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Original article

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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ABSTRACT

Background: Treatment with positive airway pressure devices improved signs and symptoms of obstructive sleep apnea syndrome (OSA); however, auto-adjusting positive pressure (APAP) device was not as effective as continuous positive airway pressure (CPAP) in reducing arterial blood pressure and insulin resistance. The role played by autonomic cardiac regulation remains to be clarified.
We aimed to test the effects of CPAP and APAP on autonomic regulation and cardiorespiratory coupling during sleep.
Methods: We retrospectively analyzed full-night polysomnographic studies. 19 patients newly diagnosed with severe OSA (AHI > 30) and 7 obese subjects without OSA (CON) were enrolled. Each OSA subject was assigned to CPAP or APAP treatment and underwent a sleep study after 1 week of treatment. Spectral and cross-spectral analyses of heart rate variability (HRV) and respiration were performed to assess autonomic profile and coherence (K^2) between respiration and HF oscillation during sleep in CPAP, APAP and CON groups.
Results: In CPAP and CON, LFnu and LF/HF, markers of sympathetic modulation, decreased from N2 to N3 and increased during REM sleep ($p < 0.001$), while in APAP group, sympathetic modulation was significantly higher compared with those of CPAP and CON during all sleep stages. K^2 values were lower in APAP compared with those in CPAP and CON.
Conclusion: APAP treatment was characterized by a greater sympathetic activation and it was associated with a lower cardio-respiratory coupling compared with CPAP. This might account for the different effects on cardiovascular risk factors induced by the two treatments.

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.

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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].