Acute effects of autoadjusting and fixed continuous positive airway pressure treatments on cardiorespiratory coupling in obese patients with obstructive sleep apnea

Vincenzo Patruno [a,b,1], Eleonora Tobaldini [a,1], Anna M. Bianchi [c], Martin O. Mendez [c,d], Orietta Coletti [b], Giorgio Costantino [a], Nicola Montano [a,*]

[a] Department of Biomedical and Clinical Sciences, University of Milan, Division of Medicine and Pathophysiology, L. Sacco Hospital, Milan, Italy
[b] Division of Pulmonary Rehabilitation, I.M.F.R., Udine, Italy
[c] Department of Electronics, Information and Bioengineering, Politecnico di Milano, Milano, Italy
[d] Faculty of Sciences, Autonomous University of San Luis Potosi, Mexico

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1. Introduction

Obstructive sleep apnea (OSA) is significantly associated with increased cardiovascular morbidity and mortality [1,2]. One of the most quoted potential links between OSA and cardiovascular diseases is thought to be the increased sympathetic drive [3]. Other recognized mechanisms are intermittent hypoxia, metabolic abnormalities, oxidative stress [4], systemic inflammation [5], coagulation abnormalities [6] and endothelial dysfunction [7].

Continuous positive airway pressure (CPAP) is the first choice treatment in OSA patients [8]: it effectively abolishes OSA symptoms and improves cardiovascular outcomes [9]. CPAP is known to reduce nighttime and daytime sympathetic activation [10], as well as arterial pressure [11], inflammatory markers [6], insulin resistance [12] and coagulation factors [13].

The use of autoadjusting-CPAP (APAP) is growing, due to its efficacy in reducing sleep respiratory disorder (mainly apnea–hypopnea index, AHI) and diurnal hyper-somnolence [14], associated with a reduction of the costs of titration [15]. However, contrasting results showed only a marginal benefit of APAP over CPAP in terms of subjective sleepiness [16], as well as a non-superiority of APAP in terms of efficacy, adherence and outcomes [17].

We have previously reported that in severe OSA patients, CPAP and APAP long-term treatments have different effects on cardiovascular risk factors, such as arterial blood pressure, insulin resistance and C-reactive

Abbreviations: AHI, apnea–hypopnea index; APAP, autoadjusting continuous positive airway pressure; BMI, body-mass index; CPAP, continuous positive airway pressure; CT 90, cut-off time 90 (total sleep time with SaO_2 <90%); DAP, diastolic blood pressure; ESS, Epworth Sleepiness Scale; HF, high frequency; HRV, heart rate variability; LF, low frequency; Mean-SaO_2, mean oxygen saturation; Nadir-SaO_2, lower oxygen saturation; ODI, oxyhemoglobin desaturation index; SAP, systolic blood pressure.

* Corresponding author at: Department of Biomedical and Clinical Sciences, L. Sacco Hospital, University of Milan, Via GB Grassi 74, 20157 Milan, Italy. Tel.: +39 0250319875.
E-mail address: nicola.montano@unimi.it (N. Montano).

[1] Both authors equally contributed to the manuscript.

protein [18]. While both treatments were able to reduce respiratory events and inflammation, only CPAP was associated with a significant decrease of systolic and diastolic arterial pressure as well as insulin resistance. Therefore, we could conclude that APAP was not as effective as CPAP in reducing cardiovascular risk factors [19,20]. We hypothesized that the two devices could differently affect cardiovascular autonomic regulation during sleep. In addition, a recent paper reported that CPAP treatment, but not APAP, was able to normalize cardiovascular control [21]. Indeed, CPAP might reduce sympathetic drive not only by improving gas exchange, but also by affecting the cardiorespiratory function.

Therefore, the aim of our study was to investigate the effects of CPAP and APAP treatments on the cardiac autonomic modulation and cardiorespiratory coupling during sleep by means of spectral and cross-spectral analyses of heart rate variability (HRV) in OSA patients.

2. Methods

2.1. Population study

From the patients' record registry of our Sleep Laboratory, we retrospectively selected full-night polysomnographic studies of nineteen consecutive patients with newly diagnosed severe OSA (AHI > 30, diurnal hyper-somnolence: Epworth Sleepiness Scale > 12), with no co-morbidities, and no past treatment for OSA. Patients with an index of PLMs (periodic leg movements) >5 h/sleep were excluded from the study.

All subjects had undergone a diagnostic cardiopulmonary sleep-study (Embletta, Medcare Flaga, Reykjavik, Iceland) in the attended setting of the Sleep Lab in baseline conditions. Apneas (nasal-cannula airflow cessation > 10 s), hypopneas (abnormal respiratory event with at least a 30% reduction in thoraco-abdominal movement or airflow as compared to baseline lasting at least 10 s, and with >3% oxygen desaturation), oxygen desaturations (drops in SaO_2 > 3%), SaO_2 mean, SaO_2 nadir and CT 90 (total time of SaO_2 < 90%) were evaluated, according to the latest AASM recommendations [22]. The AHI refers to the number of apneas and hypopneas per hour of recording. ODI refers to the number of SaO_2 drops >3% from baseline.

ECG sampling rate was 128 Hz while respiration was sampled at 32 Hz.

BP was taken at the end of PSG using a manual sphygmomanometer with the participant resting supine for 5 min in a quiet, climate-controlled room with low lighting, using the first and fifth Korotkoff sounds. The second and third systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were averaged.

2.2. CPAP titration

Fixed-CPAP titration was performed in the Sleep Laboratory using a standardized polysomnography (PSG; Heritage Grass, Astro-Med, East Greenwich Ave., West Worwick, RI, USA).

We recorded EEG (F4-M1, C4-M1, O2-M1), EOG (E1-M1, E2-M2), EMG (Chin, leg-l, leg-r), EKG, flow via nasal pressure-transducer, thoracic and abdominal effort via inductive plethysmography (RespiTrace), pulse oximetry and snoring sensor. Initial CPAP pressure was set at 4 cmH_2O and then increased progressively by increments of 1 cmH_2O until obstructive apneas, hypopnea, snoring and flow limited breathing associated with arousals disappeared. Obstructive events were identified by the presence of increased chest–abdominal movements and/or paradoxes associated with abolition or decrease in instantaneous flow. Each titration procedure was obtained with the subjects reaching REM sleep and sleeping supine.

After CPAP titration, all subjects were assigned to receive either a fixed-level (Autoset T, ResMed, North Ryde, Australia, in fixed mode) CPAP or an autoadjusting CPAP device (the same device but in auto mode). In the latter mode, the device works administering a variable CPAP levels, starting from a minimum of 4 cmH_2O, and increasing pressure after automatic detection of hypopnea or apnoea (evaluated by reduction or absence of flow signal, respectively). As unobstructed breathing is resumed, pressure decreases and so on. In auto mode, the instruments were set to deliver pressure levels until the maximum of 15 cmH_2O. In fixed mode, the instruments were set at the level obtained during the titration study.

2.3. Polysomnographic study under positive airway pressure treatment

At the end of the first week of the training period either under APAP or CPAP treatment, all subjects repeated a full-night attended polysomnographic (PSG) study in the Sleep Laboratory.

The sleep studies were blindly scored by an expert sleep technician according to standard international criteria [22]. From each PSG, we extract the following data: the amount of non-REM 2 (N2), non-REM 3 (N3) and REM sleep (expressed as % of total sleep time, TST), the arousal index (per hour of sleep), SpO_2 mean, SpO_2 nadir, TC90 (time with SpO_2 <90%), ODI (oxyhemoglobin desaturation index, with drop >3% on baseline).

2.4. Control group

We also collected and analyzed the PSG studies of seven consecutive obese subjects, without any overt cardiovascular, respiratory or systemic disease, which had referred to our Sleep Lab because of snoring. A PSG study was performed to exclude any sleep disorders and all the subjects had a PSG study negative for OSA (AHI < 5). This Control group was matched for BMI, gender and arterial blood pressure with the OSA group.

2.5. Spectral analysis

ECG and respiratory traces were derived from PSG recordings and then divided into Wake (W), N1, N2, N3 and REM stages. For each sleep stage, we analyzed a minimum of 5 segments (range 5–8) lasting 180 s. For all the three groups, we considered the first two complete NREM–REM sleep cycles. Traces were carefully checked to avoid any ectopic beats, arousals, leg movements or body artifacts. Only segments characterized by stable breathing were considered for the analysis.

RR interval time series were extracted from the ECG signal using an algorithm that implements a parabolic interpolation in the round of the R peak. Stationary RR interval sequences of 180–350 beats were selected. The respiratory signal extracted from thorax movements was resampled in correspondence of each R peak, in order to obtain a respirogram. Autoregressive monovariate batch analysis was applied to tachogram and respirogram for the calculation of the spectral components of interest and coherence function [23,24].

On the heart period time series, three main oscillatory components can be identified: very low frequency (VLF, frequency band below 0.04 Hz), low frequency (LF, frequency band bounded between 0.04–0.15 Hz, index of sympathetic modulation) and high frequency component (HF, synchronous with respiration and index of vagal modulation).

The power of the spectral components was expressed in absolute as well as normalized units, calculated as follow: LFnu = LF absolute units / (total power − VLF) and HFnu = HF absolute units / (total power − VLF). LF/HF ratio was also calculated and considered as a global index of the sympathovagal balance.

We also applied the bivariate autoregressive analysis to evaluate how the two signals, ECG and respiration were correlated to each other: thus, we calculate the maximum coherence at both LF and HF bands (LFC and HFC respectively). The maximum coherence between HF_{RR} and respiration (K^2) can be used as a surrogate index of cardiorespiratory coupling [25].

2.6. Statistical analysis

Data are expressed as mean ± SD. Statistical analyses were performed using Sigma Stat 3.11 (Jandel Scientific). Repeated measures ANOVA was used to evaluate spectral variables during sleep stages within groups. A two-way ANOVA analysis was used to compare spectral indexes during sleep stages between treatments. Bonferroni's post-hoc test analysis was applied if significant statistic differences were found. A p value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline measurements

The final analyses were thus carried out in three groups: APAP group (APAP, n = 9), CPAP group (CPAP, n = 10) and Control group (CON, n = 7).

Table 1 illustrates the characteristics of the study populations. Age, sex distribution, BMI, heart rate (HR), systolic and diastolic arterial blood pressure (SAP and DAP) were similar in the three groups. The two OSA groups did not differ at baseline in terms of ESS and severity of OSA (i.e. AHI, ODI, SaO_2 mean, SaO_2 nadir, CT 90, and ESS). Finally, CPAP titration values were similar in the APAP and CPAP groups (11 ± 2 cmH_2O and 10 ± 2 cmH_2O, respectively).

3.2. Effects of treatments

Data are reported in Table 2. Compliance to therapy during the one-week in-hospital training was similar in APAP and CPAP groups. During therapeutic PSG, APAP and CPAP patients showed similar sleep stages profile, as shown in details in Table 2.

Both APAP and CPAP had the same efficacy in reducing AHI (4.6 ± 1.4 and 3.4 ± 1.1, respectively), ODI (3.3 ± 0.8 and 3.0 ± 0.7, respectively), and in improving mean SpO_2 (94 ± 0.8% and 94 ± 0.9%, respectively) and sleepiness symptoms.

3.3. Spectral and cross-spectral analyses of HRV

Table 3 summarizes the results of spectral analysis of HRV for the three groups throughout the different sleep stages.

Comparing the three groups, during wake no differences in total HRV and LF/HF ratio, index of the sympathovagal balance, were detected between APAP, CPAP and Controls. However, both LF power and LF/HF ratio (Fig. 1), indices of sympathetic modulation, were significantly higher in all sleep stages in APAP compared with those in CPAP and Controls. CPAP and Controls were similar in terms of spectral profile throughout the night.

Considering the changes of spectral indices during the night, we found that LF/HF ratio progressively decreased from wake to N3 and then it returned to wake levels during REM, similarly in CPAP and Controls, as expected. However, in the APAP group, this index of the sympatho-vagal balance decreased in N3 compared with that in N2 and then increased again during REM, remaining constantly higher compared with those of CPAP and Controls across the night (see Fig. 1).

Considering the differences among the groups, coherence between ECG and respiration (K^2–HF) was significantly decreased in the APAP group during all the sleep stages compared with CPAP and Control groups (Fig. 2, Table 3). As to the differences between sleep stages, K^2–HF increased from W to N2 and N3 while it decreased in REM sleep in all the three groups.

Table 1
Baseline characteristics of the study population.

	APAP group (n = 9)	CPAP group (n = 10)	Control group (n = 7)
Patients (M–F)	9 (8–1)	10 (7–3)	7 (5–2)
Age (years)	45 ± 10	50 ± 12	48 ± 10
BMI (kg/m^2)	37 ± 4	36 ± 2	36 ± 1
ESS	13 ± 1*	13 ± 1*	3 ± 2
AHI (n°/h)	47 ± 15*	46 ± 15*	2 ± 2
ODI (n°/h)	42 ± 15	38 ± 13	2 ± 2
MeanSaO_2(%)	90 ± 3	89 ± 5	95 ± 2
NadirSaO_2(%)	72 ± 11	70 ± 12	91 ± 3
CT 90 (%)	43 ± 28	55 ± 29	0.4 ± 0.6
SAP (mmHg)	124 ± 9	126 ± 10	128 ± 10
DAP (mmHg)	76 ± 5	80 ± 4	75 ± 7
Neck circumference (cm)	43.6 ± 2.6	42 + 3.1	40.8 ± 5.3

Data are expressed as mean ± SD unless otherwise indicated. Abbreviations: BMI: body-mass index; ESS: Epworth Sleepiness Scale; AHI: apnea/hypopnea index; ODI: oxyhemoglobin desaturation index; mean-SaO_2: mean oxygen saturation; nadir-SaO_2: lower oxygen saturation; CT 90: cut-off time 90, i.e. total sleep time with SaO_2 <90%; HR: heart rate; SAP: systolic arterial pressure; DAP: diastolic arterial pressure.
* $p < 0.05$ vs Controls.

Table 2
Sleep and sleep–breathing parameters during therapeutic PSG after one-week training.

	APAP group (n = 9)	CPAP group (n = 10)
Compliance (h/night)	6.9 ± 4.2	7.2 ± 3.3
AHI (no./h)	4.6 ± 1.4	3.4 ± 1.1
ODI (no./h)	3.3 ± 0.8	3.0 ± 0.7
Mean SaO_2(%)	94 ± 0.8	94 ± 0.9
N1(%TST)	5.7 ± 2.8	7.2 ± 2.8
N2 (%TST)	42.6 ± 11.9	37.4 ± 8.7
N3 (%TST)	21 ± 3.3	31.6 ± 12
REM (%TST)	30.7 ± 8.3	22.9 ± 3.9
Arousal index	5.7 ± 2.3	3.5 ± 3.3

Data are expressed as mean ± SD. Abbreviations as in Table 1.

4. Discussion

The major finding of the present study is that APAP treatment was not as effective as CPAP in reducing the sympathetic modulation during sleep in OSA patients. Secondly, the different effect of the two

Table 3
Spectral and cross-spectral parameters during wake and sleep in the three groups, APAP, CPAP and Controls.

	APAP (n = 9)	CPAP (n = 10)	Controls (n = 7)
Wake			
Mean RR (ms)	1042 ± 34	905 ± 45	924 ± 36
Variance (ms^2)	1422 ± 910	1506 ± 320	2325 ± 510
LFnu	39 ± 6	34 ± 4	26 ± 6
HFnu	47 ± 7	54 ± 5	66 ± 7
K^2–HF	0.73 ± 0.04	0.84 ± 0.03	0.91 ± 0.04
N2			
Mean RR (ms)	1046 ± 14	928 ± 13	906 ± 11
Variance (ms^2)	1623 ± 1055	1040 ± 108	2115 ± 105
LFnu	53 ± 2*,#	33 ± 2	28 ± 2
HFnu	46 ± 3	64 ± 2	58 ± 2
K^2–HF	0.88 ± 0.01*,#	0.94 ± 0.01	0.91 ± 0.01
N3			
Mean RR (ms)	1094 ± 14	934 ± 14	906 ± 18
Variance (ms^2)	1490 ± 110	1030 ± 95	1420 ± 210
LFnu	38 ± 2*,#	23 ± 2	21 ± 3
HFnu	51 ± 2	70 ± 3	68 ± 3
K^2–HF	0.89 ± 0.01*,#	0.94 ± 0.01	0.94 ± 0.01
REM			
Mean RR (ms)	997 ± 13	982 ± 14	925 ± 16
Variance (ms^2)	2930 ± 305	3010 ± 290	3025 ± 410
LFnu	53 ± 3*,#	44 ± 3	43 ± 4
HFnu	33 ± 3	44 ± 3	46 ± 3
K^2–HF	0.63 ± 0.02*,#	0.80 ± 0.02	0.78 ± 0.02

Data are presented as mean ± SE. Abbreviations: LF: low frequency; HF: high frequency; K^2: coherence; nu: normalized units.
* $p < 0.05$ vs CPAP group.
# $p < 0.05$ vs Control group.

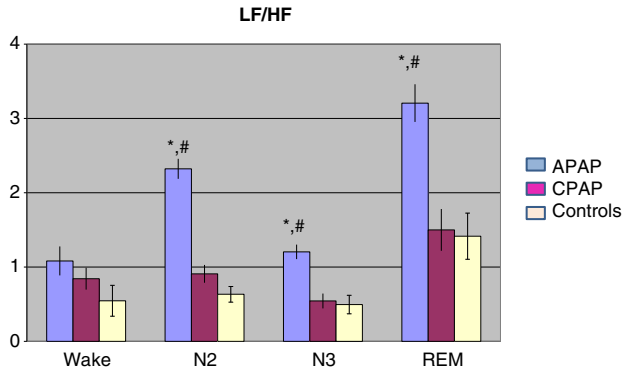

Fig. 1. Sympathovagal balance of the three groups during sleep stages N2, N3 and REM. LF/HF is lower in CPAP and Control groups compared with that in APAP group during all the sleep stages. *$p < 0.05$ vs CPAP; #$p < 0.05$ vs Controls.

treatments on cardiac autonomic regulation seems to be related to a different cardiorespiratory coupling during sleep.

Previous studies on sympathetic neural activity in OSA patients proved that sympathetic activation increases during the course of the apneas, persists during daytime and contributes to the increased cardiovascular risk in these patients [2,26].

In OSA patients, CPAP therapy is known to decrease sympathetic activity during sleep and daytime, probably by eliminating intermittent nocturnal hypoxemia and post-obstructive arousals, which are responsible of sleep disruption [8]. The therapy of OSA with autoadjusting device is also known to eliminate obstructive respiratory events and associated with intermittent nocturnal hypoxemia [27].

The qualitative analysis of sleep studies showed that the two groups, APAP and CPAP, had similar compliance to therapy and sleep stages profile, as well as a similarly reduced AHI and an improved mean SpO_2 and sleepiness symptoms. These results suggest that the two devices are equally effective in OSA patients in ameliorating sleep–breathing parameters. However, the analysis of HRV revealed that APAP and CPAP differently affect the autonomic cardiac control and the relation between heart period and respiration, i.e. the cardiorespiratory coupling.

In fact, when considering the differences between the three groups, the LFnu and the LF/HF ratio were significantly higher in the APAP group compared with those in CPAP and CON during all the sleep stages, suggesting a predominant sympathetic modulation regulating autonomic cardiac control. This different effect on autonomic profile is in line with our previous data, which showed that CPAP, but not APAP, was capable of affecting the cardiovascular risk factors, such as hypertension, inflammation and insulin resistance [18].

We hypothesize that this fact may be due to the different modalities of action between CPAP and APAP devices. In fact, while in CPAP there is one level of positive pressure delivered to fix the opening of the upper airways, on the contrary, APAP is characterized by a continuous "waxing and waning" of expiratory positive pressure around the critical pressure level of the upper airway to minimize the whole pressure delivery during the night [27]. In other words, the APAP device, during the pressure delivering decreasing step, may tolerate some brief flow-limitation events while, during the pressure delivery increasing step, may predispose to "overshooting" breathing efforts, even though without criteria for respiratory event scoring.

Considering this important difference, we assumed that APAP could affect the cardiorespiratory coupling in a different way. In fact, our results showed that, although the level of coherence in the three groups was significant, being greater than 0.5 in the HF band, it was considerably lower in the APAP group compared with those in CPAP and CON groups in both LF and HF bands. This effect can be explained by the fact that in APAP device, increasing and decreasing of the inspiratory flow, may result in shortening or lengthening of neural inspiratory time [28,29].

We hypothesized that this fine-tuning alteration of the respiratory pattern could interfere with the physiological setting of respiration during sleep, possibly contributing to maintain a higher level of sympathetic modulation during sleep and explain the lack of reduction in arterial pressure and insulin resistance induced by APAP treatment. This sympathetic overactivity can be related to the alteration of the breathing pattern during sleep (i.e., inspiratory/expiratory time ratio) induced by

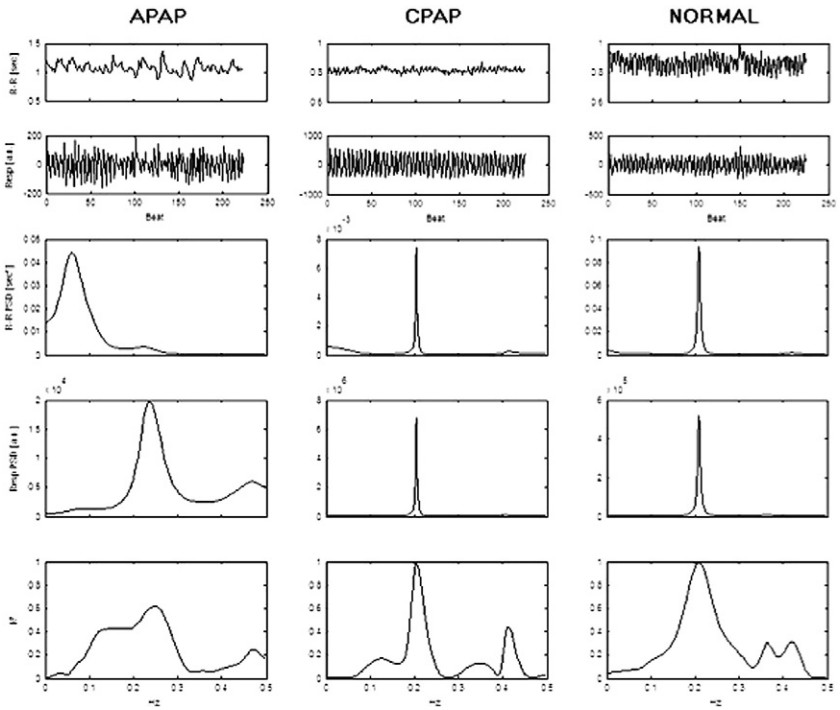

Fig. 2. Spectral and cross-spectral analysis of HRV signal and respiration during N3 in one patient under APAP, one under CPAP and in a Control subject. Notice that, accordingly to the well-known parasympathetic predominance during N3, the LF component of RR, index of sympathetic modulation, is almost undetectable in CPAP and normal, while it is still predominant in APAP. Respiration is extremely irregular and coherence between HF of RR and respiration is lower in APAP.

APAP treatment, which may subsequently lead to a reduction in baroreflex sensitivity. It has been established that the gain of baroreflex activation depends on the phase of breathing, and the cardio-inhibitory response to baroreflex stimulation is smaller during inspiration, due to a reduction in vagal cardiac motoneuron responsiveness [30]. Thus, the prolongation of inspiratory time during flow-limited respiratory events could lead to a reduction in baroreflex sensitivity and consequently to an autonomic sympathetic predominance. However, as we did not analyze the changes in the inspiratory/expiratory time ratio, this hypothesis still needs further evaluation. Another possibility is that the changes in intrathoracic pressure during brief flow-limited respiratory events may lead to a reduction in baroreflex sensitivity as a consequence of the concomitant activation of the Bainbridge reflex, which is elicited by activation of atrial stretch receptors due to an increased venous return, such as those accompanying the increasing respiratory efforts [31].

Finally, we can speculate that this respiratory variability is an "intrinsic" characteristic of APAP treatment, depending on the peculiar algorithm regulating the trigger of increased pressure and the timing of increased/decreased phases. However, it is worth noting that in a recent study, Karasulu et al. found similar results using a different APAP device [21].

4.1. Limitations

The present study has few limitations. First, the patients were not randomized to CPAP or APAP treatment but, conversely, they were retrospectively selected based on a new diagnosis of severe OSA. Furthermore, the present results are not transferable to other autoadjusting devices because another autoadjusting device, based on a different algorithm, may minimize brief flow-limited events as well as overshooting breathing.

5. Conclusions

The use of a specific APAP treatment in OSA patients is associated with a predominant cardiac sympathetic modulation during sleep when compared with CPAP and Control groups. This effect is likely to be associated with important changes of cardio-respiratory coupling, suggesting a high degree of variability of respiratory efforts interacting with the HRV signal. Thus, a reduction in cardiopulmonary coupling even in the absence of apneas and oxygen desaturations seems to be able to increase cardiac sympathetic drive during sleep.

Conflict of interests

Each author has no financial or other potential conflicts of interest to disclose.

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