Influence of the severity of obstructive sleep apnea on nocturnal heart rate indices and its association with hypertension

Tıkayıcı uyku apnesi ciddiyetinin gece kalp hızı indeksleri üzerine etkisi ve hipertansiyon ile ilişkisi

Özcan Özeke, Mutlu Güngör, Serap Bilen Hızel, Dilek Aydın*, Özcan Ertürk*, Mehmet Kutlu Çelenk, Hazım Dinçer, Gürler İliçin, Fuat Özgen*, Can Özer*

From Clinics of Cardiology and *Sleep Disorder Center, Bayındır Hospital, Ankara-*Turkey*

ABSTRACT

Objective: Both heart rate (HR) and blood pressure parameters provide important information on the pathophysiology of the cardiovascular regulatory mechanisms, and are mainly affected by the autonomic nervous system. We sought to clarify whether the severity of obstructive sleep apnea (OSA) affects nocturnal HRs and whether there is a relationship between nocturnal HRs and the presence of hypertension.

Methods: We retrospectively reviewed medical records of all patients who performed nocturnal polysomnography with monitoring of HRs, and examined whether there is a relationship among the nocturnal HRs, the severity of OSA and the presence of hypertension.

Results: A total of 540 patients were included in the study. Nocturnal mean and maximal HRs were significantly higher in severe OSA group than in moderate (p=0.002 and p>0.05 in females; p<0.049 and p=0.044, in males, respectively) and mild OSA groups (p<0.001 and p=0.003, respectively in females, p<0.001 and p=0.004, respectively in males); and there was a positive correlation between the nocturnal mean HR and apnea-hypopnea index (Pearson's p=0.504, p<0.001 in female group; Pearson's p=0.254, p<0.001 in male group) and again the nocturnal mean HR and the presence of HT (Spearman's p=0.090, p=0.394 in female group; Spearman's p=0.272, p<0.001 in male group) in both gender groups.

Conclusion: We found that nocturnal mean and maximal HRs to be associated with severity of OSA and the presence of hypertension. We speculated that increased nocturnal mean and maximal HRs caused by sympathetic nervous system activation in OSA might be one of the mechanisms in explaining the hypertension and OSA association. *(Anadolu Kardiyol Derg 2011; 11: 509-14)*

Key words: Nocturnal heart rate, sleep apnea, hypertension, sympathetic nervous system activation

ÖZET

Amaç: Kalp hızı ve kan basıncı ölçümleri otonom sinir sistemi kontrolündeki kardiyovasküler düzenleyici mekanizmaların patofizyolojisi hakkında önemli veriler sağlarlar. Uyku apnesi gerek sempatik sinir sistemi aktivasyonu gerekse hipertansiyon ile ilişkili yeni bir kardiyovasküler risk faktörü olarak kabul edilmektedir. Bu çalışmada uyku apnesi ciddiyetinin gece kalp hızı değerleri üzerine etkisi ve gece kalp hızı değerlerinin hipertansiyon varlığı ile ilişkisi araştırıldı.

Yöntemler: Hastanemizde gece kalp hızlarını da kaydeden polisomnografi cihazı ile uyku apnesi tanısı konulan tüm hastaların tıbbi kayıtları ve polisomnografik verileri retrospektif olarak değerlendirildi. Gece en düşük, ortalama ve en yüksek kalp hızları ile uyku apnesi alt gruplarındaki değişkenlik ve hipertansiyon varlığı arasındaki ilişki araştırıldı.

Bulgular: Çalışmaya toplam 540 hasta alındı. Ciddi uyku apneli bireylerde, gece "ortalama" ve "en yüksek" kalp hızları, orta (sırasıyla, p=<0.049 ve p=0.044, erkeklerde; sırasıyla, p=0.002 ve P=NS, kadınlarda) ve hafif uyku apneli (sırasıyla, p=<0.001 ve p=0.004, erkeklerde; sırasıyla, p=<0.001 ve p=0.003, kadınlarda) olan gruplara göre istatistiki anlamlı olarak daha yüksekti. Yine gece ortalama kalp hızı ile apne hipopne indeksi (Pearson's p=0.504, p<0.001 kadınlarda; Pearson's p=0.254, p<0.001 erkeklerde) ve hipertansiyon varlığı (Spearman's p=0.090, p=0.394 kadınlarda; Spearman's p=0.272, p<0.001 erkeklerde) arasında pozitif korelasyon mevcuttu.

Sonuç: Bu çalışmada gece ortalama ve en yüksek kalp hızı değerlerinin uyku apnesi ciddiyeti ve hipertansiyon varlığı ile ilişkili olduğu saptandı. Uyku apneli hastalardaki artmış sempatik sinir sistemi aktivasyonuna bağlı artan ortalama ve en yüksek kalp hızlarının, uyku apnesi ve hipertansiyon varlığı arasındaki ilişkiyi açıklayan mekanizmalardan biri olabileceği ileri sürüldü. *(Anadolu Kardiyol Derg 2011; 11: 509-14)*

Anahtar kelimeler: Gece kalp hızı, uyku apnesi, hipertansiyon, sempatik sinir sistemi aktivasyonu

Address for Correspondence/Yazışma Adresi: Dr. Özcan Özeke, Clinic of Cardiology, Bayındır Hospital, Söğütözü, 06520, Ankara-*Turkey*
Phone: +90 505 383 67 73 Fax: +90 312 285 07 33 E-mail: ozcanozeke@gmail.com
Accepted Date/Kabul Tarihi: 05.04.2011 **Available Online Date/Çevrimiçi Yayın Tarihi:** 25.07.2011

doi:10.5152/akd.2011.135

Introduction

Obstructive sleep apnea (OSA) is the most common sleep-related breathing disorder and is characterized by repetitive narrowing or collapse of the pharyngeal airway during sleep with decreases in oxygen saturation leading to a series of pathological events, primarily in the cardiovascular system (1-4). The mechanisms by which OSA affects the cardiovascular system may involve mechanical effects on intrathoracic pressure, sympathetic overstimulation, intermittent hypoxia, oxidative stress, inflammation, hyper coagulation, metabolic dysregulation and endothelial dysfunction (3, 5). The repetitive respiratory events cause hypoxia, hypercapnea, arousals, or disrupted sleep singly or in combination (6-10). These abnormal physiologic events result in increased sympathetic outflow and alterations in blood pressure control mechanisms. In particular, abnormal autonomic control and chronic sympathetic nervous system (SNS) activation appear to be key factors in the causal pathway linking OSA to cardiovascular disease (11-14).

It is well known that OSA is an independent risk factor for systemic hypertension (HT), however, the understanding of the pathogenic mechanisms linking both conditions is limited. It is probably multifactorial, with environmental, dietary, neural, humoral, mechanical and hemodynamic components and genetic inputs involved (15-18). The role that the autonomic nervous system plays in mediating these cardiovascular changes has been the focus of intensive research activity. One of the most important effects of OSA is an activation of SNS, which persists during the day and is thought to play a key role in the association of OSA and elevated systemic blood pressure (18, 19).

Both heart rate (HR) and blood pressure parameters provide important information on the pathophysiology of the cardiovascular regulatory mechanisms, and are mainly affected by the autonomic nervous system with its sympathetic and parasympathetic components. Elevated HR is an important risk factor for cardiovascular disease (20, 21). Previous studies, including large-scale cohort studies such as such the CASTEL and Framingham studies, have demonstrated a positive association between elevated HR at rest and adverse cardiovascular events in both the general population and the population with cardiovascular disease (22-25). There have been several reports on the results of spectral analysis of heart rate variability in OSA patients (26, 27), but a few published on the HR of OSA (28-30). Patients with OSA have found to have faster HRs during 24 hours, suggesting an increased cardiac sympathetic drive and the severity of OSA has been independently associated with increased mean HRs during 24 hours (29, 30).

However, the association between the severity of OSA and nocturnal HR indices has not yet been fully investigated in patients with OSA.

Accordingly, we sought to clarify whether the severity of OSA affects nocturnal HRs and whether there is a relationship between nocturnal HRs and the presence of HT.

Methods

Study population

We retrospectively reviewed medical records of all patients who underwent nocturnal polysomnography (PSG) (Somnologica, Iceland) at Bayındır Hospital Sleep Disorders Center between January 2005 and January 2010.A total 864 patients had nocturnal PSG. Of them, 540 met the inclusion criteria. The ratio of male to female was about 1 to 5. Those patients who had the "first night effect", which is the alteration of the sleep structure in the unfamiliar environment of a sleep laboratory (31); those receiving drugs affecting cardiac conduction (such as beta blockers, dihydropyridines or verapamil) and those had inadequate or incomplete data were excluded from study.

Hypertension was defined as taking antihypertensive without regard to the actual measurement of blood pressure, or having a systolic blood pressure reading greater than 140 mm Hg or a diastolic blood pressure reading greater than 90 mm Hg (32); and the systolic and diastolic blood pressure measurements at the day of PSG were recorded.

Polysomnography

The international standard for reading PSG results was used for the sleep stages and events (33, 34).

Nocturnal HRs was recorded as mean, minimal and maximal HRs during sleep by PSG. The OSA is accepted when a patient has a total apnea-hypopnea index (AHI; number of apneas and hypopneas per hour of sleep) $\geq$5 and symptoms of excessive daytime sleepiness; and severity of OSA were categorized into three groups according to the AHI: AHI <15/h (mild OSA group), AHI <30/h (moderate OSA group), and AHI $\geq$30/h (severe OSA group) (33, 34).

Statistical analysis

The SPSS statistical software package (version 16.0; SPSS Inc, Chicago, Ill, USA) was used to perform all statistical calculations. Continuous variables were expressed as mean±SD. The independent samples t-test or Mann-Whitney U test were used to compare continuous variables, when appropriate according to normality test results. Categorical variables were expressed as numbers and percentages, and compared using the Chi-square test. Since the frequency and severity of OSA are greater in men than women (35, 36), all comparisons were made separately for both genders by two steps. First, we compared the basal clinical and polysmonographic data between the men and women using independent sample t-test. Second, the analysis of variance (ANOVA) with post hoc Tukey's HSD test was used for the statistical analysis of the results. Relationships between the continuous variables were evaluated by Pearson's correlation analysis when data were normally distributed or by Spearman's correlation analysis when they were not normally distributed. For all tests, a value of $p < 0.05$ was considered significant.

Results

Since there were significant differences including age and body mass index between the both gender groups (p<0.001); all comparisons were made separately (Table 1).

In comparison of groups regarding severity of OSA, there was statistically important difference in nocturnal mean HR (p<0.001 for both genders), maximal HR (p=0.004 in females; p=0.003 in males), the presence of HT (p=0.026 in females, p<0.001 in males) and systolic (p=0.004 in females, p<0.001 in males) and diastolic (p=NS in females; p<0.001 in males) blood pressure among OSA subgroups in both gender groups (Table 2).

Nocturnal mean and maximal HRs were significantly highest in severe OSA group (Table 2). For HT, systolic and diastolic blood pressures, and maximal and mean HRs, we also performed a post hoc Tukey test to evaluate intergroup differences in detail, and found a statistically significant difference as regard mean HR among all OSA subgroups in males; but not only between the mild and moderate OSA groups in females (Table 3).

The Spearman correlation analyses showed a significant positive correlation between the nocturnal mean HR and AHI in both gender groups (Pearson's p=0.504, p<0.001 in female group; Pearson's p=0.254, p<0.001 in male group), and between the nocturnal mean HR and HT in males but not females (Spearman's p=0.090, p=0.394 in female group; Spearman's p=0.272, p<0.001 in male group).

Table 1. Basal demographic, clinical characteristics and polysomnographic results according to gender

Variables	Female (n=92)	Male (n=448)	p*
Demographics features			
Age, years	54.0±8.8	48.5±10.8	<0.001
Height, cm	159.12±6.56	174.07±7.31	<0.001
Weight, kg	80.8±15.3	91.6±14.1	<0.001
BMI, kg/m^2	31.9±5.9	30.3±4.5	<0.001
Hypertension, n (%)	33 (37)	160 (36)	NS
Hyperlipidemia, n (%)	46 (50)	232 (52)	NS
Diabetes mellitus, n (%)	40 (43)	179 (40)	NS
Current smoking, n (%)	50 (55)	268 (60)	NS
SBP, mmHg	136.47±25.7	134.52±24.66	NS
DBP, mmHg	84.34±13.67	84.63±12.88	NS
Polysomnographic results			
AHI /hour	29.7±29.9	35.4±26.6	NS
Obstructive AI/hour	11.6±21.3	15.8±21.0	0.015
Central AI/hour	0.36±1.53	0.88±4.31	NS
Mixed AI/hour	0.30±1.38	1.57±4.67	0.004
HI/hour	17.7±16.7	17.3±13.0	0.046
ODI/hour	31.1±31.3	33.7±26.9	NS
Average oxygen saturation, %	92.3±3.1	92.2±2.6	NS
Lowest oxygen saturation, %	79.4±9.4	80.3±8.7	NS
The percentage sleep time with SaO_2<90%	14.3±23.4	13.5±20.2	NS
The percentage of SP	42.8±25.9	36.6±25.3	0.005
The percentage of LSSP	20.8±17.9	25.2±19.5	0.016
The percentage of RSSP	35.4±24.4	39.7±20.8	NS
LM	27.2±21.8	27.9±23.4	NS
PLM	16.6±20.2	14.9±20.0	NS
Snoring, %	18.5±20.6	21.3±20.2	NS
Average HR, bpm	66.7±8.3	66.5±8.3	NS
Lowest HR, bpm	50.3±9.4	48.3±9.5	NS
Maximum HR, bpm	90.0±18.6	94.5±19.5	NS
HR range, maximum-minimum HR	39.7±21.8	46.1±21.4	0.016

Data are presented as mean±SD and number (percentage)
*Unpaired Student's t-test and Chi-square test
AHI - apnea hypopnea index, AI - apnea index, BMI - body mass index, bpm-beats per minute, DBP - diastolic blood pressure, HR - heart rate, HI - hypopnea index, LM - leg movements, LSSP - left side sleeping position, ODI - oxygen desaturation event index, PLM - periodic leg movements, RSSP - right side sleeping position, SP - supine position, SBP - systolic blood pressure

Discussion

In the presented study, nocturnal mean and maximal but not minimal HRs found to be well correlated with AHI and the presence of HT in patients with OSA. Our findings suggested that increased nocturnal sympathetic activation determined by nocturnal mean and maximal HRs may be responsible for one of the mechanisms in explaining the HT and OSA association.

There have been few reports on the association of HRs and OSA (28-30). Whereas some of them have reported no difference in the HRs between patients with OSA and normal controls, and no difference in the HR among OSA patients before and with nocturnal continuous positive airway pressure (nCPAP) treatment (27, 28); the others reported that the severity of OSA has been independently associated with increased mean HRs during 24 hour and the favorable effect of nCPAP on HR indices in patients with OSA (29, 30). These conflicting results may have been obtained due to the characteristic pattern of bradycardia and tachycardia during sleep in OSA patients.

In presented study, mean and maximal HRs were correlated with the OSA severity. This elevation in mean HR in patients with OSA has been thought to be due to activated sympathetic nervous system (SNS). Brief episodes of apnea/hypopnea increase SNS activation by suspending the tonic inhibition of sympathetic outflow by pulmonary stretch receptors (37) and by the stimulation of peripheral and central chemoreceptor (14, 38). The SNS is activated even during wakefulness in patients with OSA (13, 39). The mechanisms for the activation of the SNS during 24 hour are not fully understood, but one possibility is that increased chemoreflex gain by OSA results in tonic chemoreflex activation even during normoxia, with consequent increased sympathetic activity (26). Effective treatment of OSA by CPAP has been shown to markedly and acutely decrease BP and the mean HR throughout the

Table 2. A comparison of clinical and polysomnographic variables among OSA subtypes according to gender

Severity of OSA/ Variables	Mild	Moderate	Severe	F*	p*
Female	**(n=42)**	**(n=25)**	**(n=25)**		
Age, years	52.1±9.1	54.0±8.3	56.4±8.7	1.501	NS
BMI, kg/m^2	29.7±5.6	31.6±6.6	35.9±3.5	10.371	<0.001
Hypertension, %	21	44	56		0.026
Hyperlipidemia, n (%)	22 (52)	12 (48)	12 (48)		NS
Diabetes mellitus, n (%)	17 (41)	11 (44)	12 (48)		NS
Current smoking, n (%)	21 (50)	14 (56)	15 (60)		NS
SBP, mmHg	125±17	146±28	145±27	8.620	<0.001
DBP, mmHg	84±11	92±17	92±13	5.890	0.004
AHI /hour	9.8±3.1	22.6±4.9	70.3±2.9	120.821	<0.001
Mean HR, bpm	63.5±6.9	65.7±8.2	72.9±7.1	13.333	<0.001
Lowest HR, bpm	50.6±8.6	50.6±10.0	49.4±10.2	0.143	NS
Maximum HR, bpm	84.4±10.2	89.6±15.8	99.6±27.0	5.784	0.004
Male	**(n=124)**	**(n=122)**	**(n=202)**		
Age, year	47.8±10.8	47.9±10.2	49.3±11.3		NS
BMI, kg/m^2	28.6±3.7	29.7±3.6	31.6±5.1		<0.001
Hyperlipidemia, n (%)	65 (52)	65 (53)	102 (51)		NS
Diabetes mellitus, n (%)	47 (38)	48 (39)	84 (41)		NS
Current smoking, n (%)	73 (59)	73 (60)	122 (60)		NS
Hypertension, %	27	31	51		<0.001
SBP, mmHg	125±20	132±19	141±28	17.282	<0.001
DBP, mmHg	79±10	83±10	88±14	19.276	<0.001
AHI /hour	9.5±3.1	22.6±4.2	59±2.3	481.364	<0.001
Mean HR, bpm	63.7±8.6	66.2±7.8	68.3±7.8	13.297	<0.001
Lowest HR, bpm	48.8±9.3	49.4±8.6	47.4±10.0	1.886	NS
Maximum HR, bpm	90.9±17.2	92.6±15.6	98.0±22.3	5.925	0.003

Data are presented as mean±SD and number (percentage)
*One-way ANOVA test
AHI - apnea hypopnea index, BMI - body mass index, bpm-beats per minute, DBP - diastolic blood pressure, HR - heart rate, OSA - obstructive sleep apnea, SBP - systolic blood pressure

day, suggesting a possible improvement cardiovascular consequences in short and long term after the NCPAP therapy probably by restoration of SNS (13, 30). The elimination of tonic chemoreflex drive by administration 100% oxygen in OSA significantly lowers sympathetic activity and resting HR during wakefulness, suggesting that the activation of the SNS contributes mainly to elevated HR and blood pressure in patients with OSA (13, 40). These data are also in agreement with the other clinical studies reporting beta blockers (atenolol) has been shown to reduce the nocturnal pressure slightly more than the other drugs, although there is no current evidence that any specific antihypertensive drug has direct effects on attenuating sleep apnea severity (41). Similar to this finding, it has been showed that also the BP increase can be attenuated by pharmacological blockade of the autonomic nervous system with hexamethonium, indicating that it is mediated by the SNS rather than by mechanical factors related to changes in intrathoracic pressure. Somers et al. (15) proposed baroreflex impairment, mainly found in patients with arterial HT, to be susceptible for excessive autonomic response in patients with OSA, which has been proposed as an independent risk factor for the development of essential HT (1, 2, 42).

Study limitations

The main limitation of the present study resides in its retrospective design. Secondly, there was a relatively small sample size in female group. Thirdly; the relationship between sleep apnea severity and hypertension was based on office blood pressure measurements made once on the PSG day. However, it is well known in that morning and evening blood pressure measurements may differ and sleep apnea patients even demonstrate much higher blood pressure levels during sleep. The paper is not powered enough to address this relationship.

Table 3. A results of post hoc Tukey test in both gender groups

Variables	OSA severity	Mild		Moderate		Severe	
		Female	Male	Female	Male	Female	Male
Hypertension	Mild	-	-	NS	0.015	0.012	<0.001
	Moderate	NS	0.015	-	-	NS	NS
	Severe	0.012	<0.001	NS	NS	-	-
SBP	Mild	-	-	0.002	NS	0.003	<0.001
	Moderate	0.002	NS	-	-	NS	0.003
	Severe	0.003	<0.001	NS	0.003	-	-
DBP	Mild	-	-	0.021	0.025	0.011	<0.001
	Moderate	0.021	0.025	-	-	NS	0.004
	Severe	0.011	<0.001	NS	0.004	-	-
Mean HR	Mild	-	-	NS	0.036	<0.001	<0.001
	Moderate	NS	0.036	-	-	0.002	0.049
	Severe	<0.001	<0.001	0.002	0.049	-	-
Maximal HR	Mild	-		NS	NS	0.003	0.004
	Moderate	NS	NS	-	-	NS	0.044
	Severe	0.003	0.004	NS	0.044	-	-

AHI - apnea hypopnea index, bpm - beats per minute, DBP - diastolic blood pressure, HR - heart rate, SBP - systolic blood pressure

Conclusion

In presented study, we found that nocturnal mean and maximal HRs to be associated with severity of OSA and the presence of HT. Patients with OSA experience significant physiologic stress at night, in which low oxygen levels activate the SNS, which may also contribute to elevation of blood pressure and heart rate. Considered together, we believe that increased nocturnal mean and maximal HRs caused by SNS activation in OSA might be one of the mechanism in explaining the hypertension and OSA association.

Conflict of interest: None declared.

References

1. Turgut Çelen Y, Peker Y. Cardiovascular consequences of sleep apnea: I- Epidemiology. Anadolu Kardiyol Derg 2010; 10: 75-80.
2. Somers VK, White DP, Amin R, Abraham WT, Costa F, Culebras A, et al. Sleep apnea and cardiovascular disease: an American Heart Association/American College of Cardiology Foundation Scientific Statement from the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. J Am Coll Cardiol 2008; 52: 686-717.
3. Turgut Çelen Y, Peker Y. Cardiovascular consequences of sleep apnea: II-Cardiovascular mechanisms. Anadolu Kardiyol Derg 2010; 10: 168-75.
4. Dursunoğlu D, Dursunoğlu N. Cardiovascular diseases in obstructive sleep apnea. Tuberk Toraks 2006; 54: 382-96.
5. Fletcher EC. Effect of episodic hypoxia on sympathetic activity and blood pressure. Respir Physiol 2000; 119: 189-97.
6. Leung RS. Sleep-disordered breathing: autonomic mechanisms and arrhythmias. Prog Cardiovasc Dis 2009; 51: 324-38.
7. Koehler U, Becker HF, Grimm W, Heitmann J, Peter JH, Schäfer H. Relations among hypoxemia, sleep stage, and bradyarrhythmia during obstructive sleep apnea. Am Heart J 2000; 139: 142-8.
8. Aytemir K, Deniz A, Yavuz B, Uğur Demir A, Şahiner L, Çiftçi Ö, et al. Increased myocardial vulnerability and autonomic nervous system imbalance in obstructive sleep apnea syndrome. Respir Med 2007; 101: 1277-82.
9. Pinsky MR. Sleeping with the enemy: the heart in obstructive sleep apnea. Chest 2002; 121: 1022-4.
10. Shepard JW Jr. Cardiopulmonary consequences of obstructive sleep apnea. Mayo Clin Proc 1990; 65: 1250-9.
11. Wolf J, Lewicka J, Narkiewicz K. Obstructive sleep apnea: an update on mechanisms and cardiovascular consequences. Nutr Metab Cardiovasc Dis 2007; 17: 233-40.
12. Zwillich CW. Sleep apnea and autonomic function. Thorax 1998; 53: S20-4.
13. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest1995; 96: 1897-904.
14. Somers VK, Mark AL, Zavala DC, Abboud FM. Contrasting effects of hypoxia and hypercapnia on ventilation and sympathetic activity in humans J Appl Physiol 1989; 67: 2101-6.
15. Somers VK, Mark AL, Abboud FM. Potentiation of sympathetic nerve responses to hypoxia in borderline hypertensive subjects. Hypertension 1988; 11: 608-12.
16. Somers VK, Dyken ME, Mark AL. Parasympathetic hyperresponsiveness and bradyarrhythmias during apnea in hypertension. Clin Auton Res 1992; 2: 171-6.
17. Gonçalves SC, Martinez D, Gus M, de Abreu-Silva EO, Bertoluci C, Dutra I, et al. Obstructive sleep apnea and resistant hypertension: a case-control study. Chest 2007; 132: 1858-62.

18. Narkiewicz K, Somers VK. The sympathetic nervous system and obstructive sleep apnea: implications for hypertension. J Hypertens 1997; 15: 1613-9.
19. Narkiewicz K, Somers VK. Obstructive sleep apnea as a cause of neurogenic hypertension. Curr Hypertens Rep 1999; 1: 268-73.
20. Palatini P and Julius S. Heart rate and the cardiovascular risk. J Hypertens 1997; 15: 3-17.
21. Palatini P, Julius S. Association of tachycardia with morbidity and mortality: pathophysiological considerations. J Hum Hypertens 1997; 11(Suppl 1): 19-27.
22. Kannel WB, Kannel C, Paffenbarger RS Jr, Cupples LA. Heart rate and cardiovascular mortality: the Framingham Study. Am Heart J 1987; 113: 1489-94.
23. Gillman MW, Kannel WB, Belanger A, D'Agostino RB. Influence of heart rate on mortality among persons with hypertension: the Framingham Study. Am Heart J 1993; 125: 1148-54.
24. Benetos A, Rudnichi A, Thomas F, Safar M, Guize L. Influence of heart rate on mortality in a French population: role of age, gender, and blood pressure. Hypertension 1999; 33: 44-52.
25. Greenland P, Daviglus ML, Dyer AR, Liu K, Huang CF, Goldberger JJ, et al. Resting heart rate is a risk factor for cardiovascular and noncardiovascular mortality: the Chicago Heart Association Detection Project in Industry. Am J Epidemiol 1999; 149: 853-62.
26. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK. Altered cardiovascular variability in obstructive sleep apnea. Circulation 1998; 98: 1071-7.
27. Roche F, Gaspoz JM, Court-Fortune I, Minini P, Pichot V, Duverney D, et al. Screening of obstructive sleep apnea syndrome by heart rate variability analysis. Circulation 1999; 100: 1411-5.
28. Bonsignore MR, Romano S, Marrone O, Chiodi M, Bonsignore G. Different heart rate patterns in obstructive apneas during NREM sleep. Sleep 1997; 20: 1167-74.
29. Kawano Y, Tamura A, Watanabe T, Kadota J. Influence of the severity of obstructive sleep apnea on heart rate. J Cardiol 2010; 56; 27-34.
30. Sumi K, Chin K, Takahashi K, Nakamura T, Matsumoto H, Niimi A, et al. Effect of nCPAP therapy on heart rate in patients with obstructive sleep apnoea-hypopnoea. QJM 2006; 99: 545-53.
31. Gouveris H, Selivanova O, Bausmer U, Goepel B, Mann W. First-night-effect on polysomnographic respiratory sleep parameters in patients with sleep-disordered breathing and upper airway pathology. Eur Arch Otorhinolaryngol 2010; 267: 1449-53.
32. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, et al. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003; 42: 1206-52.
33. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep 1999; 22: 667-89.
34. American Academy of Sleep Medicine. International Classification of Sleep Disorders. In: Diagnostic and Coding Manual. Westchester, Ill: American Academy of Sleep Medicine; 2005.
35. Ye L, Pien GW, Weaver TE.Gender differences in the clinical manifestation of obstructive sleep apnea. Sleep Med 2009; 10: 1075-84.
36. Dancey DR, Hanly PJ, Soong C, Lee B, Shepard J Jr, Hoffstein V. Gender differences in sleep apnea: the role of neck circumference. Chest 2003; 123: 1544-50.
37. Bradley TD, Tkacova R, Hall MJ, Ando S, Floras JS. Augmented sympathetic neural response to simulated obstructive apnoea in human heart failure. Clin Sci (Lond) 2003; 104: 231-8.
38. Morgan BJ, Denahan T, Ebert TJ. Neurocirculatory consequences of negative intrathoracic pressure vs. asphyxia during voluntary apnea. J Appl Physiol 1993; 74: 2969-75.
39. Carlson JT, Hedner J, Elam M, Ejnell H, Sellgren J, Wallin BG. Augmented resting sympathetic activity in awake patients with obstructive sleep apnea. Chest 1993; 103: 1763-8.
40. Narkiewicz K, van de Borne PJ, Montano N, Dyken ME, Phillips BG, Somers VK. Contribution of tonic chemoreflex activation to sympathetic activity and blood pressure in patients with obstructive sleep apnea. Circulation 1998; 97: 943-5.
41. Kraiczi H, Hedner J, Peker Y, Grote L. Comparison of atenolol, amlodipine, enalapril, hydrochlorothiazide, and losartan for antihypertensive treatment in patients with obstructive sleep apnea Am J Respir Crit Care Med 2000; 161: 1423-8.
42. Brooks D, Horner RL, Kozar LF, Render-Teixeira CL, Phillipson EA. Obstructive sleep apnea as a cause of systemic hypertension. Evidence from a canine model. J Clin Invest 1997; 99: 106-9.