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Clinical research

Benefits of obstructive sleep apnoea treatment in coronary artery disease: a long-term follow-up study☆

Olivier Milleron[a,*], Rémy Pillière[a], Arlette Foucher[b], Florence de Roquefeuil[a], Philippe Aegerter[c], Guillaume Jondeau[a], Bernadette G. Raffestin[b], Olivier Dubourg[a]

[a] *Division of Cardiology, Ambroise Paré Teaching Hospital, AP-HP, UFR Paris-Ile de France-Ouest, Université de Versailles-Saint Quentin en Yvelines, 92104 Boulogne, France*
[b] *Sleep Laboratory Unit, Ambroise Paré Teaching Hospital, AP-HP, UFR Paris-Ile de France-Ouest, Université de Versailles-Saint Quentin en Yvelines, 92104 Boulogne, France*
[c] *Biostatistics and Medical Informatics Unit, Ambroise Paré Teaching Hospital, AP-HP, UFR Paris-Ile de France-Ouest, Université de Versailles-Saint Quentin en Yvelines, 92104 Boulogne, France*

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See page 709 for the editorial comment on this article†

KEYWORDS
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Aim The aim of this long-term prospective study was to evaluate the effect of treating obstructive sleep apnoea (OSA) on the rate of cardiovascular events in coronary artery disease (CAD).

Methods and results We prospectively studied 54 patients (mean age 57.3 ± 10.1 years) with both CAD ($\geqslant$70% coronary artery stenosis) and OSA (apnoea–hypopnoea index $\geqslant$15). In 25 patients, OSA was treated with continuous positive airway pressure $(n = 21)$ or upper airway surgery $(n = 4)$; the remaining 29 patients declined treatment for their OSA. The median follow-up was 86.5 ± 39 months. The two groups were similar at baseline in age, body mass index, smoking history, hypertension, hypercholesterolaemia, diabetes mellitus, number of diseased vessels, left ventricular ejection fraction, and CAD therapy. Treatment of risk factors other than OSA was similar in the two groups. The endpoint (a composite of cardiovascular death, acute coronary syndrome, hospitalisation for heart failure, or need for coronary revascularisation) was reached in 6 (6/25, 24%) and 17 (17/29, 58%) patients with and without OSA treatment, respectively $(P < 0.01)$. OSA treatment significantly reduced the risk of occurrence of the composite endpoint (hazard ratio 0.24; 95% confidence interval, 0.09–0.62; $p < 0.01$) and of each of its components.

Conclusions Our data indicate that the treatment of OSA in CAD patients is associated with a decrease in the occurrence of new cardiovascular events, and an increase in the time to such events.

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* Corresponding author. Tel.: +33-1-49-09-56-11; fax: +33-1-49-09-58-85.
E-mail address: olivier.milleron@apr.ap-hop-paris.fr (O. Milleron).

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Introduction

Obstructive sleep apnoea (OSA) is a common disorder characterised by episodes of upper airway obstruction during sleep that lead to repeated episodes of apnoea or hypopnoea lasting 10 s or longer. A widely accepted definition of OSA is an apnoea–hypopnoea index (AHI) of 15 or more, AHI being the mean number of episodes of apnoea or hypopnoea per hour of sleep. In a prospective population-based study, 9% and 4% of middle-aged men and women, respectively, had an AHI greater than 15.[1] Several studies have found far higher prevalences, as much as 30–50%, in patients with systemic hypertension or coronary artery disease (CAD).[2–5] The association of OSA with CAD is not fully explained by known confounding factors such as obesity, age, and sex, and research is producing a growing body of evidence supporting a causal link between OSA and cardiovascular morbidity and mortality.

Treatment of OSA with nasal continuous positive airway pressure (nCPAP) has been shown to alleviate daytime sleepiness, a frequent complaint of OSA patients, and to improve quality of life. Some studies suggest that nCPAP may reduce morbidity and mortality.[6,7] In patients free of hypertension or other cardiovascular disease at the initiation of treatment for OSA, Peker et al.[8] recently reported a significant decrease in the occurrence of cardiovascular disease as compared to patients with untreated OSA. In addition, a recent double-blind randomised study found that diurnal and nocturnal blood pressures dropped by approximately 10 mm Hg after 9 weeks of nCPAP.[9] This blood pressure-lowering effect would be expected to significantly diminish CAD event rates. However, the long-term effect of OSA treatment on cardiovascular event rates in patients known to have CAD at the time of OSA diagnosis has not been evaluated.

We therefore studied the impact of OSA treatment on cardiovascular outcomes of patients with CAD. To this end, we compared rates of new cardiovascular events over a 5-year period in patients with treated versus untreated OSA.

Methods

Patients

Recruitment was prospective at our institution between September 1991 and June 1999. All patients admitted to the cardiology department for a selective coronary angiogram and found to have a stenosis of a major coronary artery of 70% or more were considered for the study. Revascularisation was performed by the attending cardiologist, if deemed necessary. The patients were eligible for the study if they were subsequently referred to our institution's sleep laboratory for evaluation of symptoms consistent with OSA and an AHI of 15 or more was found by overnight polysomnography, thus confirming the diagnosis. Polysomnography (PSG) was performed when the patient was in a stable clinical condition (at least 4 weeks after coronary angiography and hospital discharge). Polysomnography was recorded with either a 16-channel polygraph at a chart speed of 15 mm/s (Reega 2000, Alvar, France) or a computerised sleep recording system (Medatec, Belgium). The recordings included a two-channel electroencephalogram, electro-oculogram, electrocardiogram, chin electromyogram, body position, chest and abdominal excursions, nasal and oral airflow assessed by thermocoupling or a nasal cannula, and oxyhaemoglobin saturation (finger pulse oximetry). Sleep stages were scored manually. Apnoea was defined as a cessation of oronasal airflow lasting at least 10 s and hypopnoea as a reduction by at least 50% in oronasal airflow, as compared to the previous period of normal breathing, lasting at least 10 s and followed by a transient EEG arousal. Electroencephalographic arousals were scored according to standard criteria published by the American Sleep Disorder Association. The AHI was calculated as the mean number of apnoea or hypopnoea episodes per hour of sleep.

Risk factor definitions

"Hypertension" was defined as current use of antihypertensive medications and/or as recording during the hospital stay of a systolic blood pressure (SBP) value $\geqslant$140 mm Hg and/or a diastolic blood pressure (DBP) value $\geqslant$90 mm Hg being measured with a standard sphygmomanometer on three different occasions, with the subject in supine position. Hypertension was considered uncontrolled when SBP was $\geqslant$140 mm Hg and/or DBP $\geqslant$90 mm Hg at the end of the study follow-up period.

Hypercholesterolaemia was defined as current use of cholesterol-lowering medications and/or a total cholesterol value $>$5.2 mmol/l and/or an LDL-cholesterol value $>$3.4 mmol/l in a plasma sample drawn after an overnight fast. Uncontrolled hypercholesterolaemia was defined as a total cholesterol value $>$5.2 mmol/l and/or an LDL-cholesterol value $>$3.4 mmol/l at the end of the study follow-up period.

Diabetes mellitus was defined as a need for insulin or oral hypoglycaemic agents or as a fasting blood glucose concentration $>$7.0 mmol/l on two separate occasions.

Excess weight was defined as a body mass index (BMI) $\geqslant$25 but $<$30 and obesity as a BMI $\geqslant$30 kg/m^2.

The subjects were classified as current smokers, former smokers (defined as patients who stopped smoking at least 6 months before study inclusion), and nonsmokers.

Treatment of OSA

All the patients were offered treatment for their OSA. Either upper airway surgery or nCPAP was recommended, according to the severity of OSA and results of the otorhinolaryngologic evaluation. The patients were divided into two groups based on whether they accepted or refused treatment for their OSA. The treated group comprised all the patients who initially accepted treatment for OSA, including those who changed their mind later on and those who received nCPAP but complied poorly with this treatment modality. When nCPAP was recommended, titration was performed in our sleep laboratory, according to our usual manual standardised procedure, which includes nCPAP monitoring. Compliance with nCPAP was estimated based on the time counter on the device and on clinical effectiveness. The untreated group was composed of the patients who refused treatment for their OSA from the outset.

Follow-up

Follow-up started at the time of OSA diagnosis. Throughout follow-up, data were gathered at 6-month intervals, either during visits to the cardiologist or by phone calls to the patient, relatives, or general practitioner. The following information was

collected: cardiovascular death (i.e., sudden cardiac death or death due to myocardial infarction, unstable angina, heart failure, or cardiac arrhythmia), acute coronary syndrome (ischaemic symptoms and development of abnormal Q waves on the EKG, or EKG changes indicating ischaemia or total creatine kinase elevation to more than twice the upper limit of normal), hospitalisation for heart failure, and revascularisation procedures. When a patient had more than one coronary event during follow-up, only the first coronary event was used in the analysis. Cardiovascular treatments were administered at the cardiologist's discretion. Endpoint classification was made without knowledge of the OSA treatment group.

Statistical analysis

Continuous variables are presented as mean ± SD or median (first quartile—third quartile). Groups were compared for continuous variables using the Student's *t* test, or the Mann—Whitney nonparametric test when the frequency distribution was skewed. Categorical variables were compared using χ^2 statistics or the Fisher exact test. Cardiovascular event-free survival curves were calculated with the Kaplan—Meier method and compared with the log-rank test. All tests were two-sided. Prognostic factors associated with a *P* value of less than 0.2 were then introduced in a Cox proportional hazards model with descending stepwise procedure. Major interactions were explored. Final *P* values smaller than 0.05 were considered statistically significant. All analyses were performed with Statview 4.5 software (Abacus, Berkeley, CA).

Results

Between September 1991 and June 1999, 54 patients fulfilled our entry criteria and were included in the study. Among them, 25 accepted treatment for their OSA, either nCPAP (21 patients) or surgery (turbinectomy in 4 patients, complemented by ethmoidectomy in 1 patient and septoplasty in another), and 29 refused treatment. Reasons for refusal were concern that nCPAP would adversely affect quality of life and reluctance on the part of the general practitioner.

Clinical characteristics and cardiovascular features at the time of OSA diagnosis were similar in the two groups (Table 1). All the patients but one were men. Most patients had cardiovascular risk factors and the proportions of patients with a positive smoking history, hypertension, diabetes mellitus, hypercholesterolaemia, or obesity were similar in the two groups, as was the number of risk factors per patient (Table 2). In both groups, most patients had experienced several cardiovascular events; thus, 60% had a history of myocardial infarction and all but one had undergone percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG).The left ventricular ejection fraction (LVEF) at baseline was near normal in most patients in both groups, being below 35% in only 3 OSA-treated patients (3/25, 12%) and 3 OSA-untreated patients (3/29, 10%). Median time from the diagnosis of CAD to the diagnosis of OSA was 16.0 months (range 6.25—53.75 months) in the OSA-treated group and 19.0 months (range 10.75—33.75 months) in the OSA-untreated group (P>0.05). The median time between the last coronary event and OSA diagnosis was 4 months (range 1.75—13.25 months) and 6 months (range 1—13 months), respectively, in the treated and untreated groups ($P > 0.05$). The percentage of patients who underwent coronary revascularisation at this time did not differ significantly between the 2 groups, being 88% and 86% in the OSA-treated and un-

Table 1 Characteristics at the time of OSA diagnosis

	OSA-treated group, $N = 25$	OSA-untreated group, $N = 29$
Age, year	57.7 ± 10.1	57.0 ± 10.2
Sex, M/F	24/1	29/0
BMI, kg/m^2	28.4 ± 4.2	28.2 ± 3.4
	No. of patients (%)	
Treatments		
Platelet inhibitor	24 (96)	28 (96)
Beta-blocker	18 (72)	24 (82)
Statin	11 (44)	9 (31)
ACE inhibitor	11 (44)	9 (31)
Calcium antagonists	8 (32)	11 (37)
Patients with previous		
Myocardial infarction	15 (60)	19 (65)
PTCA	20 (80)	28 (96)
CABG	8 (32)	7 (24)
LV ejection fraction	57.5 ± 14.7	54.6 ± 14.1
Number of vessels with CAD		
One	8 (32)	11 (38)
Two	6 (24)	10 (34)
Three	11 (44)	8 (27)

Plus/minus values are means ± SD. There were no significant differences between the two groups for any of the variables. Body mass index (BMI) is the weight in kilograms divided by the square of the height in meters. ACE, angiotensin-converting enzyme; CAD, coronary artery disease; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery by-pass graft; LV, left ventricle.

Table 2 Risk factors at the time of OSA diagnosis

	OSA-treated group, $N = 25$	OSA-untreated group, $N = 29$
	No. of patients (%)	
BMI >30 kg/m^2	9 (36)	9 (31)
Current smoker	6 (24)	9 (31)
Hypercholesterolaemia	19 (76)	20 (68)
Diabetes mellitus	4 (19)	7 (24)
Hypertension	10 (40)	15 (51)
Family history of CAD	13 (52)	16 (55)
Number of risk factors		
One	7 (28)	7 (24)
Two	10 (40)	14 (48)
Three	2 (8)	3 (10)
Four	3 (12)	4 (14)

treated group, respectively. There was a nonsignificant trend toward a higher proportion of CABG in the OSA-untreated group (20% vs. 13.6%).

The severity of OSA at baseline was similar in the two groups: mean AHI was 33.7 ± 16.8 and 29.0 ± 12.8 ($P = 0.25$), the lowest O_2 saturation was $82 \pm 8\%$ and $85 \pm 8\%$, and the percent of nocturnal sleep time spent with an O_2 saturation below 90% was $8.1 \pm 11.5\%$ and $4.5 \pm 7.5\%$ in the OSA-treated and OSA-untreated groups, respectively. The oxygen desaturation ($\geqslant 4\%$) index did not differ between the 2 groups, with a median of 10/h (range 2.1—21.0/h) versus 2.15/h (range 0.4—12.9/h) in the OSA-treated and OSA-untreated groups, respectively. However, there was a nonsignificant trend toward a higher proportion of patients with severe OSA (AHI >30) in the OSA-treated group (52% vs. 44.8%).

Follow-up

The median duration of follow-up did not differ between the OSA-treated and OSA-untreated groups (median time: 86 months [range 62.75—96.00 months] and 90 months [range 49.50—99.75 months]), respectively ($p > 0.05$). During follow-up, 3 patients who initially used nCPAP stopped this treatment, 2 after 18 months and 1 after 5 years; these 3 patients were kept in the OSA-treated group for the initial analysis. In the remaining OSA-treated patients, nCPAP use was at least 3 h per night with a mean time of 5.7 ± 1.5 h per night for the entire group. The therapeutic effect of nCPAP was assessed in 20 of the 21 patients treated with nCPAP, all of whom had a mean AHI $\leqslant 10$, with a decrease from 33.7 ± 16.8/h at baseline to 3.9 ± 2.9/h. Of the 4 patients treated surgically, one had an AHI of 0 and 2 had an AHI of 8; PSG could not be repeated in remaining patient. Polysomnography was not performed during follow-up in the group in which OSA was not treated.

At the end of follow-up, neither cardiovascular treatments nor risk factor control differed significantly between the two groups (Table 3). As shown in Fig. 1, at least one cardiovascular event occurred during follow-up in 6 (24%) OSA-treated patients and in 17 OSA-untreated patients (58%) ($P < 0.01$). The first cardiovascular event in the OSA-treated group was acute coronary syndrome in 5 patients and PTCA in 1 patient (for a positive stress test without symptoms); the first event in the OSA-untreated group was cardiovascular death in 1 patient, hospital admission for heart failure in 1 patient, PTCA in 2

Table 3 Risk factors and cardiovascular treatments at the end of follow-up

	OSA-treated group, $N = 25$	OSA-untreated group, $N = 29$
BMI, kg/m^2	29.1 ± 3.9	28.2 ± 3.4
	No. of patients (%)	
BMI >25 kg/m^2	21 (83)	21 (71)
Current smoker	4 (16)	6 (21)
Uncontrolled hypercholesterolaemia	7 (28)	4 (14)
Uncontrolled hypertension	2 (8)	5 (17)
Treatments		
Platelet inhibitor	23 (92)	29 (100)
Beta-blocker	15 (60)	19 (66)
Statin	17 (68)	22 (76)
ACE inhibitor	14 (56)	17 (59)
Calcium antagonists	10 (40)	13 (45)

Plus/minus values are means $\pm$ SD. There were no significant differences between the two groups for any of the variables. Body mass index (BMI) is the weight in kilograms divided by the square of the height in meters. ACE, angiotensin-converting enzyme.

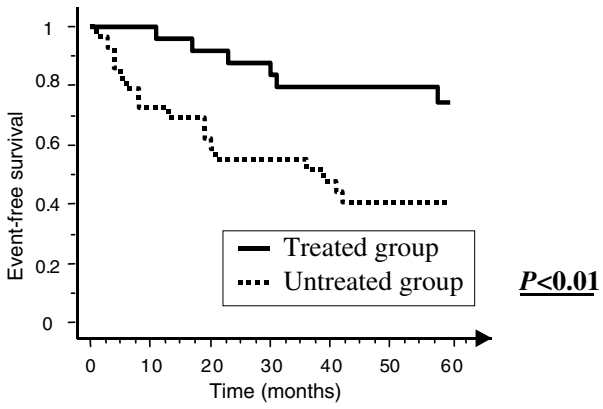

Fig. 1 Kaplan–Meier analysis: event-free survival in the groups with and without treatment for obstructive sleep apnea.

patients (for a positive stress test without symptoms), and acute coronary syndrome in 13 patients. The 3 OSA-treated patients (ages 41, 45, and 67 years) with none of the risk factors listed in Table 2 remained event-free during follow-up, whereas the only OSA-untreated patient (age 63 years) with no risk factors experienced unstable angina during follow-up. All 3 cardiovascular deaths observed during follow-up were in OSA-untreated patients, 2 being preceded by a first coronary event.

The time from OSA diagnosis to the first event was significantly longer in the OSA-treated group than in the OSA-untreated group (median time: 26.5 months [range 17–31 months] vs. 13.0 months [4.75–24.75 months], respectively, $P < 0.05$).

One of the patients who discontinued nCPAP after 18 months had a coronary event 13 months after stopping treatment. The other 2 remained free from a new cardiovascular event. When these 3 patients were excluded from the analysis, the difference between survival free from new cardiovascular event remained significant $(P < 0.01)$.

We tested separately hypertension, current smoking, hypercholesterolaemia, diabetes mellitus, age >60 years, BMI >25 kg/m^2, AHI >30, LVEF <45% as predictors of coronary events. As the *P*-values were <0.2 for BMI, hypertension, hypercholesterolaemia, age, AHI, and OSA treatment, we introduced them in a Cox model in order to adjust treatment effect on these prognostic factors. In the final model, only treatment for OSA had a significant influence on the survival free of a new coronary event. The risk for experiencing a cardiovascular event during follow-up was significantly decreased in the OSA-treated group as compared to the OSA-untreated group (hazard ratio 0.24; 95% confidence interval, 0.09–0.62; $P < 0.01$).

Discussion

The main finding of our study is that the treatment of OSA in CAD patients was associated with a significant decrease in cardiovascular events, defined as cardiovascular death, acute coronary syndrome, hospitalisation for heart failure, or need for coronary revascularisation. In addition, the time to events was longer in the group of patients who accepted OSA treatment. These data strongly suggest that OSA has a deleterious effect on CAD outcomes and that this effect can be abolished by specific treatment.

That OSA is associated with an increased risk of cardiovascular events in CAD patients has been reported previously. Mooe et al.[10] observed a 62% relative increase and a 10.1% absolute increase in a composite endpoint of cardiovascular events (death, cerebrovascular events, and myocardial infarction) in patients with CAD and OSA during a median follow-up of 5.1 years. In a 5-year prospective follow-up study, OSA independently predicted cardiovascular mortality after an acute coronary syndrome and was associated with a 3-fold increase in the risk of death after adjustment for other risk factors.[11] Similarly, we found a 3-fold increase in cardiovascular events in patients with untreated OSA as compared to treated patients.

The worse cardiovascular outcomes in CAD patients with OSA cannot be entirely explained by the effects of risk factors associated with OSA, such as age and obesity. Each apnoeic episode is associated with arterial oxygen desaturation, which causes sympathetic system overactivity that is responsible for tachycardia and transient SBP elevation.[12] Thus, large oscillations in systemic blood pressure and episodes of hypoxia-reoxygenation occur repeatedly throughout the night. The increase in myocardial O_2 consumption due to tachycardia and SBP elevation at a time when the O_2 supply is decreased can be expected to be particularly deleterious in patients with CAD. Indeed, nocturnal myocardial ischaemic events commonly occur during the rebreathing phase in apnoeic patients with CAD.[13,14] Sympathetic activity, which remains increased during the day in OSA patients as compared to nonapnoeic obese subjects of similar age,[12,15] may contribute to the increased platelet activation and aggregation associated with OSA.[16–18] Treatment with nCPAP reduces sympathetic activity,[19,20] diminishes platelet activation and aggregation, and decreases nocturnal ischaemic events.[13]

Repeated episodes of hypoxia-reoxygenation may also result in oxidative stress causing abnormal lipid peroxidation.[21] In patients with severe OSA, oxidation of low density lipoprotein (LDL) particles normalises after nCPAP treatment.[21] Similarly, the increased production of reactive oxygen species in neutrophils and monocytes seen in OSA is normalised by nCPAP.[22] Altogether, these data point to increased oxidative stress in OSA, which may result in endothelial dysfunction[23,24] and enhanced atherogenesis, but responds favourably to nCPAP.

Circulating levels of C-reactive protein, fibrinogen, and IL-6 are elevated in apnoeic patients and decrease significantly with effective nCPAP.[25–28] Plasma levels of these markers for inflammation have been associated with mortality in patients with CAD. In addition, the expression of soluble adhesion molecules has also been found to be increased in OSA patients with or without CAD[29,30] and to be associated with an increased risk of

myocardial infarction in apparently healthy men. All these data are consistent with the hypothesis that the pathogenic effects of OSA may promote atherosclerosis but may be reversed by effective treatment of the breathing disorder.

However, direct demonstration of an independent role of OSA is difficult because cardiovascular risk factors such as obesity are associated with OSA. Moreover, OSA has been identified as an independent risk factor for the development of hypertension[31–33] and is common in patients with uncontrolled hypertension.[34] In addition, severe OSA predicts poor blood pressure control with medications[35] and nCPAP may significantly lower both day-time and night-time blood pressure values.[9] Interestingly, we found a trend toward better blood pressure control in OSA-treated patients, although this variable was similar in the two groups at baseline. Therefore, we cannot rule out the possibility that part of the reduction in cardiovascular events with OSA treatment was related to improved blood pressure control. This effect, together with abolition of the negative intrathoracic pressure swings that accompany apnoea, may have significantly reduced left ventricular afterload and myocardial O_2 requirement.

The main limitations of this study are the absence of randomisation and the small number of patients. However, using sham CPAP during the long period needed to allow assessment of clinical endpoints would be ethically questionable. The two groups did not differ significantly for known risk factors or treatment during follow-up, except for OSA therapy, but we cannot exclude that small differences failed to reach statistical significance because of the small size of the population. Nevertheless, our findings are strengthened by the fact that each component of the composite endpoint (cardiovascular death, acute coronary syndrome, hospitalisation for heart failure, PTCA, and bypass surgery) was less common in the treated than in the untreated group.

This is the first study, to our knowledge, indicating a beneficial effect of OSA treatment on event-free survival in CAD patients. Although not randomised, our study strongly supports the importance of recognising and treating OSA in this population.

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