ความแปรปรวนของการเต้นของหัวใจในผู้ป่วยไทยที่มีภาวะหยุดหายใจขณะนอนหลับจากการอุดกั้น

โสภิดา สัณฐมิตร[1], วิไลวรรณ กฤษณะพันธ์[1*], วรรณภา อิชิดะ[1], อรพิน ผาสุริย์วงษ์[1], ธิชานนท์ พรหมศรีรสุข[1], วัชรา บุญสวัสดิ์[2], เบญจมาศ อินทรโภคา[3], อุไรวรรณ แซ่อุย[4]
[1]*ภาควิชาสรีรวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น จ.ขอนแก่น 40002*
[2]*ภาควิชาอายุรศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น จ.ขอนแก่น 40002*
[3]*โรงพยาบาลบำรุงราษฎร์ จังหวัดกรุงเทพมหานคร 10110*
[4]*โรงพยาบาลศรีนครินทร์ คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น จ.ขอนแก่น 40002*

Heart Rate Variability in Thai Patients with Obstructive Sleep Apnea

Sopida Santamit[1], Wilaiwan Khrisanapant[1*], Wannapa Ishida[1], Orapin Pasurivong[1], Tichanon Promsrisuk[1], Watchara Boonsawat[2], Banjamas Intarapoka[3], Uraiwan Zaeoue[4]
[1]*Department of Physiology, Faculty of Medicine, Khon Kaen University 40002*
[2]*Department of Medicine, Faculty of Medicine, Khon Kaen University 40002*
[3]*Bumrungrad International Hospital, Bangkok 10110*
[4]*Srinagarind Hospital, Faculty of Medicine, Khon Kaen University 40002*

หลักการและวัตถุประสงค์: ภาวะหยุดหายใจขณะนอนหลับจากการอุดกั้น (OSA) มีความสัมพันธ์กับความผิดปกติของระบบประสาทออโตโนมิคหรือไม่ยังคงเป็นที่ถกเถียงกันอยู่ การศึกษาครั้งนี้จึงมีวัตถุประสงค์ในการประเมินการเปลี่ยนแปลงของระบบประสาทออโตโนมิค โดยใช้ความแปรปรวนของการเต้นหัวใจ (HRV) ในผู้ป่วย OSA ทั้งเพศชาย และหญิง

วิธีการศึกษา: ศึกษากลุ่มผู้ป่วย OSA และกลุ่มคนปกติ กลุ่มละ 18 ราย ที่ไม่ได้รับการรักษา มีระดับความรุนแรงของโรคอยู่ในระดับปานกลางถึงรุนแรง อายุระหว่าง 30-70 ปี เทียบเคียงเพศและอายุเท่ากัน การศึกษา HRV ได้วิเคราะห์ท่านอนและท่าเอียง 70 องศา

ผลการศึกษา: พบว่าผู้ป่วย OSA มีค่าดัชนีมวลกายมากกว่า ($p<0.05$) และมีการลดลงของค่าร้อยละค่าเฉลี่ย ความอิ่มตัวของออกซิเจนในเลือด ($p<0.05$) แม้ว่าดัชนีการหยุดหายใจและหายใจแผ่ว (AHI) คือ 17.8 $\pm$ 3.7ครั้งต่อชั่วโมง ซึ่งเป็นตัวบ่งชี้ถึงความรุนแรงของโรคระดับปานกลาง ดัชนีการตื่น คือ 32.0 $\pm$ 9.7 ครั้งต่อชั่วโมงบอกถึงระดับความรุนแรงของโรคเมื่อเทียบกับกลุ่มคนปกติ พบว่าค่าความถี่สูง (HF) ไม่แตกต่างกันระหว่างกลุ่มผู้ป่วย OSA กับกลุ่มคนปกติ ในขณะที่ผู้ป่วย OSA มีการเพิ่มขึ้นของค่า SDNN, LF/HF ratio ($p<0.05$) และการลดลงของค่า RMSSD ($p<0.001$) ทั้งในท่านอนราบและท่าเอียง 70 องศา นอกจากนี้ค่า LF ในผู้ป่วย OSA ยังมีการเพิ่มขึ้นในท่าเอียง 70 องศาเมื่อเปรียบ

Background and Objectives: Whether obstructive sleep apnea (OSA) is associated with abnormal function of autonomic nervous system is still debatable. The purpose of this study was to evaluate the presence of autonomic modulation using heart rate variability (HRV) in both male and female OSA patients.

Methods: Eighteen untreated moderate to severe OSA patients aged between 30 to 70 years old and 18 gender- and age-matched non-OSA patients were studied. HRV was analyzed at rest and a 70° head-up tilt.

Results: Body mass index was higher ($p<0.05$) and mean oxygen saturation (%) was lower ($p<0.05$) in OSA patients. Although the mean AHI was 17.8 $\pm$ 3.7 events/hour which is indicative of moderate OSA, the arousal index of 32.0 $\pm$ 9.7 events/hour signifies severe OSA. Non-OSA and OSA patients were comparable for HF whereas OSA patients exhibited significant increased SDNN and LF/HF ratio ($p<0.05$) and decreased RMSSD ($p<0.001$) in either supine or 70° head-up tilt positions. Furthermore, LF was significantly greater in a tilt position in OSA compared to non-OSA patients. In comparison with supine, the tilt position showed

***Correspondence :** Associate Professor Dr. Wilaiwan Khrisanapant, Department of Physiology, Faculty of Medicine, Khon Kaen University, Khon Kaen 40002, Thailand, Tel: +66 (0) 43 363263 Email: wilkhr@kku.ac.th

เทียบท่านอนกับท่า เอียง 70 องศา พบว่ามีการเพิ่มขึ้นของค่า LF (p<0.001), LF/HF ratio (p<0.001) และมี การลดลงของค่า HF (p<0.001) ในกลุ่มคนปกติ ขณะที่ กลุ่มผู้ป่วย OSA ที่มีการเพิ่มขึ้นของค่า SDNN (p<0.05), LF (p<0.001) และ LF/HF ratio (p<0.001) อย่างไรก็ตามค่า LF/HF ratio มีการเพิ่มขึ้นในกลุ่ม OSA เมื่อเทียบกับ กลุ่มคนปกติ (2.6 ± 1.1 และ 1.5 ± 0.4) (p<0.001)

สรุป: ผลการศึกษาครั้งนี้แสดงให้เห็นว่า ภาวะหยุดหายใจขณะนอนหลับจากการอุดกั้นอาจทำให้การควบคุมการทำงานของหัวใจด้วยระบบประสาทออโตโนมิคบกพร่องได้

คำสำคัญ: ความแปรปรวนของการเต้นของหัวใจ ภาวะหยุดหายใจขณะนอนหลับจากการอุดกั้น

significant increased LF (p<0.001) and LF/HF ratio (p<0.001), and decreased HF (p<0.001) in the non-OSA group while significant increased SDNN (p<0.05), LF (p<0.001) and LF/HF ratio (p<0.001) were observed in the OSA group. Nevertheless, LF/HF ratio were greater in the OSA compared to that of the non-OSA group in a head-up tilt (2.6 ± 1.1 vs. 1.5 ± 0.4) (p<0.001).

Conclusion: Our findings demonstrate that cardiac autonomic control may be attenuated by OSA.

Keywords: Heart rate variability, Obstructive sleep apnea

ศรีนครินทร์เวชสาร 2558; 30 (5): 518-526. ♦ Srinagarind Med J 2015; 30 (5): 518-526.

Introduction

Obstructive sleep apnea (OSA) is a common disorder affecting at least 2-4% of the Caucasian population and 3.5-5.3% of Thais[1]. The signs, symptoms and consequences of OSA are a direct result of the derangements due to repetitive collapses of the upper airway: hypoxemia and increased sympathetic activity[2]. Previous studies have reported that in OSA, the recurrence of apneas all through the night elicits a typical and cyclic heart rate pattern consisting of cyclical bradycardia and tachycardia. Possible mechanisms proposed to explain these changes are the potentially pro-arrhythmic contributions of apnea-induced hypoxia and increased sympathetic nervous system (SNS)[3, 4].

Cardiac autonomic function can be non-invasively assessed by analyzing the heart rate variability (HRV), which quantifies the changes in beat-to-beat intervals influenced by the effects of the SNS and parasympathetic nervous systems (PNS) on the sino-atrial nodes, and hence, heart rate (HR)[3, 5]. Early in the investigation of OSA patients, it is recognized that the events of apnea and hypopnoea are accompanied by concomitant cyclic variations in HR[6]. The OSA patients have baroreflex and central respiratory-cardiovascular neuron activity damage[7]. Nonetheless, conflicting results have been reported. Regarding low frequency power (LF), high frequency power (HF) or square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD) and LF/HF represents SNS, PSN and sympathovagal balance, respectively. In patients with OSA, LF and LF/HF ratio was higher while HF was lower compared to those of the control group[8, 9]. On the other hand, RMSSD, HF, LF was lower whereas LF/HF was greater in the OSA patients than the non OSA group[10]. HF was greater whereas LF and, hence, LF/HF was lower[3], and LF was greater while HF and LF/HF ratio were not different compared to the control group[2].

A previous study demonstrated in healthy subject's measurement of HRV in postural supine to tilt-testing caused significant increases in LF, LF/HF ratio indicating increased SNS and decreased HF indicating decreased PNS[11-13]. The head-up tilt table test used to assess the sympathovagal balance has never been previously studied in the OSA patients.

Materials and Methods

Study design and population

The study was treatment, non-randomized and open-labeled approved by the Human Research Ethics Committee, Khon Kaen University, and informed assent was obtained from each participant. Eighteen OSA patients aged between 30 to 70 years old volunteered to participate in the study and 18 age-matched non-OSA subjects of both genders were analyzed. All patients were recruited from the Sleep Disorder Clinics, the Faculty of Medicine (Srinagarind Hospital, Khon Kaen University). Patients were diagnosed with medical specialists by the polysomnography (PSG), provided that the test results within a period not exceeding one month. Clinically, patients with an apnea–hypopnea index (AHI) $\geq$ 15 per hour with no history of cardiovascular (i.e. coronary heart disease and myocardial infarction) were studied. Patients with history of central sleep apnea, autoimmune conditions and symptoms of respiratory tract infection 6 weeks prior to the study were excluded.

Experimental Protocols

Each participant was asked to have a visit to our Laboratory Unit. On the visit, physical examinations, measurements of anthropometry and HRV were obtained. Height and weight were measured for each participant, according to the WHO guidelines. The BMI was calculated as weight (kg) divided by height (m^2).

HRV measurement

HRV was measured by an autoregressive power spectral analysis of R-R electrocardiographic interval acquisition (LapChart 7, Power Lab 26TADINSTRUMENTS, Australia). The test involved lying quietly on a bed (V.S. ENGINEERING, US.) for 10 min and being tilted at angles (70^0) for a period of 7 min while EKG was monitored. HRV was analysed during the 5-min period just before tilt during supine rest and during the 5-min period immediately after tilt. All participants were prepared for electrode placement to measure R-R interval via a 3-lead EKG. HRV can be assessed in two ways: by calculation of indices based on statistical operations on R-R intervals (time domain analysis) or by spectral (frequency domain) analysis of an array of R-R intervals.

Time domain analysis

Parameters of the time domain are standard deviation of all NN intervals (SDNN), standard deviation of the averages of NN intervals (SDANN) and RMSSD. SDNN and RMSSD represent total power and parasympathetic activity.

Frequency domain analysis

To evaluate the ANS activity in each subject of the present study, low frequency (0.04 – 0.15 Hz), high frequency (0.15 – 0.4 Hz), and total power (0 – 0.4 Hz) were analyzed by integrating the spectrum for the respective bandwidth. The ratio between low- and high-frequency spectra (LF [ms^2]/HF [ms^2]) is used as an estimation of the interaction between vagal and sympathetic influences on the cardiac pacemaker[14].

Statistical Analyses

Data were expressed as mean $\pm$ SD. The Stata 10 Statistical software was used to perform the statistical analysis. Unpaired t-test was used to compare differences in characteristics and all parameters between OSA patients and control group. A value of $p<0.05$ was taken to be the threshold of statistical significance.

Results

Clinical characteristics of 18 OSA patients and 18 aged matched non-OSA controls are summarized in Table 1. Of the 18 OSA patients and non-OSA group, 13 were males whereas 5 were females. As can be seen, mean oxygen saturation (%) was significantly decreased in OSA compared to non-OSA group ($p<0.05$). The OSA group had a significant increase in BMI ($p<0.05$) in comparison with non-OSA group. Besides, 11 and 7 presented with controlled hypertension and normotension, respectively. AHI was 17.8$\pm$3.7 events/hoor of TST which is indicative of moderate OSA, the arousal index of 32.0 $\pm$ 9.7 events/hour signifies severe OSA.

Comparisons of HRV between patients with OSA and Non-OSA groups

Time and frequency domain variables of HRV among the patients with OSA and non-OSA group are listed in Table 2 and Fig. 1, 2 and 3. OSA patients showed significant increases in SDNN and LF/HF ratio ($p<0.05$) but RMSSD was significantly decreased compared to non-OSA group ($p<0.001$). Moreover, LF and HF were not different between the 2 groups in a supine position. In a tilt position, OSA patients showed significant increases in SDNN ($p<0.05$), LF ($p<0.001$) and LF/HF ratio ($p<0.001$) whereas RMSSD was significantly decreased but not HF compared to non-OSA group ($p<0.001$). In the OSA patients, a tilt position resulted in no changes in RMSSD and HF, increased SDNN, LF and LF/HF ratio ($p<0.05$) (Table 2 & Fig. 2). Additionally, the non-OSA group showed increases in LF and LF/HF ratio and decreases HF ($p<0.001$) and no changes in SDNN and RMSSD (Table 2).

Table 1 Clinical characteristics in OSA and non-OSA.

	OSA	non-OSA
Subjects (n)	18	18
Age (yrs)	53.8 ± 10.5	53.7 ± 10.4
BMI (kg/m^2)	28.8 ± 6.5*	23.4 ± 1.7
Gender (M/F)	13/5	13/5
AHI (events/h of TST)	17.8 ± 3.7	0
Arousal index (events/h)	32.0 ± 9.7	0
Mean oxygen saturation (%)	97.1 ± 1.2*	97.7 ± 0.4
HR at rest (beats/min)	77.1 ± 12.6	75.2 ± 11.9
MAP (mm Hg)	96.4 ± 9.2	89.5 ± 11.4
Controlled hypertension (n)	11	0
Normotension(n)	7	18

group (mean ± SD). OSA, obstructive sleep apnea; BMI, body mass index; AHI, apnea hypopnea index; TST, total sleep time; HR, heart rate; MAP, mean arterial pressure; M, male; F, female.*p<0.05, OSA vs non-OSA

Discussion

In the present study, OSA patients had higher BMI compared to non-OSA group which similar to previous studies[2, 3, 6]. However, some studies demonstrated no significant difference in BMI between patients with OSA and non-OSA group[8, 15].

The main findings of this study were (i) increases in SDNN and LF/HF ratio and decreases in RMSSD in supine position in OSA group; (ii) increases in SDNN, LF and LF/HF ratio in tilt-testing in OSA group; (iii) increases in LF and LF/HF ratio together with decreases HF in tilt-testing in non-OSA group and (iv) similar increases in SDNN, LF and LF/HF ratio in tilt-testing in OSA comparison to non-OSA group.

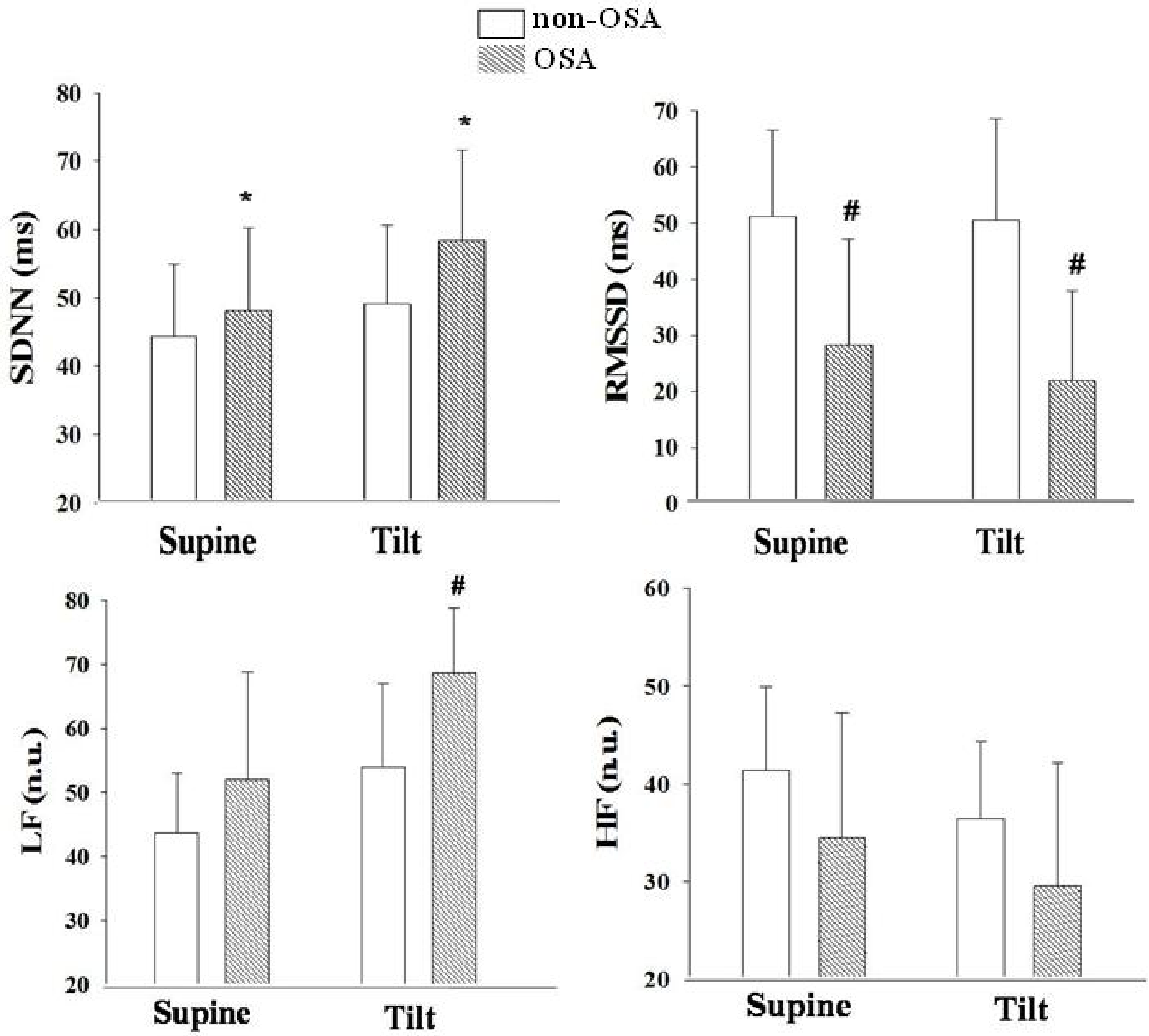
Table 2 The measurement of HRV assessed in supine and tilt positions in non-OSA and OSA group. OSA, obstructive sleep apnea; SDNN, standard deviation of all NN intervals; RMSSD, square root of the mean squared differences of successive NN intervals; LF, low frequency; HF, high frequency.

Position		OSA	non-OSA
Supine	Time domain		
	SDNN (ms)	48.1 ± 12.1*	44.3 ± 10.7
	RMSSD (ms)	28.3 ± 18.8$^\#$	51.1 ± 15.4
	Frequency domain		
	LF (n.u.)	52.1 ± 16.8	43.8 ± 9.2
	HF (n.u.)	34.5 ± 12.8	41.4 ± 8.5
	LF/HF ratio	1.8 ± 1.1*	1.1 ± 0.2
Tilt	Time domain		
	SDNN (ms)	58.4 ± 13.3$^{*,\prime}$	49.1 ± 11.5
	RMSSD (ms)	21.9 ± 16.1$^\#$	50.6 ± 17.9
	Frequency domain		
	LF (n.u.)	68.8 ± 10.1$^{\#,\prime}$	54.1 ± 13.0$^{\prime\prime}$
	HF (n.u.)	29.5 ± 12.6	36.5 ± 7.9$^{\prime\prime}$
	LF/HF ratio	2.6 ± 1.1$^{\#,\prime}$	1.5 ± 0.4$^{\prime\prime}$

*p<0.05, OSA vs non-OSA; $^\#$p<0.001, OSA vs non-OSA; $^\prime$p<0.05 supine vs tilt in OSA; $^{\prime\prime}$p<0.001, supine vs tilt in non-OSA

HF and LF are generally regarded as a reflection of vagal tone, and albeit less pure, of sympathetic tone. The LF/HF ratio can therefore be regarded as sympathovagal balance or the ratio of sympathetic to vagal tone measured by periodic fluctuations in HR[15].

In supine rest, the present study found that significantly increased of SDNN in patients with severe OSA compared to non-OSA group which is in lines with previous studies[3, 6, 8]suggesting a significant increase in overall autonomic nervous activity. Similarly, these studies also recruited moderate to severe OSA patients with controlled hypertension and obesity. On the contrary, a significant decrease in SDNN in patients with mild to severe OSA compared to that of non-OSA groups has been reported[10]. This study also found that RMSSD was significantly decreased in patients with OSA compared to non-OSA group. This finding is consistent with previous studies[3, 6, 9, 10] but not with studies which reported a significant increase[2] or no difference in RMSSD[7, 8]. Our observation that no difference in LF in



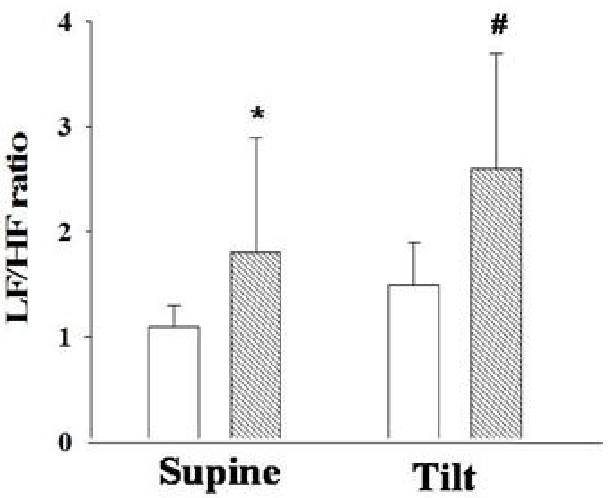


Figure 1 Comparison of the time and frequency domain variables between non-OSA and OSA group. SDNN, standard deviation of all NN intervals; RMSSD, square root of the mean squared differences of successive NN intervals; LF, low frequency; HF, high frequency $^{*}p<0.05$, non-OSA vs OSA; $^{\#}p<0.001$, non-OSA vs OSA

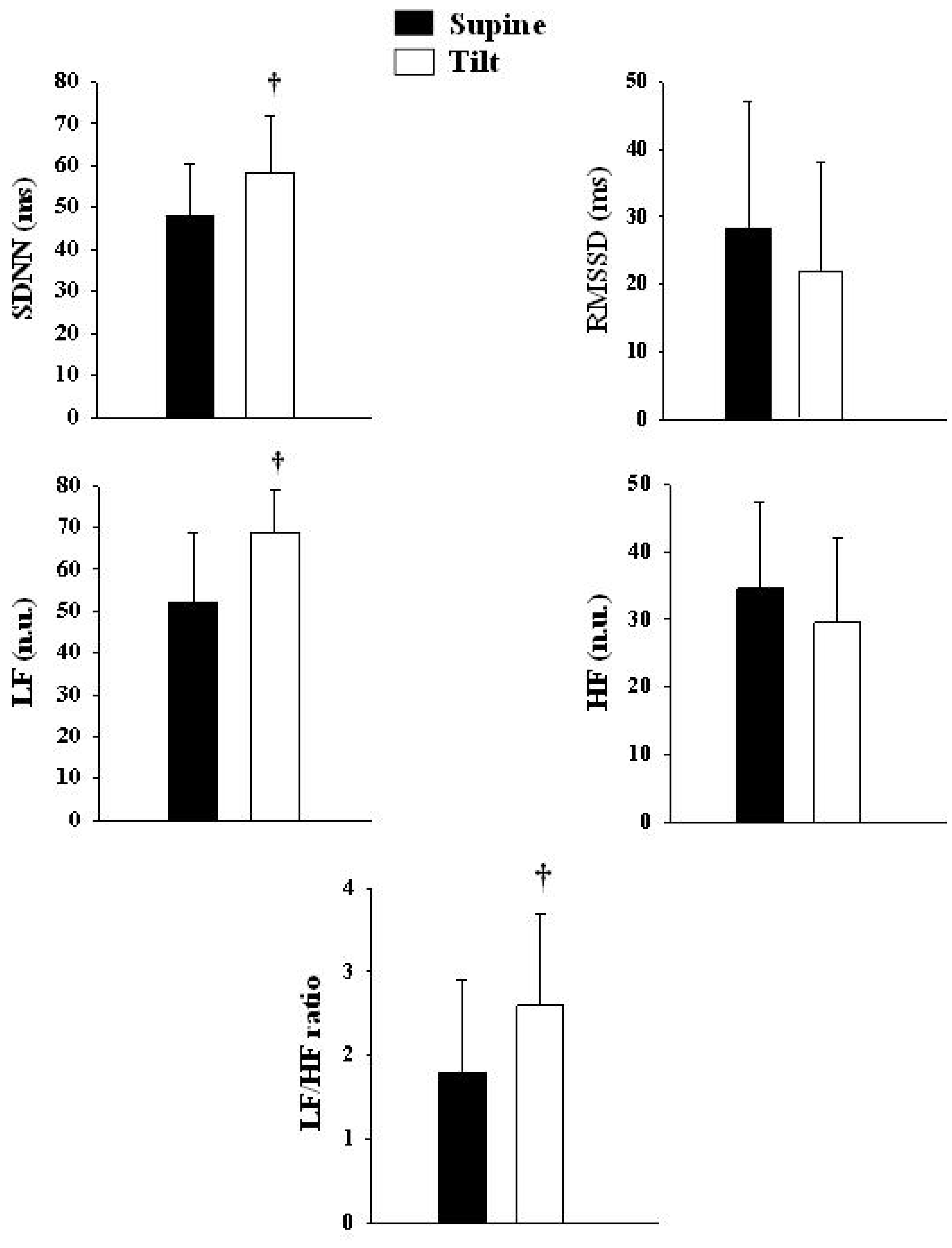


Figure 2 Comparison of the time and frequency domain variables between supine and tilt positions in patients with OSA. SDNN, standard deviation of all NN intervals; RMSSD, square root of the mean squared differences of successive NN intervals; LF, low frequency; HF, high frequency $p<0.05$, supine vs tilt

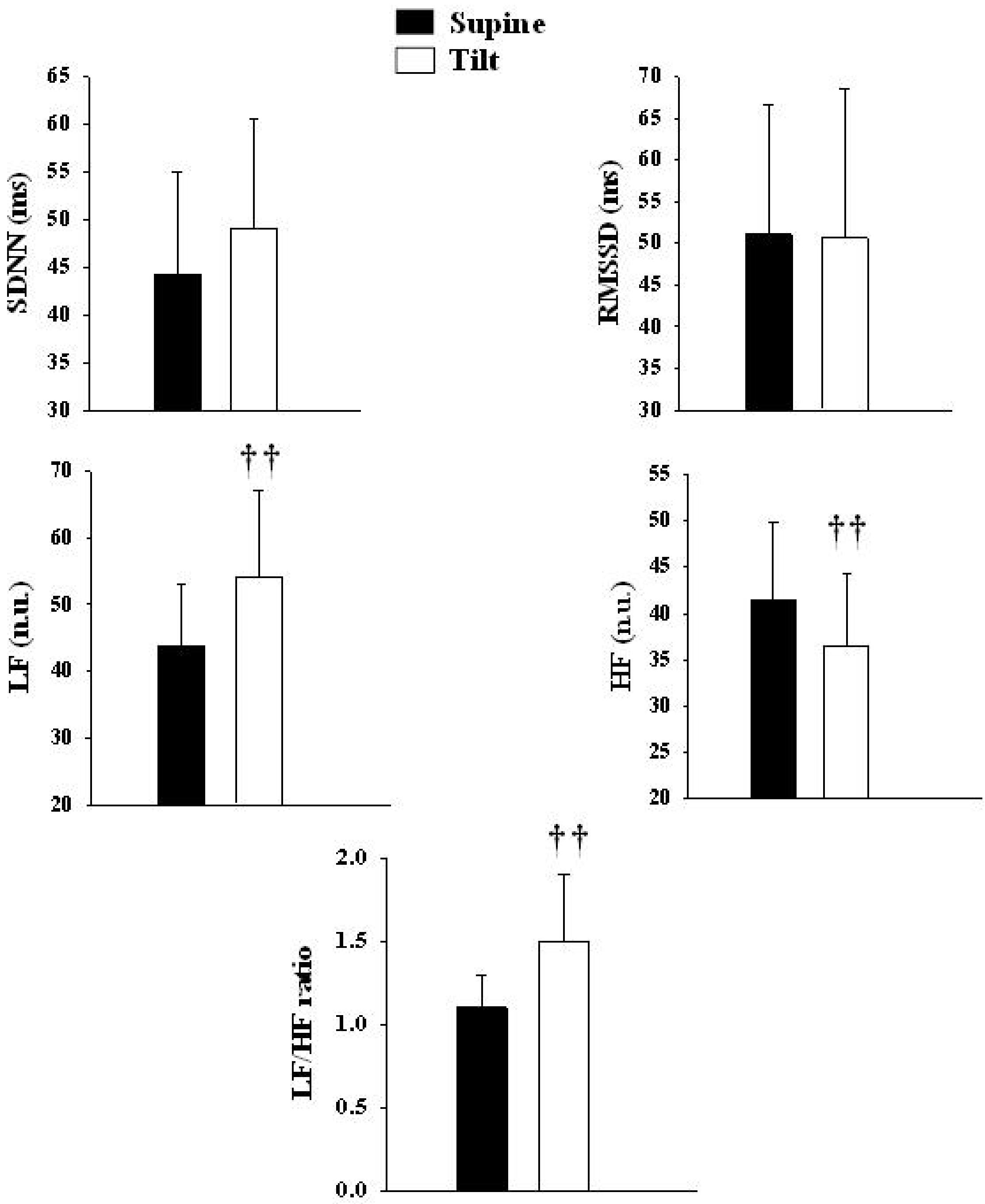


Figure 3 Comparison of the time and frequency domain variables between supine and tilt positions in non-OSA group. SDNN, standard deviation of all NN intervals; RMSSD, square root of the mean squared differences of successive NN intervals; LF, low frequency; HF, high frequency ' p<0.001, supine vs tilt

patients with OSA compared to non-OSA group is consistent with a study in 2011[6]. On the other hand, either increased LF[2, 8, 9] or decreased LF[3, 10] has been demonstrated previously. Moreover, there was no difference in HF in patients with OSA compared to non-OSA groups in our study – the finding being consistent with several studies[2, 6] but not with studies reporting either increased HF[3]or decreased HF[8, 9, 10]. Observation that LF/HF ratio, a value indicative of sympathovagal balance, was significantly greater in OSA compared to non-OSA groups is in agreement with the previous studies[3, 8, 10, 2, 6]. These discrepancies between studies are probably due to severity of OSA, controlled hypertension or normotension, male to female ratio, duration of OSA and age of OSA patients recruited.

In comparison to a supine position, the non-OSA group increased SDNN, LF and LF/HF ratio, and decreased RMSSD and HF observed in the present study being similar to several studies[16-19]. It is a result of an increased sympathetic activity in combination with a decrease in vagal activity due to sino-aortic baroreflexes. In the OSA patients, only increased SDNN, LF and LF/HF ratio not a decreased RMSSD or HF were found. Further, sympathovagal balance was greater in the OSA group compared to the non-OSA group. Clearly, there was an increased sympathetic activity but no reduction in vagal activity. This study suggests that the OSA patients may have impairment of sino-baroreflexes hypothesized by other studies[2,3, 8].

In conclusion, the present study has demonstrated impaired cardiac autonomic control in Thai patients with OSA. Nevertheless, greater number of observation is crucial before definite conclusion can be drawn.

Acknowledgements

This study was supported by the KKU Graduate Research Fund (57211110), Invitation Research Grant (I58152), the Faculty of Medicine, Khon Kaen university. I would like to thank Ms. Uraiwan Zaeoue, nursing teams at the Chest Unit, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University and Mr. Puttapol Chanchalad for his excellent technical support.

References

1. Suwanprathes P, Won C, Komoltri C, Nana A, Kotchabhakdi N, Guilleminault C. Epidemiology of sleep-related complaints associated with sleep-disordered breathing in Bangkok, Thailand. Sleep Med 2010; 11: 1025-30.
2. Galai I. Nocturnal heart rate variability analysis as a screening tool for obstructive sleep apnea syndrome. Egy J Chest Diseases and Tubercul 2012; 61: 187-95.
3. Trimer R, Cabidu R, Sampaio LL, Stirbulov R, Poiares D, Guizilini S, et al. Heart rate variability and cardiorespiratory coupling in obstructive sleep apnea: elderly compared with young. Sleep Med 2014; 15: 1324-31.
4. Song MK, Ha JH, Ryu SH, Yu J, Park DH. The effect of aging and severity of sleep apnea on heart rate variability indices in obstructive sleep apnea syndrome. Psychiatry Investig 2012; 9: 65-72.
5. Stein PK, Pu Y. Heart rate variability, sleep and sleep disorders. Sleep Med Rev 2012; 16: 47-66.
6. Khandoker AH, Karmakar CK, Palaniswami M. Comparison of pulse rate variability with heart rate variability during obstructive sleep apnea. Med Eng Phys 2011; 33: 204-9.
7. Neves C, Tufik S, Monteiro MA, Chediek F, Jose FF, Roizenblatt S. The effect of sildenafil on sleep respiratory parameters and heart rate variability in obstructive sleep apnea. Sleep Med 2010; 11: 545-51.
8. Aydin M, Altin R, Ozeren A, Kart L, Bilge M, Unalacak M. Cardiac autonomic activity in obstructive sleep apnea: time-dependent and spectral analysis of heart rate variability using 24-hour Holter electrocardiograms. Tex Heart Inst J 2004; 31: 132-6.
9. Park DH, Shin CJ, Hong SC, Yu J, Ryu SH, Kim EJ, et al. Correlation between the severity of obstructive sleep apnea and heart rate variability indices. J Korean Med Sci 2008; 23: 226-31.
10. Balachandran JS, Bakker JP, Rahangdale S, Yim-Yeh S, Mietus JE, Goldberger AL, et al. Effect of mild, asymptomatic obstructive sleep apnea on daytime heart rate variability and impedance cardiography measurements. Am J Cardiol 2012; 109: 140-5.
11. Nicola MM, Tomaso GR, Alberto PB, Federico LM, Massimo PM, Alberto MM. Power Spectrum Analysis of Heart Rate Variability to Assess the Changes in Sympathovagal Balance During Graded Orthostatic Tilt. Circulation 1994; 90: 1826-31.
12. Heikki VH, Matti JN, Sirkku OM, Asko RM, Markku JI, Airaksinen KE. Circadian Rhythms of Frequency Domain Measures of Heart Rate Variabilit in Healthy Subjects and Patients With Coronary Artery Disease Effects of Arousal and Upright Posture. Circulation 2009; 90: 121-6.

13. Gianfranco P, Filippo LF, Emanuela V, M. V. Age-adjusted normal confidence intervals for heart rate variability in healthy subjects during head-up tilt. Int J Cardiol 2009; 50: 117-24.
14. Heart rate variability. Standards of measurement, physiological interpretation, and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Eur Heart J 1996; 17: 354-81.
15. Gula LJ, Krahn AD, Skanes A, Ferguson KA, George C, Yee R, et al. Heart rate variability in obstructive sleep apnea: a prospective study and frequency domain analysis. Ann Noninvasive Electrocardiol. 2003; 8: 144-9.
16. Koskinen T, Kahonen M, Jula A, Laitinen T, Keltikangas-Jarvinen L, Viikari J, et al. Short-term heart rate variability in healthy young adults: the Cardiovascular Risk in Young Finns Study. Autonomic neuroscience : basic & clinical 2009; 145: 81-8.
17. Piccirillo G, Fimognari FL, Viola E, Marigliano V. Age-adjusted normal confidence intervals for heart rate variability in healthy subjects during head-up tilt. International journal of cardiology 1995; 50: 117-24.
18. Cardenas M, Vallejo M, Romano-Riquer P, Ruiz-Velasco S, Ferreira-Vidal AD, Hermosillo AG. Personal exposure to PM2.5 air pollution and heart rate variability in subjects with positive or negative head-up tilt test. Environmental research 2008; 108: 1-6.
19. Badilini F, Maison-Blanche P, Coumel P. Heart rate variability in passive tilt test: comparative evaluation of autoregressive and FFT spectral analyses. Pacing Clin Electrophysiol 1998; 21: 1122-32.