RESEARCH ARTICLE

AUTONOMIC FUNCTION IN ADULTS WITH OBSTRUCTIVE SLEEP APNEA

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DOI: 10.5455/ijmsph.2013.170820131 **Received Date: 11.08.2013** **Accepted Date: 17.08.2013**

ABSTRACT

Background: Obstructive Sleep Apnea (OSA) is the most prevalent form of sleep disordered breathing and could become an important public health issue in India. Patients with OSA have high levels of sympathetic nerve activity during sleep. The autonomic alterations persist during wakefulness and are considered to contribute to the cardiovascular disorders associated with OSA.

Aims & Objective: The aim of the present study was to study autonomic function in adults with Obstructive Sleep Apnea using autonomic cardiovascular tests.

Material and Methods: 30 normal controls (Group I) and 30 patients with Obstructive Sleep Apnea (Group II) of both sexes in the age group of 35-45 years were subjected to a battery of autonomic function tests. The heart rate response to standing (30:15 ratio), heart rate response to deep breathing (E:I ratio), and the Valsalva ratio were used to assess parasympathetic function while the isometric hand- grip exercise and cold pressor tests were used to assess sympathetic function. Statistical analysis was done using SPSS 17 and unpaired student t test.

Results: The 30:15 ratio, E:I ratio and Valsalva Ratio were significantly lower (p value < 0.001) in the patients with OSA when compared to the controls, while the diastolic pressure difference in the isometric hand-grip exercise test and the cold pressor tests were significantly higher (p value < 0.001) in the patients with OSA.

Conclusion: Our study revealed that there was sympatho-vagal imbalance in adult patients with Obstructive Sleep Apnea, with decreased parasympathetic and increased sympathetic activity.

Key-Words: Autonomic Cardiovascular Tests; Autonomic Function; Obstructive Sleep Apnea (OSA)

Introduction

Changes in autonomic function occur during sleep. Normal subjects have lower sympathetic nerve activity, blood pressure and heart rate when they are in deep non-Rapid Eye Movement (NREM) sleep than when they are awake; while during Rapid Eye Movement (REM) sleep, sympathetic nerve activity increases although blood pressure and heart rate return to normal.[1] Obstructive Sleep Apnea (OSA) is the most prevalent form of sleep disordered breathing[2] and is characterized by recurrent episodes of upper airway collapse during sleep. A definition of "sleep induced upper airway narrowing leading to symptomatic sleep disturbance" has been proposed as being the only current valid definition of OSA Syndrome.[3] Obstructive Sleep Apnea Syndrome (OSAS) could become an important public health issue in India due to the obesity epidemic, increasing urbanization and consequent lifestyle changes and there is no significant difference in its prevalence in India when compared to the West.[4] The prevalence of OSAS and OSA has been reported as being 3.6% and 13.7% respectively in a semi-urban North Indian population;[5] 2.8% and 9.3% respectively in an urban population in South Delhi[6] and 7.5% and 19.5% respectively in a hospital based study involving urban men in Western India.[7]

Patients with Obstructive Sleep Apnea have high levels of sympathetic nerve traffic, caused by chemoreceptor reflexes triggered by repetitive episodes of hypoxia, hypercapnia and obstructive apnea.[8] This elicits humoral vasoconstrictor responses and manifests as raised blood pressure.[9] The autonomic alterations are carried over into wakefulness, and the increase in blood pressure persists due to baroreflex and chemoreflex dysfunction, vasoconstrictor effect of nocturnal endothelin and endothelial dysfunction.[8] The carrying over of autonomic nervous system alterations into wakefulness

contributes to the cardiovascular disorders associated with OSA.[10] Although the chronic sympathetic activation is considered the main link between OSA and cardiovascular disorders factors like inflammation, hypercoagulability , stimulation of the renin-angiotensin system[11], increased oxidative stress and metabolic dysregulation too contribute.[12]

It is difficult to measure autonomic activity directly, especially in sleep, since invasive approaches are needed. Recently, muscle sympathetic nerve activity and surrogate markers of ANS activity like Heart Rate Variability (HRV) analysis, beat- to- beat blood pressure monitoring, peripheral artery tonometry and blood and urine catecholamine estimation are used.[2] Researchers have used HRV with time-domain and frequency-domain measures to study OSA patients and have found evidence of reduced Heart Rate Variability in patients with OSA[13-15] which improves after treatment with Continuous Positive Airway pressure (CPAP).[16]

Autonomic cardiovascular tests like the heart rate response to Valsalva manoeuvre, deep breathing and standing and the blood pressure response to standing are also used to study autonomic function in OSA. Ito et al. attempted to confirm the relationship between OSAS and autonomic nervous system dysfunction and found that while the baseline heart rate of OSAS patients was significantly higher than that of the controls, the Valsalva ratio (VR) and baroreflex sensitivity (BRS) in patients with OSAS were significantly lower.[17] Ryan et al. found that spontaneous baro-reflex sensitivity (BRS) was significantly lower in patients with severe OSAS than in patients with mild-to-moderate OSAS and in non-OSAS subjects and concluded that this may contribute to the cardiovascular pathophysiology in OSAS patients.[18] Montesano et al. found a lower 30:15 index, greater blood pressure variability during the supine-to-orthostatic posture change and less heart rate variability during deep breathing in children with OSAS when compared to controls although there was no difference in the Valsalva ratio.[19] Hakim et al. state that there is conclusive evidence that OSA components pathologically activate the sympathetic nervous system and cause the high blood pressure, arrhythmias and congestive heart failure in adults and the changes in heart rate responses and increased blood pressure in children.[2]

In view of above studies, and in view of the fact that we had also done frequency-domain analysis of Heart Rate Variability (HRV) by fast-Fourier transformation using the electrocardiographic data obtained during Polysomnography in our OSA patients and found evidence of increased sympathetic activity and parasympathetic attenuation[20], we were interested in studying autonomic function using simple cardiovascular tests in our adult patients with OSA. The aim of the present study was therefore to study autonomic function in adults with Obstructive Sleep Apnea using autonomic cardiovascular tests.

Materials and Methods

This study was done in the Institute of Physiology & Experimental Medicine, Madras Medical College, Chennai, India.

Sample Size: 30 normal controls (Group I) and 30 patients with Obstructive Sleep Apnea (Group II) of both sexes in the age group of 35-45 years participated in the study.

Inclusion Criteria: The patients with Obstructive Sleep Apnea (OSA) in the age group 35-45 years from various Departments in Government General Hospital, Chennai, who were diagnosed based on history, clinical examination and overnight Polysomnographic recordings using RMS software, on the basis of an apnea-hypopnea index (AHI) of $\geq$ 10 episodes of apnea or hypopnea per hour of sleep were chosen for the study. Age, gender and BMI matched controls were also chosen.

Exclusion Criteria: Individuals with co-existing diseases like Systemic Hypertension, Ischemic Heart Disease, Congestive Cardiac Failure, Diabetes Mellitus, renal disease and neuromuscular disorders and history of intake of drugs acting on the autonomic nervous system were excluded.

Informed consent was obtained and controls and patients were subjected to the following battery of autonomic function tests using standard techniques

described by Ewing et al. and Deepak et al.[21,22] In the heart rate response to standing test, the 30:15 R-R ratio was calculated from ambulatory ECG recording and Nivequre software by determining the longest R-R interval occurring 30 beats after standing divided by the shortest R-R interval occurring 15 beats after standing up from a supine position. In the heart rate response to deep breathing test, participants were asked to take deep breaths at a rate of 6 per minute and the E:I ratio was calculated by dividing the mean of the maximum R-R intervals during deep expiration by the mean of the minimum R-R intervals during deep inspiration. Inspiratory and expiratory periods were identified with the help of stethographic respiratory tracings recorded in a physiograph connected to a polygraph compatible ECG recorder and ECG was also recorded continuously by connecting the ECG leads to the ECG recorder which in turn was connected by the signal processing unit to the computer. The participants were then asked to perform the Valsalva manoeuvre by exhaling forcefully into a mercury manometer and maintaining the pressure at 40 mm Hg and the Valsalva Ratio was calculated by dividing the longest R-R interval after the manoeuvre by the shortest R-R interval during the manoeuvre.

In the isometric hand-grip exercise test, participants were given a hand-grip dynamometer and asked to maintain 30% of their maximum activity for 1.5 minutes. The change in diastolic pressure was calculated as the difference between the last value recorded in the opposite limb before the release of hand-grip pressure and the mean resting value obtained before starting the exercise (ΔDBP_{IHG}). The cold pressor test was done by asking participants to immerse their hand in cold water of 10^0C for one minute. The blood pressure was recorded in the opposite limb and the difference in diastolic blood pressure compared to the resting value was determined (ΔDBP_{CPT}). Blood pressure was recorded manually using a Riva Rocci sphygmomanometer according to standard procedure.

Statistical Analysis:

Data thus collected was subjected to statistical analysis using SPSS 17. Values were expressed as Mean ± SD. Unpaired Student t test was used to compare the variables between the controls (Group I) and OSA patients (Group II). A 'p' value of < 0.05 was considered significant.

Results

This study done to compare the autonomic function in 30 adult patients with Obstructive Sleep Apnea (Group II) and 30 normal controls (Group I) using autonomic cardiovascular tests revealed that the 30:15 ratio, E:I ratio and Valsalva Ratio were significantly lower (p value < 0.001) in the patients with OSA when compared to the controls, while the diastolic pressure difference in the isometric hand-grip exercise test (ΔDBP_{CPT}) and the cold pressor tests (ΔDBP_{CPT}) were significantly higher (p value < 0.001) in the patients with OSA (Table - 1).

Table-1: Comparison of the Autonomic Cardiovascular Test Variables between Controls (Group I) and Obstructive Sleep Apnea (OSA) Patients (Group II)

Autonomic Cardiovascular Test Variables	Group I	Group II	p value
Heart rate response to standing (30:15 ratio)	1.17 ± 0.08	1.03 ± 0.109	< 0.001*
Heart rate response to deep breathing (E:I ratio)	1.20 ± 0.06	1.07 ± 0.067	< 0.001*
Valsalva maneuver (Valsalva Ratio)	1.27 ± 0.05	1.19 ± 0.04	< 0.001*
Isometric hand- grip exercise test (Diastolic pressure difference - ΔDBP_{IHG})	7.37 ± 1.97	10.20 ± 1.65	< 0.001*
Cold pressor test (Diastolic pressure difference- ΔDBP_{CPT})	6.20 ± 1.35	9.17 ± 2.60	< 0.001*

Results expressed as mean and standard deviation of the Autonomic cardiovascular test variables of the two groups; Group I: Controls; Group II: Obstructive Sleep Apnea patients; 30:15 ratio: ratio of maximum R-R interval at 30th beat to minimum R-R interval at 15th beat following standing from supine position; E:I Ratio: ratio of maximum R-R interval during expiration to minimum R-R interval during inspiration following deep breathing; Valsalva Ratio: longest R-R interval after the Valsalva maneuver by the shortest R-R interval during the Valsalva maneuver; ΔDBP_{IHG}: maximum rise in diastolic blood pressure (in mm Hg) above baseline following sustained hand-grip; $\Delta DBP_{CPT:}$ maximum rise in diastolic blood pressure (in mm Hg) above baseline following immersion of the hand in cold water;*p< 0.05 being considered significant.

Discussion

Our study revealed that there were significant differences in the 30:15 ratio, E:I ratio and Valsalva Ratio between controls (Group I) and Obstructive Sleep Apnea patients (Group II),with the values of OSA patients in Group II being lower; these ratios being obtained from the heart rate response to standing, heart rate response to deep breathing and Valsalva manoeuvre tests respectively. The heart rate analysis during

standing (the 30:15 ratio), heart rate variation with deep breathing, and the Valsalva ratio are tests of parasympathetic cardio-vagal regulation.[23] In the heart rate response to standing test, normally, the heart rate increases immediately on standing from supine position, reaches a maximum at about the 15th beat and then slows down at about the 30th beat.[24] Heart rate varies with respiration (sinus arrhythmia), increasing during inspiration and decreasing during expiration mainly due to the parasympathetic innervation of the heart, the pulmonary stretch receptors, cardiac mechanoreceptors and baroreceptors.[24] The Valsalva ratio assesses the parasympathetic function more than the sympathetic function as the parasympathetics are both the afferents and the efferents while the sympathetics are part of the efferents.[24]

Our study also revealed that the diastolic pressure difference in the isometric hand-grip exercise test and the cold pressor tests were significantly higher (p value < 0.001) in the patients with OSAS compared to the controls. The isometric hand-grip exercise test and the cold pressor tests are tests of sympathetic adrenergic vascular regulation.[23] In the isometric hand-grip test, heart rate and blood pressure increase due to increase in sympathetic activity and decrease in parasympathetic activation as a result of central motor command and mechanical changes in response to muscle contraction.[24] The cold pressor test assesses sympathetic activity as submersion of the hand in cold water increases systolic and diastolic blood pressure due to afferents in the somatic pathway and efferents in the sympathetic pathway.[24]

Our findings therefore suggest that there is a sympatho-vagal imbalance during wakefulness in patients with OSA when compared to controls, with parasympathetic blunting and sympathetic over activity. Patients with OSA have been shown to have a high level of sympathetic activity during sleep possibly due to the episodes of hypoxia and hypercapnia that they experience triggering chemoreceptor reflexes.[8] The autonomic changes have been shown to persist even during wakefulness, even though there is normoxia,[8,10-12] and many mechanisms have been proposed. These findings of our study are therefore in agreement with the findings of other researchers. Comparison of the results of our study with other researchers who specifically used cardiac autonomic function tests to study patients with OSA, also revealed similar results. Ito et al. also found that the Valsalva ratio was significantly lower in OSAS patients when compared to controls.[17] Baroreflex sensitivity had also been proven to be lowered.[17,18] We however, had not used beat- to beat- monitoring of blood pressure (BP) and did not assess baroreflex sensitivity. Results of a study using cardiovascular autonomic function tests in children with OSAS were similar to our study in that Montesano et al. found that the 30:15 ratio was lower in children with OSAS and there was less heart rate variability during deep breathing; but differed from our study in that they did not find any difference in the Valsalva ratio while we found that the Valsalva ratio also was lower in patients with OSA.[19]

Our findings have to be considered in the context that the carrying over of the autonomic system alterations into wakefulness in OSA patients are considered to contribute to cardiovascular disorders in adults[10] and children,[2] and the possibility that Obstructive Sleep Apnea syndrome could become an important public health issue in India.[5] However, the limitations of our study include the small sample size; use of a sphygmomanometer to record BP instead of beat-to beat- BP monitoring (which would have helped determine BP variability and baroreceptor sensitivity) and use of the isometric hand- grip test which is considered insensitive in assessing sympathetic activity.

Conclusion

This study done with the aim of assessing autonomic function in adults with Obstructive Sleep Apnea (OSA) using autonomic cardiovascular tests revealed that there was sympatho-vagal imbalance in patients with OSA, with decreased parasympathetic and increased sympathetic activity. Further studies in larger samples can be planned using beat- to beat- blood pressure monitoring and results of Heart Rate Variability (HRV) analysis using time-domain and frequency-domain methods can be interpreted simultaneously. Muscle sympathetic nerve

activity, peripheral artery tonometry and blood and urine catecholamine estimation could also be done.

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Cite this article as: Jagannathan S, D'cruz SM, Kumar AS, Badanidiyur VR. Autonomic function in adults with obstructive sleep apnea. Int J Med Sci Public Health 2013; 2:1027-1031.
Source of Support: None
Conflict of interest: None declared