

## BENEFIT OF ATRIAL PACING IN SLEEP APNEA SYNDROME

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### ABSTRACT

**Background** Many patients with sleep apnea syndrome have nocturnal bradycardia, paroxysmal tachyarrhythmias, or both, which can be prevented by permanent atrial pacing. We evaluated the effect of using cardiac pacing to increase the heart rate during sleep in patients with sleep apnea syndrome.

**Methods** We studied 15 patients (11 men and 4 women; mean [ $\pm$ SD] age,  $69\pm 9$  years) with central or obstructive sleep apnea who had received permanent atrial-synchronous ventricular pacemakers for symptomatic sinus bradycardia. All patients underwent three polysomnographic evaluations on consecutive nights, the first night for base-line evaluation and then, in random order, one night in spontaneous rhythm and one in dual-chamber pacing mode with atrial overdrive (basic rate, 15 beats per minute faster than the mean nocturnal sinus rate). The total duration and number of episodes of central or obstructive sleep apnea or hypopnea were analyzed and compared.

**Results** The mean 24-hour sinus rate during spontaneous rhythm was  $57\pm 5$  beats per minute at base line, as compared with  $72\pm 3$  beats per minute with atrial overdrive pacing ( $P<0.001$ ). The total duration of sleep was  $321\pm 49$  minutes in spontaneous rhythm, as compared with  $331\pm 46$  minutes with atrial overdrive pacing ( $P=0.48$ ). The hypopnea index (the total number of episodes of hypopnea divided by the number of hours of sleep) was reduced from  $9\pm 4$  in spontaneous rhythm to  $3\pm 3$  with atrial overdrive pacing ( $P<0.001$ ). For both apnea and hypopnea, the value for the index was  $28\pm 22$  in spontaneous rhythm, as compared with  $11\pm 14$  with atrial overdrive pacing ( $P<0.001$ ).

**Conclusions** In patients with sleep apnea syndrome, atrial overdrive pacing significantly reduces the number of episodes of central or obstructive sleep apnea without reducing the total sleep time. (N Engl J Med 2002;346:404-12.)

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**S**LEEP apnea syndrome is a common and often undiagnosed disorder associated with substantial cardiovascular morbidity and mortality.<sup>1-8</sup> Other consequences include an increased incidence of traffic accidents,<sup>9-11</sup> social and family disruption,<sup>9,10,12</sup> and bradyarrhythmias or tachyarrhythmias.<sup>13-15</sup> Treatments such as nasal continuous positive airway pressure<sup>16-18</sup> and oral administration of theo-

phylline<sup>19</sup> reduce the number of episodes of apnea but produce side effects such as palpitations. Surgical therapy involving the ablation of tissue, such as uvulopalatopharyngoplasty,<sup>20,21</sup> has also been proposed for patients with apnea that is predominantly obstructive.

We observed that some patients who had received a pacemaker with atrial overdrive pacing in order to reduce the incidence of atrial tachyarrhythmias<sup>22,23</sup> reported a reduction in breathing disorders after the implantation of the pacemaker. We therefore undertook a study to investigate the efficacy of atrial overdrive pacing in the treatment of sleep apnea syndrome in consecutive patients who required a pacemaker for conventional indications.

### METHODS

#### Study Population

A total of 152 patients with dual-chamber pacemakers that had been implanted at least one year previously were screened. A total of 47 patients with problems related to sleep-disordered breathing, snoring, daytime sleepiness, frequent arousals at night, sleep apnea, or some combination of these symptoms were asked to undergo polysomnography in a sleep laboratory. Of these 47 patients, 26 provided written informed consent, and in 15 of them, polysomnographic recordings revealed sleep apnea syndrome, as defined by an apnea index (the total number of episodes of apnea divided by the number of hours of sleep) of 5 or higher and an apnea-hypopnea index (the total number of episodes of either apnea or hypopnea divided by the number of hours of sleep) of 15 or higher.<sup>24-26</sup> These 15 patients, who did not engage in regular physical exercise, presented with snoring, daytime sleepiness, fatigue during the morning, and frequent arousals at night; they became the study group. They had no clinical evidence of heart failure, perhaps because they were sedentary, but 11 patients (73 percent) had a left ventricular ejection fraction on echocardiography ranging from 40 to 56 percent within the six months before the study. None of the patients were dependent on the pacemaker.

#### Polysomnography

Polysomnography was performed in the sleep laboratory with monitoring that included electroencephalography, electromyography of the chin and legs, electro-oculography, oronasal air-flow tracing, recording of the movement of the chest wall and abdomen, finger oximetry, and electrocardiography with a Holter monitor.<sup>27</sup> Air flow was monitored qualitatively with an oronasal thermocouple. An episode of apnea was defined as a complete cessation of air flow for at least 10 seconds.<sup>19,27</sup> An episode of hypopnea was

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defined as a decrease of 50 percent or more in the oronasal air flow associated with a 4 percent decrease in arterial oxyhemoglobin saturation. An obstructive event was recorded if there were rib-cage excursions, abdominal excursions, or both during an episode of apnea. The simultaneous absence of air-flow thermistor tracing and respiratory movements was considered to indicate the presence of central apnea.<sup>19,27</sup> The number of episodes of arousal due to disordered breathing per hour of sleep was referred to as the arousal index. All polysomnographic recordings were scored by a pneumologist who was unaware of the pacing configuration and not otherwise involved in the study.

### Study Protocol

The 15 patients spent three consecutive nights in the sleep laboratory. Their medications were not changed during the study. All polysomnographic recordings were performed with use of the same procedures. The polysomnographic recording of the first night represents the base line (basic pacing rate, 55 to 60 beats per minute), which established the diagnosis of sleep apnea syndrome. The patients were randomly assigned to undergo one of two sets of procedures on the next night and the other set on the night after that. During one of the two nights, the basic ventricular rate of the pacemaker (not synchronized with the atrial activity) was programmed to 40 beats per minute with the aim of recording spontaneous rhythm for a high percentage of the sleep time in order to assess measures of breathing in the absence of pacing (the no-pacing phase). During the other night, atrial overdrive stimulation was provided at a rate that was 15 beats per minute faster than the mean nocturnal heart rate (recorded by the memory function of the pacemaker during the base-line nocturnal assessment) in order to assess the effect of pacing on breathing (the pacing phase). This level of pacing was chosen on the basis of its therapeutic effect on vagally induced atrial arrhythmias, as reported in recent studies.<sup>22,23</sup>

### Statistical Analysis

Data obtained during the base-line recordings were compared with those obtained during the no-pacing and pacing phases. Values are reported as means  $\pm$ SD. Because of the small sample size, the Mann-Whitney nonparametric test for paired data was used to compare intrapatient differences between the outcome variables during the no-pacing phase and the outcome variables during the pacing phase. In order to assess the effects of the order of the two phases of the study (assessment of period effects), the patients were divided into two groups — one with no pacing on night 2 and pacing on night 3 and the other with pacing on night 2 and no pacing on night 3. Period-effects analysis was performed by means of the Mann-Whitney nonparametric test for independent samples. This test consisted of comparing the two groups in terms of the mean differences in the data between the pacing phase and the no-pacing phase for each variable studied. A two-tailed *P* value of less than 0.05 was considered to indicate statistical significance. Calculations were performed with the use of Statistica software (StatSoft, Tulsa, Okla.).

## RESULTS

### Base-Line Polysomnographic Assessment

The base-line characteristics of the patients are summarized in Table 1. Nine patients had sinus node disease (60 percent), and six (40 percent) had bradycardia-tachycardia syndrome. Six patients were randomly assigned to receive no pacing on night 2 and nine to receive no pacing on night 3. The 24-hour mean spontaneous heart rate during the base-line phase was similar for all the patients ( $57 \pm 5$  beats per

minute). All patients presented with episodes of both obstructive and central apnea; the study group had a higher central-apnea index ( $12 \pm 14$ ) than obstructive-apnea index ( $7 \pm 4$ ), but the difference was not statistically significant ( $P=0.09$ ) (Table 1). Seven patients (Patients 1 through 7) had apnea that was predominantly obstructive (central-apnea index,  $5 \pm 4$ ; obstructive-apnea index,  $8 \pm 4$ ). The other eight patients (Patients 8 through 15) had apnea that was predominantly central (central-apnea index,  $18 \pm 16$ ; obstructive-apnea index,  $6 \pm 3$ ) (Table 1). The left ventricular ejection fraction was 56 percent or lower in 11 patients (73 percent) and 65 percent or higher in 4 patients (27 percent). The percentage of total sleep time during which oxyhemoglobin saturation was below 90 percent was  $12 \pm 8$  percent, and the mean arousal index was  $21 \pm 12$ .

### No-Pacing Phase

Data collected during the no-pacing phase and the pacing phase are shown in Table 2. Pacemaker stimulation was used during  $1.0 \pm 0.5$  percent of the no-pacing phase because five patients had short episodes of bradycardia with a heart rate of less than 40 beats per minute. The mean total sleep time during the no-pacing phase was  $321 \pm 49$  minutes, the mean apnea-hypopnea index was  $28 \pm 22$ , and the mean arousal index was  $18 \pm 9$ .

### Pacing Phase with Atrial Overdrive Pacing

Atrial pacing at a rate 15 beats per minute faster than the mean nocturnal heart rate resulted in a significant reduction in the number of episodes of all types of apnea (Table 2). In 13 patients (87 percent), the apnea-hypopnea index was reduced by more than 50 percent. The two remaining patients had smaller reductions in the apnea-hypopnea index: one patient had an index of 21 with no pacing and an index of 12 with pacing (a 43 percent reduction), and the index of the other patient was reduced from 79 to 47 (a 41 percent reduction).

An example of a polysomnographic recording during the no-pacing phase from a patient (Patient 9) who presented with sleep apnea that was predominantly central is shown in Figure 1A. The heart-rate recording shows large variations, with a heart rate below 50 beats per minute during episodes of apnea and an increased heart rate (up to 100 beats per minute) during arousals. In contrast, the recording in Figure 1B shows a substantial reduction in the number of episodes of central apnea and hypopnea associated with much less variation in the heart rate when the basic pacing rate was set at 72 beats per minute. An example of polysomnographic recordings from a patient (Patient 3) with a large number of episodes of obstructive apnea is shown in Figure



TABLE 2. SLEEP-DISORDERED BREATHING EVENTS AND ARTERIAL OXYGEN SATURATION VALUES DURING THE NO-PACING PHASE AND THE PACING PHASE.\*

VARIABLE	PATIENTS WITH PACING ON NIGHT 2 (N=9)			PATIENTS WITH PACING ON NIGHT 3 (N=6)			ALL PATIENTS (N=15)		
	NO-PACING PHASE	PACING PHASE	P VALUE	NO-PACING PHASE	PACING PHASE	P VALUE	NO-PACING PHASE	PACING PHASE	P VALUE
Heart rate (beats/min)									
24-hour mean	55±8	73±6	<0.001	54±6	71±5	<0.001	54±7	72±3	<0.001
Nocturnal mean	53±9	74±2	<0.001	48±8	67±6	<0.001	51±8	72±4	<0.001
Total sleep time (min)	318±65	328±61	11±18	322±60	334±58	14±17	321±49	331±46	10±28
Breathing-event index (no. of episodes/hr)									
Apnea or hypopnea	32±26	14±17	0.002	24±7	10±7	<0.001	28±22	11±14	<0.001
Central apnea	17±21	9±11	0.003	8±6	3±2	0.009	13±17	6±7	-7±10
Obstructive apnea	4±4	2±2	0.04	9±4	3±3	0.007	6±4	3±1	-4±2
Hypopnea	11±4	3±2	0.009	7±8	4±3	0.03	9±4	3±3	-6±3
Arousal due to disordered breathing	23±21	13±12	0.009	18±7	9±5	0.006	18±9	11±7	-7±5
Oxyhemoglobin saturation									
Base line (%)	92±7	94±6	2±2	95±5	95±6	1±1	94±3	95±2	1±2
Lowest value (%)	81±11	90±7	9±4	84±8	85±7	1±1†	83±8	87±5	4±3
<90% (% of total sleep time)	11±8	6±4	0.008	10±7	7±4	0.04	10±6	6±4	-4±2

\*Plus-minus values are means ±SD. P values for the comparisons between the no-pacing phase and the pacing phase in the group of patients indicated were calculated by the Mann-Whitney nonparametric test for paired data.

†P=0.04 by the Mann-Whitney nonparametric test for independent series for the comparison between the mean differences in the two subgroups.

2A; the number of episodes was markedly reduced when the heart rate was stabilized at 75 beats per minute (Fig. 2B).

The effect of atrial overdrive pacing on the obstructive-apnea index and the central-apnea index of each of the 15 patients is shown in Figure 3. Regardless of the severity of the sleep apnea syndrome, there was a reduction in both indexes in every patient. The reduction in the number of episodes of apnea and hypopnea was associated with a significant increase in the arterial oxyhemoglobin saturation during sleep, reflected by a reduction of the total sleep time during which the oxygen saturation was less than 90 percent (from 10±6 percent to 6±4 percent, P=0.04) (Table 2), in addition to a significant increase in the lowest oxygen saturation value from 83±8 percent to 87±5 percent (P=0.02). There was also a significant decrease in the number of arousals due to periodic breathing that were recorded on electroencephalography, but the typical Cheyne-Stokes pattern was found only in Patient 10 and was present at all three evaluations.

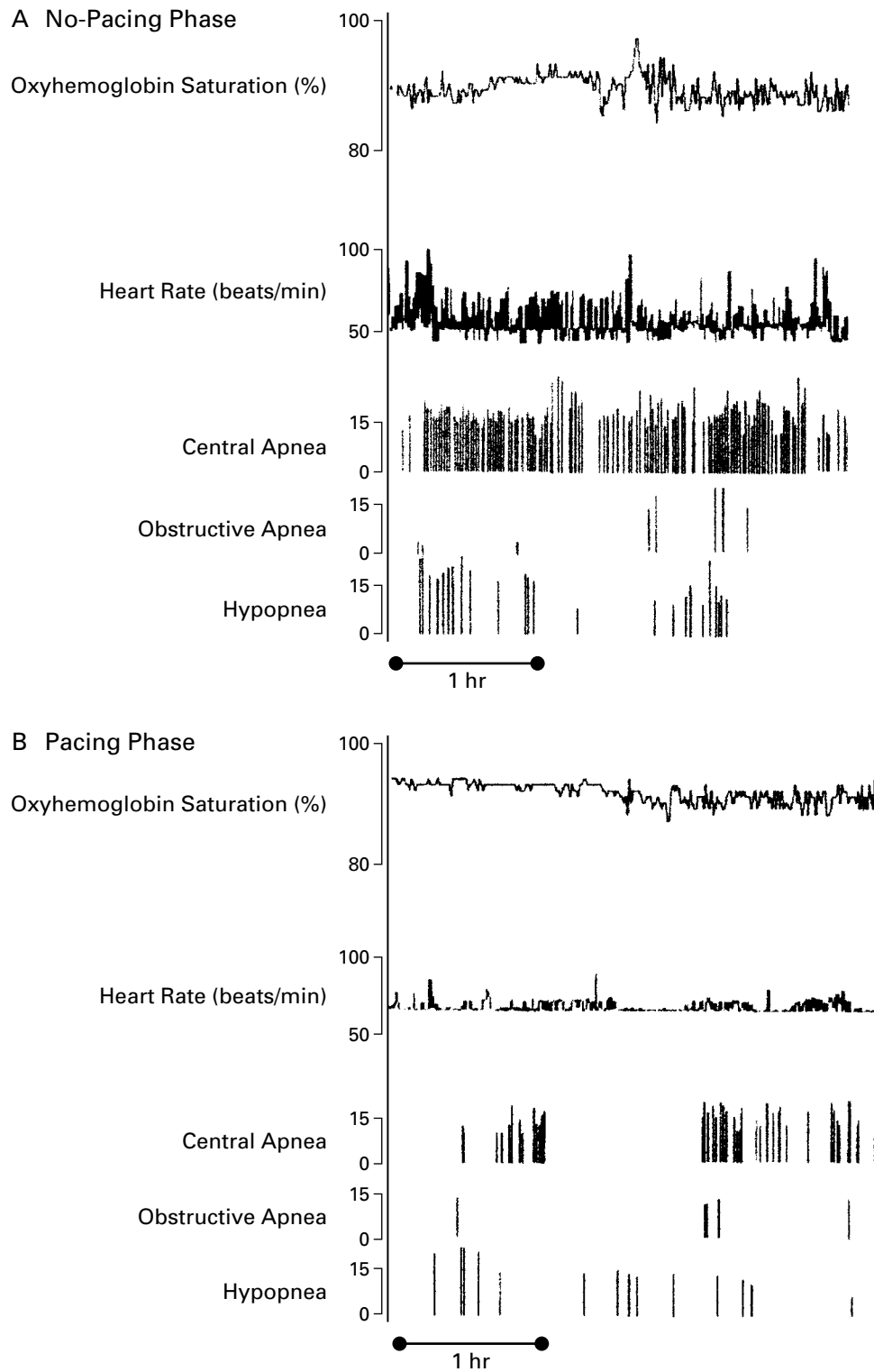
The statistical analysis revealed only two significant period effects (Table 2): there was a significantly greater reduction in the obstructive-apnea index among patients assigned to pacing on night 3 (P=0.04) and a significantly greater increase in the lowest oxyhemoglobin saturation value among patients assigned to pacing on night 2 (P=0.04).

**Cardiac Rhythm**

All the patients tolerated the protocol well: the total sleep time was similar at base line and during the pacing and no-pacing phases. The Holter monitor tracing and the recordings of the memory function of the pacemaker revealed a significant increase in the mean nocturnal heart rate during the atrial overdrive (pacing) phase (Table 2). The numbers of episodes of atrial arrhythmia that occurred during the pacing and no-pacing phases were similar. Three patients had an episode of atrial arrhythmia (one lasting 21 minutes, one lasting 35 minutes, and one lasting 6 minutes) during the no-pacing phase, and two patients had such an episode (one lasting 18 minutes and the other lasting 27 minutes) during the pacing phase. There were no differences in the number of isolated premature ventricular contractions per hour of sleep (13±24 at base line, 16±31 during the no-pacing phase, and 12±25 during the pacing phase). Neither ventricular couplets nor episodes of ventricular tachycardia were observed during the base-line assessment or during the pacing or no-pacing phase of the study.

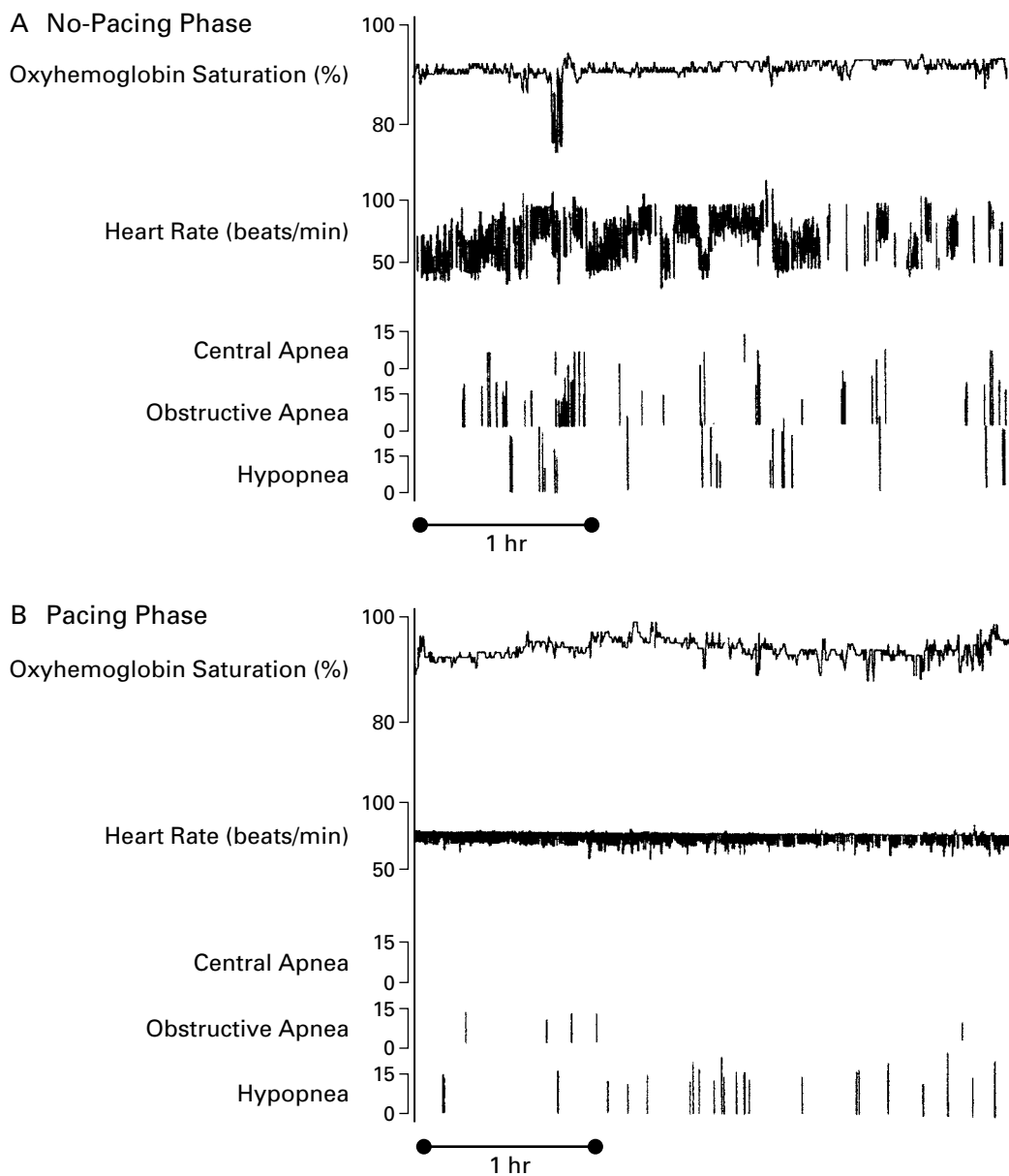
**DISCUSSION**

Our observations show that in patients with sleep apnea syndrome who have an atrial pacemaker, atrial



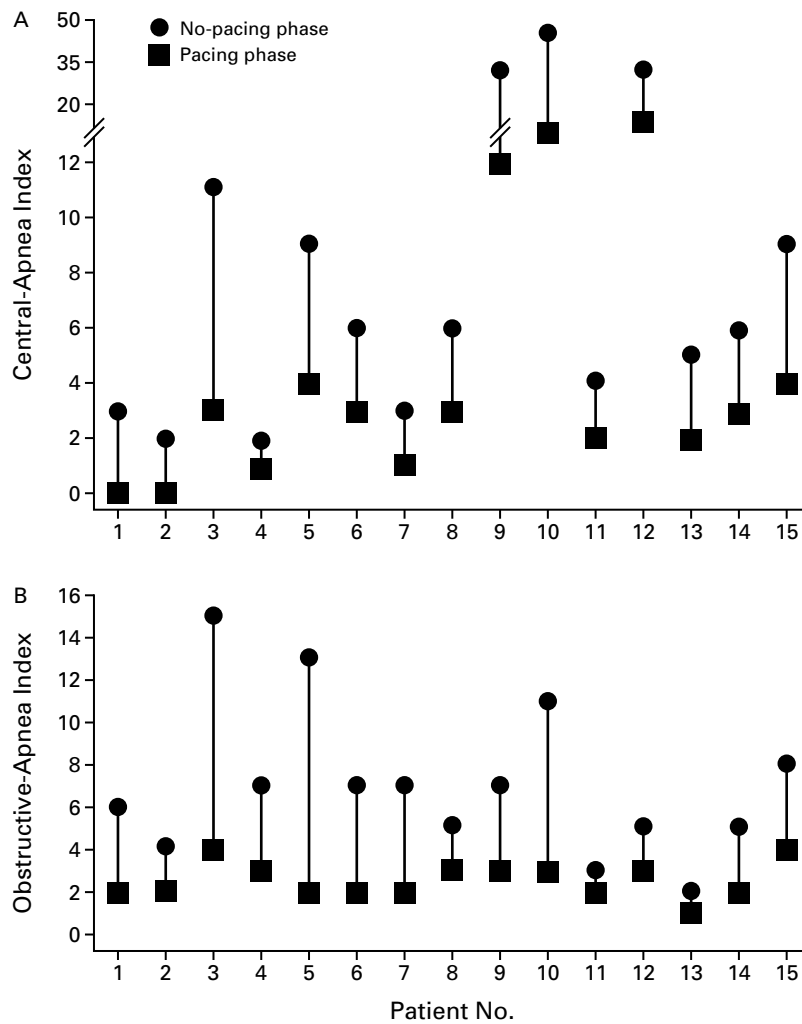
**Figure 1.** Polysomnographic Recordings in a Patient with Predominantly Central Apnea Obtained with the Pacemaker Programmed to a Fixed Basic Rate of 40 Beats per Minute (No-Pacing Phase) (Panel A) and with Atrial Overdrive Pacing at 72 Beats per Minute (Pacing Phase) (Panel B).

Patient 9 presented with very frequent episodes of central sleep apnea. Each episode of apnea or hypopnea is represented by a vertical line; the height of the line indicates the duration of the episode in seconds.



**Figure 2.** Polysomnographic Recordings in a Patient with Predominantly Obstructive Apnea Obtained with the Pacemaker Programmed to a Fixed Basic Rate of 40 Beats per Minute (No-Pacing Phase) (Panel A) and with Atrial Overdrive Pacing at 75 Beats per Minute (Pacing Phase) (Panel B).

At presentation, the majority of the episodes of sleep apnea in this patient (Patient 3) were obstructive. Each episode of apnea or hypopnea is represented by a vertical line; the height of the line indicates the duration of the episode in seconds.



**Figure 3.** Effect in the 15 Patients of Atrial Overdrive Pacing on Episodes of Central Sleep Apnea (Panel A) and Episodes of Obstructive Sleep Apnea (Panel B).

The central- and obstructive-apnea indexes were calculated as the number of episodes divided by the number of hours of sleep.

overdrive pacing significantly reduces the number of episodes of obstructive and central sleep apnea and increases arterial oxyhemoglobin saturation without altering total sleep time. A reduction of more than 50 percent in the number of episodes of apnea and hypopnea was achieved with atrial overdrive pacing in most patients (13 of 15), irrespective of whether they had obstructive or central sleep apnea, and was associated with a reduction in the number of arousals and an increase in arterial oxyhemoglobin saturation. These variables returned to the base-line values defining sleep apnea syndrome when the pacemaker was turned off.

Episodes of apnea are associated with hypoxemia,

the retention of carbon dioxide, bradycardia, and a decrease in blood pressure that is, in turn, associated with an increase in vagal tone leading to periodic variations in heart rate.<sup>24-27</sup> Our data show that reducing the variations in heart rate markedly reduced the number of episodes of sleep apnea in our study population. These periodic variations in heart rate may result in part from changes in autonomic tone and may influence the incidence of central sleep apnea. Consequently, atrial pacing at a high rate relative to that of spontaneous sinus bradycardia may counteract sustained increases in vagal tone by maintaining sympathetic activity.

This hypothesis is compatible with the results of

recent studies<sup>28-30</sup> showing the efficacy of atrial overdrive pacing in the treatment of vasovagal syncope. In addition, clinical studies have demonstrated that atrial overdrive pacing can suppress vagally induced episodes of atrial fibrillation.<sup>22,23,31</sup> The hypothesis is further supported by a previous study suggesting that the therapeutic effects of theophylline in patients with central sleep apnea may be mediated by adenosine antagonism.<sup>32</sup> The beneficial effect of theophylline on sleep apnea syndrome might be at least partially explained by its ability to reduce vagal tone.

In contrast to the effect on central sleep apnea, the mechanism of the amelioration of obstructive sleep apnea by atrial overdrive pacing is not clear. Obstructive apnea is caused mainly by the presence of excessive soft tissue (i.e., the soft palate, the tonsils, and the base of the tongue) or by hypotonia of the pharyngeal muscles during sleep.<sup>33-36</sup> We did not expect that atrial overdrive pacing would reduce the obstructive-apnea index, since this type of apnea results primarily from anatomical obstruction. The mechanisms involved remain to be explained.

We observed a reduction of more than 50 percent in the apnea-hypopnea index with atrial overdrive. Thus, in our population of patients with symptomatic bradycardia, cardiac pacing could be considered as an alternative to treatment with continuous positive airway pressure or oral theophylline.<sup>16-19,37</sup> The ablation of tissue has been proposed as a surgical method for the treatment of snoring and obstructive apnea. Improvement has been achieved in 38 to 50 percent of the patients who have undergone such a surgical procedure.<sup>38-41</sup>

In our study, cardiac pacing was effective in patients with symptomatic bradyarrhythmias and frequent variations in heart rate. Whether similar beneficial effects could be achieved with atrial pacing in patients who had no indications for pacemaker implantation (typically, sinus node disease or bradycardia-tachycardia syndrome) remains to be determined. In addition, all but four of our patients presented with a reduced left ventricular ejection fraction. Therefore, our results cannot yet be extrapolated to patients with normal cardiac function who have sleep apnea syndrome, even though our four patients with normal cardiac function had more than a 50 percent reduction in the sleep-apnea index.

Atrial overdrive pacing substantially reduced the number of episodes of central and obstructive apnea in patients with pacemakers that had previously been implanted for the treatment of the sick sinus syndrome or the bradycardia-tachycardia syndrome. Further studies are needed to elucidate the mechanisms involved in achieving these reductions and to assess the precise role of cardiac pacing in preventing symptoms, disability, and death in the general population of patients with sleep apnea syndrome.

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**CORRECTION**

**Benefit of Atrial Pacing in Sleep Apnea Syndrome**

Benefit of Atrial Pacing in Sleep Apnea Syndrome . On page 404, the name of the sixth author should have read, "Chantal Raheison," not "Chantal Raheisson," as printed. In the original Web publication of this article, the name was spelled correctly.