Is there a chronic sleep stage-dependent linear and nonlinear cardiac autonomic impairment in obstructive sleep apnea?

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Introduction

Obstructive sleep apnea (OSA) is a respiratory disorder char-acterized by recurrent airflow obstruction caused by total or partial collapse of the upper airway [1–3]. Epidemiological studies have shown a 33 % prevalence of OSA among the 50–70 year-old population [2, 4]. Chronic loud snoring, excessive daytime sleepiness [5], personality changes [6], and deterioration of quality of life [7] are the most common symptoms of OSA.

Previous research has demonstrated OSA has a negative impact on cardiac autonomic function [5]. Specifically, autonomic nervous system (ANS) (sympathetic and para-sympathetic) control of heart rate (HR) appears unstable in patients with OSA and has been linked with an increased risk of cardiovascular events and mortality [8–13]. A non-invasive and clinically valuable measure providing insight

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into ANS balance is heart rate variability (HRV) [14, 15]. Studies have proposed the use of HRV assessed from ECG recordings, which is part of polysomnographic monitoring, as a simple and economical solution for the diagnosis of OSA [16–18].

Traditionally, HRV has been measured in the time and frequency domain [19, 20]. More recently, nonlinear HRV analysis has been receiving increasing recognition, as it appears to be more sensitive in detecting autonomic dysfunction compared to other diagnostic approaches. For example, Mäkikallio et al. [21] reported that some nonlinear indices are able to detect subtle changes in HR dynamics better than conventional linear analyses and suggested that the mechanisms involved in cardiovascular regulation are better characterized in a nonlinear fashion.

Most of these HRV studies are based on a full night of HR signal analysis, comparing OSA with healthy subjects or OSA subgroups according to disease severity with the goal of discovering physiologic measures that allow for distinction among them. Lado and colleagues [22] conducted a HRV investigation during an apnea-free sleep period to determine if HRV changes represent a chronic autonomic imbalance in OSA. These authors showed that spectral analysis could discriminate mild from severe OSA. In this context, to our knowledge, the combination of linear and additional nonlinear analysis was not investigated, which could potentially detect ANS dysfunction in even less severe, earlier, stages of the disease.

In addition, differences in HRV during different sleep stages throughout the night have been demonstrated [21]. Although HRV may be influenced by sleep stages, some investigators posit that these changes do not differ significantly when comparing OSA to NonOSA cohorts [23]. Moreover, these sleep stage recordings used to support this hypothesis did not use apnea-free samples. More specifically, no studies have investigated (1) the existence of linear and nonlinear HRV changes using HR signal intervals without apneic episodes in patients affected by OSA or (2) if the change in HRV is sleep stage-dependent. Thus, our specific aims were to investigate whether the ANS alterations in OSA patients are a chronic condition (evaluating linear plus nonlinear HRV indices during an apnea-free sleep period) and to discover if these changes vary depending on the different sleep stages [i.e., stage 2 and rapid eye movement (REM) sleep] in earlier stages of the disease, specifically mild and moderate OSA.

We hypothesize that (1) OSA may affect linear and nonlinear ANS modulation, even during sleep periods that were free from apnea events, and (2) there is a linear and nonlinear HRV difference between apparently healthy subjects and OSA subjects during the different sleep stages analyzed.

Methods

This was a single-center, cross-sectional, retrospective study involving patients with mild and moderate OSA. Subjects were selected from the sleep institute database of our institution between February and December 2012. The study protocol was approved by the local ethics review committee (401/2010), and all participants signed written informed consent forms prior to enrollment, and the study was conducted in full accordance with the Declaration of Helsinki. The trial was registered in RBR-3jbm6d.

Patients and polysomnographic recordings

The database used in the present study consisted of in-laboratory overnight polysomnography (PSG) recordings of 58 patients referred to our sleep laboratory for evaluation of apnea, snoring, and excessive daytime sleepiness. Exclusion criteria were as follows: patients younger than 18 years, permanent or paroxysmal atrial fibrillation, permanent ventricular or atrial pacing, current tobacco use, pulmonary disease, periodic leg movements, and participation in trials with continuous positive airway pressure devices in the previous 6 months. PSGs with insufficient REM time sleep or those that displayed an insufficient quality of their ECG recordings were also excluded.

Overnight PSG recordings were performed using the iCelera Fast-Poli 26i (Homed, São Paulo, Brazil) device that allowed for electroencephalogram, electrooculogram, oronasal flow by thermistor, transducer nasal pressure, thoracoabdominal movement, electrocardiogram, and snoring and body position monitoring [24]. A sleep specialist blinded to study analyzed the data of visually scored polysomnographic records for sleep stages and apnea events. Total sleep time, number and duration of REM periods, and number and duration of arousals were also measured [25].

Sleep stages, hypopneas, apneas, and arousals were scored using the standard recommended by the American Academy of Sleep Medicine (AASM) [26]. Apnea was defined as the absence of airflow for more than 10 s, and hypopnea as the reduction of respiratory flow for at least 10 s accompanied by a decrease of 4 % or more in the saturation of hemoglobin.

After overnight PSG, OSA was diagnosed by the apnea–hypopnea index (AHI), calculated by dividing the number of apneas and hypopneas by the number of hours of sleep [27]. Subjects were then categorized into three groups: moderate OSA ($n=20$; $15<\text{AHI}<30$), mild OSA ($n=20$, $5<\text{AHI}<15$), and NonOSA ($n=18$, $\text{AHI}<5$) groups [24].

Linear and nonlinear analysis of HRV

Electrocardiographic signals were acquired using the PSG device at a sampling rate of 128 Hz. After acquisition, the

signals were visually inspected and corrected for ectopic beats. Only segments with >90 % pure sinus beats were included in the final analysis. The data were entered into Kubios HRV Analysis Software (MATLAB, version 2 beta, Kuopio, Finland). HRV analysis was performed during REM and stage 2 non-REM sleep.

In order to standardize the selection of the segments, the whole PSG recording (≈6 h) was divided into three parts (≈2 h). Five-minute apnea-free sleep segments were selected within each PSG recording part (1/3, 2/3, and 3/3 of overnight data length) of REM and stage 2 non-REM sleep. The HRV indices were analyzed in 5-min segments, and the average of each was considered for statistical analysis.

The nonlinear analysis of the Poincaré plot of RR intervals (RRis) was applied, and the following two descriptors of the Poincaré plot were used: standard deviation (SD1), usually interpreted as a measure of short-term HRV, which is mainly caused by respiratory sinus arrhythmia (parasympathetic modulation), and SD2, which is interpreted as a measure of both short- and long-term HRV (overall HRV) [28]. These indices can infer the notion of different temporal effects of changes in the vagal and sympathetic modulation of the HR on the subsequent R–R intervals without a requirement for a stationary quality of the data [28–30].

A recurrence plot (RP) analysis was performed as well, and the following indices were assessed: mean line length (Lmean), recurrence rate (REC), determinism (DET), and Shannon entropy (ShanEn) [29, 30]. These measures are related with the predictability and complexity of the deterministic structure in the system [29–31].

Linear frequency domain HRV was computed by fast Fourier transformation. Two spectral components were obtained: low frequency (LF), from 0.04 to 0.15 Hz, and high frequency (HF), from 0.15 to 0.4 Hz. The spectral components were expressed in normalized units (nu). Normalization is obtained by dividing the absolute power of a spectral component (LF or HF) by the total power minus the power of the component, with a frequency range between 0 and 0.03 Hz (very low frequency), and then multiplying this ratio by 100 [32, 33].

Statistical analysis

Statistical analysis was conducted to verify possible differences among the groups (mild and moderate OSA patients and control group) and between sleep stages (stage 2 and REM) within groups. Results were reported as mean values and SDs. Paired *t* tests were performed for within-patients HRV comparisons between sleep stages, and one-way ANOVA (post hoc Tukey) was used to test for differences among groups (HRV indices and polysomnographic and demographic parameters). The Pearson product–moment correlation coefficient was computed to assess the relationship between the nonlinear and linear HRV indices. A p value less than 0.05 was considered significant for all tests. The analyses were performed with SigmaPlot version 11.0 (Systat Software, Germany).

Results

The study groups consisted of 20 mild and 20 moderate OSA patients as well as 18 NonOSA subjects serving as controls. The demographic characteristics and polysomnographic parameters are summarized in Table 1. There were no significant differences in age and sleep efficiency among studied groups. As expected, mild and moderate OSA patients presented with higher AHI index values compared to the NonOSA group. The AHI index was also higher in the moderate OSA group compared to that in the mild OSA group. The moderate OSA group also presented with higher values of oxygen desaturation index (ODI) compared to both mild OSA and NonOSA groups. Regardless of severity, subjects with OSA also displayed a longer time with oxygen saturation below 90 % compared to NonOSA subjects.

Figure 1 shows the results of the HRV nonlinear DET index and linear spectral indices for each group in sleep stages 2 and REM. As expected, NonOSA subjects presented with higher values for both LF and LF/HF in REM sleep compared to stage 2 sleep, while the mild OSA group did not demonstrate the same autonomic behavior between these sleep stages. Moderate OSA patients also presented with higher values for both LF and LF/HF in REM sleep when compared with stage 2 and REM sleep of controls. Regardless of the comparison, the moderate OSA group demonstrated higher values for the DET index during REM compared to stage 2 sleep.

Table 1 Demographic and polysomnographic parameters in control group and mild OSA and moderate OSA groups

	NonOSA (N=18)	Mild OSA (N=20)	Moderate OSA (N=20)
Men	8 (44 %)	6 (30 %)	13 (65 %)
Age (years)	36±8	37±14	39±8
BMI (kg/m^2)	25±3	27±5	30±5
AHI (events/h)	2.8±1.2	8.4±2.5[a]	19.6±3.7[a, b]
Sleep efficiency (%)	92±3	85±7	88±4
ODI (4 % level)	3.6±2.5	6.9±3.3	23.4±8.0[a, b]
T90 (min)	2.1±3.5	7.7±12[a]	17.7±16[a, b]

Data are expressed as mean ± SD

OSA obstructive sleep apnea, *BMI* body mass index, *AHI* apnea/hypopnea index, *ODI* oxygen desaturation index, *T90* cumulative time spent below 90 % saturation

[a] Differences in NonOSA group

[b] Difference in mild OSA group

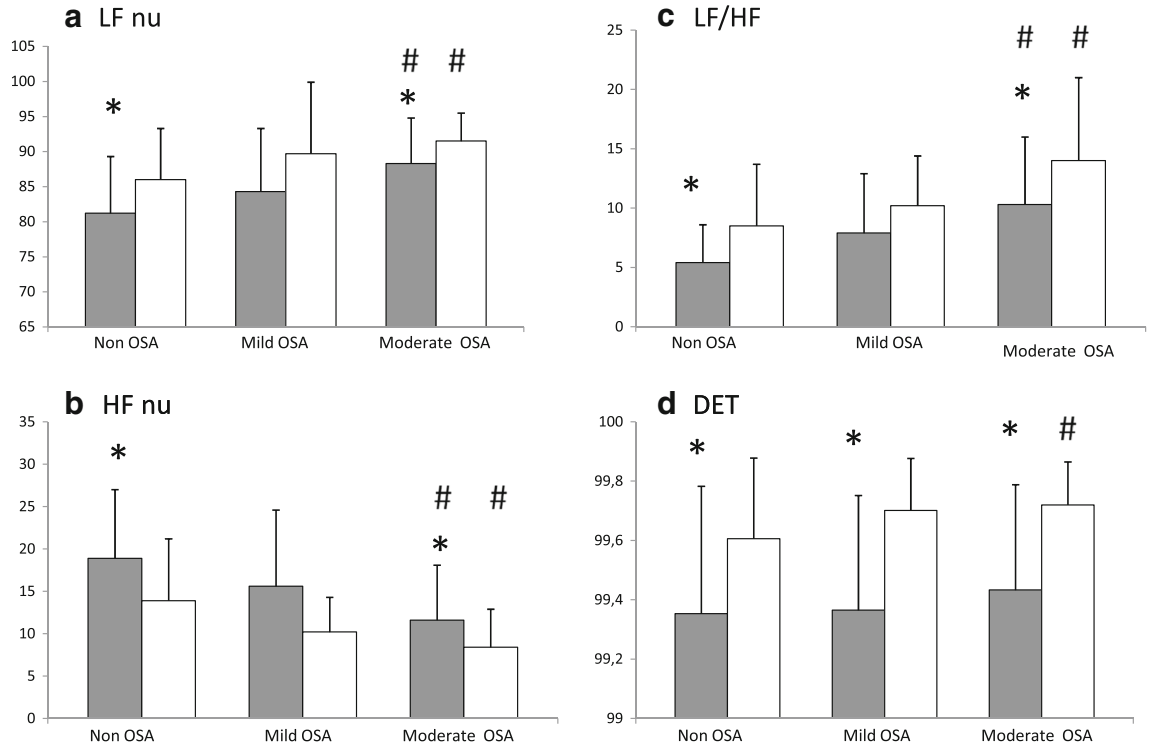

Fig. 1 Linear and nonlinear indices in sleep stage 2 (*gray bars*) and REM (*white bars*) for OSA and NonOSA groups in **a** LF nu, **b** HF nu, **c** LF/HF ratio, and **d** DET. *Asterisk* indicates a difference between sleep stages within patients ($p<0.05$), and *number sign* indicates difference vs. NonOSA

The Poincaré and recurrence plot analysis results for each group and sleep stages studied are shown in Table 2. HRV differences between sleep stages are apparent among all groups. The REM sleep stage demonstrated higher values for HRV indices (SD2, Lmean, REC, and ShanEn) compared to sleep stage 2 in all groups, with the exception of the SD1 index.

The Pearson coefficient demonstrated a significant correlation between DET and HF during sleep stage 2 ($r=-0.58$, $p=<0.01$) and REM ($r=-0.22$, $p=<0.05$). Moreover, a significant relationship between DET and LF during sleep stage 2 ($r=0.58$, $p=<0.01$) and REM ($r=0.22$, $p=<0.05$) were also found.

Discussion

The present study was undertaken to investigate possible chronic sleep stage-dependent changes in ANS modulation in OSA patients. To our knowledge, this is the first study to

Table 2 Linear and nonlinear HRV indices in sleep stage 2 and REM for OSA and NonOSA groups

	NonOSA		Mild OSA		Moderate OSA	
	Stage 2	REM	Stage 2	REM	Stage 2	REM
SD1, ms	7.2±2.7	7.9±3.2	7.48±2.4	8.1±2.5	7.8±2.9	8.1±2.3
SD2, ms	35.4±16	51.2±26[a]	36.0±13	60.2±26[a]	38.4±16	65.0±29[a]
Lmean (beats)	12.17±2.52	15.88±4.39[a]	12.20±3.08	17.57±3.91[a]	13.61±4.32	16.67±4.32[a]
REC (%)	38.56±5.78	43.25±7.47[a]	37.72±6.95	45.56±5.18[a]	40.57±7.37	45.08±5.94[a]
ShanEn	3.22±0.33	3.46±0.34[a]	3.21±0.36	3.58±0.18[a]	3.34±0.26	3.51±0.20[a]

Data are presented as mean ± SD

OSA obstructive sleep apnea, *SD1* the standard deviation measuring the dispersion of points in the plot perpendicular to the line of identity, *SD2* the standard deviation measuring the dispersion of points along the identity line, *Lmean* mean line length, *REC* recurrence rate, *DET* determinism, *ShanEN* Shannon entropy

[a] Significant differences between stage 2 and REM

reveal an ANS impairment in OSA patients, even during apnea-free sleep periods, and this change is dependent on the sleep stage analyzed.

This main finding was verified by different linear and nonlinear HRV indices among groups in periods free of respiratory events. The moderate OSA group presented higher values of linear (LF and LF/HF) and nonlinear (DET) indices compared to the NonOSA group in both sleep stages analyzed as well as lower values of the linear parasympathetic index (HF), suggesting that this severity level of OSA produces sympathetic hyperactivity. In addition, the mild OSA patients failed to show the expected difference between sleep stages in the LF and LF/HF ratio, as observed in NonOSA patients, which may represent the early onset of autonomic impairment at this level of OSA. Thus, as we hypothesized, ANS modulation may already demonstrate a characteristic of chronic impairment in the early stages (i.e., mild OSA).

A number of studies have shown that OSA has a close relationship with cardiovascular disease [2, 34–36]. In these patients, ANS abnormalities including an increased resting HR, decreased cardiac rhythm activity, and increased sympathetic tone are considered to be involved in the development of cardiovascular diseases [37]. Therefore, the assessment of ANS cardiac modulation in OSA patients has potential clinical utility as, among other things, a means to identify individuals at highest risk for untoward events.

It is known that deleterious changes in cardiovascular function accompany every apnea event [38]. During the apnea episode, a relative bradycardia is observed, while after the event, reconstitution of respiration and a relative tachycardia ensues [39, 40]. Nonetheless, the measurement of HRV during segments with apnea can be difficult because the events, per se, cause dramatic alterations in HRV, which violates the stationary condition required for frequency domain analysis [17]. In this study, we used apnea-free sleep periods for linear and nonlinear HRV analyses, which have been only recently investigated in other chronic conditions such as post-myocardial infarction (MI) [42].

Most of the studies evaluate ECG signals that included apnea and arousal events, and a few studies have analyzed HRV during an apnea-free sleep period. Song and colleagues [20] studied the influence of OSA on HRV, by analyzing time and frequency domain analysis in moderate and severe OSA. These investigators found that the LF/HF ratio, which is closely related to sympathetic nervous system activity, may be affected by the severity of sleep apnea. However, in this study, HR signals were only reported to be free of artifacts, while no detailed information about the HR signal period analyzed was provided.

Vanoli et al. [43] compared frequency domain HRV between post-MI and controls in REM and non-REM sleep. They observed reduced vagal activity following MI in non-REM sleep and pronounced sympathetic activity during REM sleep. In our study, we found similar results in moderate OSA patients, although with distinct methodological differences, specifically, monitoring HR signals without events.

Dingli et al. [18] applied frequency domain HRV analysis to 2-min windowed RRi centered at the end of apneic events and found that HRV results were consistent with SNS enhancement during sleep due to apnea, which may help explain the increased cardiac risk. In a recent study, Jilek and colleagues [19] also demonstrated that patients with OSA presented with sympathetic overdrive not only during phases of hypopnea and obstructive apnea but also in nonapnea intervals, before and after events. Their results also demonstrate higher values for the LF/HF ratio during hypopnea and obstructive apnea episodes.

In mild OSA, we did not observe differences between sleep stage 2 and REM patients by linear HRV indices. This is an interesting result that may be interpreted as an early identification of impaired cardiac ANS modulation since the varying sleep stage response (i.e., stage 2 vs. REM) was expected, as observed in NonOSA subjects. We also did not observe differences in these values when compared to NonOSA subjects, which contrasts from the results observed in the study by Lado et al. [22]. Specifically, they observed that mild and severe OSA subjects presented with lower values of linear indices compared to controls when evaluated throughout the night.

In the moderate OSA group, subjects presented with higher values of indices related to sympathetic predominance and sympathovagal balance (LF and LF/HF ratio) and nonlinear indices during REM sleep compared to stage 2.

Another study [22] calculated HRV indices in 5-min-long intervals to investigate whether there were differences between intervals with and without apnea episodes. Consistent with our results, this study showed that HRV spectral indices in both apneic and normal breathing intervals are statistically different between OSA patients and healthy controls, demonstrating lower HRV in OSA subjects throughout the night. These results contributed to the hypothesis that cardiovascular risk remains constant for OSA patients. One difference in the present study was the additional analysis of nonlinear HRV indices.

In our study, the HRV measurements were made only during apnea-free periods, representing an important methodological difference. Thus, it was possible to demonstrate that independent of the HRV alterations that occur during apnea episodes, there is a chronic change in cardiac ANS modulation in both mild and moderate OSA patients. While these changes were more apparent in moderate OSA, subjects with mild OSA did also present with differences compared to subjects without OSA. Specifically, cardiac ANS modulation in subjects with mild OSA did not respond to different sleep stages in the same way individuals without OSA did. This can be considered useful information for recognition of patients with

OSA who have established or emerging increase in risk for cardiovascular events.

In this context, choosing an apnea-free ECG period for analysis presents an interesting possibility for HRV analysis during sleep, reflecting a more stable condition, which, however, may be difficult depending of severity of OSA. Patients with more severe OSA do not have long event-free periods during sleep, and many have subclinical events that are not scored but are still associated with significant disruptions in cardiac ANS function. In this study, we analyzed the ECG signal from three parts of the night, with 5 min averages corresponding to the stages studied (stage 2 and REM) to improve the HRV analysis of patients. Furthermore, the present study did not include patients with severe OSA, who could present with instability of normal breathing and potential arrhythmias produced by oxygen desaturation, which could be interpreted as a methodological bias.

To our knowledge, some studies have evaluated HRV only by spectral analysis during different sleep stages. Scholz et al. [41] and Cabiddu et al. [42] already demonstrated that in NonOSA subjects, REM sleep is marked for an increased sympathetic modulation observed in HRV spectral analysis. They observed that LF/HF ratio was higher during REM sleep when compared to stage 2 of sleep. In our study, although the mild OSA group presented the same behavior of the other groups in the analysis, we could not see statistical difference within stage 2 and REM. We believed that this finding is important instead that in a relative small number of subjects, we have been able to observe differences. However, in contrast with the present study, Scholz et al. [41] and Cabiddu et al. [42] did not study nonlinear HRV indices, and they did not exclude apnea intervals during the HRV analysis.

In relation to nonlinear analysis, the Poincaré plot SD2 descriptor displayed larger values during REM in all subjects when compared with sleep stage 2. This index is inferred by overall HRV and demonstrated a higher variation in REM sleep in OSA and NonOSA patients. When we applied recurrence plot analysis, we also observed that Lmean, recurrence rate, and Shannon entropy were higher in the REM stage in all subjects as well as the DET.

Among all nonlinear indices, only DET demonstrated intergroup differences, with higher values in REM sleep in moderate OSA subjects compared to the NonOSA group, which can be attributed to overactive sympathetic activation in this moment since we observed a significant and positive relationship between DT and LF. These results suggest that nonlinear HRV may not be as sensitive of an indicator for ANS dysfunction during the earlier stages of OSA compared to linear domain frequency indices.

The nonlinear analysis of HRV can be characterized as random or correlated HR patterns. Thus, two patients could have the same values for RRi, but one could have a very normal, organized HR pattern, and the other could have a highly random and disorganized HR pattern. In this way, nonlinear indices can be useful to detect dynamic changes in HRV in OSA patients [29, 30].

Limitations of study

A limitation of the study was the relatively small sample size, no formal calculation to find the needed number of patients for comparison, and no prior knowledge about precision for HRV nonlinear measurements and skewness of their distribution. Another limitation of this study was the exclusion of severe OSA due to difficulty in obtaining enough HR signals free of events. Moreover, the first-night effect was not considered in this study. Increased sleep latency, decreased overall sleep time, increased wake frequency, and invasion of alpha in non-REM sleep may occur due to first-night effects [43]. However, polysomnography was conducted under the same conditions on all subjects, and thus, first-night effects likely did not influence the comparisons among groups. Another possible limitation is the fact that in this study, we only analyzed the subjects during sleep, and thus, we could not compare HRV values obtained while the subjects were awake. The measure of sympathetic activation during wakefulness in the resting state would be complementary to our analysis as well as the analysis of ANS modulation during other conditions such as physical exercise.

Conclusion

In subjects with OSA, there is a chronic and sleep stage-dependent impairment of linear and nonlinear cardiac ANS modulation. Interestingly, this impairment can be identified in the early stages of the disease.

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References

1. Kapur VK (2010) Obstructive sleep apnea: diagnosis, epidemiology, and economics. Respir Care 55(9):1155–1164
2. Park JG, Ramar K, Olson EJ (2011) Updates on definition, consequences, and management of obstructive sleep apnea. Mayo Clin Proc 86(6):549–555
3. Caples SM, Gami AS, Somers VK (2005) Obstructive sleep apnea. Ann Intern Med 1 142(3):187–197

4. Tufik S, Santos-Silva R, Taddei JA, Bittencourt LRA (2010) Obstructive sleep apnea syndrome in the Sao Paulo epidemiologic sleep study. Sleep Med 11:441–446
5. Resta O, Foschino-Barbaro MP, Legari G, Talamo S, Bonffito P, Palumbo A, Minenna A, Giorgino R, De Pergola G (2001) Sleep-related breathing disorders, loud snoring and excessive daytime sleepiness in obese subjects. Int Obes Relat Metab Disord 25(5): 669–675
6. Gugliemi O, Sánchez AL, Jurado-Gámez B, Buela-Casal G, Bardwell WA (2011) Obesity and sleep quality: the predictors of depression and anxiety in obstructive sleep apnea syndrome patients. Rev Neurol 52(9):515–521
7. Bradley TTD, Floras JS (2003) Sleep apnea and heart failure: part I: obstructive sleep apnea. Circulation 107(12):1671–1678
8. Drager LF, Bortolotto LA, Lorenzi MC, Figueiredo AC, Krieger EM, Lorenzi-Filho G (2005) Early signs of atherosclerosis in obstructive sleep apnea. Am J Respir Crit Care Med 172:613–618
9. Figueroa MS, Peters JI (2006) Congestive heart failure: diagnosis, pathophysiology, therapy, and implications for respiratory care. Respir Care 51(4):403–412
10. Marshall NS, Wong KKH, Liu PY, Cullen SRJ, Knuiman MW, Grustein RR (2008) Sleep apnea as an independent risk factor for all-cause mortality: the Busselton Health Study. Sleep 31(8): 1079–1085
11. Gami AS (2005) Day-night pattern of sudden death in obstructive sleep apnea. N Engl J Med 352(12):1206–1214
12. Narkiewicz K, van de Borne PJ, Montano N, Dyken ME, Phillips BG, Somers VK (1998) Contribution of tonic chemoreflex activation to sympathetic activity and blood pressure in patients with obstructive sleep apnea. Circulation 97:943–945
13. Narkiewicz K, Montano N, Cogliati C, van de Borne PJ, Dyken ME, Somers VK (1998) Altered cardiovascular variability in obstructive sleep apnea. Circulation 98:1071–1077
14. Park DH, Shin CHJ, Hong SCH, Yu J, Ryu SH, Kim EJ, Shin HB (2008) Correlation between the severity of obstructive sleep apnea and heart rate variability indices. J Korean Med Sc 23:226–231
15. Shamsuzzaman AS, Gersh BJ, Somers VK (2009) Obstructive sleep apnea: implications for cardiac and vascular disease. JAMA 290: 1906–1914
16. Gula LJ, Krahn AD, Skanes A, Ferguson KA, George C, Yee R, Klein JG (2003) Heart rate variability in obstructive sleep apnea: a prospective study and frequency domain analysis. Ann Noninvasive Electrocardiol 8:144–149
17. Stein PK, Pu Y (2012) Heart rate variability sleep and sleep disorders. Sleep Med Rev 16:47–66
18. Dingli K, Assimakopoulos T, Wraith PK, Fietze I, Witt C, Douglas NJ (2003) Spectral oscillations of RR intervals in sleep apnoea/ hypopnoea syndrome patients. Eur Respir J 22:943–950
19. Jilek C, Gebauer J, Muders F, Arzt M, Riegger G, Pfeifer M, Wensel R (2012) Polysomnography underestimates altered cardiac autonomic control in patients with obstructive sleep apnea. Herzschr Elektrophys 23:45–51
20. Song MK, Hyun Ha J, Ryu SH, Yu J, Park DH (2012) The effect of aging and severity of sleep apnea on heart rate variability indices in obstructive sleep apnea syndrome. Psychiatry Investig 9:65–72
21. Mäkikallio TH, Tapanaine JM, Tulppo M, Huikuri HV (2002) Clinical applicability of heart rate variability analysis by methods based on non linear dynamics. Card Electrophysiol Rev 6(3):250–255
22. Lado MJ, Mendez AJ, Rodrıguez-Linares L, Otero A, Vila XA (2012) Nocturnal evolution of heart rate variability indices in sleep apnea. Comput Biol Med 42:1179–1185
23. Penzel T, Kantelhardt JW, Lo CC, Voigt K, Vogelmeier C (2003) Dynamics of heart rate and sleep stages in normals and patients with sleep apnea. Neuropsychopharmacology 28(Suppl 1):S48–S53
24. Bradley VV, Giallanza P (2008) Technical review of polysomnography. Chest 134:1310–1319
25. Patil SP (2010) What every clinician should know about polysomnography. Respir Care 55(9):1179–1193
26. Redline S, Budhiraja R, Kapur V, Marcus CL, Mateika JH, Mehra R, Parthasarthy S, Somers VK, Strohl KP, Sulit LG, Gozal D, Wise MS, Quan SF (2007) The scoring of respiratory events in sleep: reliability and validity. J Clin Sleep Med 3(2):169–200
27. Silber MH, Ancoli-Israel S, Bonnet MH, Chokroverty S, Grigg-Damberger HM, Kapen S, Keenan SA, Kryger MH, Penzel T, Pressaman MR, Iber C (2007) The visual scoring of sleep in adults. J Clin Sleep Med 3(2):121–13
28. Piskorsk J, Guzik P (2007) Geometry of the Poincaré plot of RR intervals and its asymmetry in healthy adults. Physiol Meas 28: 287–300
29. Rajendra Acharya U, Paul Joseph K, Kannathal N, Lim CM, Suri SJ (2006) Heart rate variability: a review. Med Bio Eng Comput 44: 1031–1051
30. Webber CL Jr, Zbilut JP (1994) Dynamical assessment of physiological systems and states using recurrence plot strategies. J Appl Physiol 76(2):965–973
31. Voss A, Shulz S, Schroeder R, Baumert M, Caminal P (2009) Methods derived from nonlinear dynamics for analysing heart rate variability. Phil Trans R Soc A 277–296
32. No authors listed (1996) 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. Eu Heart J. 17(3):354–81
33. Malliani A, Pagani M, Lombardi F, Cerutti S (1991) Cardiovascular neural regulation explored in the frequency domain. Circulation 84(2):482–492
34. Kasai T, Bradley D (2011) Obstructive sleep apnea and heart failure: pathophysiologic and therapeutic implications. J Am Coll Cardiol 57:119
35. Punjabi NM, Caffo BS, Goodwin JL, Gottlieb DJ, Newman AB, O'Connor GT, Rapoport DM, Redline S, Resnick HE, Robbins JA, Shahar E, Unruh ML, Samet JM (2009) Sleep-disordered breathing and mortality: a prospective cohort study. PLoS Med 6(8):e1000132
36. Botros N, Concato J, Mohsenin V, Selim B, Doctor K, Yaggi HC (2009) Obstructive sleep apnea as a risk factor for type 2 diabetes. The Am J Med 122:1122–1127
37. Parish JM, Sommers VK (2004) Obstructive sleep apnea and cardiovascular disease. Mayo Clin Proc Aug 79(8):1036–1046
38. Somers VK, Mark AL, Zavala DC, Abboud FM (1989) Contrasting effects of hypoxia and hypercapnia on ventilation and sympathetic activity in humans. J Appl Physiol 67:2101–2106
39. Somers VK, Mark AL, Zavala DC, Abboud FM (1989) Influence of ventilation and hypocapnia on sympathetic nerve responses to hypoxia in normal humans. J Appl Physiol 67:2095–2100
40. Guilleminault C, Poyares D, Rosa A, Huang YS (2005) Heart rate variability, sympathetic and vagal balance and EEG arousals in upper airway resistance and mild obstructive sleep apnea syndromes. Sleep Med 6(5):451–457
41. Scholz UJ, Bianchi AM, Cerutti S, Kubicki S (1997) Vegetative background of sleep: spectral analysis of the heart rate variability. Physiol Behav 62(5):1037–4
42. Cabiddu R, Cerutti S, Viardot G, Bianchi AM WS (2012) Modulation of the sympatho-vagal balance during sleep: frequency domain study of heart rate variability and respiration. Frontiers in physiology 3(45):1–10
43. Vanoli E, Adamson PB, Ba-Lin PGD, Lazzara R, Orr WC (1995) Heart rate variability during specific sleep stages. Circulation 91: 19181922