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Overdrive atrial pacing does not improve obstructive sleep apnoea syndrome

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ABSTRACT: The aim of this study was to assess the ability of overdrive atrial pacing to reduce sleep apnoea severity.

A total of 17 unselected patients (12 males; mean±SD age 71±10 yrs; body mass index 27±3 kg·m^{-2}) who had received permanent atrial-synchronous ventricular pacemakers for symptomatic bradyarrhythmias and not known to have central or obstructive sleep apnoea syndrome (OSAS) were studied. Using a crossover study design, patients were or were not in pacing mode with atrial overdrive (15 beats·min^{-1} faster than mean baseline nocturnal cardiac frequency) for 1 month. Patients were paced only during sleep periods, identified by a specific algorithm included in the pacemaker. Patients underwent three overnight polysomnographic evaluations 1 month apart. The first was performed for baseline evaluation. The patients were then randomly assigned to either 1 night in spontaneous rhythm or to 1 night in pacing mode with atrial overdrive. Two patients refused to continue the study after the first polysomnographic evaluation.

OSAS was highly prevalent in this population: 10 of the 15 (67%) patients exhibited an apnoea–hypopnoea index of >30 events·h^{-1}. The nocturnal spontaneous rhythm was 59±7 beats·min^{-1} at baseline, compared to 75±10 beats·min^{-1} with atrial overdrive pacing. The apnoea–hypopnoea index was 46±29 events·h^{-1} in spontaneous rhythm, compared to 50±24 events·h^{-1} with atrial overdrive pacing. Overdrive pacing changed none of the respiratory indices, or sleep fragmentation or sleep structure parameters.

In conclusion, atrial overdrive pacing has no significant effect on obstructive sleep apnoea.

KEYWORDS: Obstructive sleep apnoea, overdrive pacing, pacemaker

In patients implanted with dual-chamber pacemakers for bradyarrhythmias, GARRIGUE *et al.* [1] reported a 60% reduction in both central and obstructive sleep apnoea severity by overdriving atrial pacing at 15 beats·min^{-1} faster than the mean baseline nocturnal cardiac frequency. The mechanisms underlying such an improvement are still the subject of debate [2–5].

Central sleep apnoea syndrome (CSAS) is generally related to cardiac failure and the associated hypocapnia, chronic hyperventilation and high sensitivity of loop gain that are classical patterns of the disease [6–8]. Efficient therapies for cardiac failure (*i.e.* β-blockers, cardiac transplantation, *etc.*) are also able to improve the related CSAS [6]. Overdrive cardiac pacing probably leads to an increase in cardiac output in patients with the lower baseline cardiac frequency [9], and might, in turn, improve CSAS.

Conversely, in patients with moderately altered cardiac function, short episodes of periodic breathing associated with reduced cardiac output could lead to secondary aggravation of obstructive sleep apnoea syndrome (OSAS) severity [10]. An associated upper airway size reduction and/or increase in upper airway compliance are probably needed for the occurrence of sleep-induced upper airway obstruction. Again, by improving cardiac function and avoiding periodic breathing episodes, overdrive cardiac pacing could reduce the number of secondary obstructive events.

Are the haemodynamic effects of overdrive cardiac pacing (*i.e.* an increase in cardiac frequency of >15 beats·min^{-1}) demonstrated? In dogs, acute cardiac frequency increases induced by pharmaceutical means lead cardiac output to increase curvilinearly [11]. In healthy subjects, after saline loading, pacing tachycardia is also associated with increases in ejection fraction [12]. Conversely, cardiac frequency increases during left ventricular distension had detrimental effects in dilated myocardiopathy patients [12]. The haemodynamic effects of pacing are likely to depend on baseline cardiac frequency and the

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characteristics of the underlying cardiac disease. GARRIGUE *et al.* [13], examining the potential mechanism of sleep apnoea improvement due to overdrive pacing, proposed that cardiac output increases, circulation time shortens and pulmonary congestion decreases. These changes would account for the reduction in central sleep apnoea. For obstructive events, pacing, by reducing vagal tone, might increase upper airway muscle activity. Moreover, in some patients, increases in cardiac output may improve local circulation at the pharyngeal level, thereby improving muscle function [13]. Finally, it should be noted that no randomised studies are available in the literature on the long-term haemodynamic effects of pacing.

Overall, these data suggest that cardiac pacing overdrive could be effective mainly or exclusively in CSAS patients, and in OSAS patients only if they exhibit a certain degree of cardiac failure. In the article published by GARRIGUE *et al.* [1], a reduction in left ventricular ejection fraction (LVEF; <56%) was reported in 11 of their 15 subjects and the prevalence of CSAS was >50%. Thus, the present authors hypothesised that, in patients with normal LVEF and obstructive respiratory events, pacing would not be effective. Therefore, a new subset of 17 patients was studied in order to further evaluate overdrive pacing indications in the sleep apnoea field.

MATERIAL AND METHODS

Study population

A total of 17 unselected patients (12 males; mean±SD age 71±10 yrs; body mass index (BMI) 27±3 kg·m^{-2}) were recruited by the Cardiac Pacing Unit of Grenoble University Hospital (Grenoble, France), and showed classical indications for requiring dual-chamber pacemakers. They were included in the study 1 month after implantation of a Talent DR213^{TM} pacemaker (ELA Medical, Le Plessis-Robinson, France) for symptomatic bradyarrythmias. The patients were not known to have CSAS or OSAS.

The study was conducted in accordance with institutional guidelines, and all patients gave written informed consent.

Protocol

Study design

The study design included baseline overnight polysomnography followed by a crossover clinical trial design in which the two test conditions (overdrive pacing *versus* spontaneous rhythm) were applied for 1 month in randomised order.

Pacing period

The pacemakers used in the present study were able to estimate minute ventilation by means of a transthoracic impedance sensor. It has previously been demonstrated that a sustained 39% decrease in minute ventilation distinguishes nocturnal sleep/rest from daytime activity [14]. More recently, it was demonstrated that the difference between pacemaker estimates and polysomnographic measurements of sleep duration was <15% [15]. Therefore, using this algorithm in the present study, patients were or were not overdrived (crossover study design) for 1 month, and, when overdrived, only during sleep periods detected by associated reductions in minute ventilation. The paced rhythm was used 100% of the time during the overdrive pacing night and 0% of the time during the baseline and nonpacing test nights.

Evaluation of sleep apnoea severity

Continuous recordings were made of electroencephalograpy (using electrode positions C3/A2, C4/A1 and Cz/O1 of the international 10–20 electrode placement system), eye movements, chin electromyography and ECG with modified V2 lead. Airflow was measured *via* nasal pressure, associated with the sum of the buccal and nasal thermistor signals. Respiration was monitored using uncalibrated inductance plethysmography. An additional signal of respiratory effort (*i.e.* pulse transit time) was recorded concurrently. Oxygen saturation was measured using a pulse oximeter (Biox-Ohmeda 3700; Ohmeda, Liberty Corner, NJ, USA). Polysomnographic studies were scored using standard techniques and criteria [16–18]. An apnoea–hypopnoea index (AHI) of >15 events·h^{-1} is the validated value separating normal from apnoeic subjects when using nasal pressure [19]. An AHI of 30 events·h^{-1} has been proposed for separating moderate from severe OSAS by the American Academy of Sleep Medicine Task Force [17]. Hypopnoeas were scored following the recommended rules of the American Sleep Disorders Association [17]. Briefly, a hypopnoea was accepted when a >50% reduction in amplitude occurred during the inspiratory phase of nasal pressure measurements. A hypopnoea was also scored when a >30% reduction in nasal pressure signal was associated with a desaturation of >3% and/or a microarousal [17]. Central hypopnoeas were identified based on pulse transit time effort measurements, as previously validated [20], and the shape of the nasal pressure inspiratory curve.

Two patients refused to continue the study after their first polysomnographic evaluation. Complete data are, therefore, available for 15 patients (11 males; age 71±9 yrs; BMI 27.7±2.9 kg·m^{-2}).

Cardiac function evaluation

LVEF was determined for all patients *via* echocardiography in the trademark mode using the Teicholz formula [21].

Statistical analysis

Quantitative variables were described using mean±SD. Normality of distribution was assessed by skewness and kurtosis tests. No order effect was detected for cardiac frequency and polysomnographic variables. Thus, comparison between pacing and nonpacing phases was made using a paired t-test or Wilcoxon test. Comparison between data from the paper by GARRIGUE *et al.* [1] and that collected during the present study was performed using a t-test or the Mann-Whitney U-test.

RESULTS

OSAS was highly prevalent in the present population: 13 (87%) and 10 (67%) of the 15 patients exhibited an AHI of >15 and >30 events·h^{-1}, respectively (AHI 46±29 events·h^{-1}; BMI 27.7±2.9 kg·m^{-2}; table 1). The nocturnal rhythm during the nonpacing phase was 64±6 beats·min^{-1} at baseline, compared to 75±10 beats·min^{-1} with atrial overdrive pacing ($p<0.001$). The AHI was 43±27 events·h^{-1} during the nonpacing phase, compared to 50±24 events·h^{-1} with atrial overdrive pacing (nonsignificant). The LEVF was 64±13%, with five of the 15 (33%) patients exhibiting an LVEF of <56%. Overdrive pacing changed none of the respiratory indices, or sleep fragmentation or sleep structure parameters in these OSAS patients (fig. 1; table 2).

TABLE 1 Cardiac frequency (f_C) and polysomnographic and oximetric data at baseline

f_C beats·min^{-1}	59±7
Polysomnographic data	
TST min	302±78
Stage 1–2 % TST	78±10
SWS % TST	2±3
REMS % TST	20±10
Respiratory microarousals index events·h^{-1}	32±26
Nonrespiratory microarousals index events·h^{-1}	6±4
Total microarousals index events·h^{-1}	38±24
OAI events·h^{-1}	3.6±8.1
MAI events·h^{-1}	0.6±0.9
HI events·h^{-1}	36.3±22.8
CHI events·h^{-1}	0.05±0.17
CAI events·h^{-1}	1.9±2.0
IFLI events·h^{-1}	3.9±3.9
Total AHI events·h^{-1}	46.3±28.5
Oximetric data	
Mean nocturnal Sa,O_2 %	93.7±1.5
Minimal nocturnal Sa,O_2 %	85.4±5.8

Data are presented as mean±SD. TST: total sleep time; SWS: slow-wave sleep; REMS: rapid eye movement sleep; OAI: obstructive apnoea index; MAI: mixed apnoea index; HI: hypopnoea index; CHI: central hypopnoea index; CAI: central apnoea index; IFLI: inspiratory flow limitation index; AHI: apnoea–hypopnoea index; Sa,O_2: arterial oxygen saturation.

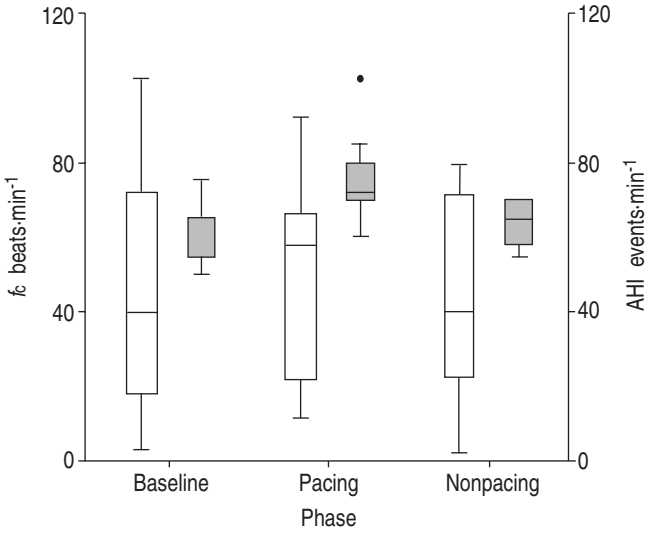

FIGURE 1. Box-plot showing cardiac frequency (f_C; ■) and sleep apnoea severity (apnoea–hypopnoea index (AHI); □) during the pacing and nonpacing phases. Boxes represent median and interquartile range and whiskers range (points represent outliers). The nocturnal spontaneous cardiac rhythm was 59±7 beats·min^{-1} (mean±SD) at baseline, compared to 75±10 beats·min^{-1} with atrial overdrive pacing ($p<0.001$ by ANOVA) and 64±6 beats·min^{-1} during the nonpacing phase. The AHI was 46±29 events·h^{-1} during spontaneous rhythm, compared to 50±24 events·h^{-1} with atrial overdrive pacing (nonsignificant) and 43±27 events·h^{-1} during the nonpacing phase. Overdrive pacing changed none of the respiratory indices, or sleep fragmentation or sleep structure parameters.

TABLE 2 Cardiac frequency (f_C) and polysomnographic and oximetric data during pacing and nonpacing phase

	Pacing	Nonpacing	p-value#
f_C beats·min^{-1}	75±10	64±6	0.001
Polysomnographic data			
TST min	303±74	307±96	NS
Stage 1–2 % TST	77±10	77±9	NS
SWS % TST	3±3	4±5	NS
REMS % TST	20±10	20±7	NS
Respiratory microarousals index events·h^{-1}	33±20	32±23	NS
Nonrespiratory microarousals index events·h^{-1}	6±6	5±4	NS
Total microarousals index events·h^{-1}	39±17	37±20	NS
OAI events·h^{-1}	4.2±4.7	4.6±10.6	NS
MAI events·h^{-1}	0.5±0.8	0.6±0.8	NS
HI events·h^{-1}	37.4±21.0	32.0±22.7	NS
CHI events·h^{-1}	0.0±0.0	0.8±3.2	NS
CAI events·h^{-1}	1.8±2.4	0.9±1.4	0.09
IFLI events·h^{-1}	6.2±7.3	5.2±4.6	NS
Total AHI events·h^{-1}	50.1±24.1	43.3±27.0	NS
Oximetric data			
Mean nocturnal Sa,O_2 %	93.3±1.2	93.5±1.8	NS
Minimal nocturnal Sa,O_2 %	83.7±6.4	83.3±5.3	NS

Data are presented as mean±SD, unless otherwise stated. TST: total sleep time; SWS: slow-wave sleep; REMS: rapid eye movement sleep; OAI: obstructive apnoea index; MAI: mixed apnoea index; HI: hypopnoea index; CHI: central hypopnoea index; CAI: central apnoea index; IFLI: inspiratory flow limitation index; AHI: apnoea–hypopnoea index; Sa,O_2: arterial oxygen saturation; NS: nonsignificant. #: paired t-test or Wilcoxon test.

DISCUSSION

The prevalence of unrecognised sleep apnoea syndrome was very high in the population studied. In pacemaker patients, complaints related to sleep quality and sleepiness are generally very few. In a recent report, in a group of 98 long-term pacemaker implant patients, 60% of whom suffered from undiagnosed sleep apnoea, the score on the Epworth Sleepiness Scale was 7±5 and only few patients complained of symptoms related to sleep apnoea [22]. Finally, cardiologists do not routinely ask patients about symptoms such as snoring, nonrefreshing sleep or sleepiness. Such a high prevalence should lead to specific diagnostic strategies. Thus, some pacemakers have now been designed to detect abnormal respiratory events during sleep [15].

No improvement related to overdrive atrial pacing was found in the present OSAS patients. These results could appear contradictory to those previously published [1]. However, as summarised in table 3, a careful comparison of the data from the two studies permits a better understanding of which subgroup of sleep apnoea patients could experience benefits from overdrive atrial pacing.

Patients in the two studies did not differ in terms of sex, age, BMI and clinical indications for atrial pacing. In the initial

TABLE 3 Anthropometric, cardiac frequency (f_c) and function, and polysomnographic data[#]

	Previous	Present	p-value[¶]
Anthropometric data			
Age yrs	69±9	71±9	NS
Males/females n	11/4	11/4	NS
BMI kg·m^{-2}	26.5±1.4	27.7±2.9	NS
Cardiac frequency and function			
LVEF %	54±11	64±13	0.04
f_c beats·min^{-1}	57±5	59±7	NS
Between-phase[+] Δf_c beats·min^{-1}	18±4	11±11	<0.05
Polysomnographic data			
OAI events·h^{-1}	7±4	4±8	0.0005
HI events·h^{-1}	9±3	36±23	0.0003
CAI events·h^{-1}	12±14	2±2	0.0004
Total AHI events·h^{-1}	27±16	46±29	0.04
Between-phase[+] ΔAHI % nonpacing	-61	16	NA

Data are presented as mean±SD, unless otherwise stated. BMI: body mass index; LVEF: left ventricular ejection fraction; Δ: difference; OAI: obstructive apnoea index; HI: hypopnoea index; CAI: central apnoea index; AHI: apnoea–hypopnoea index; NS: nonsignificant; NA: not available. [#]: comparison between a previous study by GARRIGUE *et al*. [1] and the present study; [¶]: paired t-test or Mann-Whitney U-test; [+]: pacing and nonpacing.

study, patients were included as they reported symptoms suggestive of sleep apnoea. In the present report, the only inclusion criterion was previous implantation of a dual-chamber pacemaker.

There were marked differences in the polysomnographic patterns of the two populations (table 3). The present report studied the effects of overdrive atrial pacing in moderate-to-severe predominantly obstructive apnoeic patients. In the study of GARRIGUE *et al.* [1], more than half of the patients exhibited CSAS, and all presented with a significant number of central events. However, the polysomnographic data are difficult to compare between the two studies, since the present study used more sensitive tools for identifying hypopnoeas and a 3 *versus* a 4% threshold for oxygen desaturations.

In association with prominent CSAS, a large number of patients exhibiting reduced ejection fractions were reported in the initial study (11 out of 15 (73%) *versus* five out of 15 (33%) in the present report). In terms of patient recruitment in the two studies, LVEF was significantly higher in the present group of patients than in the initial report (64±13 *versus* 54±11%; p=0.04). Another important finding when comparing the two studies (table 3) was that the mean difference in cardiac frequency between the pacing and nonpacing phase was higher in the initial study (18±4 *versus* 11±11 beats·min^{-1}; p<0.05).

It has been suggested that cardiac pacing itself can change sleep structure in a way that would explain the reduction in AHI [4]. In the present report, detailed data in terms of sleep structure and sleep fragmentation are provided. Neither the non-REM/REM sleep ratio nor nonrespiratory-related micro-arousal indices were modified by pacing (table 2).

The occurrence of obstructive respiratory events during sleep is determined by two main factors: ventilatory control instability, and upper airway anatomy and collapsibility. Ventilatory control instability can be assessed by the amplitude of the response (*e.g.* hyperpnoea) to perturbation (*e.g.* apnoea or hypopnoea). The rate of response, described as the loop gain, can vary from nearly 0 (stable ventilatory system) to almost 1 (high susceptibility to CSAS) [8]. The more severe the cardiac failure, the closer to 1 the loop gain. Depending on upper airway anatomy and collapsibility, loop gain modulates the occurrence of respiratory events. When the upper airway is highly collapsible, obstructive events occur, regardless of the loop-gain value. This was probably the case in the patients included in the present study. When the upper airway is less collapsible, overdrive atrial pacing could reduce loop gain by improving cardiac function, thereby limiting obstructive events. This was probably the case in the study of GARRIGUE *et al.* [1], in which the patients were less severe in terms of obstructive events, but frequently demonstrated associated reduced ejection fractions and, thus, probably high loop gain.

Conclusions and summary

According to current knowledge, atrial overdrive pacing has no significant effect on obstructive sleep apnoea.

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