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Reduced heart rate variability and increased saliva cortisol in patients with TMD

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ABSTRACT

Temporomandibular disorders (TMD) are the most common source of non-dental pain. The pathogenesis of TMD is multifactorial, involving biological, psychological and behavioral factors. Those factors are involved with alterations of the autonomic nervous system (ANS) and stressful conditions. Heart rate variability (HRV) has been used as a marker of ANS function. Increased cortisol level (a stress indicator), has been found in chronic pain. Therefore, the present study aimed to compare pain intensity, HRV, psychological factors, and salivary cortisol level between TMD patients and a control group. Twenty-one TMD patients and twenty-three healthy control subjects participated in the study. All participants underwent 24-h-Holter monitoring to record HRV. Morning unstimulated saliva samples were collected from each participant for cortisol analysis. The pain intensity was assessed using a visual analog scale. The participants were evaluated for anxiety and depression via the Hospital Anxiety and Depression Scales. We found that pain intensity and psychological distress in the TMD group were significantly greater than those of the control ($p < 0.01$). Pain intensity showed a positive correlation with psychological distress ($p < 0.01$). HRV parameters in the TMD group were significantly lower than those in the control, suggesting reduced HRV in TMD patients. Pain intensity was negatively associated with HRV. Salivary cortisol level of the TMD group was greater than that of control. Our findings indicate that reduced HRV with higher psychological distress and increased salivary cortisol levels were observed in the TMD group. Therefore, TMD patients may benefit from interventions that can restore ANS function and stress balance.

1. Introduction

Temporomandibular disorders (TMD) are classified as chronic pathological conditions, involving disorders in masticatory muscles, temporomandibular joints (TMJs) and associated structures (de Leeuw & Klasser, 2013). Orofacial pain is the most common complaint in patients with TMD and the most regular diagnosis of TMD includes myofascial pain. Myofascial pain is characterized by muscle pain with referred pain in any area of the face or spreading entirely within the originating muscle group (Dworkin, 2010; Dworkin & LeResche, 1992).

Although several studies have shown that the etiology of TMD is multifactorial (de Leeuw & Klasser, 2013), the exact pathophysiology of TMD remains unclear. It has been shown that the autonomic nervous system (ANS) plays an important role in the modulation of the sensation of pain (Haugen, 1968; Randich & Maixner, 1984). The functional interaction between the ANS and pain perception has been shown to be an important contributor in the pain regulatory process (Bruehl & Chung, 2004; Sodervall et al., 2013).

Heart rate variability (HRV) is the variation in the beat-to-beat interval of the heart, which is greatly influenced by input from the ANS. HRV is a reliable noninvasive way to assess ANS activity (Eze-Nliam, Quartana, Quain, & Smith, 2011). The parameters of HRV include the time and frequency domains. A series of time domain variables include the standard deviation of the R-R intervals over a 24-h period (SDNN). The reduction in the parameter values can be interpreted as reduced variability. The frequency domain of HRV includes low frequency (LF) and high frequency (HF). A LF value is related to the overall autonomic nervous activity, whereas a HF value is used as a measure of parasympathetic nervous activity. The ratio of LF/HF ratio measures the balance of action of the ANS (Akselrod et al., 1981; Malik & Camm, 1993). An elevated LF/HF ratio represents reduced variability, indicating an imbalance between sympathetic and parasympathetic nervous activities. Typically, reduced variability arises from increased sympathetic nervous activity or, equivalently, decreased

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parasympathetic nervous activity. Previous studies have demonstrated that various chronic pain conditions are associated with altered ANS function. Assessments were made using the HRV indices. Findings included: 1) Patients with fibromyalgia have a lower HRV (Cohen et al., 2001) and blunted autonomic response to an orthostatic challenge (Cohen et al., 2001); 2) Decreased HRV occurred in patients with complex regional pain syndrome (Terkelsen et al., 2012) and among chronic neck pain patients (Hallman, Lindberg, Arnetz, & Lyskov, 2011). Although Eze-Nliam et al. showed that myofascial TMD patients revealed lower nocturnal HRV than pain-free controls (Eze-Nliam et al., 2011), the fluctuations in 24-h HRV in TMD patients has not yet been investigated. In addition, a recent study by de Almeida et al showed that the oxidative stress index recorded from saliva, but not total oxidative stress in saliva, of patients with TMD was significantly greater than that of pain-free control (de Almeida & Amenabar, 2016). The authors also found that there was no correlation between VAS and oxidative stress in saliva. These findings were inconsistent with previous studies, showing that blood and synovial fluid from the TMJ have been used to detect free radicals and joint disease markers of patients with TMD (Basi et al., 2012; Etoz, Akcay, Neselioglu, Erel, & Alkan, 2012). The possible explanation may be due to the lower sensitivity of the method used (Erel's method) for measuring total oxidative status in saliva. A recent study reported that salivary cortisol could be useful as a pain biomarker in healthy subjects (Sobas et al., 2016). However, the correlation between salivary cortisol, HRV, and pain perception in patients with TMD has never been investigated. Therefore the present study was aimed to: 1) investigate the correlation between 24-h variability and the pain status or the psychological stress of patients with experiencing pain due to TMD, relative to members of the healthy, pain-free control group, and 2) to determine salivary cortisol levels in patients with painful TMD, compared with the control group.

2. Materials and methods

2.1. Participants and study protocol

The protocol used in the study was approved by the Human Experimentation Committee of the Faculty of Dentistry, Chiang Mai University, Chiang Mai, Thailand in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki)(Number:08/2557). Forty-four participants (age range from 20 to 40 years old) were included in this study. Participants with cardiovascular diseases, pregnancy or taking anti-inflammatory medication were excluded. All participants gave their written and informed consent before participating in the study. The descriptive data of all participants are summarized in Table 1. The TMD participants (n = 21) were recruited by a specialist at the TMJ pain clinic at the Faculty of Dentistry, Chiang Mai University. All TMD participants had reported ongoing and persistent pain lasting longer than three months. The clinical diagnosis of "Myofascial Pain" was made in accordance with the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) (Dworkin, 2010; Dworkin & LeResche, 1992). Participants in the control group were volunteer dental students from the Faculty of Dentistry, Chiang Mai University. The inclusive criteria for the control group were aged from 20 to 40 years old, in good health with no myofascial TMD pain. Participants with cardiovascular diseases, pregnancy or taking anti-inflammatory drugs were excluded.

Table 1
Descriptive data of control subjects and patients with myofascial TMD.

	control	TMD
Number of participants	23	21
Age (mean ± SEM)	22.00 ± 0.62	26.05 ± 1.34**
Gender		
Female (%)	13 (56.52%)	19 (90.48%) **

**p < 0.01 compared to control group; *p < 0.05 compared to control group; TMD: temporomandibular disorders.

The study focused on baseline measurements of pain sensitivity and autonomic nervous function. All participants underwent an extra/intraoral examination, followed by an examination to assess TMD, including palpation on TMJs and masticatory muscles, and, mandibular movement measurement. Pain intensity was assessed using a visual analog scale (VAS). The measure of pain from the VAS was the current pain intensity. The present study determined VAS via the line, 10 cm in length, on the questionnaire paper. Scale "0" was set at the left side as no pain at all and scale "10" was set at the right side as the worst pain as imaginable. All participants were instructed how to determine their pain status and they marked their pain status on the line. Anxiety and depression were evaluated using Thai anxiety and depression questionnaires. The Thai anxiety and depression questionnaires were adapted from the Hospital Anxiety and Depression Scales (HADS). The questions in these questionnaires consist of 14 questions, including questions to determine anxiety (7 questions) and depression (7 questions). Each question has four scores (0 (no symptoms), 1 (mild symptoms), 2 (moderate symptoms), and 3(severe symptoms). The total score for either anxiety or depression is 21. Scores of anxiety and depression can be determined as: 0–7 (none); 8–11 (doubtful); and 11–21 (positive). Thai HADs is not the Thai version of the SCL-90-R recommended, the RDC/TMD, since the Thai version of the SCL-90-R is still in process of validation, however the Thai HADs has been validated by a previous study (Lotrakul & Sukanich, 1999; Nilchaikovit, Lotrakul, & Phisansuthideth, 1996) and has been used to good effect in several previous reports (Boonyanaruthee et al., 2001; Prasithsirikul et al., 2017; Viwattanakulvanid et al., 2014).

To measure HRV, all participants were required to wear a Holter monitor for a 24-h period. HRV-related variables were obtained from the analysis of the recorded data. To determine the salivary cortisol level, unstimulated saliva samples were collected over a five-minute period. The Holter monitor was attached to participants and saliva collection made from each participant at the same time of the day. Participants were fitted with a Holter monitor on day 1 of the study (between 9–11 a.m.). The monitor was removed 24 h afterwards, when a saliva sample was collected. All saliva samples were collected within a 2-h period (9–11 a.m.) on day 2, 24 h after a Holter monitor was fitted.

2.2. Heart rate variability measurement

For each participant, a 24-h electrocardiogram (ECG) was recorded using a SEER Light Holter system (GE Healthcare, Milwaukee, WI, USA). Rhythmic disturbances and QRS complexes were identified from the recorded data using MARS software (version 7, GE Healthcare, Milwaukee, WI, USA). Excessive noises and artifacts were noted, and any ectopy quantified.

Time-domain analyses included average heart rate, average R-R intervals (NN), standard deviation of the R-R intervals over a 24-h period (SDNN), standard deviation of all five-minute mean R-R intervals (SDANN), average standard deviation of all five-minute R-R intervals (ASDNN), the percentage of R-R intervals with more than 50-ms variation (pNN50), and the square root of the mean squared differences of successive R-R intervals (RMSSD).

Frequency-domain analyses were performed with the same analytical software using Fast-Fourier Transform analysis. Frequency-domain indices obtained included the total power (0–0.4 Hz), high-frequency (HF, 0.15–0.4 Hz) power spectral density, low-frequency (LF, 0.04–0.15 Hz) power spectral density, and very-low-frequency (VLF, 0.003–0.04 Hz) power spectral density. Total power expresses the magnitude of the entire heart rate variability, whereas HF power reflects the parasympathetic tone, and LF power indicates the sympathovagal interactions (Hallman & Lyskov, 2012; Schmidt & Carlson, 2009).

The designated physician who operated and fitted the Holter