Heart Rate Variability in Thai Patients with Obstructive Sleep Apnea

ความแปรปรวนของการเต้นของหัวใจในผู้ป่วยไทยที่มีภาวะหยุดหายใจขณะนอนหลับจากการอุดกั้น

Sopida Santamit (โสภิดา สัณฐมิตร)* Dr.Wilaiwan Khrisanapant (ดร.วิไลวรรณ กฤษณะพันธ์)**
Dr.Wannapa Ishida (ดร.วรรณภา อิชิดะ)** Dr.Watchara Boonsawat (ดร.วัชรา บุญสวัสดิ์)***
Orapin Pasurivong (อรพิน ผาสุริย์วงษ์)**** Dr.Banjamas Intarapoka (ดร.เบญจมาศ อินทรโภคา)*****
Uraiwan Zaeoue (อุไรวรรณ แซ่อุย)******

ABSTRACT

Heart rate variability (HRV) has been used to assess cardiac autonomic function. Whether obstructive sleep apnea (OSA) is associated with abnormal function of autonomic nervous system is still debatable. This study aimed to compare HRV in 8 OSA patients and 8 age-matched non-OSA subjects in both genders, 30 to 70 years old. Low frequency (LF) and high frequency power (HF) represent sympathetic and parasympathetic activity, respectively. We observed no differences in HRV variables in supine position among the 2 groups. Upon changing from supine to tilt positions (70^0), the OSA group showed no changes in SDNN and HF, decreased RMSSD and increased LF and LF/HF ratio ($p<0.05$) whereas the non-OSA group showed increases in LF and LF/HF ratio and decreases in SDNN, RMSSD and HF ($p<0.05$). Nevertheless, LF/HF ratio were 2-folds greater, in the OSA compared to that of the non-OSA group ($p<0.05$). We suggest that cardiac autonomic control may be attenuated by OSA.

บทคัดย่อ

ความแปรปรวนของการเต้นของหัวใจ (HRV) ได้นำมาใช้ในการประเมินการทำงานของระบบประสาทอัตโนมัติหัวใจ ภาวะหยุดหายใจขณะนอนหลับจากการอุดกั้น (OSA) มีความเกี่ยวข้องกับความผิดปกติระบบประสาทอัตโนมัติหัวใจหรือไม่ยังคงเป็นที่ถกเถียง การศึกษาครั้งนี้มีวัตถุประสงค์ในการเปรียบเทียบ HRV ในผู้ป่วย OSA กับคนปกติ ทั้งเพศชาย และเพศหญิง อายุ 30-70 ปี เทียบเคียงอายุเท่ากัน โดย LF เป็นการวัดการทำงานของระบบประสาทซิมพาเทติก และ HF เป็นการวัดการทำงานของระบบประสาทพาราซิมพาเทติก พบว่าตัวแปร HRV ในท่านอนไม่แตกต่างกันระหว่าง 2 กลุ่ม และเมื่อเปลี่ยนจากท่านอนเป็นท่ายืน 70 องศา พบว่ากลุ่มผู้ป่วยไม่มีการเปลี่ยนแปลง SDNN, HF แต่ RMSSD ลดลง LF และ LF/HF ratio เพิ่มขึ้น ($p<0.05$) ในขณะที่กลุ่มคนปกติพบว่า RMSSD และ LF/HF ratio เพิ่มขึ้น ($p<0.05$) แต่ SDNN, RMSSD และ HF ลดลง ($p<0.05$) อย่างไรก็ตามพบว่าการเพิ่มขึ้นของ LF/HF ratio ในกลุ่มผู้ป่วยสูงเป็น 2 เท่าของค่าในกลุ่มคนปกติจึงเป็นไปได้ว่าภาวะหยุดหายใจขณะนอนหลับจากการอุดกั้นทำให้การควบคุมการทำงานของหัวใจด้วยระบบประสาทอัตโนมัติบกพร่องได้

Key Words: Heart rate variability, Obstructive sleep apnea
คำสำคัญ: ความแปรปรวนของการเต้นของหัวใจ ภาวะหยุดหายใจขณะนอนหลับจากการอุดกั้น

** Student, Master of Science Program in Medical Physiology, Faculty of Medicine, Khon Kaen University*
*** Associate Professor, Department of Physiology, Faculty of Medicine, Khon Kaen University*
**** Associate Professor, Department of Medicine, Faculty of Medicine, Khon Kaen University*
***** Assistant Professor, Department of Physiology, Faculty of Medicine, Khon Kaen University*
****** Lecturer, Bumrungrad International Hospital, Bangkok*
****** Nurse, Srinagarind Hospital, Faculty of Medicine, Khon Kaen University*

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 (Suwanprathes *et al.*, 2010). 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 (Galal, 2012). 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) (Song *et al.*, 2012; Trimer *et al.*, 2014).

Cardiac autonomic function can be non-invasively assessment 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) (Stein and Pu, 2012; Trimer *et al.*, 2014). 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 (Khandoker *et al.*, 2011). The OSA patients have baroreflex and central respiratory-cardiovascular neuron activity damage (Neves *et al.*, 2010). Nonetheless, conflicting results have been reported. Regarding low frequency power (LF), high frequency power (HF), 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 (Aydin *et al.*, 2004; Park *et al.*, 2008). On the other hand, RMSSD, HF, LF was lower whereas LF/HF was greater in the OSA patients than the non OSA group (Balachandran *et al.*, 2012). HF was greater whereas LF and, hence, LF/HF was lower (Trimer *et al.*, 2014), and LF was greater while HF and LF/HF ratio were not different compared to the control group (Galal, 2012).

A previous study demonstrates 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 (Gianfranco P. *et al.*, 2009; Nicola M. *et al.*, 2010). The head-up tilt table test used to assess the sympathovagal balance has never been previously studied in the OSA patients.

Objective of the study

To evaluate whether resting cardiac autonomic control was impaired in 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. Ten OSA patients aged between 30 to 70 years old volunteered to participate in the study. There were 2 OSA patients excluded due to technical problems during EKG recording before data analysis. Thus, 8 OSA patients and 8 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) ≥ 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 in 6 weeks prior to the study were excluded.

Experimental Protocols

Participants were asked to have 1 visit to our Laboratory Unit. On the visit, physical examinations, measurements of anthropometry and HRV were obtained.

Body mass index (BMI)

Height and weight were measured for each participant, according to the WHO guidelines. Participants wore light clothing without shoes. Weight was determined using a digital scale, to the nearest tenth. Height was measured standing with feet together and arms relaxed at the sides. The BMI was calculated as weight (kg) divided by height (m^2).

HRV measurement

HRV was measured by an autoregressive power spectral analysis of RR 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 RR 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 (1996).

Statistical Analyses

Data were expressed as mean ± 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 8 OSA patients and 8 non-OSA aged between 30 to 70 years old are summarized in Table 1. Of the 8 OSA patients, 6 were males whereas 2 were females. The 8 subjects in the non-OSA group were females. As can be seen, mean saturation (%) of the former group was slightly but not significantly different from that of the latter group. The OSA group had higher BMI and MAP than the non-OSA group ($p<0.05$). Besides, 3 and 5 presented with controlled hypertension and normal hypertension, respectively. AHI was 19.2±5.1 events/h of TST which is indicative of moderate OSA.

Table 1 Clinical characteristics in OSA and non-OSA subjects (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

	OSA	Non-OSA
Subjects (n)	8	8
Age (yrs)	55.0±10.0*	63.3±8.7
BMI (kg/m^2)	30.3±8.6*	23.0±17.0
Gender (M/F)	6:2	0:8
AHI (events/h of TST)	20.0±5.0	0
Mean saturation (%)	96.5±1.7	98.3±0.5
HR at rest (beats/min)	76.5±13.1	75±9.5
MAP	97.1±11.8*	83.5±9.6
Controlled hypertension (n)	3	0
Normotension(n)	5	8

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. Both time and frequency domain variables were not significantly different between OSA and non-OSA groups in a supine position and LF/HF ratio significantly increases between OSA and non-OSA in a tilt position. In the OSA group, postural supine to tilt-testing resulted in no changes in SDNN and HF, decreased RMSSD and increased LF and LF/HF ratio ($p<0.05$) (Table 2 & Fig. 1). Similarly, the non-OSA group showed increases in LF and LF/HF ratio and decreases in SDNN, RMSSD and HF ($p<0.05$) (Table 2).

Table 2 The measures of HRV (mean ± SD) 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. #$p<0.05$, OSA vs non-OSA *$p<0.05$, supine vs tilt in OSA; ¥$p<0.05$, supine vs tilt in non-OSA

Position		OSA	Non-OSA
Supine	*Time domain*		
	SDNN (ms)	26.2±11.1	40.0±16.8
	RMSSD (ms)	19.4±8.7	37.9±28.4
	Frequency domain		
	LF (n.u.)	44.0±18.0	44.3±5.5
	HF (n.u.)	40.5±21.5	45.2±6.4
	LF/HF ratio	1.5±1.1	1.0±0.1
Tilt	*Time domain*		
	SDNN (ms)	23.3±11.3	31.8±18.0¥
	RMSSD (ms)	12.0±5.0*	25.7±22.1¥
	Frequency domain		
	LF (n.u.)	59.5±13.6*	60.4±12.4¥
	HF (n.u.)	27.0±15.5	38.0±6.5¥
	LF/HF ratio	2.8±1.3#,*	1.6±0.4¥

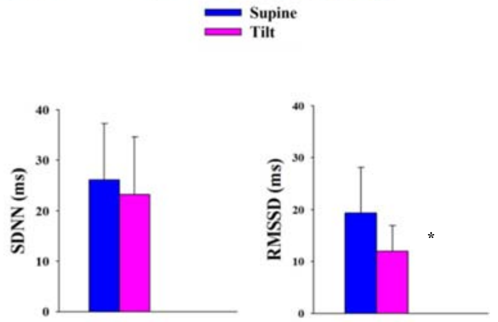

Figure 1 Comparison of the time domain variables between supine and tilt positions in patients with OSA. SDNN, standard deviation of all NN intervals; RMSSD, square root of the mean squared differences of successive NN intervals *p<0.05, supine vs tilt

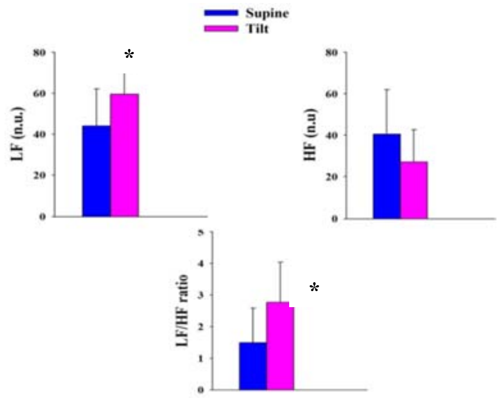

Figure 2 Comparison of the frequency domain variables between supine and tilt positions in patients with OSA. LF, low frequency; HF, high frequency *p<0.05, supine vs tilt

Discussion

The main findings of this study were (i) no differences in HRV variables in supine position among non-OSA and patients with OSA; (ii) increases in LF and LF/HF ratio in tilt-testing in OSA; (iii) increases in LF and LF/HF ratio together with decreases in SDNN, RMSSD and HF in tilt-testing in non-OSA group and (iv) similar increases in LF but a 2-fold increase in LF/HF ratio in tilt-testing in OSA in comparison to non-OSA groups.

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 (Gula *et al.*, 2003).

In supine rest, the present study found that SDNN was not different in patients with OSA compared to non-OSA group. This is not in lines with previous studies suggesting a significantly increased of SDNN (Galal, 2012; Khandoker *et al.*, 2011) opposite a significantly decreased of SDNN in patients with OSA compared to non-OSA groups (Balachandran *et al.*, 2012). Similar RMSSD in patients with OSA compared to non-OSA group observed in our study is comparable to that reported previously (Galal, 2012). In contrast, a significant increase in RMSSD (Khandoker *et al.*, 2011) and a significant decrease SDNN (Balachandran *et al.*, 2012) in patients with OSA compared to non-OSA groups have been reported. Our observation that no difference in LF in patients with OSA compared to non-OSA group is consistent with a study in 2011 (Khandoker *et al.*, 2011). On the other hand either increased LF (Aydin *et al.*, 2004; Galal, 2012; Park *et al.*, 2008) or decreased LF (Balachandran *et al.*, 2012; Trimer *et al.*, 2014) 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 (Galal, 2012; Khandoker *et al.*, 2011) but not with studies reporting either increased HF (Trimer *et al.*, 2014) or decreased HF (Aydin *et al.*, 2004; Balachandran *et al.*, 2012; Park *et al.*, 2008).

We also observed that LF/HF ratio, a value indicative of a sympathovagal balance, was similar between non-OSA and OSA patients. This is in agreement with some studies (Galal, 2012; Khandoker *et al.*, 2011) but not with several studies (Aydin *et al.*, 2004; Balachandran *et al.*, 2012; Trimer *et al.*, 2014). Previous study demonstrated that no significant difference of SDNN between genders (Antelmi *et al.*, 2004; Zhang, 2007) and significantly increased of HF and LF/HF ratio in male compared to female gender (Zhang, 2007). Similar LF and LF/HF ratio in male show significant increase compared to female gender (Agelink *et al.*, 2001; Antelmi *et al.*, 2004).

Previous study demonstrated that no significant difference between BMI in patients with OSA compared to non-OSA group (Aydin *et al.*, 2004; Gula *et al.*, 2003). On the other hand either increased of BMI in patients with OSA compared to non-OSA group (Galal, 2012; Trimer *et al.*, 2014).

Although the OSA patients showed HRV variables more-or-less the same as those of non-OSA group following tilt-testing, e.g. increases in LF and LF/HF ratio, the increase in LF/HF ratio of was only 50% of that of the non-OSA group. It is possible that the OSA patients may have impairment of baroreflex and central respiratory-cardiovascular neuron activity suggested previously (Neves *et al.*, 2010).

Conclusions

We found impaired cardiac autonomic control in Thai patients with OSA during tilt-testing but not supine rest. Nevertheless, greater number of observation is crucial before definite conclusion can be drawn.

Acknowledgements

This study was supported by the Invitation Research Grant (I58152) from the Faculty of Medicine, Khon Kaen University. We would like to thank Mr.Puttapol Chanchalad for his excellent technical support.

References

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)107: 354-81.

Agelink MW, Malessa R, Baumann B, Majewski T, Akila F, Zeit T, et al. Standardized tests of heart rate variability: normal ranges obtained from 309 healthy humans, and effects of age, gender, and heart rate. Clin Auton Res 2001; (2)11: 99-108.

Antelmi I, de Paula RS, Shinzato AR. Influence of age, gender, body mass index, and functional capacity on heart rate variability in a cohort of subjects without heart disease. Am J Cardiol 2004; (3)93: 381-5.

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; (2)31: 132-6.

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; (1)109: 140-5.

Galal I. Nocturnal heart rate variability analysis as a screening tool for obstructive sleep apnea syndrome. Egyptian Journal of Chest Diseases and Tuberculosis 2012; (2)61: 187-195.

Gianfranco P., Filippo LF., Emanuela V., M. V. Age-adjusted normal confidence intervals for heart rate variability in healthy subjects during head-up tilt. InternationaJl ournaol f Cardiolog 2009; (2)50: 117-124.

Gula LJ, Krahn AD, Skanes A, Ferguson KA, George C. Heart rate variability in obstructive sleep apnea: a prospective study and frequency domain analysis. Ann Noninvasive Electrocardiol 2003; (2)8: 144-9.

Khandoker AH, Karmakar CK, Palaniswami M. Comparison of pulse rate variability with heart rate variability during obstructive sleep apnea. Med Eng Phys 2011; (2)33: 204-9.

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; (6)11: 545-51.

Nicola M. M, Tomaso R. M, Alberto P. B, Massimo P. M, Alberto M. M. Power Spectrum Analysis of Heart Rate Variability to Assess the Changes in Sympathovagal Balance During Graded Orthostatic Tilt. American Heart Association 2010; (4)90: 1826-1831.

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; (2)23: 226-31.

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; (1)9: 65-72.

Stein PK, Pu Y. Heart rate variability, sleep and sleep disorders. Sleep Med Rev 2012; (1)16: 47-66.

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; (10)11: 1025-30.

Trimer R, Cabidu R, Sampaio LL, Stirbulov R, Poiares D. Heart rate variability and cardiorespiratory coupling in obstructive sleep apnea: elderly compared with young. Sleep Med 2014; (15): 1324-31.

Zhang J. Effect of age and sex on heart rate variability in healthy subjects. J Manipulative Physiol Ther 2007; (5)30: 374-9.