpitis or unfinished root canal therapies has a profound effect in the periradicular nociceptors. Indeed, substantial apical inflammation can be observed in animal models of apical periodontitis in early phases of pulp inflammation before it succumbs to pulp necrosis. Furthermore, teeth diagnosed with previous endodontic treatment collectively had similar MA to the control group teeth. Notably, the greatest majority of the cases with previous endodontic treatment were also diagnosed with AAP, whereas the cases diagnosed with either SAP or chronic apical periodontitis had detectable MA. Nonetheless, these results suggest that teeth with previous endodontic therapy, despite the presence of

<table>
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<th>Pulpal diagnosis</th>
<th>Asymptomatic irreversible pulpitis</th>
<th>Symptomatic irreversible pulpitis</th>
<th>Necrotic pulp</th>
<th>Previously initiated</th>
<th>Previously treated</th>
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<tbody>
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<td>Number of participants (n) and percentage of total</td>
<td>6 (8.6)</td>
<td>20 (28.6)</td>
<td>8 (11.4)</td>
<td>15 (21.4)</td>
<td>21 (30.0)</td>
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</table>

<table>
<thead>
<tr>
<th>Periapical diagnosis</th>
<th>Normal</th>
<th>Asymptomatic apical periodontitis</th>
<th>Symptomatic apical periodontitis</th>
<th>Chronic apical abscess</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of participants (n) and percentage of total</td>
<td>3 (4)</td>
<td>24 (34)</td>
<td>37 (53)</td>
<td>6 (9)</td>
</tr>
</tbody>
</table>
radiolucency, have greater bite force thresholds than unfilled teeth (pulp necrosis or previously initiated therapy) with a similar apical diagnosis. Although there is poor correlation between pulp and periradicular histology and diagnostic testing, the MA quantification method provides data that directly relate to the established diagnosis, but it also provides a degree of severity that is a snapshot of the pulpal and/or periradicular inflammatory process sensitizing periodontal nociceptors.

The currently used American Association of Endodontists consensus periradicular diagnostic terms are symptomcentric but also take into consideration the presence of radiolucency, swelling, or sinus tracts. MA was detected in all periradicular diagnoses included in this study with the exception of normal periradicular diagnosis in healthy volunteers. Thus, the digital bite force transducer was sensitive enough to detect reduced bite forces even in the absence of percussion sensitivity. Indeed, a study reported that 57% of patients with irreversible pulpitis had sensitivity to the percussion test, whereas MA was detected in 100% of patients diagnosed with irreversible pulpitis in the current study using the digital force transducer. Interestingly, patients with teeth diagnosed with CAA often report little to no symptoms. Surprisingly, they displayed similar lowered mechanical pain thresholds to patients with SAP. This is possibly due to the reduction of spontaneous pain with a draining sinus tract with persistence of tenderness to biting. In addition, patients may develop compensatory behaviors such as avoidance of using the offending tooth during chewing because infections with the development of a draining sinus tract are typically long-standing. Although this difference in clinical presentation is hard to detect by subjective percussion or biting tests, the use of the bite force transducer provided quantitative differences between CAA, SAP, and AAP compared with normal healthy teeth.

One of the findings in this study is a significant association between CS and MA. It is known that CS is marked by increased excitability of central neurons, which results from a barrage of impulses from C nociceptors evoking changes in central pain circuitry. The release of neuropeptides and brain-derived

FIGURE 1 – Mechanical pain withdrawal threshold quantification in patients with different pulpal and periradicular diagnoses. (A) Teeth diagnosed with asymptomatic irreversible pulpitis (AIP), SIP, pulp necrosis (NEC), and previously initiated therapy (P-Int) had marked MA seen as a reduction in ipsilateral bite withdrawal threshold. (B) Only SIP and P-Int were associated with MA contralateral to the offending tooth. (C) Teeth diagnosed with AAP, SAP, and CAA had marked MA, (D) whereas only SAP and CAA were associated with MA contralateral to the offending tooth. The Kruskal-Wallis with Dunn post hoc test: \( * P < .05, ** P < .01, *** P < .001, **** P < .0001 \), and n.s. = not statistically significant. The numbers in white circles denote the sample size for each group. The dashed horizontal line denotes the mean bite withdrawal threshold of healthy teeth. CTRL, control; P-Tx, previous endodontic treatment.
neurotrophic factor, among other molecules, has been implicated in the initiation and maintenance of CS in the medullary dorsal horn\textsuperscript{15}. The ultimate result of these central changes is a heightened state of nociception caused by the facilitation of excitatory signals and a possible decrease in inhibitory descending signals from the central nervous system\textsuperscript{20–22}. Although CS is expected in endodontic pain because it is usually of great intensity and duration, it is seldom detected or studied. This study detected contralateral MA (ie, CS) in teeth with a pulp diagnosis of SIP or previously initiated therapy or with a periradicular diagnosis of SAP and CAA. These findings agree with Khan et al\textsuperscript{3}, since that study also found CS in irreversible pulpitis and SAP. Thus, this study also confirms that pulp inflammation and the sensitization of pulpal nociceptors can result in central changes that ultimately lead to a reduced mechanical activation threshold of periaxial nociceptors. In addition, the current study expands the findings on CS to teeth diagnosed with previously initiated therapy and the periradicular diagnosis of SAP and CAA. Therefore, pulp and periradicular diagnoses were strong predictors of the development of CS. These findings suggest that teeth diagnosed with SIP and SAP must be treated as soon as possible to minimize the time of primary afferent barrage and decrease the development of CS. Also, pulpectomies should be immediately followed by definitive treatment because the previously initiated therapies included in this study also presented with significant CS.

Patient sex has been identified as a major predictor of endodontic pain, with female patients showing greater levels of preoperative and postoperative pain in certain studies\textsuperscript{13,23} but not all\textsuperscript{11,12}. In the current study, female patients had a greater reduction of the mechanical pain threshold across all diagnoses for both the ipsi- and contralateral sides compared with male patients. In addition, multivariate regression analysis revealed that, only in female patients, there was an association between age, pain intensity, and duration and the development of ipsilateral MA and CS, leading to contralateral MA. The findings of this study agree with a previous study that also used the digital bite force transducer and showed sexually dimorphic differences in MA in patients diagnosed with SIP\textsuperscript{1}. Importantly, the duration and intensity of preoperative pain have been both identified as predictors of persistent postoperative pain after endodontic therapy\textsuperscript{15,12,14,23}. In the current study, these factors were found to be positively associated with CS only in female patients, despite the relatively limited sample sizes. These results argue that females are at risk for the development of CS and subsequently persistent pain if presented with pain with high intensity for a longer duration. Although the mechanisms of this sexually dimorphic presentation are not fully understood, there is mounting evidence that some pain-modulating molecules may be directly involved in sex differences in nociception\textsuperscript{24–26}.

A limitation of this study is that the sample size in some of the groups did not allow for the evaluation of MA in all possible combinations of pulpal and periradicular diagnoses. Also, the impact of endodontic therapy on the measured magnitude of MA was not evaluated in the present study. A recent study evaluated the presence of MA in adjacent and contralateral teeth and concluded that teeth adjacent to a diseased tooth had greater association with MA than the contralateral teeth\textsuperscript{17}. Notably, teeth adjacent to a diseased tooth could also be affected by peripheral sensitization because of their proximity to the inflammatory milieu. Nonetheless, this study provided further evidence that CS is involved in the development of MA in the disease tooth but also in adjacent and contralateral teeth. Moreover, MA has been detected even in distant extraoral sites in patients with odontogenic pain\textsuperscript{30}, a finding that can be reproduced in animal models of CS subsequent to apical periodontitis\textsuperscript{31,32}. It is known that the activation of pulpal neurons produces CS that persists for a while even after removing the stimulus\textsuperscript{5,7} and that preoperative pain greater than 1 week before treatment significantly increased the risk of developing persistent pain over 6 months\textsuperscript{12}. Therefore, given the robust effect of CS on MA on a diseased tooth, surrounding tissues, and even distant intraoral and extraoral sites, additional studies using quantitative methods are needed to evaluate the effect of endodontic therapy on the resolution of MA and CS. It is noteworthy that the quantitative assessment used in this study\textsuperscript{7} has been shown to be a sensitive method that can be
FIGURE 3 – Scatterplot matrices for (A) women and (B) men showing the bivariate relationship between the ipsi- and contralateral mechanical pain threshold (y-axis) with age, visual analog scale, and tooth pain duration (x-axis). The ipsilateral mechanical pain threshold (IMPT, x-axis) depicts a significant correlation with contralateral thresholds in both sexes. R values show the correlation coefficient between the variables. Note that all variables in women, except for IMPT, were inversely correlated with the ipsi- and contralateral mechanical pain thresholds. (A) For female patients, all associations were significant with the exception of ipsilateral MA and age, whereas no significant associations were found in male patients, except for IMPT and contralateral pain threshold. Pearson correlation coefficient, $P < .05$. 

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used in future studies evaluating the kinetics of the recovery of both peripheral sensitization and CS after endodontic treatment. Collectively, this study shows the novel finding that MA and CS vary with different pulpal and periapical diagnoses with greater magnitude in female patients, being associated with age, intensity, and duration of preoperative pain. This study has strong clinical significance because patients with greater CS are expected to have longer recovery periods, allowing clinicians to properly inform patients of expectations and provide a more individualized treatment regimen.

**CREDIT AUTHORSHIP CONTRIBUTION STATEMENT**

**Ahmed A. Alelyani**: Investigation, Writing - original draft. **Pardis S. Azar**: Investigation. **Asma A. Khan**: Conceptualization, Validation, Resources, Writing - review & editing. **Vanessa Chrepa**: Investigation, Writing - review & editing. **Anibal Diogenes**: Conceptualization, Methodology, Validation, Resources, Writing - original draft, Writing - review & editing, Supervision, Project administration, Funding acquisition.

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The authors deny any conflicts of interest related to this study.

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