Different Effects of CPAP and APAP Therapies on the Autonomic Nervous System in OSA Patients

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Abstract

Obstructive Sleep Apnea (OSA) is a common sleep disorder which causes the reduction of the upper airways muscular tone collapsing the same. This disorder is associated with bad sleep quality leading to excessive daytime sleepiness and increased risk of cardiovascular diseases. The main therapies are the Continuous Positive Airways Pressure (CPAP) and Auto-CPAP which are devices that force a positive pressure in the upper airways in different manner. The aim of this work was to evaluate the different response of the cardiovascular autonomic nervous system to the therapies. We applied mono and bivariate autoregressive time invariant spectral estimation methods to the Heart Rate Variability and respiratory signals coming from polisomnography executed on 12 patients: 4 during APAP, 4 during CPAP and 4 in basal condition as group of control. We principally found significant differences between groups in HRV variance, low-to-high frequencies ratio (LF/HF) and different coherence levels between signals. These preliminary results seem to suggest different effects of the therapies, with a greater sympathetic activation for APAP group and a better efficacy of CPAP in bringing back pathological condition closer to normality.

1. Introduction

In normal condition everyone usually incurs in some apneic events during sleep every night. However, in about 5% of the population, this situation grows to pathological levels becoming dangerous for the health. Most of this population is affected by the Obstructive Sleep Apnea (OSA) syndrome which is a respiratory disorder characterized by the reduction of the muscular tone of the upper airways and the consequent interruption of the air-flow toward lungs. OSA is associated with daytime sleepiness and its chronic happening results an independent risk factor for cardiovascular diseases such as hypertension, congestive heart failure and arrhythmias. The most common treatments for OSA are the CPAP therapy, which forces a pre-fixed air pressure level on the upper airways, and the APAP, which auto-set the given pressure level to the upper airways correspondingly to the obstruction severity, giving a better compliance to the patient than CPAP. Both methods provide similar clinical results in the reduction of some parameters as Apnea-Hypopnea index, oxygen saturation and reduction of sleepiness [1]. Nevertheless, APAP patients did not show a reduction of blood pressure values and other hypertension markers after three month of treatment as CPAP does [2]. The cardiovascular functions are largely controlled by the Autonomic Nervous System (ANS) whose activity may be evaluated non-invasively by spectral decomposition of the Heart Rate Variability (HRV) signal. In fact, it has been found out that spectral components in the band between 0.04 and 0.15 Hz, called Low Frequencies (LF), represent mainly sympathetic activity; frequency components between 0.15 and 0.45 Hz are indication of parasympathetic effects and are strongly affected by the respiratory process. So their ratio, the LF/HF index is considered as an indicator of the simpatho-vagal balance of the ANS [3-4]. Some non parametric (i.e. Fourier Transform, Time-Frequency Analysis and Wavelets) and parametric (i.e. Autoregressive models, Time-Varying Autoregressive models) approaches have been applied to the HRV with the purpose of evaluating the behavior of the ANS in different conditions and pathologies, some examples are shown in [5-9]. Each approach presents advantage and disadvantages depending on the time series characteristics and the information that is required to extract from the signal. The autoregressive Batch Analysis (BA) presents fine features when it is necessary to decompose a stationary signal in its different frequency components with very low computational cost. In its simplest form (monovariate) BA is usually applied to detect HRV spectral components. In its bivariate form it allows to evaluate how two signals are correlated each other. In the present study it is used for quantifying the frequency correlation between R-R intervals and respiratory signals.

In this study we applied autoregressive BA, in both mono and bivariate form, to R-R intervals and chest respiratory signal in order to evaluate the response of the ANS in group of patients with OSA subdue to CPAP and APAP therapies.

2. Methods

Data come from polisomnographic registration from 12 males and females patients (4 CPAP, 4 APAP and 4 group of control), matched for age and BMI (48±5 years, 35±2 Kg/m^2). Their average Apnea Hypoapnea Index (AHI), evaluated during the eventual therapy, is always lower than the pathological limit fixed at 7-8 AHI per hour: 3.6 in APAP, 1.4 in CPAP and 1.3 in overweight with no OSA. The registration was performed after one night of adaptation in the same conditions of the domiciliary therapy, meaning same diet, drugs and environmental condition. The polygraph was a Grass Telefactor and the signals were recorded at a sampling rate of 100 Hz. *Protocol:* Registrations obtained with the polysomnography were divided in the typical Wake, 2, 3, 4 and REM sleep stages by experts whose applied Rachtshaffen and Kales rules. Then the R-R intervals were extracted from ECG using an own developed algorithm, which implements a parabolic interpolation in the round of the R peak to reduce the low sampling rate error [6]. Stationary sequences of the R-R intervals between 180 to 450 beats were searched to guarantee the correctness of the analysis through Autoregressive model. The respiratory signal extracted form thorax movements was re-sampled in correspondence to each R peak in order to obtain the respirogram. Batch analysis mono and bivariated were applied at the respirogram and tacogram for the calculation of the spectral components of interest and coherence function. Applying the monovariate BA to the tacogramm were obtained the following spectral indexes: Total Power (TP), Very Low Frequencies Power in 0.003 – 0.04 Hz (VLF), Low Frequency 0.04 – 0.15 Hz (LF) and High Frequency 0.15 – 0.5 Hz (HF) components in absolute and normalized units; Low to High frequency ratio (LF/HF) was also computed. The indexes computed with the bivariate BA applied to tacogram and respirogram were: maximum Coherence at both LF and HF (LFC and HFC respectively), frequency of maximum coherence at LF and HF (FMC in LF and HF) [10]. *Data Analysis:* One-Way ANOVA test were performed to compare indexes grouped by therapies and Repeated Measure ANOVA to evaluate the indexes grouped by sleep stages. Bonferroni's post hoc test analysis were performed if significant statistic differences were found. Values of $P<0.05$ were considered statistically significant.

3. Results

Table 1 shows the results of the statistically significant indexes (mean ± standard error) for all the group of patients. Variance of the HRV signal is significantly greater in APAP group in all the sleep stages, and there are no statistic differences between CPAP and normal subjects. It can also be noticed that the average value of this index shows a "trend" that varies according to the sleep stage. It is lower in the slow wave sleep and is greater in the REM sleep.

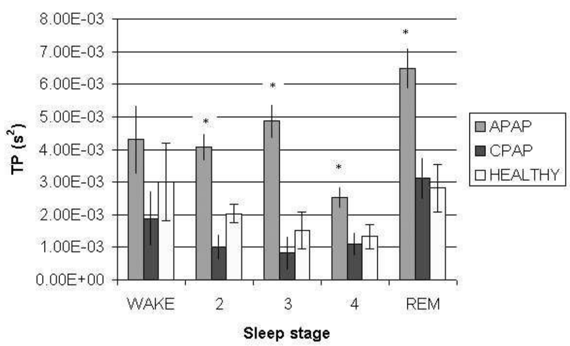

Fig 1: Total Power of the HRV signal obtained from the APAP, CPAP and healthy subjects. Values reported are mean±SE. An * means statistical difference between the selected group and the healthy subjects.

The LF/HF ratio, shows greater values in APAP patients, caused by greater power level in the range between 0.04 and 0.15Hz. It has also a characteristic trend which shows lower power ratio in the deep sleep stages and greater in REM phase, also greater than Wake levels.

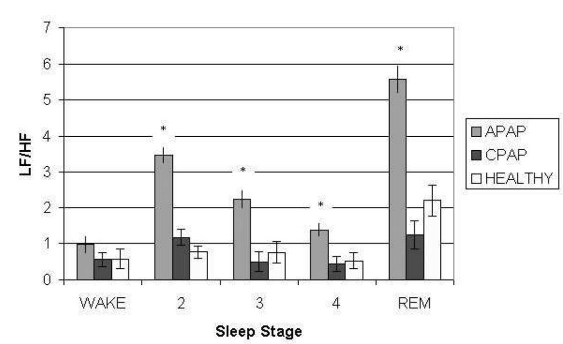

Fig 2: LF/HF ratio in APAP, CPAP and healthy subjects. Values reported are mean±SE An * means statistically difference between the selected group and the healthy subjects.

TABLE I

Table 1. Index obtained applying autoregressive mono e bivariate batch analysis in health overweight subjects and patients subdue to APAP ands CPAP therapy.

Subjects	Index	Stage WAKE	Stage 2	Stage 3	Stage 4	Stage REM
	Mean R-R (ms)	1112±39	1128±14*	1129±16*	1095±22*	1080±13*
	TP (ms^2)	4311±1056	4066±412*	4863±526*	2525±336	6495±625*
	LF/HF	0.979±0.243	3.487±0.234*	2.238±0.277*	1.386±0.201*	5.578±0.388*
APAP	LFC	0.320±0.055	0.191±0.026*	0.201±0.030*	0.103±0.037*	0.160±0.026*
	HFC	0.617±0.079*	0.747±0.033*	0.660±0.048*	0.659±0.037*	0.496±0.040*
	FMC in LF (Hz)	0.088±0.010*	0.100±0.005*	0.091±0.007*	0.094±0.007*	0.096±0.006
	FMC in HF (Hz)	0.296±0.020	0.278±0.006*	0.275±0.010*	0.278±0.011*	0.306±0.010*
	Mean R-R (ms)	979±31	1034±13*	1034±16*	1017±23*	1059±14*
	TP (ms^2)	1879±847	1017±388	826±526	1111±354	3109±633
	LF/HF	0.563±0.195	1.173±0.220	0.504±0.277	0.442±0.211	1.241±0.393
CPAP	LFC	0.242±0.044*	0.219±0.025*	0.220±0.030*	0.210±0.039*	0.247±0.027
	HFC	0.721±0.063	0.908±0.031	0.892±0.048	0.908±0.039	0.649±0.040
	FMC in LF (Hz)	0.088±0.008*	0.108±0.005*	0.105±0.007*	0.116±0.007	0.112±0.006
	FMC in HF (Hz)	0.263±0.016	0.253±0.006*	0.265±0.010*	0.254±0.011	0.279±0.010*
	Mean R-R (ms)	980±44	881±10	899±18	898±24	895±16
	TP (ms^2)	3000±1197	2034±284	1517±570	1324±364	2815±722
	LF/HF	0.575±0.275	0.767±0.161	0.760±0.300	0.523±0.218	2.201±0.448
HEALTHY	LFC	0.456±0.055	0.884±0.022	0.953±0.052	0.974±0.040	0.783±0.046
	HFC	0.923±0.079	0.884±0.022	0.953±0.052	0.974±0.040	0.783±0.046
	FMC in LF (Hz)	0.138±0.010	0.136±0.004	0.145±0.007	0.137±0.008	0.108±0.007
	FMC in HF (Hz)	0.249±0.020	0.205±0.004	0.217±0.011	0.226±0.011	0.214±0.011

Data are presented as mean ± SE. TP : Total Power, LF/HF : Low to High frequency ratio, LFC : LF maximum level of Coherence, HFC : HF maximum level of Coherence, FMC : Frequency of Maximum Coherence, APAP : Automatic Positive Airways Pressure, CPAP : Continuous Positive Airways Pressure, * statistical difference of either APAP or CPAP patients respect the healthy subjects, $p<0.05$;

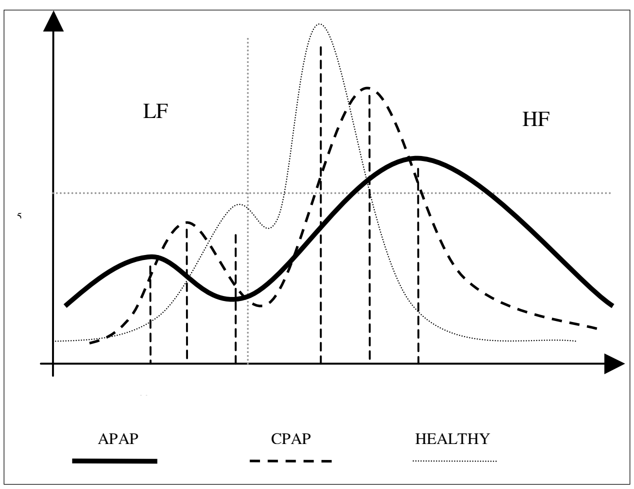

Fig 3: draft of the coherence trend in the APAP, CPAP and healthy subjects obtained with the bivariate analysis between the HRV and the chest respiratory signal. LF is the band between 0.04 and 0.15 Hz and HF the frequencies component between 0.15 and 0.45 Hz. Values over 0.5 means significant coherence.

The data obtained from bivariate analysis display a behavior shown in Fig 3 that qualitavely represents the coherence between tachogram and respirogram in the three groups during slow-wave sleep. There are no statistic differences between groups, neither in coherence level nor in frequency of maximum coherence, but it can be noticed that the greatest coherence level between HRV and the chest respiratory signal is obtained in healthy subjects, followed by CPAP patients' and APAP's in both LF and HF. Moreover, the maximum coherence peaks of healthy subjects are closer in frequency, seeming a single bell centered at 0.15 Hz, while the behavior of CPAP and APAP patients shows peaks separated.

4. Discussion and conclusions

We worked on a pilot population of patients in order to assess the CPAP and APAP therapies effects toward the autonomic nervous system in subjects with OSA. The main findings were: the group with CPAP presented similar values to the control subjects of both the total power and the sympatho-vagal balance indexes, the APAP group showed a greater increment in the LF/HF ratio than normal and CPAP groups, and finally the subjects treated with CPAP presented a similar coherence between the R-R intervals fluctuations and respiratory signal ones than the normal subjects in all the sleep stages.

The HRV indexes obtained by the time-invariant monovariate analysis showed significant greater values in TP and LF/HF for APAP group (Table 1), evidencing a major sympathetic activation [3-4]. Thus, nevertheless the APAP therapy is able to reduce the sleepiness levels, number of apneas during sleep, and other variables [1], this therapy seems to maintain some risk of heart failure and other disease produced by a permanent hypertension condition. In addition, the typical patterns of reduction of all the spectral indexes in the sleep phase 3-4 and the overshoot of them in the REM ones, are tracked by both therapies [4].

Moreover the results obtained with the bivariate analysis suggest other interesting indications. In all groups there is a significant level of coherence greater than 0.5 in the HF band, between chest respiratory signal and R-R intervals fluctuations, meaning that the respiratory mechanism seems to work correctly. But in APAP population we found that the coherence level is lower than normal and CPAP groups in both LF and HF. Those results could suggest that the APAP device influences the patients' breathing and consequently the whole respiratory system, uncoupling the normal chronobiological courses among the various rhythmical physiological systems during deep sleep (Fig 3) [11]. In other words, the coherence level detected in CPAP and normal subject seems to be distributed around a single peak, centered on the respiratory frequency which mean that amplitude is close to 1. In APAP, instead the coherence seems to be distributed into two peaks, that indicate a synchronization both at the HF and at LF. In addition the peaks have lower levels, indicating a lower degree of coupling. It is worth noting that this could be a typical reaction to the not regular air pressure level exerted by the APAP device on the upper air ways. This is extremely evident after a frequency analysis of the respiratory signal, which is spread on the whole frequency axis.

These observations could be considered as a possible index of an induced hyper-activation of the sympathetic nervous system of APAP patients due to an irregular respiratory effort, and this could be a possible cause of the general inflammatory state detected in recent studies about the long term effects of this OSA therapy [2]. Moreover, the CPAP induces a kind of physiological function closer to the one detected on normal subjects and seems to be a preferable therapy for this syndrome.

In conclusion in this work we applied mono and bivariate time-invariant methods of spectral estimation, in a pilot group of healthy subjects and patients that suffer OSA treated with either CPAP or APAP therapies, in order to evaluate the behavior of the autonomous nervous system at the different therapies. On the basis of our results, we found an hyper-activation of the cardiovascular autonomic nervous system of APAP patients due to irregular respiratory efforts that interact with the HRV signal. So CPAP therapy seems to be a preferable treatment for OSA patients.

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