

# Acute response to 7-day therapy with CPAP in patients with moderate to severe obstructive sleep apnea and cardiac arrhythmia

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## ABSTRACT

**Introduction:** Obstructive Sleep Apnea (OSA) has been associated with an elevated risk of cardiac arrhythmia. Continuous positive airway pressure (CPAP) is the selected treatment for moderate to severe OSA and could improve arrhythmias in the long term. However, the acute effect of CPAP has not been studied in detail. **Methods:** We conducted a prospective study with 25 patients with moderate to severe OSA diagnosed by home respiratory polygraphy (RP) and arrhythmia and/or pauses in 24-hour Holter ECG. We analyzed inflammatory parameters and the rate of arrhythmias/pauses after 7 days of auto-adjusting CPAP. **Results:** 92.5% of the patients were men with a mean age of  $61.7 \pm 1.9$  years. Body mass index (BMI) was  $59.5 \pm 2.2$  kg/m<sup>2</sup>, with a mean apnea hypopnea index (AHI) of  $37.7 \pm 3.8$  events/hour (ev/h), and a residual AHI (AHIr) of  $5.3 \pm 0.53$  ev/h. After short treatment with CPAP we observed a tendency to improvement in both the severity and number of ventricular extrasystoles (VE) ( $1595.0 \pm 850.3$  vs.  $926.4 \pm 434.5$  respectively), pauses and the inflammatory parameters (CRP  $3.9 \pm 3.1$  vs.  $1.7 \pm 1.2$ , glycemia  $131.4 \pm 11.6$  vs.  $121.9 \pm 9.8$ , HOMA  $24.4 \pm 3.1$  vs.  $21.7 \pm 2.8$ , insulin  $7.6 \pm 1.4$  vs.  $7.2 \pm 1.2$  ( $p > 0.5$ )). **Conclusion:** We didn't find significant changes in pauses, VE and inflammatory parameters with CPAP short therapy in CPAP naive patients recently diagnosed with OSA.

**Keywords:** Arrhythmias, Cardiac; Blood Chemical Analysis; Sleep Apnea, Obstructive.

## INTRODUCTION

Obstructive Sleep Apnea (OSA) is characterized by repetitive episodes of partial or complete upper airway obstruction during sleep. OSA may cause several consequences, including daytime sleepiness, non-restorative sleep, and heart disease or metabolic syndrome associated with a sleep AHI >5 ev/h. OSA is highly prevalent in the general population and often under-diagnosed<sup>1,2</sup> and more over high frequently in cardiology outpatient setting (66% in this population)<sup>3</sup>. Tufik et al.<sup>3</sup> have shown that OSA prevalence was 32.8%; predominantly in women 55% and with body mass index >25 kg/m<sup>2</sup> in more than 60% of the general population. Even though OSA has traditionally been confirmed with polysomnography (PSG), respiratory polygraphy (RP) is currently accepted as a valid diagnostic tool<sup>4-6</sup>.

It has been demonstrated that OSA patients have a higher risk of heart disease, hypertension, and metabolic syndrome as well as endothelial injury, platelet and coagulation disorders, tissue remodeling, and even activation of a powerful inflammatory factor called NFκ-β (nuclear transcription factor)<sup>7,8</sup>.

Atrial fibrillation (AF) is described as the most common sustained arrhythmia in clinical practice. It accounts for one third of arrhythmia-related hospital admissions. There is very high prevalence of OSA in patients with AF, estimated at approximately 32-49%. OSA is associated with significant cardiovascular morbi-mortality. It is estimated that two thirds of the patients with AF could suffer from OSA<sup>9</sup>.

Several studies have evaluated the use of CPAP (from 3 months to 7.5 years) in patients with arrhythmia and OSA, particularly the effect of CPAP in cardiovascular morbi-mortality<sup>10-12</sup>. However, short-term use of CPAP (= 7 days) and its effect on inflammatory mediators and VE in CPAP-naive patients have not been studied extensively.

McEvoy et al.<sup>13</sup> reported effects of CPAP in patients with moderate to severe OSA and cardiovascular or cerebrovascular disease. This study has compared the effect in CPAP group *vs.* no CPAP group. After a 3 year follow up period the CPAP group did not prevent cardiovascular events.

Obesity and insulin resistance are also present in OSA. Central obesity and the accumulation of visceral fat have been described as independent factors of insulin resistance<sup>14-16</sup>. Iftikhar et al.<sup>7</sup> conducted a meta-analysis of 6 trials with a total number of 340 non-diabetic patients with insulin resistance and OSA; 172 in the CPAP arm (between 1 and 24 weeks) and 168 in the control arm. They measured the effect of CPAP in homeostasis and insulin resistance (HOMA-IR) and found a significant reduction of - 0.43 ( $p < 0.008$ ) in favor of the CPAP arm.

On the other hand, the C-reactive protein (CRP) has been correlated with an increased risk of cardiovascular disease, inflammation, and arteriosclerosis<sup>17</sup>. Taheri et al.<sup>18</sup> studied CRP and cardiovascular risk factors, inflammatory parameters, and

sleep-related breathing disorders and found that the CRP was higher in women and it was strongly and significantly correlated with age and BMI ( $p < 0.0001$ ). However, they observed no relationship between OSA syndrome and CRP.

The main objective of this study was to evaluate the short-term effects of auto-adjusting CPAP (administered for one week) in patients with cardiac arrhythmias and a recent diagnosis of moderate to severe OSA (diagnosed through self-administered home respiratory polygraphy and Holter). The secondary aims was assess the changes in the inflammatory and metabolic parameters.

## METHODS

### Design

This prospective study included derivatives patients from the physician's Cardiologists and Pulmonologist working as co-authors in this protocol at Hospital Británico (Buenos Aires, Argentina).

The protocol was approved by the Ethics Committee and the Independent Institutional Review Board of "Hospital Británico de Buenos Aires" (HBC). All the procedures that involved human subjects followed the ethical standards of national laws/institutions and the Declaration of Helsinki. All patients signed an informed consin.

### Patients

All adult patients with a clinical suspicion of OSA based on cardinal symptoms (i.e. snoring, observed apneas, or excessive daytime sleepiness) were referred for home respiratory self-administered RP according to current HBC<sup>5</sup> protocol and enrolled in the study between June 2015 and August 2016 (12 months).

Patients with moderate and severe OSA and arrhythmias were enrolled in the study group.

The following were exclusion criteria: mild OSA, no sign of arrhythmia after 24-hour ECG, <4 hours/night of CPAP, pacemaker due to bradyarrhythmia, hospitalization for any cause in the previous three months, neuromuscular disease, known diagnosis of COPD, chronic use of corticosteroids or immunosuppressant drugs, use of CPAP, ventilation devices, or supplemental oxygen.

### Holter (ECG)

We used 24-hour Holter monitoring to detect tachyarrhythmia and bradyarrhythmia, ventricular or supraventricular extrasystoles (VE or SVE) in couplets, triplets, or runs. Outpatient ECG monitoring was performed before treatment with CPAP and after 7 nights of auto-adjusting CPAP. We used Cardio Vex (MMC10D) equipment. Obtained data was processed using specific software and the resulting reports were prepared by cardiologists specialized in cardiac electrophysiology.

## Respiratory Polygraphy (RP)

Upon clinical suspicion of OSA due to any one of three cardinal symptoms, patients were assessed with a one-night self-administered home RP. The portable monitors used were Apnea Link Air (ResMed) and Alice Nighth One (Philips-Respironics). When patients picked up the polygraphy device, they completed a Spanish-language version of Epworth Sleepiness Scale (ESS)<sup>19</sup>, the Berlin questionnaire<sup>20</sup>, and STOP-BANG questionnaire<sup>21</sup> and received personalized training on the correct use of the device, which included a practical demonstration and illustrations. Recordings were downloaded the following day.

## Manual scoring

Recordings were analyzed with specialized software Apnea Link (ResMed, Australia) and G3 (Philips, USA) in 3/5 minute epochs. Respiratory events were corrected manually when necessary. Recording sections with low quality signals or transient disconnections were removed. Apnea was defined as a >80% drop from baseline airflow for = 10 seconds, and hypopnea as a 50% drop for = 10 seconds associated to = 3% oxygen desaturation<sup>22</sup>. The AHI was calculated as the number of apneas/hypopneas per hour of valid total recording time (TRT). Patients were classified as normal (AHI <5/h), mild (AHI = 5 and <15), moderate (AHI = 15 and <30), severe (AHI = 30).

## Lab tests

A 3 ml venous blood sample was tested at Hospital Británico central laboratory. We analyzed two morning samples, taken before and after seven nights of treatment with auto-adjusting CPAP. We monitored the following inflammatory and metabolic mediators: insulin (Cobas e-411 Roche *Electrochemiluminescence*), CRP (Vitros 5600 serum chemistry), HOMA and glycemia (Vitros 5600 serum chemistry).

## Treatment with CPAP

We used the System One Series auto-adjusting CPAP (Philips-Respironics) with oro-nasal or nasal mask with forehead support according to practical demonstration on interface choice conducted by trained physiotherapists. Used pressures were preset between 4-14 cmH<sub>2</sub>O. A pulse oximetry module was connected to the CPAP.

Data were collected and read after seven days using Encore Pro II software: visual analysis of time-pressure curve to detect leaks of < 30 l/m. Only recordings with a mean use of > 4 hours/night were accepted. The data checked were: mean leak, AHI<sub>r</sub>, effective titration pressure, and oximetry indicators.

Previously mentioned variables were analyzed for each patient, considering both pre- and post-treatment data. Variables were expressed as mean and standard deviation. Overall results were compared using a nonparametric statistical test (Mann Whitney) and Graph Pad Prism 5 software.

## RESULTS

We analyzed data from 27 patients (61.7±1.9 years old). Two patients were excluded (one did not have the second

Holter and the other did not comply with the required number of CPAP hours). Finally, 25 patients were included in the study (Figure 1). Characteristics were summarized in Table 1. Only 50% of the patients take antihypertensive medications. Figure 2, show comorbid and medications conditions.

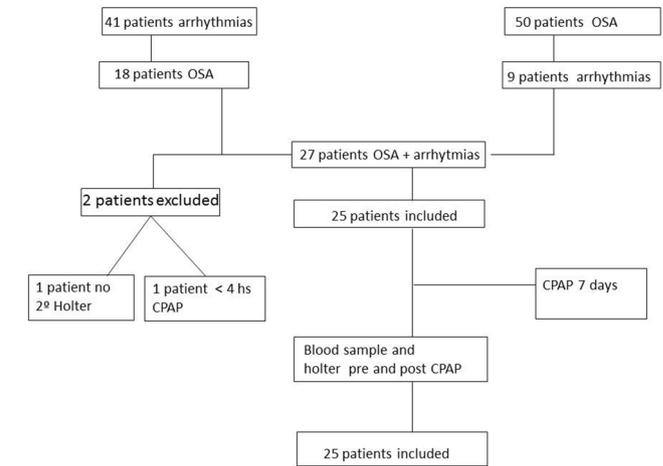


Figure 1. Patients flow chart.

Table 1. Respiratory polygraphy indicators.

25 PATIENTS ASSESSED THROUGH RP	
MEAN AGE (YEARS OLD)	61.7±1.9 (36-86)
BMI KG/M <sup>2</sup>	59.5±2.2 (40.4-85.7)
MEN	92.5%
MEAN AHI	37.7±3.8 (17-83)
T < 90 %	27.2±3.9 (1-77)

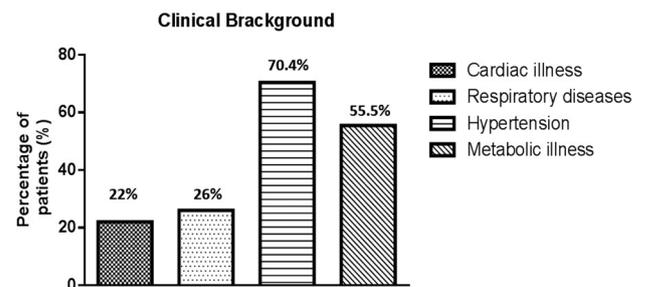


Figure 2. Clinical background.

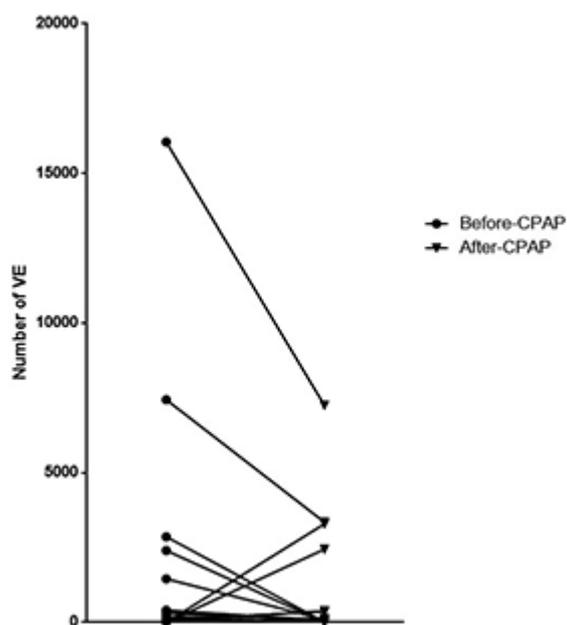
The group was made up of 16 (64%) patients with systemic hypertension (SAH), 13 (52%) with ischemic cardiopathy and 9 (36%) with diabetes. Furthermore, 9 (36%) were social drinkers (mostly wine) and 20 (80%) were smokers or former smokers (20 packs/year on average).

Table 2 shows adherence and efficacy of auto-adjusting CPAP therapy. After treatment, there was a tendency to improve the absolute numbers of VE (1595±850 vs. 926.4±434.5) (Figure 3) and in complexity (bigeminal, couplets, triplets, and non-sustained ventricular tachycardia)  $p=0.5$  (Figure 4). In addition, there was also a tendency to improve the number of

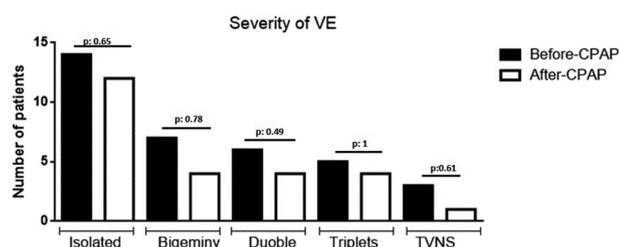
pauses ( $3.2 \pm 0.7$  vs.  $2.5 \pm 1.6$ ) which was not statistically significant ( $p=0.5$ ). However, there was no change in SVE ( $1193 \pm 558.7$  vs.  $1043 \pm 485.7$ )  $p=0.5$ . Likewise, there was a tendency to improve in the inflammatory parameters after seven days of CPAP treatment ( $p=0.5$ ) (Table 3).

**Table 2.** CPAP titration results.

RESULTS 7 NIGHTS WITH CPAP	
TRT (minutes)	$397 \pm 16.9$ (214-617)
EFFECTIVE PRESSURE CM H <sub>2</sub> O	$8.7 \pm 0.4$ (1.7-12)
RESIDUAL AHI EV/H	$5.3 \pm 0.53$ (0.6-10)



**Figure 3.** Number of ventricular extrasystoles pre and post CPAP.



**Figure 4.** Complexity of ventricular extrasystoles pre and post CPAP.

**Table 3.** Inflammatory parameters before and after CPAP.

LABORATORY	BEFORE CPAP	AFTER CPAP	<i>p</i>
CRP	$3.9 \pm 3.1$	$1.7 \pm 1.2$	0.88
GLYCEMIA	$131.4 \pm 11.6$	$121.9 \pm 9.8$	0.49
HOMA	$24.4 \pm 3.1$	$21.7 \pm 2.8$	0.9
INSULIN	$7.6 \pm 1.4$	$7.2 \pm 1.2$	0.69

$p=0.5$

After short term treatment with CPAP we not found any significant changes in the outcomes proposal.

## DISCUSSION

In spite of the small sample size from patients, prospective, non-randomized design, lack of echocardiographic data, our findings showed that there could be an improvement in the rate of ventricular arrhythmias (i.e. a reduction in their number and complexity), a drop in the number of pauses, and an improvement of inflammatory parameters after 7 days of auto-adjusting CPAP in recently diagnosed CPAP-naïve patients.

The advantage of super-simplified strategy based on self-administered, home RP and unsupervised short-term titration with automatic devices (a week), lies in its applicability in limited resource settings and hospital units with long waiting lists. Mc Evoy et al. and others also used apnea link and unsupervised CPAP titration but for a mean follow up of 3.7 years. They didn't find significant cardiovascular effect including cardiac arrhythmias, moreover they found a reduction in snoring and daytime sleepiness<sup>13</sup>.

Ours patients with OSA referred for CPAP showed proper adherence to treatment (6.6 hours per night), though they were not previously adapted before the training program on mask selection and other basic information delivered during the first week of therapy. We have to highlight that our population have high BMI<sup>23</sup>.

Kanimozhi et al.<sup>8</sup> showed a significant reduction in systolic and diastolic pressure in 20 patients recruited with severe OSA and metabolic syndrome, who used CPAP for one night. Clinical measurements and inflammatory parameters were measured before and after CPAP therapy during short periods. Lipids, however, were not significantly reduced and there was a non-significant statistical reduction in insulin resistance.

Even though inflammatory parameters and insulin resistance did not improve significantly in our study, it is worth highlighting that there was a downward trend (possible sample-related restriction) after short-term CPAP therapy, which is consistent with the literature. Different studies evidence an improvement in arrhythmias and inflammatory parameters after several months of CPAP treatment. Short-term use, however, has not been broadly studied.

High prevalence of AF has been observed in OSA patients, independently from other arrhythmias. In their work using 24-hour Holter in 400 patients with moderate and severe OSA, Guilleminault et al. found the AF prevalence rate was 3 times as high as the general population. Recently, a Sleep Heart Health Study found similar results showing 4 times much prevalence<sup>24,25</sup>. Kanagala et al.<sup>26</sup> have shown CPAP improved the recurrence rate of AF one year after effective cardioversion: 82 vs. 42%, respectively. In a study conducted on 458 patients, arrhythmias had a prevalence of 58% in OSA patients and 42% in non-OSA patients ( $p<0.001$ ). Moreover, in that same study, patients with AHI  $>40$  ev/h presented a higher prevalence of arrhythmias (70%), as compared to those with AHI  $<10$  (42%)<sup>27</sup>. Undoubtedly, the largest body of evidence has focused

on the study of AF, even though specific phenomena such as VE and SVE are frequent causes of consultation requiring pharmacological treatment.

On the other hand, OSA causes intermittent hypoxemia associated with hemodynamic changes in ventricular function, which may alter diastolic function in relation with structural and functional alterations in the atria. All these alterations favored by the increase in intra-thoracic pressure, the severity of hypoxemia from apneas, and adrenergic changes could be partially reverted by treating apneas with CPAP<sup>28</sup>, though the effect on serum mediators may take longer.

Complex ventricular arrhythmias are usually referred for testing when they prevail at night in Holter recordings and are usually treated with antiarrhythmic drugs. The effect of CPAP on these events has been scarcely explored<sup>26,28</sup>, but our data suggest CPAP may have a protective effect. Abe et al.<sup>29</sup> in 316 Japanese patients with OSA (diagnosed through polysomnography) and titrated with CPAP, found a significant reduction of paroxysmal AF ( $p < 0.001$ ), VE ( $p < 0.016$ ), sinus bradycardia ( $p < 0.001$ ), and sinus pauses ( $p < 0.004$ ).

However, a prospective, randomized, placebo-controlled trial (Sham CPAP) in patients with arrhythmias showed a reduced heart rate at rest (sympathetic tone) but failed to show changes in the occurrence of VE, SVE, and AF after 30 days (acute effect)<sup>30</sup>. Also, our data didn't show relevant changes in VE, SVE and pauses, nevertheless it tended to dropdown. Therefore, it may take longer to observe some electrophysiological changes.

## CONCLUSION

In our experience, we could not prove the acute effect of CPAP therapy could contribute to a reduction in pauses, ventricular events and inflammatory mediators. Longer trials are needed to evaluate the effect of short treatment with CPAP in patients with arrhythmias.

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