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Long-term Effects of Nasal Continuous Positive Airway Pressure Therapy on Cardiovascular Outcomes in Sleep Apnea Syndrome*

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Background: **Obstructive sleep apnea syndrome (OSAS) has been associated with increased morbidity and mortality, principally from cardiovascular disease, but the impact of nasal continuous positive airway pressure (CPAP) therapy is unclear.**
Methods: **We performed a long-term follow-up study of 168 patients with OSAS who had begun receiving CPAP therapy at least 5 years previously, most of whom had been prospectively followed up, having been the subject of an earlier report on cardiovascular risk factors in OSAS patients. The average follow-up period was 7.5 years. We compared the cardiovascular outcomes of those patients who were intolerant of CPAP (untreated group, 61 patients) with those continuing CPAP therapy (107 patients).**
Results: **CPAP-treated patients had a higher median apnea-hypopnea index score than the untreated group (48.3 [interquartile range (IQR), 33.6 to 66.4] vs 36.7 [IQR, 27.4 to 55], respectively; $p = 0.02$), but age, body mass index, and time since diagnosis were similar. Deaths from cardiovascular disease were more common in the untreated group than in the CPAP-treated group during follow-up (14.8% vs 1.9%, respectively; $p = 0.009$ [log rank test]), but no significant differences were found in the development of new cases of hypertension, cardiac disorder, or stroke. Total cardiovascular events (*ie*, death and new cardiovascular disease combined) were more common in the untreated group than in the CPAP-treated group (31% vs 18%, respectively; $p < 0.05$).**
Conclusions: **The data support a protective effect of CPAP therapy against death from cardiovascular disease in patients with OSAS.** ***(CHEST 2005; 127:2076–2084)***

Key words: cardiovascular mortality; continuous positive airway pressure therapy; obstructive sleep apnea

Abbreviations: AHI = apnea-hypopnea index; BMI = body mass index; CHF = congestive heart failure; CPAP = continuous positive airway pressure; IQR = interquartile range; OSAS = obstructive sleep apnea syndrome

Obstructive sleep apnea syndrome (OSAS) has a prevalence of 2 to 4% in the adult population[1] and is associated with a reduced quality of life[2] and increased risk of road traffic accidents due to excessive sleepiness.[3] Continuous positive airway pressure (CPAP) is an effective therapy and is the most widely used modality in patients with moderate-to-severe disease.[4] OSAS is also associated with an increased risk of cardiovascular disease,[5–9] especially hypertension.[10–12] However, the evidence that OSAS is an independent risk factor for cardiovascular disease or death has been disputed[13] on the basis that some previous studies[14–16] supporting a causative association may have been too small, may have failed to take into account other known cardiovascular risk factors, or may have had an inadequate duration of follow-up. Furthermore, Veale and coworkers[17] found that, although the overall mortality rate was similar to that of the normal population, patients with OSAS who had been prescribed nasal CPAP therapy died mainly from cardiovascular disease.

If OSAS is an independent risk factor for the development of cardiovascular disease, it could be hypothesized that effective therapy for the disorder would likely reduce the long-term risk of the development and progression of such disease, and two

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reports[18,19] have supported this possibility. We have previously reported[20] the cardiovascular risk factors of 114 consecutive patients with OSAS who were assessed in our unit. Using this prospective patient cohort, together with other patients in whom OSAS had previously been diagnosed, for whom similar baseline data as those in this report were available, we performed a long-term follow-up study comparing the cardiovascular outcomes of those patients who continued to receive CPAP therapy with those who had quit therapy. The primary outcome of the study was cardiovascular morbidity and mortality, and this outcome was designated prior to the study.

Materials and Methods

Patient Selection

Approval for the study was obtained from our hospital ethics committee. Patients included the cohort of patients whose baseline data have previously been reported,[20] in addition to those patients who had OSAS diagnosed between 1990 and 1995 in our sleep laboratory, where similar baseline data were available. All patients fulfilled the entry criteria of an apnea-hypopnea index (AHI) of >15 events per hour on overnight sleep studies performed with a polysomnography system (Oxford Medilog SAC847 polysomnography system; Oxford Instruments; Oxford, UK) together with symptoms in keeping with a diagnosis of OSAS.[21,22] We excluded patients in whom OSAS had been diagnosed by overnight oximetry alone and those for whom baseline data were incomplete. The initial cohort of 114 patients was recruited as a consecutive group of patients coming through our sleep disorders unit and was prospectively followed up in our clinic on an annual basis with the intention of evaluating long-term cardiovascular outcomes. The additional patients in the present report were not consecutive, and their inclusion would properly be described as retrospective since they were not prospectively enrolled. However, all had the same baseline data as the prospective cohort and were followed up in the same manner as in our clinic. Furthermore, there was no difference between the prospective cohort and the additional group in anthropometric characteristics and OSAS severity.

Baseline Data

Baseline data consisted of age, body mass index (BMI), AHI, Epworth sleepiness scale score,[23] smoking and alcohol history, and cardiovascular history, in addition to fasting lipid levels, and fasting and 2-h blood glucose levels. The Epworth sleepiness scale is a well-recognized subjective sleepiness scale ranging from 0 to 24, and the normal range for our center is ≤ 8. Excess alcohol consumption was defined as $>$ 21 U weekly for men and $>$ 14 U for women. A unit of alcohol is a standard term to describe a single measure of liquor, a glass of wine or a small beer. Cardiovascular history was determined during the initial clinical assessment and from previous hospital records. The cardiovascular diseases included were hypertension, ischemic heart disease (*ie*, documented angina or a history of a myocardial infarction), congestive heart failure (CHF), cardiac arrhythmias (defined as any cardiac rhythm disturbance requiring medical intervention), and stroke. Any history of diabetes mellitus or nasal surgery was also recorded.

Follow-up Data

Follow-up information was obtained from hospital and/or clinic records, and by contact with the patient's family practitioner. A specially designed questionnaire was also posted to each patient requesting details of height and weight, the use of CPAP therapy, Epworth sleepiness scale score, smoking history, and current alcohol intake, in addition to information on any new medical diagnosis and/or ongoing use of medications since commencing CPAP therapy. Information was sought on any otolaryngologic procedure or oral appliance prescribed for the treatment of OSAS. In the event of death, the cause was determined from the patient's own physician and/or death certificate, and a close family member was contacted to seek information on the hour of death and whether the patient had continued to use CPAP. Nonresponders were sent a second and third postal reminder and were followed up by telephone. The questionnaire was mailed to the subjects at the time of the present study, and the time interval from initial enrollment was 91 months (interquartile range [IQR], 83 to 103 months), reflecting the time range over which the patients were initially recruited.

Statistical Analysis

Results are expressed as the mean $\pm$ SD for quantitative variables if normally distributed and as the median (IQR) if otherwise distributed. Qualitative variables were expressed as the absolute number (percentage). The comparison of numerical data was achieved using the unpaired Student t test, and the comparison of categoric data was achieved using the χ^2 formula. When the application conditions were not met, the Wilcoxon rank sum test and the Fisher Exact Test were used. The Kaplan-Meier method of survival analysis was applied for the calculation of survival rates, and log-rank analysis was used to detect differences between groups. A multivariate logistic regression analysis was performed to assess the predictive variables of cardiovascular mortality and other cardiovascular end points. The included variables were selected if they were significant during univariate analysis or were considered to be biologically relevant. The data were expressed as the odds ratio (confidence interval). A p value of < 0.05 was regarded as significant.

Results

Patients in whom OSAS was diagnosed were offered CPAP therapy within at least 3 months of receiving the diagnosis. A total of 223 patients satisfied the inclusion criteria. Despite repeated attempts by mail, telephone, and contacting of the family physician, which were indicated in the patient's clinical records, we were unable to collect follow-up information from 55 patients, which resulted in an overall 75% response rate. A chart review of the patients in whom follow-up information could not be obtained indicated that all had defaulted from follow-up in the sleep clinic and also with the family physician. Responders were categorized into the following two groups: those who indicated continuing use of CPAP therapy (the CPAP group); and those who never tolerated CPAP therapy or had stopped CPAP therapy for at least 5 years (the untreated group). Responders and nonre-

sponders did not differ significantly in terms of BMI, AHI, or time since the diagnosis of OSAS, but nonresponders were significantly younger than responders (Table 1). The reason for noncompliance with CPAP therapy was not recorded, but 55% of patients refused CPAP therapy outright, and the remainder refused therapy after a short period.

Baseline Data

There were no significant differences between the CPAP group and the untreated group in terms of age, BMI, and cardiovascular risk factors at baseline, but subjects in the untreated group had a significantly lower AHI, and more patients in the untreated group had undergone nasal surgery prior to the diagnosis of OSAS (Table 2). The percentage of patients receiving any cardiovascular medication (including aspirin, lipid-lowering, antianginal, antiarrhythmic, and antihypertensive agents) did not differ significantly between the two groups at baseline. Since patients were recruited during the early to mid 1990s, data on the Epworth sleepiness scale score were available in only 87 respondents (approximately 52% of each group) and therefore were not formally included in the follow-up analysis. However, an analysis of these data revealed that patients in the CPAP group showed a slight trend to be sleepier (ie, they had a higher Epworth sleepiness scale score) than those in the untreated group (15.2 ± 6.3 vs 12.6 ± 5.6, respectively; $p = 0.6$ [Wilcoxon rank sum test]). Pulmonary function was similar in the CPAP group and the untreated group (Table 2).

Follow-up Data

At follow-up, despite dietary advice being given to all patients presenting to our sleep disorders unit, the median BMI did not change significantly in either the CPAP group (31.2 kg/m^2 [IQR, 27.6 to 36.1 kg/m^2] vs 31.1 kg/m^2 [IQR, 27.5 to 35.2 kg/m^2], respectively; $p = 0.9$), or the untreated group (30.2 kg/m^2 [IQR, 26.5 to 34.5 kg/m^2] vs 29.4 kg/m^2 [IQR, 26.4 to 34.6 kg/m^2], respectively; $p = 0.9$). The median time interval between diagnosis of OSAS and the follow-up was also similar in both groups (CPAP group: median, 92 months; IQR, 82 to 104.5 months; untreated group, 90 months; IQR, 83.5 to 96.5 months; $p = 0.7$). There were no differences between the CPAP and untreated groups in the rate of subsequent otolaryngologic surgery during follow-up (7.5% vs 8.2%, respectively; $p = 0.9$), or in the numbers of patients who were continuing to smoke (11% vs 15%, respectively; $p = 0.5$). No patient was using an oral appliance.

Table 1—*Comparison of Baseline Data Among Responders and Nonresponders

Variables	Responders	Nonresponders	p Value
Patients, No.	168	55	
Men, No.	155	53	
Age, yr	51.1 ± 10.8	47.5 ± 8.7	0.03
BMI, kg/m^2	30.5 (27.4–35.4)	31.7 (27.2–35.3)	NS
AHI, events/h	46.3 (30–62.5)	53.1 (35.1–67)	0.2
Time since OSAS diagnosis, mo	91 (83–103)	94 (84–100)	NS

*Values given as mean ± SD or median (IQR), unless otherwise indicated. NS = not significant.

Cardiovascular Morbidity and Mortality

Figure 1 illustrates the changes in the prevalence of cardiovascular disease in both the CPAP group and the untreated group from baseline to follow-up. During the period of follow-up, there was a significant excess of cardiovascular deaths (nine deaths [14.8%] vs two deaths [1.9%], respectively; $p = 0.009$) and a nonsignificant increase in cardiovascular morbidity in the untreated group compared to those in the CPAP group. Furthermore, the total number of cardiovascular events (death and new cardiovascular disease combined) was significantly greater in the untreated group compared to that in the CPAP group (19 events [31%] vs 19 events [18%], respectively; $p < 0.05$). However, the difference in the total number of deaths between the two groups showed only a trend toward an increase in the untreated group (untreated group, nine deaths [14.8%]; CPAP group, eight deaths [7%]; $p = 0.3$ [log-rank test]).

Figure 2 illustrates the Kaplan-Meier survival analysis for cardiovascular death in CPAP users and nonusers. Univariate predictors of cardiovascular death in the total population were CPAP use, a history of diabetes mellitus, and a history of ischemic heart disease and CHF at baseline. Apart from heart failure, these variables remained independently predictive of cardiovascular death on multivariate analysis (Table 3).

Of those patients who died, there was no difference between the two groups in age at diagnosis, BMI, and AHI. The causes of death for patients in both groups are listed in Table 4. Of the deaths in the CPAP group, only two were possibly cardiac in nature, and one of those occurred during surgery with the patient under general anesthesia. In the untreated group, six patients were known to have died from cardiovascular causes, and in the remaining three patients a presumptive cause of cardiovascular death was made by the family physician. In all cases, cardiovascular disease was the primary cause of death given on the death certificate. Most patients

Table 2—*Baseline Data of OSAS Patients Treated With CPAP Compared to Those Untreated

Variables	CPAP-Treated Patients	Untreated Patients	p Value
Patients, No.	107	61	
Men, No.	100	55	NS
Age, yr	50.1 ± 11.4	52.8 ± 9.6	NS
BMI, kg/m^2	31.2 (27.6–36.1)	30.2 (26.5–34.5)	NS
AHI, events/h	48.3 (33.6–66.4)	36.7 (27.4–55)	0.02
Previous nasal surgery	16 (5)	17 (28)	0.04
Fasting cholesterol, mmol/L	5.8 ± 1.1	5.7 ± 1.0	NS
Fasting triglycerides, mmol/L	2.2 ± 1.5	2.2 ± 1.2	NS
Fasting glucose, mmol/L	5.8 ± 1.5	5.5 ± 0.7	NS
BP			
Systolic	139 ± 27.2	136 ± 19	NS
Diastolic	85 ± 17.7	85.4 ± 9.1	NS
Current smokers	28 (26.2)	13 (21.3)	NS
Excess alcohol intake	16 (15)	11 (18)	NS
Hypertension	25 (23.4)	12 (19.7)	NS
Ischemic heart disease	9 (8.4)	5 (8.2)	NS
Cardiac failure	3 (2.8)	2 (3.3)	NS
Cardiac arrhythmia	1 (0.9)	3 (4.9)	NS
Cerebrovascular disease	2 (1.9)	1 (1.6)	NS
Diabetes mellitus	7 (6.5)	2 (3.3)	NS
Pulmonary function†			
FEV_1, L	3.3 ± 0.94 (96)	3.2 ± 0.9 (94)	NS
FVC, L	4.19 ± 0.9 (97)	4.15 ± 0.9 (101)	NS
DLCO, mL/min	26.83 ± 5.4 (89)	26.5 ± 9.2 (93)	NS

*Values given as mean ± SD, median (IQR), or No. (%), unless otherwise indicated; DLCO = diffusion capacity of the lung for carbon monoxide. See Table 1 for abbreviation not used in the text.
†Values in parentheses are %.

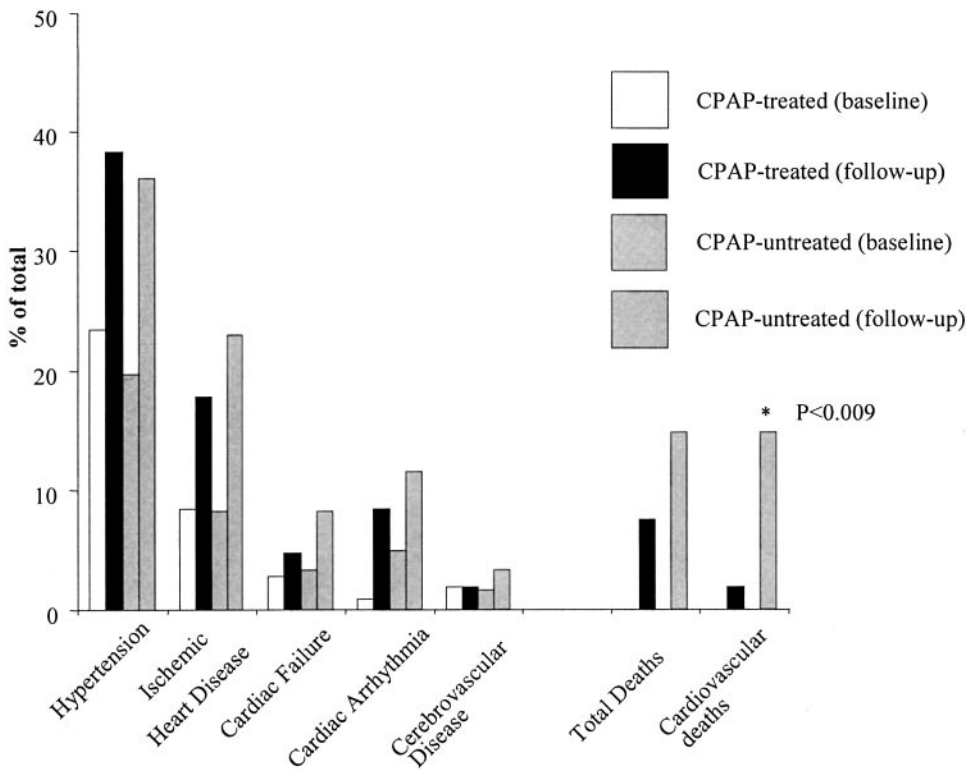

FIGURE 1. Cardiovascular disease and mortality in CPAP-treated patients and untreated patients at baseline and follow-up.

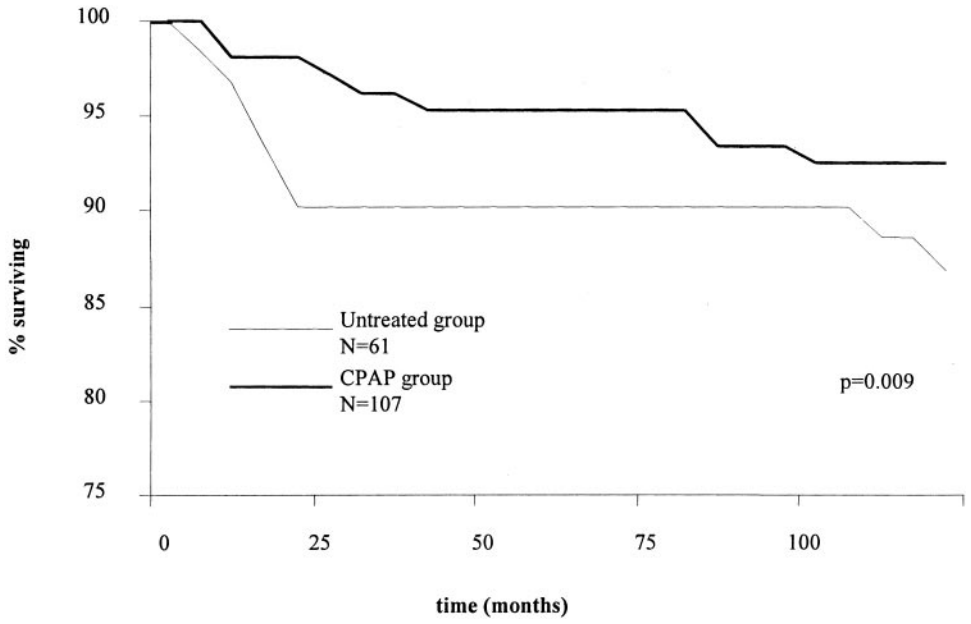

FIGURE 2. Kaplan-Meier survival curve for cardiovascular death in CPAP-treated patients and untreated patients.

Table 3—*Cox Regression Analysis of Clinical and Pathologic Features Influencing Survival in OSAS Patient Population (n = 168)**

	Univariate Analysis			Final Regression Model	
Variables†	Cases, No.	Survival, %	p Value	RR (95% CI)	p Value
Age					
A (13–47 yr)	56	94			
B (47–56 yr)	56	100	0.46		
C (56–77 yr)	56	80			
BMI					
A (19.2–28.4)	56	100			
B (28.5–33.8)	56	81.5	0.15		
C (33.8–54.1)	56	92			
AHI					
A (15–35)	56	91			
B (35–55)	56	88	0.09		
C (55.3–131.5)	56	98			
CPAP therapy					
Continued	107	93	0.009		
Stopped	61	85		0.08 (0.01–0.52)	0.008
Cigarettes					
Current smokers	41	92.7			
Ex-smokers	72	96	0.9		
Nonsmokers	55	86			
Alcohol intake					
Excess	27	89	0.25		
Social	141	92			
History					
Hypertension	43	89	0.09		
Ischemic heart disease	17	43	0.005	8.61 (1.76–42.02)	
Cardiac failure	12	43	0.02		
Cardiac arrhythmias	4	100	0.14		
Diabetes mellitus	9	89	0.008	9.65 (1.61–57.56)	0.013

*RR = relative risk; CI = confidence interval.

†Age, BMI, and AHI are expressed in tertiles (A,B,C) of 56 patients.

Table 4—*Age, BMI, AHI, and Cause of Death of Patients Who Died in CPAP Group and Untreated Group

Variables	CPAP-Treated Patients	Untreated Patients	p Value
Age at diagnosis, yr	61.6 ± 12.7	56 ± 12.7	NS
BMI, kg/m^2	31.1 (29.9–34.3)	33.8 (30.1–44.4)	NS
AHI, events/h	48.6 (40.3–53.4)	34.2 (26.8–60.4)	NS
Time from OSA diagnosis till death, mo	34.5 (18.8–75)	18 (14.5–36)	NS
Deaths, No. (% total group)	8 (7)	9 (15)	
Cause of death			
1	Myocardial infarction at 7:00 PM	Sudden unexpected death at 7:00 AM; presumed cardiac	
2	Cardiac arrhythmia during cardiac bypass surgery	Sudden unexpected death at 4:45 AM; presumed cardiac	
3	Suicide	Sudden unexpected death at 8:00 AM; presumed cardiac	
4	Exacerbation of COPD	Heart failure at 1:00 PM	
5	Postoperative hemorrhage	Myocardial infarction at 10:30 AM	
6	Lung carcinoma	Sudden unexpected death at 9:00 AM; history of valvular heart disease, coronary bypass grafting	
7	Colon carcinoma	Myocardial infarction at 1:30 PM	
8	Septicemia complicating renal cell carcinoma	Stroke at 3:00 PM; history of heart failure	
9		Stroke at 9:00 AM; history of heart failure	

*Values given as mean ± SD or median (IQR), unless otherwise indicated. See Table 1 for abbreviation not used in the text.

in the untreated group died during the night or early morning (Table 4), and four of the nine deaths were sudden and unexpected.

Discussion

This study supports a beneficial effect of long-term CPAP therapy on cardiovascular mortality in patients with OSAS, which was independent of age, BMI, smoking and alcohol history, and severity of OSAS. The only significant difference between the CPAP group and the untreated group at baseline was a higher AHI in the CPAP group, which might have been expected to predispose those patients to a higher incidence of cardiovascular disease than those in the untreated group, as has been observed.[8] Other relevant factors such as age, BMI, or the presence of other cardiovascular risk factors were similar at baseline in both groups.

Although our sample size was small, baseline population characteristics were quite similar to those of previously published studies,[14–19] and, therefore, we believe, it was representative of the OSAS population as a whole. Furthermore, our conclusions support and extend the findings of other published studies. Peker et al[18] reported the 7-year follow-up of 60 OSAS patients and 122 non-OSAS subjects who were free of cardiovascular disease at baseline. They found a significant increase in the incidence of cardiovascular disease among incompletely treated OSAS patients compared to those who were efficiently treated after adjusting for age, BMI, BP, and smoking, although the untreated patients were significantly older than the treated patients. Marti et al[19] reported the long-term survival of a historical cohort of 444 patients with OSAS who had been followed up for 4 to 14 years to be 65% in the group of 98 untreated patients compared to 90% in the treated group, with the statistics for the latter group being similar to those of the general population. Treatment consisted of CPAP, diet, and/or surgery. Veale et al[17] reported the mortality rate of 5,669 OSAS patients who had been treated with CPAP over a period of 2 to 11 years to be similar to the general French population, but compliance with CPAP was significantly worse in patients who died. Finally, Lindberg at al[24] reported the 10-year follow-up of a sample of 3,100 middle-aged men who responded to a postal questionnaire and found a significantly higher mortality rate among those who reported snoring and sleepiness compared to those of nonsleepy snorers and those who had reported neither symptom.

We believe that the present study has a number of strengths when compared to previous reports in that both groups were contemporaneous, detailed baseline data were available on all patients, and there were no potentially confounding differences in baseline data between groups. Furthermore, patients in the untreated group were only given dietary and lifestyle advice, and none were managed by use of a mandibular advancement device since such therapy has only become available through our center in more recent years. Since this general dietary and lifestyle advice was also given to those patients in the CPAP group, the only major difference in manage-

ment between groups was CPAP therapy. Thus, those patients in the untreated group might be considered to be a reasonable control group for comparison purposes in this particular setting.

An important limitation of the present study is that we did not randomly allocate our control group to conservative therapy, and that the control patients were those who were noncompliant with CPAP therapy. However, we strongly believe that such a randomized long-term follow-up study would be unethical in a group of patients with severe OSAS, given the available evidence[25,26] on accident risk and the related benefits of CPAP therapy in such patients. Another limitation is that only a part of the study population was selected and followed up in a prospective fashion, namely, the 114 patients included in a previous report from this department.[20] The remaining patients were included at a later date, but had the same baseline data collected and were followed up in our clinic in the same manner as that of the prospective cohort. In addition, this latter group was no different from the prospective cohort in terms of anthropometric characteristics, OSAS severity, CPAP adherence, and cardiovascular complications.

We recognize that since the untreated group had failed to comply with CPAP therapy, it could be argued that this group might be noncompliant in general, and thus noncompliant with cardiovascular medications, where prescribed, and with general dietary and lifestyle advice. However, both groups were very similar at baseline, and neither group demonstrated a significant change in BMI at follow-up. Furthermore, it is our clinical experience that most patients are intolerant of CPAP therapy because of feelings of claustrophobia and blocked nasal passages rather than because of a negative attitude toward therapy in general. In this regard, it is noteworthy that significantly more patients in the untreated group gave a history of previous nasal surgery at baseline (Table 2), suggesting a higher prevalence of nasal obstruction in this group. In most cases, CPAP therapy compliance was self-reported since most patients were supplied with a CPAP device that did not contain a built-in time clock. However, patients are more likely to overestimate rather than underestimate their CPAP use,[27] therefore any possible cardioprotective effect of CPAP therapy is also likely to be underestimated. It could also be argued that since the method of deriving information from postal questionnaires depends on accurate self-reporting by the patient, the prevalence of cardiovascular disease also may be misrepresented. We feel that this is unlikely because questions were phrased with minimal ambiguity, and information was double-checked against recent hospital records and/or with the family physician.

Baseline data in the majority of responding patients have previously been reported,[20] and the present report allows a comparison with the risk prediction for future cardiovascular disease identified in this earlier report. The rate of development of new-onset ischemic heart disease in the untreated group (14% for an average 8-year follow-up) was similar to the 10-year predicted risk of 13.4% that had been calculated in the previous report, whereas only 5% of patients in the CPAP group developed new-onset ischemic heart disease. These data support a protective effect of CPAP therapy on the future development of ischemic heart disease, although we recognize that the relatively small number of patients in our study makes it difficult to draw confident conclusions in this regard. A surprising finding was the number of patients in the CPAP group who died from noncardiovascular causes such as carcinoma. One could speculate that patients dying in the untreated group did so earlier during the course of follow-up from cardiovascular causes, whereas a putative protective effect of CPAP on cardiovascular mortality might have resulted in these patients dying at a later stage from other causes. Some support for this hypothesis comes from the fact that the time interval from diagnosis to death in the untreated CPAP group was approximately half that of those who died in the continuing CPAP group, although the difference was not statistically significant (Table 4).

The mechanisms by which OSAS predisposes a person to cardiovascular disease are not fully understood, but they likely include elevated sympathetic drive[28] secondary to recurrent hypoxias and arousals from sleep, with loss of the resetting of the baroreceptor control, and increased oxidative stress secondary to recurring oxygen desaturation and resaturation. The repetitive hypoxia and reoxygenation episodes that are characteristic of the OSAS result in the increased production of reactive oxygen species[29] which is associated with a differential expression of specific genes through the activation/up-regulation of redox-activated transcription factors including hypoxia inducible factor-1 and nuclear factor κB, among others. This up-regulation results in the increased production of an array of proteins including vascular endothelial growth factor. Circulating vascular endothelial growth factor levels are elevated in OSAS patients and fall with nasal CPAP therapy.[30] Furthermore, levels of nitric oxide, which is regarded as protective against vascular endothelial damage, are reduced in OSAS and increase with CPAP therapy.[31]

These changes likely take many years to evolve, which emphasizes the need for long-term follow-up to establish relationships of OSAS with cardiovascular disease and the potential benefits of CPAP therapy. While there is now clear evidence that OSAS is an independent risk factor for hypertension,[10–12] the evidence of an independent association with cardiac disease and stroke is less clear-cut. However, the Sleep Heart Health cohort study[5,12] reported an increased risk of hypertension, cardiac failure, stroke, and ischemic heart disease in patients with even mild OSAS, independent of age and BMI. While there is now evidence from short-term randomized controlled trials that CPAP therapy lowers BP levels in OSAS patients,[32] there is only limited evidence that CPAP therapy benefits patients with other forms of cardiovascular morbidity. The possibility of a direct beneficial effect on cardiac function rather than relief of obstructive sleep apnea as a potential mechanism of benefit from CPAP therapy in the present patient population can be considered in light of previous reports[33,34] that CPAP therapy benefits left ventricular function in selected patients with CHF. However, we believe this to be unlikely since only a very small proportion of our patients had CHF and there are differing views on the potential benefit of CPAP in such patients.[33–37] Furthermore, Sin et al[38] reported that CPAP therapy improved cardiac function in patients with both CHF and Cheyne-Stokes breathing, but not in those with CHF alone. These data suggest that the mechanism of benefit was predominantly related to the relief of a sleep-related breathing disturbance rather than a direct benefit on cardiac function *per se*.[38]

The predominance of nocturnal or early morning death in patients in the untreated group provides some support for an association with sleep-related events, and the high prevalence of sudden and unexpected deaths raises the possibility of a fatal arrhythmia in these cases. However, these possibilities must be regarded as purely speculative in view of the relatively small number of patients who died and the lack of objective information about the circumstances surrounding death. Furthermore, the reliance on death certification for the cause of death in such cases raises the possibility of error on the part of the certifying physician in cases in which a postmortem examination was not performed. In conclusion, the present study supports the hypothesis that OSAS is an independent risk factor for cardiovascular disease and that treatment with CPAP therapy reduces this risk.

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