

ORIGINAL ARTICLE

Atrial Overdrive Pacing for the Obstructive Sleep Apnea–Hypopnea Syndrome

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ABSTRACT

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BACKGROUND

The role of atrial overdrive pacing (AOP) in sleep apnea remains uncertain. We prospectively evaluated the effect of AOP after 24 hours and after one month in patients with the obstructive sleep apnea–hypopnea syndrome and compared it with the use of nasal continuous positive airway pressure (n-CPAP).

METHODS

We studied 16 patients with a moderate or severe case of the obstructive sleep apnea–hypopnea syndrome (baseline mean apnea–hypopnea index, 49) and normal left ventricular systolic function in whom a dual-chamber pacemaker had been implanted. After 48 hours, the patients were randomly assigned to AOP (pacing at 15 bpm above the spontaneous mean nocturnal heart rate) or backup atrial pacing (pacing at a heart rate below 40 bpm); the latter group began n-CPAP therapy one day later. After one month, the two groups switched therapies and were followed for an additional month. Polysomnographic studies were performed at baseline, on the first night after randomization, at crossover, and at the end of the study.

RESULTS

During AOP, no significant changes were observed in any of the respiratory variables measured. The change in the apnea–hypopnea index at one month with AOP was +0.2 (95 percent confidence interval, –2.7 to +2.3; $P=0.87$). In contrast, all variables improved significantly after one month of n-CPAP (change in the apnea–hypopnea index, –46.3; 95 percent confidence interval, –56.2 to –36.5; $P<0.001$).

CONCLUSIONS

Nasal continuous positive airway pressure therapy is highly effective for the treatment of the obstructive sleep apnea–hypopnea syndrome, whereas AOP has no significant effect.

THE OBSTRUCTIVE SLEEP APNEA-HYPOPNEA syndrome is a condition characterized by repeated episodes of upper-airway occlusion during sleep, with consequent excessive daytime sleepiness, impairment of quality of life, and abnormalities in cardiopulmonary function. It is the most common sleep-related breathing disorder and is associated with considerable morbidity and mortality.^{1,2}

Our understanding of the pathophysiology of the obstructive sleep apnea-hypopnea syndrome is somewhat limited. Anatomical narrowing of the airway, increased collapsibility of the airway tissues, a disturbance in the reflexes that affect the caliber of the upper airway, and abnormalities of pharyngeal-muscle function all contribute to upper-airway occlusion during sleep.³ However, it has also been suggested that the obstructive sleep apnea-hypopnea syndrome is a systemic illness associated with the metabolic syndrome, rather than simply a local airway abnormality.⁴

Treatments that have been used for the obstructive sleep apnea-hypopnea syndrome include upper-airway surgery, weight loss, oral appliances, and nasal continuous positive airway pressure (n-CPAP). Since 1981, n-CPAP has been considered first-line therapy and has proved to be highly effective in alleviating symptoms, reducing morbidity and mortality, and improving the quality of life.⁵⁻⁷ However, patients' compliance with n-CPAP is low (ranging from 65 percent to 80 percent) because of problems with the nasal-mask interface, limited acceptance of treatment, and inadequate educational programs before n-CPAP titration.^{8,9}

Accordingly, all efforts to develop new approaches to treatment are welcome. In one study, atrial pacing at a rate 15 beats higher than the mean sinus rate (atrial overdrive pacing [AOP]) during sleep was found to reduce significantly the number of episodes of apnea and hypopnea in a cohort of patients in whom pacing for conventional indications was already being used and who also had sleep apnea.¹⁰ Although a tentative pathophysiological explanation was given for these results, further investigation is necessary to confirm them and to determine whether they also apply over longer periods.

Our aim was to evaluate prospectively the effect of AOP after 24 hours and after one month in patients with the obstructive sleep apnea-hypopnea syndrome. We also sought to compare AOP with n-CPAP, the established form of therapy.

METHODS

PATIENTS

The study population included patients with moderate or severe obstructive sleep apnea-hypopnea syndrome and sleep-related bradyarrhythmias (sinus pauses longer than six seconds or transient atrioventricular block) who on initial consultation reported more than two episodes of syncope during the preceding year (Fig. 1). Patients with heart failure, left ventricular systolic dysfunction (ejection fraction, <50 percent), or sleep apnea of the central type were excluded from the study. Patients were enrolled in the trial after written informed consent had been obtained.

Diagnosis of the obstructive sleep apnea-hypopnea syndrome was based on polysomnographic data.¹² Recordings were performed overnight, with continuous monitoring of the electroencephalogram, electro-oculogram, electromyograms at the chin and anterior tibialis, oronasal airflow (with use of a thermistor), chest and abdominal respiratory movements, arterial oxyhemoglobin saturation (by pulse oximetry), electrocardiogram, body position, and snoring noise (Alice 4, Respironics). All records were scored manually. Respiratory and electroencephalographic indexes were measured by polysomnographic evaluation. Candidates for enrollment also underwent echocardiography to permit exclusion of those with left ventricular systolic dysfunction.

STUDY DESIGN

In all patients, a dual-chamber pacemaker was implanted because of a history of syncope and the presence of bradyarrhythmias on polysomnography (Fig. 1). Although these findings are not considered standard indications for pacing, it is our practice to suggest pacing in this select population. The consent form for participation in the study noted that pacemaker implantation would not be universally recommended under these circumstances.

All pacemakers in study participants were initially programmed to initiate atrial pacing only when the intrinsic heart rate fell below 40 bpm. Two days later, the patients were randomly assigned with equal probability to one of two groups by means of a computer algorithm. In the first group, the pacemakers were programmed for AOP (pacing at a rate 15 bpm greater than the spontaneous mean nocturnal heart rate); in the second group, the program-

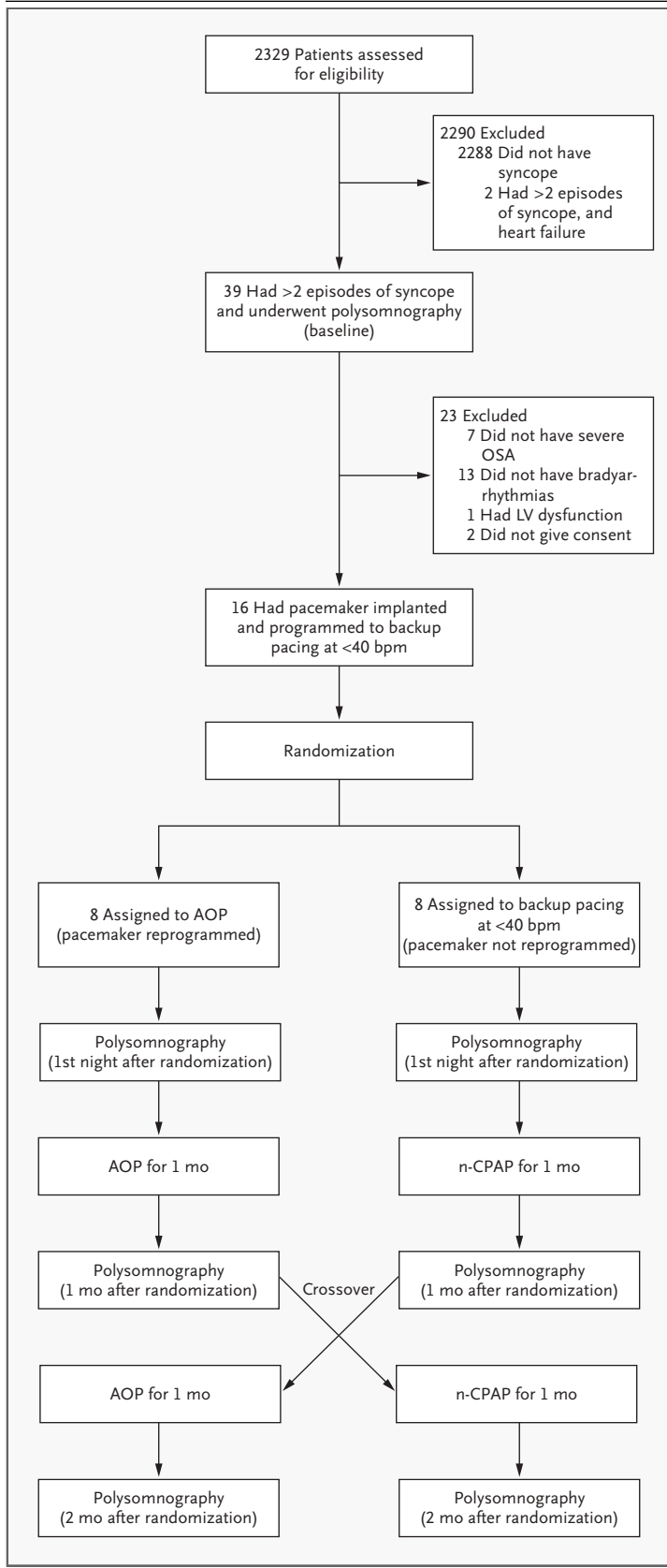


Figure 1. Plan of the Trial.

A total of 16 patients were enrolled; 8 were randomly assigned first to AOP, and 8 were randomly assigned first to n-CPAP. At one month, all patients switched therapies and were followed for an additional month. All patients completed both one month of AOP and one month of n-CPAP. This figure is based on the Consolidated Standards of Reporting Trials guidelines.¹¹ OSA denotes obstructive sleep apnea, and LV left ventricular.

ming was not changed, such that backup atrial pacing at less than 40 bpm was continued (Fig. 1).

Twenty-four hours after randomization, the patients in the backup-pacing group began n-CPAP therapy after n-CPAP titration. Those in the AOP group did not receive n-CPAP. One month later, the two groups of patients switched therapies (i.e., the patients in the AOP group began n-CPAP, and the patients in the n-CPAP plus backup-pacing group began AOP), and follow-up was continued for an additional month (Fig. 1).

Before commencement of n-CPAP therapy, the patients underwent an educational session from a qualified nurse in the n-CPAP clinic, who provided detailed explanation of the use of the n-CPAP device, adequate fitting of one of several types of available mask, and familiarization with the sensation of receiving n-CPAP. All patients spent two additional nights in the sleep laboratory after the initial n-CPAP setup so that any problems could be quickly identified and solved. Patients were instructed to contact the n-CPAP clinic nurse daily by telephone within the first week. Subsequently, they were seen two weeks and four weeks after the initiation of n-CPAP therapy. The bed partner (e.g., spouse) was included in the n-CPAP educational sessions and training and in the follow-up visits. In addition, a nurse from a home health care agency visited patients at home when needed.

Polysomnographic studies were performed at baseline, the first night after randomization, at crossover, and at the end of the study period. Compliance with n-CPAP was examined subjectively, on the basis of patients' responses on questionnaires, and objectively, on the basis of data downloaded from the built-in timer on the n-CPAP machine (Auto-CPAP Respirationics). Information about sleep history and the score on the Epworth Sleepiness Scale (an eight-item questionnaire to evaluate subjectively the severity of daytime sleepiness; scores can range from 0 to 24, with higher scores indicating excessive daytime sleepiness) were also recorded at baseline, at crossover, and at the time of the

final polysomnographic studies. The study was approved by the hospital ethics committee.

STATISTICAL ANALYSIS

To compare the effects of the two treatments, we used a classic crossover design in which the patients served as their own controls. In this repeated-measures design, each patient received one of the two treatments (AOP or n-CPAP) during different one-month periods (Fig. 1). The treatment order was randomly assigned (either AOP followed by n-CPAP or n-CPAP followed by AOP).

Descriptive statistics for continuous variables are given as means ±SD. Ninety-five percent confidence intervals around the difference between the values for each intervention, as well as between the values for each intervention and baseline, were constructed to provide additional information about the magnitude of true mean differences. Repeated-measures analysis of variance was used to determine whether there was any treatment effect or order effect. Where findings for any variable were significant, post hoc

Bonferroni adjusted tests for multiple comparisons (baseline vs. AOP, baseline vs. n-CPAP, and AOP vs. n-CPAP) were performed to pinpoint the differences. In case the distribution of any of the variables violated analysis-of-variance assumptions, Friedman’s nonparametric test was also applied to confirm the significance of the results. A P value of less than 0.05 was considered to indicate statistical significance.

RESULTS

There were 2329 consecutive patients referred to our hospital between July 2002 and October 2004 for the evaluation of symptoms related to sleep apnea (Fig. 1). Of these, 41 had had more than two episodes of syncope during the preceding year. Twenty-three were excluded for other reasons, including refusal to participate (2 patients); thus, 16 patients were enrolled in the trial. The patients’ baseline characteristics are listed in Table 1. Twelve of the participants were men, and the patients’ mean

Table 1. Baseline Characteristics of the Patients.*

Patient No.	Sex	Age	Reason for Pacemaker Implantation	LVEF	Mean Heart Rate	Apnea-Hypopnea Index†	Arousal Index‡	SaO ₂ during Sleep	
								%	Lowest %
		yr		%	bpm				
1	M	69	Sinus pause	63	52	39	40	91	83
2	F	75	Sinus pause	61	55	58	47	89	76
3	M	37	Sinus pause	58	67	66	52	90	82
4	M	76	Sinus pause	67	57	46	32	90	81
5	F	60	Complete heart block	65	53	54	31	90	77
6	M	44	Sinus pause	57	57	97	93	77	61
7	M	66	Sinus pause	56	51	62	44	85	73
8	F	64	Sinus pause	62	63	24	27	92	82
9	M	56	Complete heart block	55	66	40	37	89	81
10	M	50	Sinus pause	58	51	53	30	88	71
11	M	73	Complete heart block	57	50	44	36	91	82
12	M	46	Complete heart block	60	52	47	36	87	76
13	M	58	Sinus pause	60	60	53	55	82	70
14	M	60	Sinus pause	55	58	22	25	90	83
15	M	58	Sinus pause	56	54	23	25	91	84
16	F	69	Sinus pause	57	49	56	42	88	73
Overall	NA	60±11	NA	59±4	55±6	49±19	41±17	88±4	77±6

* Plus-minus values are means ±SD. LVEF denotes left ventricular ejection fraction, SaO₂ arterial oxyhemoglobin saturation, M male, F female, and NA not applicable.

† The apnea-hypopnea index is the mean number of episodes of apnea and hypopnea per hour of sleep.

‡ The arousal index is the mean number of arousals per hour of sleep.

(\pm SD) age was 60 \pm 11 years. The mean apnea–hypopnea index (the mean number of episodes of apnea and hypopnea per hour of sleep) was 49 \pm 19. Twelve patients had sinus pauses (mean duration, 13 \pm 3 seconds), and four had episodes of complete heart block.

Eight patients were randomly assigned to receive AOP first, and eight to receive n-CPAP first. All patients completed all the evaluations in both intervention periods. Basic clinical characteristics, such as body-mass index, mean intrinsic nocturnal heart rate, and patients' habits (including smoking status and alcohol consumption) did not change during the study period (data not shown).

During AOP, consistent pacing was suggested by a significant increase in the mean heart rate on the polysomnographic electrocardiographic recordings. The mean nocturnal heart rate during AOP in each patient was at least 11 bpm higher (mean in-

crease, 17 bpm; range, 11 to 21) than the mean nocturnal heart rate at baseline and at least 14 bpm higher (mean increase, 18 bpm; range, 14 to 25) than the corresponding heart rate during n-CPAP therapy. Patients' rate of compliance with n-CPAP therapy was 100 percent.

SHORT-TERM EFFECTS OF AOP

During the second polysomnographic study, two nights after pacemaker implantation, no significant changes were observed in the apnea–hypopnea index, arousal index (the mean number of arousals per hour of sleep), mean or lowest arterial oxyhemoglobin saturation, total sleep time, or partial pressure of arterial carbon dioxide in either the AOP group or the backup-pacing group (Table 2). The desaturation index decreased significantly ($P=0.02$) in the latter group, and the duration of rapid-eye-movement (REM) sleep decreased in seven of the

Table 2. Short-Term Effects of AOP and Backup Atrial Pacing on Selected Variables.*

Technique and Variable	Mean Baseline Value	Mean Value at 24 Hr	Difference between Baseline and 24-Hr Values	95% CI of Difference	P Value
AOP					
Apnea–hypopnea index [†]	55.8	56.1	+0.3	–3.4 to +4.1	0.82
Arousal index [‡]	45.8	45.7	–0.1	–4.9 to +4.9	0.99
Desaturation index [§]	58.9	59.5	+0.6	–2.6 to +3.9	0.66
Mean SaO ₂ (%)	88	87	–1.0	–1.2 to +0.9	0.78
Lowest SaO ₂ (%)	77	76	–1.0	–1.7 to +1.5	0.86
Total sleep time (min)	301.5	305.4	+3.9	–5.4 to +13.2	0.35
Duration of REM sleep (min)	8.1	5.4	–2.7	–4.8 to –0.7	0.02
PCO ₂ (mm Hg)	39.7	39.4	–0.3	–1.0 to +0.4	0.29
Backup atrial pacing[¶]					
Apnea–hypopnea index [†]	42.3	41.9	–0.4	–3.5 to +2.8	0.78
Arousal index [‡]	35.8	35.0	–0.8	–3.6 to +2.1	0.55
Desaturation index [§]	53.3	50.1	–3.2	–5.3 to –0.9	0.02
Mean SaO ₂ (%)	88	88	0	–1.5 to +1.3	0.84
Lowest SaO ₂ (%)	77	78	+1.0	–0.2 to +1.9	0.12
Total sleep time (min)	276.4	271.8	–4.6	–14.9 to +5.9	0.34
Duration of REM sleep (min)	12.0	9.0	–3.0	–5.2 to –0.8	0.01
PCO ₂ (mm Hg)	38.9	38.9	0	–0.5 to 0.5	0.95

* Plus signs indicate that the variable increased from baseline, and minus signs that the variable decreased from baseline. CI denotes confidence interval, SaO₂ arterial oxyhemoglobin saturation, REM rapid eye movement, and PCO₂ partial pressure of arterial carbon dioxide.

[†] The apnea–hypopnea index is the mean number of episodes of apnea and hypopnea per hour of sleep.

[‡] The arousal index is the mean number of arousals per hour of sleep.

[§] The desaturation index is the mean number of desaturation episodes (episodes in which the arterial oxyhemoglobin saturation drops below 90 percent) per hour of sleep.

[¶] In backup atrial pacing, pacemakers were programmed for atrial pacing only when the intrinsic heart rate fell below 40 bpm.

eight patients in each group. No differences in the apnea-hypopnea index, arousal index, desaturation index, mean or lowest arterial oxyhemoglobin saturation, total sleep time, or partial pressure of arterial carbon dioxide were observed between the two groups during the same period. Patients in the backup-pacing group, though, had significantly more REM sleep than those receiving AOP (P=0.03).

LONG-TERM COMPARATIVE EVALUATION OF AOP WITH n-CPAP

There was a striking long-term difference between AOP and n-CPAP in all the variables measured in the study except for total sleep time (Table 3 and Fig. 2). With n-CPAP, the apnea-hypopnea index decreased from 49.0 to 2.7 (net change, -46.3; 95 percent

confidence interval, -56.2 to -36.5; P<0.001). All measured variables except total sleep time improved in every patient undergoing n-CPAP. Moreover, significant clinical improvement was noticed at follow-up as measured by the patients' Epworth Sleepiness Scale score (net change, -10.2; 95 percent confidence interval, -11.7 to -8.8; P<0.001). In contrast, AOP had no measurable effect on any of the variables. With AOP, the apnea-hypopnea index increased from 49.0 to 49.2 (net change, +0.2; 95 percent confidence interval, -2.7 to +2.3; P=0.87). There also was no significant change with AOP in the patients' Epworth Sleepiness Scale score (net change, +0.1; 95 percent confidence interval, -0.24 to +0.36; P=0.67).

The order of interventions had no observable

Table 3. Long-Term Effect of AOP and n-CPAP on Selected Variables.*

Intervention and Variable	Mean Baseline Value	Mean Value during Intervention	Difference between Baseline and Intervention Values	95% CI of Difference	P Value
AOP					
Apnea-hypopnea index†	49.0	49.2	+0.2	-2.7 to +2.3	0.87
Arousal index‡	40.75	41.3	+0.55	-2.0 to +3.1	0.65
Desaturation index§	56.1	56.4	+0.3	-2.6 to +3.2	0.82
Mean SaO ₂ (%)	88.0	87.0	-1.0	-1.2 to +0.1	0.08
Lowest SaO ₂ (%)	77.0	76.0	-1.0	-1.1 to +0.5	0.40
Total sleep time (min)	288.9	283.6	-5.3	-13.1 to +2.3	0.16
Duration of REM sleep (min)	10.1	8.2	-1.9	-3.9 to +0.2	0.07
PCO ₂ (mm Hg)	39.3	39.4	+0.1	-0.4 to +0.5	0.75
Epworth Sleepiness Scale score¶	15.7	15.8	+0.1	-0.24 to +0.36	0.67
n-CPAP					
Apnea-hypopnea index†	49.0	2.7	-46.3	-56.2 to -36.5	<0.001
Arousal index‡	40.75	4.6	-36.15	-44.9 to -27.4	<0.001
Desaturation index§	56.1	3.5	-52.6	-64.8 to -40.4	<0.001
Mean SaO ₂ (%)	88.0	96.0	+8.0	+5.7 to +9.3	<0.001
Lowest SaO ₂ (%)	77.0	90.0	+13.0	+9.9 to +16.1	<0.001
Total sleep time (min)	288.9	288.3	-0.6	-11.5 to +10.1	0.89
Duration of REM sleep (min)	10.1	17.4	+7.3	+4.8 to +9.9	<0.001
PCO ₂ (mm Hg)	39.3	38.1	-1.2	-1.6 to -0.8	<0.001
Epworth Sleepiness Scale score¶	15.7	5.5	-10.2	-11.7 to -8.8	<0.001

* Plus signs indicate that the variable increased from baseline, and minus signs that the variable decreased from baseline. CI denotes confidence interval, SaO₂ arterial oxyhemoglobin saturation, REM rapid eye movement, and PCO₂ partial pressure of arterial carbon dioxide.

† The apnea-hypopnea index is the mean number of episodes of apnea and hypopnea per hour of sleep.

‡ The arousal index is the mean number of arousals per hour of sleep.

§ The desaturation index is the mean number of desaturation episodes (episodes in which the arterial oxyhemoglobin saturation drops below 90 percent) per hour of sleep.

¶ The Epworth Sleepiness Scale is a subjective measure of sleepiness; scores range from 0 to 24, with higher scores indicating excessive daytime sleepiness.

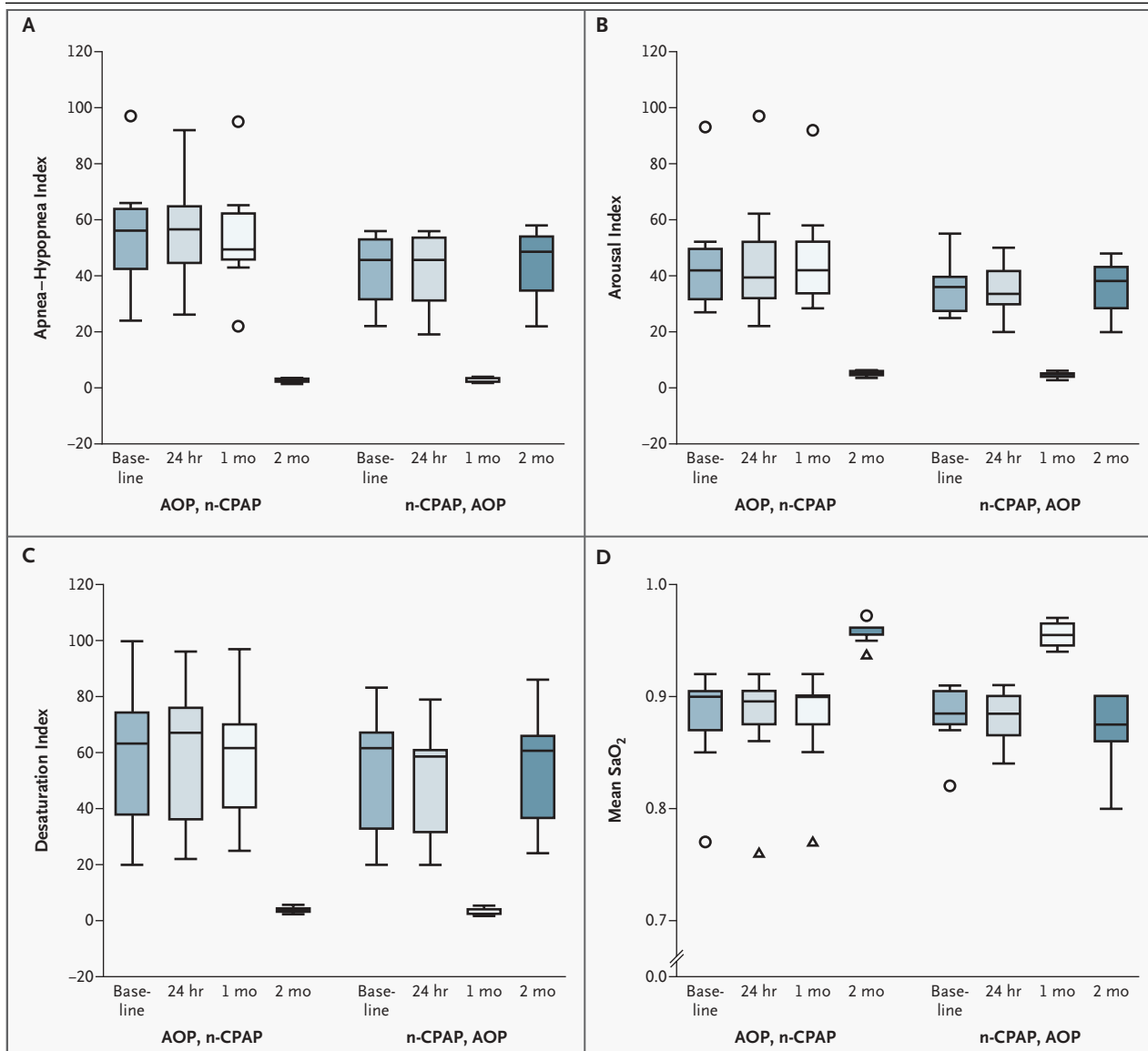


Figure 2. Box Plots of the Apnea-Hypopnea Index, Arousal Index, Desaturation Index, and Mean Arterial Oxyhemoglobin Saturation (SaO₂) over Time, According to Treatment Order.

For each variable, the left half of the plot shows data from the patients treated first with atrial overdrive pacing (AOP) and then with n-CPAP, and the right half shows data from the patients treated first with n-CPAP and then with AOP. Data are shown for each group of patients at four time points: baseline, 24 hours after randomization, one month after the initiation of the first treatment, and one month after the initiation of the second treatment (i.e., two months after the initiation of the first treatment). The advantage of one month of n-CPAP therapy is evident, regardless of the treatment order. Among the patients who were treated with n-CPAP first, the benefit of that therapy completely disappeared after n-CPAP was discontinued. The centerline of the box denotes the median, the extremes of the box the interquartile range, and the bars the upper and lower limits of 95 percent of the data. The circles represent outlying data (data points between 1.5 times the interquartile range and 3.0 times the interquartile range beyond the 25th or 75th percentile), and the triangles extreme points (data points more than 3.0 times the interquartile range beyond the 25th or 75th percentile).

effect on the apnea-hypopnea index, arousal index, desaturation index, mean or lowest arterial oxyhemoglobin saturation, duration of REM sleep, or partial pressure of arterial carbon dioxide (Fig. 2). In other words, the order in which patients were treated (n-CPAP followed by AOP or AOP followed by n-CPAP) was irrelevant as far as these variables were concerned. However, patients

who received n-CPAP therapy first had significantly less total sleep time throughout the observation period than those who received AOP first ($P=0.04$). None of the patients reported any syncope or presyncopal episodes during the study period.

DISCUSSION

The pathophysiology of the obstructive sleep apnea-hypopnea syndrome is complex and not completely understood. Treatment is aimed mainly at reducing the number of episodes of apnea and hypopnea, the number of arousals, and oxyhemoglobin desaturation during sleep. These reductions have been correlated with a decrease in the rate of motor-vehicle accidents among persons with this syndrome¹³ as well as with improvements in blood pressure,^{14,15} baroreceptor sensitivity,¹⁶ and nitric oxide derivative production¹⁷; and reductions in sympathetic nervous system activation¹⁸⁻²⁰ and cardiac arrhythmias (especially bradyarrhythmias).^{12,21,22} In recent years, the mainstay of therapy for the obstructive sleep apnea-hypopnea syndrome has been n-CPAP, which maintains a patent airway during sleep, thereby decreasing apnea. However, although n-CPAP is highly effective, compliance with the treatment is a problem.

Recently, an alternative treatment, based on the increase and stabilization of heart rate during sleep, has been proposed. The proposal followed the observation that some patients who had received a pacemaker with AOP to reduce the incidence of atrial tachyarrhythmias reported a reduction in breathing disorders after implantation of the pacemaker. Garrigue et al.¹⁰ found that in 15 patients with the sleep apnea syndrome, AOP significantly reduced the number of episodes of central or obstructive sleep apnea, without reducing total sleep time. Similar results had previously been reported by Kato et al.,²³ who found that after physiologic cardiac pacing in three patients with central or obstructive apneas (a mixed type of the syndrome), the apnea-hypopnea index decreased as the average heart rate increased. With regard to patients with central sleep apnea, these results are predictable: when the heart rate increases with the use of AOP, factors that have been related to the occurrence of central sleep apnea also improve: cardiac output increases, circulation time shortens, and pulmonary congestion decreases. Furthermore, Sinha et al.²⁴ recently reported that, in association with the im-

provement in cardiac function, cardiac-resynchronization therapy improved central sleep apnea in patients with heart failure and left bundle-branch block.

In contrast, the beneficial effect of AOP among patients with obstructive sleep apnea was somewhat unexpected. Although Garrigue et al.¹⁰ suggested several possible pathophysiological explanations, such as the vagolytic effects of pacing and the reduction of the ventilatory-loop gain and consequent stabilization of the respiratory pattern, confusion still remains: why, for example, has there been little success with theophylline in the treatment of the obstructive sleep apnea-hypopnea syndrome, even though it acts in roughly the same way as AOP. In addition, the suggested vagolytic effect of pacing has not been proved.

In our study, we used the same increase in paced heart rate as that tested by Garrigue et al.¹⁰ (15 beats above the mean nocturnal rate). Although our study was small and had power comparable to that of the study by Garrigue et al., we were unable to show any beneficial effect of pacing in reducing the number of episodes of apnea or hypopnea per hour or in increasing arterial oxyhemoglobin saturation during sleep. Moreover, there was no difference between the pacing and nonpacing phases in the number of arousals per hour. Furthermore, not only was AOP ineffective on the first night; it also showed no benefit even after one month.

The only variable that was altered by AOP at 24 hours was the duration of REM sleep. However, the same effect was also observed in patients who were not receiving AOP, which means that this alteration could be attributed to the intervention (pacemaker implantation) two days before randomization or perhaps simply to the patients' participation in the study, rather than to any particular therapy. Our results show that increasing the heart rate or reducing the variations in rate during sleep has no effect on the pathophysiology of obstructive sleep apnea, at least among patients with the characteristics of our study population — that is, middle-aged, obese patients with normal left ventricular systolic function and a purely obstructive type of the syndrome. Such persons constitute the majority of patients with obstructive sleep apnea.

In the study by Garrigue et al.,¹⁰ most of the patients were older and had mild impairment of left ventricular ejection fraction and the mixed type of the syndrome. It seems that in such patients, cardiac pacing could reduce the number of secondary ob-

structive events by improving cardiac function and preventing the periodic breathing that may have a role in the pathophysiology of some cases of the obstructive sleep apnea–hypopnea syndrome.²⁵ It should be noted that in a more recent report, Pepin et al.²⁶ state that they were unable to find beneficial effects of pacing in another, more representative population of patients who had moderate-to-severe, predominantly obstructive sleep apnea and a mean left ventricular ejection fraction of 64±13 percent and who had received a pacemaker for conventional indications. Furthermore, Luthje et al.²⁷ found that in patients with normal or impaired left ventricular function, AOP had no effect on the apnea–hypopnea index or on oxygen desaturation. The difference between the results reported by Luthje et al. and those reported by Garrigue et al. in relation to patients with impaired left ventricular function might be attributed to the higher mean nocturnal heart rate in the former study.

In our study, we preferred to compare pacing therapy with the more established n-CPAP therapy, rather than comparing pacing with no pacing in the long-term phase (one month), both for ethical

reasons and because we were seeking a comparative standard of efficacy. In contrast to AOP, n-CPAP therapy was highly effective in reducing episodes of apnea and hypopnea, arousals, and oxyhemoglobin desaturation (while increasing the mean and lowest arterial oxyhemoglobin saturation), without reducing total sleep time. These findings are consistent with the benefits of n-CPAP noted in previous studies.⁵⁻⁷ It is likely, however, that the results of our study cannot be applied to all patients with sleep-related breathing disorders. Rather, they indicate the necessity of further investigating the possible therapeutic effect of AOP in other subgroups of patients.

In conclusion, n-CPAP therapy was highly effective in the treatment of patients with obstructive sleep apnea, whereas AOP had no effect on a representative population of such patients. The findings of our study may not apply in general to all patients with the obstructive sleep apnea–hypopnea syndrome. The data suggest that further investigation is needed in order to determine in which groups of patients AOP may have some therapeutic effect.

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