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Effects of CPAP on systemic hypertension in OSAH: A monocentric, observational, cohort study

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Summary
Background: Obstructive sleep apnea-hypopnea (OSAH) is a risk factor for development of systemic arterial hypertension (SAH) and can worse the control of established SAH. We investigated the effects of long-term continuous positive airway pressure (CPAP) treatment in controlling and preventing SAH in a large cohort of subjects referred for sleep study for suspected OSAH.
Methods: In 495 subjects of whom 422 with OSAH and 73 without OSAH, the clinical history was obtained, arterial blood pressure was measured and the current anti-hypertensive drugs was recorded at diagnosis and/or at CPAP start. Subjects were interviewed after a follow-up period of (mean ± SD) 3.4 ± 2.2 yr (range 1–8 yr) and divided in patients with moderate-to-severe OSAH ($n = 125$) who referred to use CPAP regularly for at least 4 h every night (group 1), with moderate-to-severe OSAH ($n = 70$) who refused or abandoned the CPAP treatment after few weeks (group 2), with mild OSAH ($n = 227$) with no CPAP indication (group 3) and simple snorers or normals ($n = 73$) (group 4). For each group clinical status, BMI, and changes in SAH therapy and occurrence of SAH were assessed at the follow-up.
Results: At the follow-up, a higher risk of increasing treatment for SAH was found for group 2 and group 3 versus group 1 (OR = 5, 95%CI 1–20, $p < 0.01$ and OR = 3, 95%CI 1–10, $p < 0.05$), respectively. The occurrence of SAH was lower ($p < 0.001$) in the group 1 (1.9%), vs group 2 (35.9%), 3 (21.1%) and 4 (18.6%).

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Conclusions: In moderate-to-severe OSAH patients, long-term CPAP treatment significantly reduces the development of SAH and, in those with SAH at baseline, the need of anti-hypertensive drugs.

Introduction

Obstructive sleep apnea—hypopnea (OSAH) is widely recognized as an independent risk factor for the development of systemic arterial hypertension (SAH)[1–3] and today considered as the first identifiable cause of secondary SAH.[4] Several mechanisms have been invoked potentially linking OSAH to SAH: an increased nighttime and daytime sympathetic activity (due to chemoreflex stimulation by nocturnal intermittent hypoxia),[5] an impaired arterial vasodilation[5] (secondary to endothelial dysfunction and systemic inflammation)[6] and a reduced inhibitory baroreflex gain (due to an abnormal autonomic function).[7] Among other factors, the sustained arterial pressure is thought to markedly increase the cardiovascular morbility and mortality risk observed in OSAH patients.[8]

The administration of continuous positive airway pressure (CPAP) during sleep is the treatment of choice for moderate-to-severe and/or symptomatic OSAH patients. CPAP has been shown to be able to positively modify all the above mentioned "intermediate mechanisms" inducing or worsening SAH in OSAH.[9] The results of previous studies looking at the effect of CPAP treatment on the arterial blood pressure levels in OSAH patients, however, were controversial possibly because influenced by several factors such as the severity of OSAH,[5] the presence or absence of daytime sleepiness,[5] the degree and duration of SAH before the treatment[5] including the occurrence of resistant SAH,[5] CPAP proper titration,[5] the average time of the CPAP use during the night,[5] age and gender of patients[5] and finally the duration of the treatment.[5] In fact, the vast majority of these studies were conducted for weeks or few months and very few studies investigated the CPAP effects on arterial blood pressure for a longer time.[9–11]

Therefore, the objective of the present study was to assess the long-term effects of CPAP treatment on the arterial blood pressure levels in a single-center, large cohort of subjects referred for sleep study for suspected OSAH. In particular, we evaluated the occurrence of SAH and the pharmacological changes of established SAH in patients with moderate-to-severe OSAH according to the CPAP treatment adherence.

Methods

This was a monocentric, observational, cohort study performed in 820 subjects referred for clinically suspected OSAH who underwent either a full polysomnography or a cardio-respiratory monitoring at the sleep laboratory of the medical Division of the hospital of Umbertide (Perugia, Italy) between October 2000 and December 2007.

Scoring of sleep stages and associated events was made according to the recommendation of American Academy of Sleep Medicine.[12] At the time of the first visit, clinical assessment including medical history, physical examination, and office measurement of systemic arterial blood pressure was performed for each subject. Arterial blood pressure measurements were determined by averaging two readings of systolic and diastolic blood pressure obtained at 5-min interval using a mercury sphygmomanometer after subjects had been seated in a chair with the dominant arm supported at the heart level for at least 10 min.[13] Normal values were considered as lower than 130 mmHg and 85 mmHg for systolic and diastolic blood pressure, respectively and SAH was defined by arterial blood pressure values higher than 140/90 mmHg.[13] In case of subjects with SAH, the current anti-hypertensive treatment was recorded. The subjects with apnea—hypopnea index (AHI) more than 20 and those with AHI more than 5 and excessive daytime somnolence, as scored by Epworth Sleepiness Scale (ESS) as higher than 10, were subsequently titrated for optimal CPAP. The baseline clinical assessment in the first visit, the interpretation of diagnostic and titration sleep studies, and follow-up were performed by the same physician (PB) for all subjects. The flowchart of the study is shown in Fig. 1.

At the time of the interview performed in the years 2008—09, among 820 subjects who attended the sleep study, 726 were successfully contacted. After two phone calls done by physicians from a single university center, only 495 subjects accepted to give information about the clinical status including the present BMI, the last 3 values of systemic arterial blood pressure measured by their family-doctors, any changes in anti-hypertensive therapy and the compliance with CPAP treatment. Among 422 subjects with OSAH, 195 were recommended to adopt the CPAP treatment (group 1 and 2), while 227 had no indication for CPAP treatment (AHI $<$ 20, group 3); 73 were simple snorers or normals (group 4). At the follow-up 125 of 195 OSAH patients who were advised to adopt the CPAP treatment, used CPAP all nights for more than 4 h every night (group 1), while 70 refused to use CPAP since the beginning or abandoned the CPAP treatment after few weeks of initial treatment (group 2). Subjects without OSAH represented the control group (group 4). The protocol was approved by Ethic Committee of "Spedali Civili, Brescia" (no approval number available).

Statistical analysis

Continuous variables were expressed as mean $\pm$ SD, and categorical variables were expressed as a percentage. The primary outcomes were the pathological increase of systolic and diastolic arterial blood pressure (yes or not) in previously normotensive subjects as well as variations of

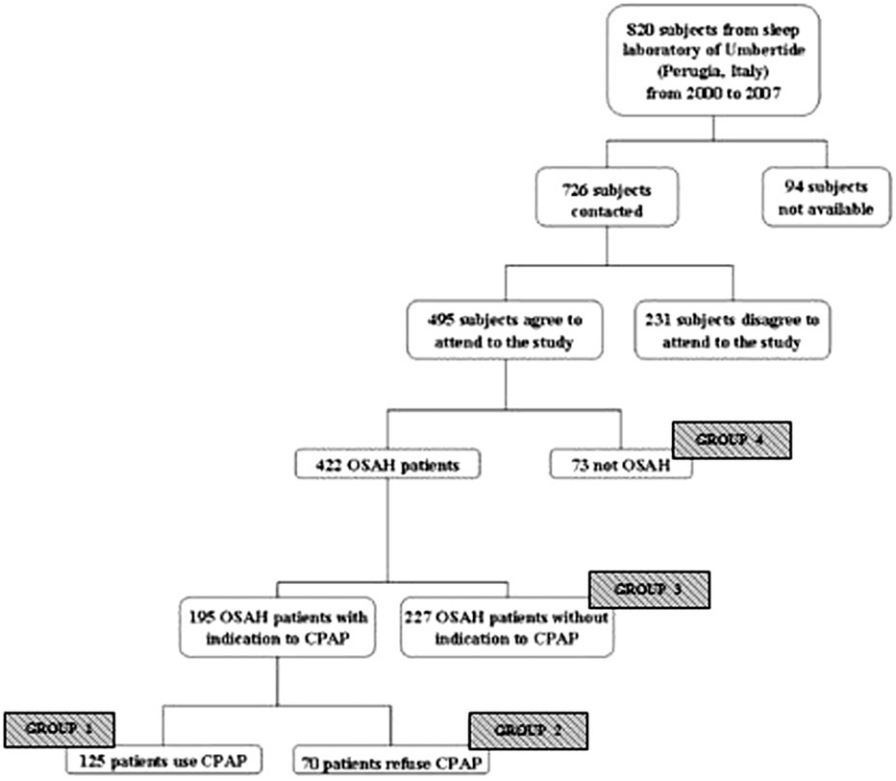

Figure 1 Flow-chart of the study with identification of each group.

anti-hypertensive treatment (more or equal-less pills/drug) in the subjects with SAH among different groups during the follow-up. We analyzed the different risk of such outcomes among various groups as odd ratios. Baseline characteristics of patients were compared by two-tailed unpaired *t*-test for continuous variables and two-tailed Fisher exact test or Chi square for nominal variables. Analysis of variance of changes of variables of interest among groups was performed after checking the normality of the data set; if significant variance was observed, multiple comparisons were performed using unpaired Student's *t*-test, corrected by the Bonferroni method.

$P < 0.05$ was considered as significant. Statistical software (SPSS version 12.0.1, Chicago, IL.) was used for data processing and statistical analysis.

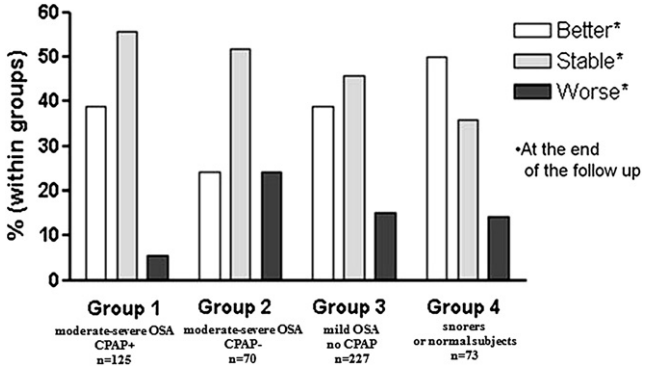

Figure 2 Changes of the anti-hypertensive treatment at the end of the follow-up in subjects with established SAH at baseline in each group. Better (white columns) means reduction of anti-hypertensive drugs or pills; stable (grey columns) means no change in anti-hypertensive therapy; worse (black columns) means increase in anti-hypertensive drugs or pills.

Results

The baseline clinical features of all the subjects are shown in Table 1 and those of each group in Table 2. The mean of the follow-up period was 3.4 ± 2.2 yr (range 1–8 yr) and was similar among the groups. Age, gender, and BMI were not different between group 1 and 2. AHI was greater in the group 1 than in the group 2, although subjects in both groups suffered from moderate-to-severe OSAH. BMI and AHI was significantly lower in groups 3 and 4 than in groups 1 and 2. Age in the group 4 was lesser than in group 2.

The prevalence of SAH at baseline is shown in Table 2. The amounts of anti-hypertensive drugs assumed by the subjects with established SAH at baseline were shown according to the different groups in Table 3.

In subjects with normal values of systemic arterial pressure (<130/85 mmHg) at the beginning of the study, the SAH incidence was 1.9% in the group 1, 35.9% in group 2 and 21.1% and 18.6% in groups 3 and 4 (Fig. 3). At the beginning the sleepiness, assessed according to the ESS, was significantly greater in the group 1 than group 2 and 3 (see Table 2).

Table 1 Baseline characteristics of population studied.

Subjects	$n = 495$
Age, yr	58.5 ± 12.9
Male	407 (82.2%)
Female	88 (17.7%)
BMI (kg/m^2)	30.1 ± 5.3
Prevalence of systemic hypertension	40.4% (200/495)

Data are expressed as mean ± SD or *n* (%).

A higher risk to develop SAH was found in the group 2 and groups 3 and 4 versus group 1 (OR = 27, 95%CI 3–216, $p < 0.0001$, OR = 14, 95%CI 2–105, $p < 0.001$ and OR = 12, 95%CI 1–96, $p < 0.01$), respectively.

During the follow-up among subjects with SAH 5% of the subjects in the group 1 increased their anti-hypertensive therapy, using more pills or more drugs, while 26% of the subjects in the group 2 needed to do it. Also 15% of subjects in the group 3 and 14% in the group 4 increased their anti-hypertensive therapy. A higher risk of increasing treatment for SAH was found for group 2 and group 3 versus group 1 (OR = 5, 95%CI 1–20, $p < 0.01$ and OR = 3, 95%CI 1–10, $p < 0.05$), respectively (Fig. 2).

At the follow-up BMI was 32.2 ± 5.3 for group 1, 31.1 ± 5.1 for group 2, 27.8 ± 4.1 for group 3, and 26.5 ± 3.3 for group 4, respectively. The changes between baseline and follow-up BMI were not significantly different among different groups.

Among patients of the group 1 who had established SAH, a significantly higher probability of reducing the number of anti-hypertensive pills and/or drugs at the follow-up (OR = 5.3, 95%IC 1.8–15.8, $p < 0.002$) was observed in those who were taking a greater amount of anti-hypertensive drugs (more than two versus two or less) at the beginning of CPAP treatment. In contrast, this was not observed for BMI, AHI and somnolence score.

At the follow-up the all-cause mortality was equal to 0.8% (1 subject) in the group 1, 5.7% (4 subjects) in the group 2 and 0.9% (2 subjects) in the group 3.

Discussion

The main finding of this study is that long-term treatment with CPAP is associated with a significant, protective effect towards SAH development and SAH worsening in subjects with moderate-to-severe OSAH versus both untreated moderate-to-severe OSAH and mild OSAH. Although this is an observational study and arterial blood pressure was not recorded as mean of 24-h ambulatory monitoring, its results are important due to the longest follow-up ever reported and the large number of subjects involved, all coming from a single center, so avoiding inter-operator variability in diagnosis of OSAH, titration of CPAP, therapeutic advices and initial control of the device use.

The effect on arterial blood pressure of CPAP treatment in OSAH, although repeatedly assessed in several small studies, has not been convincingly demonstrated due to the variable results. A recent meta-analysis performed on 12 randomized trials with a duration ranged from 1 to 12 weeks, including 572 OSAH patients, found only a small reduction on arterial blood pressure (in average less than 2 mmHg in mean 24-h arterial blood pressure) in those treated with CPAP.[14] Interestingly, some sub-populations of hypertensive OSAH patients seemed to benefit more from CPAP treatment such as those with more severe OSAH (according to AHI and/or number of arousals per hour of sleep), longer duration and gravity of SAH, greater somnolence and obviously better adherence to the treatment. Although it would have seemed reasonable to recommend CPAP treatment to OSAH patients with severe SAH (mainly in those with other cardiovascular risk factors) also with the goal of lowering SAH, nevertheless the results of the trials were too modest, possibly because of the short duration and the small number of subjects in each study, to justify the CPAP use in other groups of hypertensive OSAH patients only to obtain a better control of SAH. For instance, in a very recently published multi-centre randomized trial, involving 340 OASH patients with untreated SAH, where the effects on arterial blood pressure, assessed by a 24-h ambulatory monitoring, were

Table 2 Baseline anthropometric characteristics and apnea-hypopnea index (AHI) of each group.

	Group 1	Group 2	Group 3	Group 4
	OSAH with CPAP (AHI > 20)	OSAH without CPAP (AHI > 20)	Mild OSAH (AHI < 20)	Controls (AHI < 5)
Number	125 (25.2%)	70 (14.1%)	227 (45.8%)	73 (14.7%)
Age, yr	59.8 ± 11.1	62.2 ± 12.2	58.5 ± 12.7	58.8 ± 13.3§
Male	111 (88.8%)	62 (88.5%)	184 (81%)	50 (68.5%)
Female	14 (11.2%)	8 (11.4%)	43 (18.9%)	23 (31.5%)
BMI (kg/m^2)	33.2 ± 11.1	32.7 ± 5.5	28.6 ± 4.4**	27.1 ± 3.9**
AHI	52.8 ± 18.7	45.3 ± 22.2*	10.9 ± 10.4**	2.3 ± 1.3** °°
ESS	10.3 ± 3.9	8.6 ± 4.6§	7.2 ± 2.8 ##	/
Prevalence of SAH	57.6% (72/125 pts)	41.2% (29/70 pts)	37.4% (85/227 pts)	19.2% (14/73 pts)

Data are expressed as mean ± SD or *n* (%).
$^{\S}p < 0.05$ vs Group 1.
*$p < 0.01$ vs Group 1; $^{\#}p < 0.01$ vs Group 2; °$p < 0.01$ vs Group 3.
**$p < 0.001$ vs Group 1; ##$p < 0.001$ vs Group 2; °°$p < 0.001$ vs Group 3.
ESS = Epworth Sleepiness Score; SAH = Systemic arterial hypertension; pts = patients.

Table 3 Amount of therapy of SAH at baseline in hypertensive subjects.

Number of patients	Group 1 (72)	Group 2 (29)	Group 3 (85)	Group 4 (14)
Number of anti-hypertensive drugs				
1	28 (38.9%)	13 (44.8%)	35 (41.1%)	7 (50%)
2	24 (33.3%)	12 (41.4%)	37 (43.5%)	4 (28.6%)
3	18 (25%)	3 (10.3%)	11 (12.9%)	3 (21.4%)
4	1 (1.4%)	0 (0%)	2 (2.3%)	0 (0%)
5	1 (1.4%)	1 (3.4%)	0 (0%)	0 (0%)

compared in the group treated with CPAP for 3 months versus that assigned to sham treatment, the significant reduction of SAH in the subjects receiving CPAP was relatively small, less than 3 mmHg drop in mean 24-h ambulatory blood pressure, still questioning the clinical relevance of these results.[15] In addition, recently it has been published[16] a paper with the observation that 3 months of CPAP therapy similarly lowers blood pressure in patients with OSAH with metabolic syndrome or some of its component.

Mayer and coll. treating with CPAP 12 hypertensive OSAH patients found that daytime SAH decreased significantly only after 6 months, while nighttime SAH was acutely reduced.[17] More recently, in a sample of 98 hypertensive OSAH patients Dernaika et al. investigated the effect of the one year CPAP treatment on arterial blood pressure and reported a significant better control of blood pressure only in those with resistant SAH.[11] Again, in contrast with the findings of Robinson et al.,[18] Barbè et al. showed that in a large sample of 359 hypertensive OSAH patients without hypersomnolence, those treated for at least one year with CPAP can exhibit a significant SAH reduction if the adherence was adequate (more than 5 h per night).[9] In fact, in the present study after a mean follow-up of 3.4 yr, patients with moderate-to-severe OSAH and established SAH who declared an adequate adherence to CPAP (group 1), showed a worsening in the SAH control significantly lesser than that reported in the hypertensive OSAH patients of other groups (groups 2 and 3). Therefore, the duration of CPAP treatment seems very important to judge carefully its effects on arterial blood pressure in OSAH patients. This is in keeping with the notion that it may take more than several months of CPAP treatment to obtain a reduction of sympathetic activity in OSAH patients.[19]

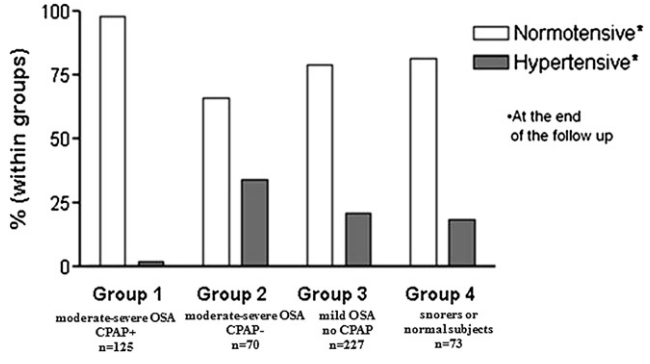

Figure 3 Absence (white columns) or presence (black columns) of established SAH at the end of the follow up in subjects with normal arterial blood pressure at baseline in each group.

In our study, very impressive was the prevention of the SAH development in normotensive moderate-to-severe OSAH patients treated with CPAP as compared to the untreated ones. This finding is in agreement with the results obtained by Campos et al.[20] and in a small randomized trial performed in 36 severe OSAH patients with similar arterial blood pressure values and percentage of pre-hypertension and masked hypertension, according to both office and 24-h monitoring measurement, who were assigned to a sham or CPAP treatment for only 3 months.[21] While no changes in arterial blood pressure were observed in the control group, the OSAH patients in the treated group showed a significant reduction of the frequency of pre-hypertension and masked hypertension, reflecting a protective effect of the active treatment.

Mild OSAH patients had a lower risk to develop SAH as compared to untreated moderate-to-severe OSAH patients, although they showed a frequency of new SAH similar to control subjects. It is somehow surprising that either group 3 (mild-to-moderate OSAH patients) or group 4 (controls) showed a higher frequency of new SAH than group 1 (moderate-to-severe OSAH patients treated with CPAP). Actually, CPAP does deeply influence and possibly may delay the effects of several pathogenic mechanisms leading to increase systemic vascular resistance and this cannot be usually offered to mild-to-moderate OSAH patients. Moreover, in this group and mainly in the group 4 less attention could be paid to favorable changes in life style such as physical activity, diet and medical checkups.

The present study has some clear limitations. Physical activity and dietary habits were not checked in our population and these could be confounding factors. However, it is highly improbable that in a long run greater physical activity and low salt and less caloric diet only pertain to the moderate-to-severe OSAH patients treated with CPAP as compared with others groups. The contrary would be more plausible considering the less favorable long-term results on arterial blood pressure in the untreated OSAH patients. On the other hand, the average decrease in BMI was similar in the different groups of OSAH patients, arguing against these potential confounders.

We have not objective measurements of the CPAP use throughout such a prolonged period of treatment. Even if the CPAP use would have been lower than one reported by group I patients, the effects we recorded on control and prevention of SAH would be even more impressive in the absence of other obvious explanations.

In conclusion, the long-term CPAP treatment is highly effective in moderate-to-severe OSAH patients to decrease the SAH occurrence in those who were normotensive and to improve the SAH control in those who were hypertensive before its implementation as compared with both untreated moderate-to-severe OSAH patients and mild-to-moderate OSAH patients.

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Conflict of interest statement

All the authors have no conflict of interest to disclose.

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None.

Authors' contribution

PB conceived the study design and collected data, LTM contributed to collecting data and did statistical analysis, MN contributed to collecting data and did statistical analysis, MBet contributed to data analysis and review of the manuscript, ER contributed to data analysis and review of the manuscript, CA coordinated polysomnography and lung function tests, MBen coordinated polysomnography and lung function tests, LC contributed to preparation of the manuscript, CT is the guarantor of the paper, conceived the study design, monitored the study protocol and wrote the article.

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