Reduced Heart Rate Variability with increased saliva cortisol in patients with TMD

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Abstract

Objective: Heart rate variability is the variation in the heart rythm, which is influenced by the autonomic nervous system (ANS). This variability has been used as a marker of ANS dysfunction. The study aimed to 1) investigate the correlation between 24-hour variability and the pain status or the psychological stress of patients with painful TMD, relative to healthy, controls, and 2) to determine salivary cortisol levels in these patients, compared with controls.

Methods: Patients and control subjects underwent 24-hour Holter monitoring to determine heart rate variability. Time and frequency domain indicators of the variability and the ratio of the domain indicators were analyzed and compared. Multiple linear regression was used to identify the influence of pain status and psychological stress on the 24-hour variability. Unstimulated saliva samples from all participants were collected to determine salivary cortisol levels.

Results: Forty-four participants were included in this study. Time-domain parameters in the TMD group (n = 21) were significantly lower than in the control (n = 23) ($p < 0.05$). The LF/HF ratio was greater in the TMD group. Pain status and psychological distress in the TMD group were significantly greater ($p<0.01$ 0. Pain status and psychological distress were positively correlated ($p<0.05$). Pain status was negatively correlated with SDANN and SDNN ($p<0.05$). Salivary cortisol level was significantly higher in the TMD group ($p<0.05$).

Conclusions: Patients with TMD demonstrate ANS imbalance and increased stress. Therefore, future management of patients with TMD may benefit from restoring normal ANS function and stress balance, possibly via psychological therapy.

Keywords: orofacial pain; autonomic nervous system; anxiety; depression

Introduction

Temporomandibular disorders (TMDs) are chronic conditions, encompassing a group of musculoskeletal and neuromuscular conditions that involve masticatory muscles, temporomandibular joints (TMJs) and associated structures (Leeuw, Klasser, & American Academy of Orofacial, 2013). Several studies have shown that signs and symptoms of TMDs are common in non-patient populations (Leeuw et al., 2013; Schiffman et al., 2014). Pain in the orofacial area is the most common chief complaint for patients with TMDs. Muscles disorders take the dominant part of these problems. Myofascial pain is the most common diagnosis in the patient group with musculoskeletal pain. This diagnosis is made when the patient reports an area of muscle pain, with referred pain in any area of the face or spreading entirely within the originating muscle group.

Multifactorial etiology concepts are widely used to help in the management of signs and symptoms of patients with TMDs. The pathophysiology of TMDs, however, remains unclear. Possible pathways include abnormality of the central nervous system, involving the trigeminal or the limbic systems, or abnormality of the peripheral nervous system (Cohen, 2000; Younger, Shen, Goddard, & Mackey, 2010).

Heart rate variability is the variation in the beat-to-beat interval of the heart, which is greatly influenced by input from the autonomic nervous system (ANS). Heart rate variability is a non-invasive marker of ANS dysfunction (Eze-Nliam, Quartana, Quain, & Smith, 2011). This variability is quantified by measuring the R-R interval, which is used to calculate a series of time domain variables, including, for example, the standard deviation of the R-R intervals over a 24-hour period (SDNN). These time domain parameters can be used as a measure of the variability, such that reduction in the parameter values can be interpreted as reduced variability. Transformation of time domain variables into the related frequency domain counterparts yields further information. A low frequency variable is related to the overall autonomic nervous activity, whereas a high frequency variable is used as a measure of parasympathetic nervous activity. The ratio of low frequency (LF) over high frequency (HF) variables (LF/HF ratio) measures the balance of action of the autonomic nervous system and is also a measure of HRV. The relationship between LF/HF ratio and heart rate variability is an inverse one, with an elevated LF/HF ratio translating to reduced variability (indicating an imbalance between

sympathetic and parasympathetic nervous activities). Typically, reduced variability arises from increased sympathetic nervous activity or, equivalently, decreased parasympathetic nervous activity.

Studies in patients with pain conditions reveal that there is a relationship between pain and lowered variability (Maixner et al., 2011). Patients with TMDs show lower variability than normal heathy subjects. This has led to variability being regarded as a more reliable biological indicator of pain in patients, compared to subjective symptoms. Considerable evidence has accumulated in support of the proposal that physiological factors, including altered pain sensitivity and autonomic dysfunction, are associated with several chronic pain conditions, including TMDs.

A study by Meeus et al. reported that fibromyalgia patients exhibited lowered heart rate variability and increased activity of the sympathetic nervous system (Meeus et al., 2013). Several other studies have also demonstrated that autonomic dysregulation plays a role in fibromyalgia and other idiopathic pains (Cohen, 2000; Younger et al., 2010). Because the symptoms of TMDs are quite similar to those of fibromyalgia and other idiopathic pain, it is possible that, TMDs and fibromyalgia may share the same pathophysiology.

The association between myofascial TMD with changes in the autonomic nervous system, as measured via heart rate variability, has not been thoroughly investigated. This study aimed to 1) investigate the correlation of 24-hour variability and the painful status or the psychological stress of patients with painful TMDs, relative to healthy, pain-free controls and 2) to determine salivary cortisol levels in patients with painful TMDs, compared with controls.

Materials and methods

Participants and study protocol

The study protocol described here was approved by the Human Experimentation Committee of the Faculty of Dentistry, Chiang Mai University, Chiang Mai, Thailand. Forty-four subjects, all between the ages of 20 and 40 years, were included in this study. Subjects with cardiovascular diseases, pregnancy or taking anti-inflammatory medications were excluded. All subjects gave written and informed consent before participating in the study. Details of the study subject groups are summarized in Table 1. All TMD group subjects have reported ongoing and persistent pain lasting longer than three months. The clinical diagnosis of "Myofascial Pain" was made by following the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) (Dworkin, 2010; Dworkin & LeResche, 1992).

The study focuses on baseline measurements of pain sensitivity and autonomic nervous function. All subjects received extra/intraoral examination, followed by the examination of TMDs, including palpation on TMJs and masticatory muscles, and, mandibular movement measurement. Pain measurement was recorded using the visual analog scale. Anxiety and depression were evaluated using Thai anxiety and depression questionnaires. To measure the heart rate variability, subjects were required to wear a Holter monitor for a 24-hour period. Heart rate variability-related variables were obtained from the analysis of the recorded data. Finally, to determine the salivary cortisol level, unstimulated saliva samples were collected over a five-minute period.

Heart rate variability measurement

For each participant, a 24-hour 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 ectopy was 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 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 (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 monitor to the patients was blinded to the patients' information to minimize biases. The subjects were fitted with the Holter monitor after saliva sample collection at the Holter unit of the Faculty of Medicine, Chiang Mai University.

Saliva collection and the measurement of salivary cortisol level

To measure salivary cortisol level, unstimulated saliva samples were collected over a five-minute period from every subject after removing the Holter monitor. Analysis of saliva samples was performed using an ab108821 – Corticosterone ELISA kit (Abcam, Cambridge, United Kingdom).

Statistical analysis

All processed data were expressed as mean ± SEM. For all comparisons, the significance of the differences in pain score, psychological distress, anxiety, heart rate variability and salivary cortisol levels were calculated using the Mann-Whitney U test. $P < 0.05$ was considered a measure of statistical significance. Statistical analysis was performed using SPSS version 13.0 for Windows (SPSS Inc., Chicago, IL, USA) under license to Chiang Mai University.

Results

Forty-four participants (n = 21 TMD; n = 23 controls) were included in the study. We found that time domain parameters, including SDNN, ASDNN and SDANN of the TMD group were significantly lower than in the control group ($p < 0.05$, Table 2). The LF/HF ratio tended to be higher in the TMD group [0.93±0.2 (TMD) versus 0.85±0.2 (control): Table 2]. The pain status and psychological distress in the TMD group were significantly higher than those in the control group ($p<0.01$: Table 3). The pain status was positively correlated with the psychological distress ($p<0.05$: Table 4), and was negatively correlated with SDANN and SDNN ($p<0.05$: Table 5). In addition, salivary cortisol was significantly higher in the TMD group, than in the control group ($p<0.05$: Figure 1).

Discussion

This study showed that subjects with TMDs have significantly greater autonomic dysfunction than pain-free control subjects. Time domain parameters of heart rate variability, including SDNN, SDANN and ASDNN, were found to be significantly lower in the TMD group compared to the control. Additionally, the LF/HF ratio was found to be higher in the TMD group. The higher, although not statistically significant, LF power observed in the TMD group suggests a possibility that the autonomic dysfunction observed in the TMD group may be caused by increased sympathetic activity. These differences were only detected using spectral analysis of heart rate variability (Maixner et al., 2011).

Additionally, the level of oxidative stress, as indicated by salivary cortisol level, was significantly greater in subjects with TMDs. These findings provide evidence of associations among oxidative stress, autonomic factors and TMDs. Future analyses should be undertaken to determine whether these autonomic factors and oxidative stress increase the risk of new onset of TMDs.

Our findings that pain status and psychological distress were significantly higher in the TMD group are consistent with the outcomes of other studies in pain and painful conditions, where chronically affected pain patients reported higher psychological distress than did healthy, pain-free controls (Carlson et al., 1993; Carlson et al., 1998; Solberg Nes, Carlson, Crofford, de

Leeuw, & Segerstrom, 2010). The negative correlation between pain status and heart rate variability observed in this study is also in agreement with other studies of heart rate variability in patients with pain (Eze-Nliam et al., 2011; Maixner et al., 2011; Meeus et al., 2013; Schmidt & Carlson, 2009).

Differences in the demographics of the two study groups (TMD and control) should be discussed. The percentage of female participants was significantly higher in the TMD group than in the control. However, such a difference was not expected to have substantial impact on the outcome and conclusions of this study, as TMDs have been found to be more common in females than in males (Dworkin, 2010; Leeuw et al., 2013). The difference in average age of participants in the two study groups, however, should be highlighted here, since heart rate variability is directly influenced by age. Finally the multifactorial nature of TMDs is a common challenge faced in TMD research (Dworkin, 2010; Leeuw et al., 2013). Patients diagnosed with forms of TMD do not necessarily share the same signs and symptoms.

Future investigation in this topic should benefit from a larger study group size, so that the impacts of confounding factors (for example, sex and age) can be further minimized. With a larger sample population, effects of other pain-related factors on heart rate variability may also become evident.

Conclusions

These findings suggest that patients with TMDs demonstrate ANS imbalance and increased stress levels. Therefore, the future therapeutic approaches for patients with TMDs should focus on restoring the ANS and stress balance, possibly via psychological therapy.

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Table 1: Descriptive data for controls and patients with myofascial TMD

	Control	TMD
Number of participants	23	21
Age (mean±SD)	22.00± 2.98	26.05± 6.14 **
Gender Female(%)	13(56.52%)	19 (90.48%) **

**p < 0.01 compared to control group

*p < 0.05 compared to control group

Table 2: Parameters of heart rate variability (HRV) in controls and patients with myofascial TMD

HRV parameter	Control	TMD
ASDNN	73.8 ± 18.4	61.3 ± 14.9*
SDANN	168.0 ± 43.9	136.4 ± 40.2**
SDNN	179.3 ± 42.2	147.5 ± 39.5**
RMSSD	48.4 ± 17.4	41.3 ± 15.6
Low power (ms*ms)	14,542.3 ± 5,205.1	16,141.8 ± 7,503.6
High power (ms*ms)	17,653.5 ± 6,822.8	17,156.3 ± 5,851.2
LF/HF ratio	0.85 ± 0.2	0.93 ± 0.2

**p < 0.01 compared to control group

*p < 0.05 compared to control group

Table 3: Pain scores and psychological parameters in controls and patients with myofascial TMD

Parameter	Control	TMD
Pain score (VAS)	11.8 ± 15.7	44.2 ± 21.8**
Anxiety score	4.3 ± 2.1	7.1 ± 2.9**
Depression score	2.1 ± 1.9	4.2 ± 3.2*
Suffering scale	1.8 ± 1.1	3.4 ± 2.3*

**p < 0.01 compared to control group

*p < 0.05 compared to control group

Table 4: Correlation between pain score (VAS) and psychological parameters in all subjects (n=44); Pearson correlation (2-tailed)

	Psychological parameter		
	Anxiety score	**Depression score**	**Suffering scale**
VAS	0.625**	0.508**	0.631**

**p < 0.01 compared to control group

*p < 0.05 compared to control group

Table 5: Correlations between HRV and pain score (VAS) and psychological parameters in all subjects (n=44); Pearson correlation (2-tailed)

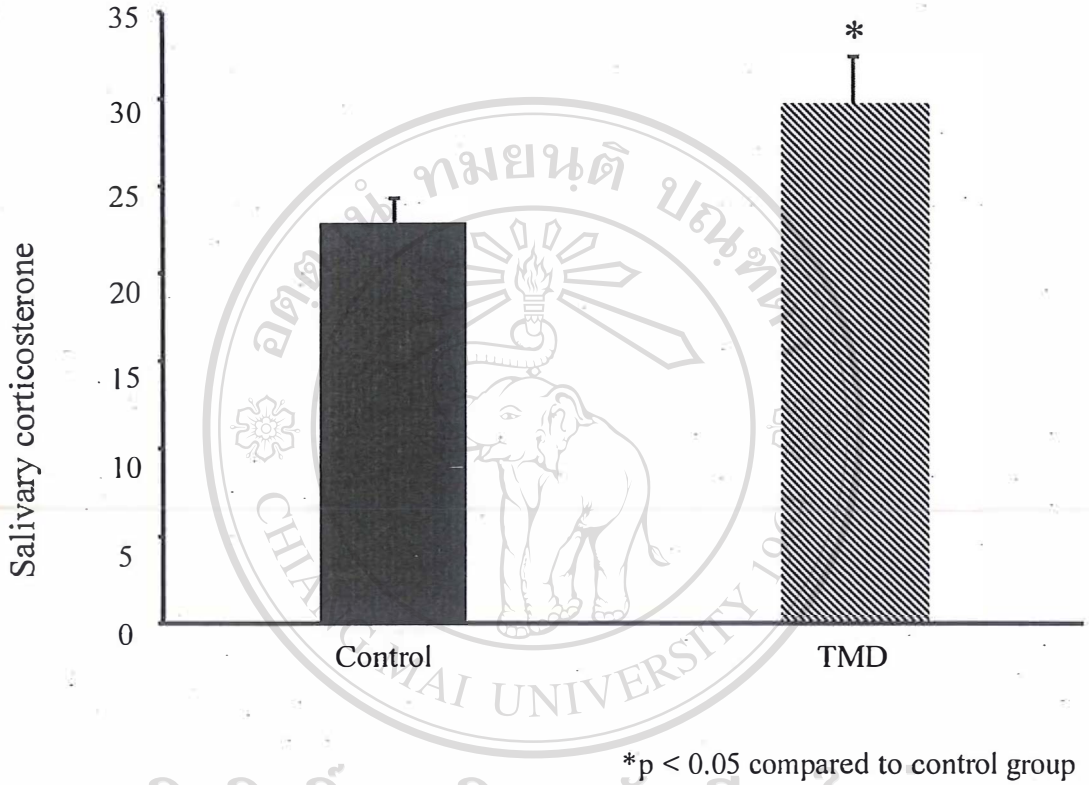
HRV parameter		Psychological parameter		
	VAS	Anxiety score	Depression score	Suffering scale
ASDNN	-0.230	-0.255	-0.138	-0.150
SDANN	-0.348*	-0.219	-0.027	-0.109
SDNN	-0.315*	-0.208	-0.035	-0.103
RMSSD	-0.104	-0.154	0.025	-0.056
Low power (ms^2)	-0.010	-0.060	-0.084	-0.169
High power (ms^2)	-0.043	-0.147	-0.069	-0.175
LF/HF ratio	0.049	0.119	-0.059	0.001

*$p < 0.05$ compared to control group

Table 6: Correlations between HRV and pain score (VAS) and psychological parameters in patients with myofascial TMD (n=21); Pearson correlation (2-tailed)

HRV parameter	VAS	Psychological parameter		
		Anxiety score	Depression score	Suffering scale
ASDNN	0.131	-0.294	0.173	0.054
SDANN	-0.090	-0.094	0.302	0.158
SDNN	-0.006	-0.076	0.314	0.177
RMSSD	0.126	-0.255	0.260	0.050
Low power(ms^2)	-0.114	-0.329	-0.099	-0.316
High power(ms^2)	-0.012	-0.435*	-0.018	-0.300
LF/HF ratio	-0.051	0.028	-0.093	-0.090

*$p < 0.05$ compared to control group



*p < 0.05 compared to control group

Figure 1: Salivary corticosterone (ng/ml) of control and patients with myofascial TMD

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