Overdrive Ventricular Pacing in Pacemaker Recipients with Permanent Atrial Fibrillation and Sleep Apnea

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SCIENTIFIC INVESTIGATIONS

Study Objectives: Cardiac pacing is ineffective in obstructive sleep apnea (SA), but it can alleviate central SA/Cheyne-Stokes respiration (CSA) in patients with heart failure (HF). We examined whether overnight overdrive ventricular pacing (OVP) has an effect on SA in pacemaker recipients with permanent atrial fibrillation (AF).

Methods: An apnea-hypopnea index (AHI) ≥ 15 was confirmed in 28/38 patients screened by finger pulse oximetry during overnight ventricular pacing at a backup rate of 40 bpm (BUV40). These patients (23 men, 77.9 ± 7.6 y, BMI 27.6 ± 5.1 kg/m²) were randomly assigned to 2 consecutive nocturnal ventilation polygraphies with BUV40 versus OVP at 20 bpm above the mean nocturnal heart rate observed during screening.

Results: During BUV40 versus OVP, (1) mean heart rate was 49 ± 8 versus 71 ± 8 bpm ($p < 0.0001$) and percent ventricular pacing $36\% \pm 38\%$ versus $96\% \pm 6\%$ ($p < 0.0001$); (2) AHI was 35.4 ± 11.9 versus 32.5 ± 15.5 ($p = \text{ns}$), central AHI 23.9 ± 11.8 versus 19.1 ± 12.7 ($p < 0.001$), and obstructive AHI 11.6 ± 13.1 versus 13.5 ± 15.9 ($p = \text{ns}$). In 15/28 patients

without HF, mean left ventricular ejection fraction (LVEF) was $51\% \pm 17\%$, AHI was 37.6 ± 11.0 during BUV40 and 39.0 ± 11.5 during OVP, versus 32.8 ± 12.9 and 24.9 ± 16.5 in 13/28 patients with HF ($p = 0.02$) and mean LVEF $35\% \pm 15\%$ ($p = 0.01$). Between the 2 subgroups, (1) central AHI was 23.6 ± 12.4 during BUV40 and 21.5 ± 14.0 during OVP versus 24.1 ± 11.6 and 16.2 ± 10.7 ($p = 0.05$); (2) obstructive AHI was 14.0 ± 13.7 during BUV40 and 17.6 ± 16.5 during OVP versus 8.8 ± 12.3 and 8.7 ± 14.3 ($p = \text{ns}$).

Conclusions: The prevalence of SA, predominantly central, was high in our pacemaker recipients with permanent AF. In those with HF, a single overnight OVP resulted in modest improvement in central events.

Keywords: Heart failure, sleep apnea, atrial fibrillation, cardiac pacing

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After a first report suggesting that cardiac pacing might alleviate sleep apnea (SA), subsequent studies have yielded conflicting results.^{1,2} An increase in pacing rate by overdrive atrial pacing, using a dual chamber pacemaker implanted for the treatment of bradycardia, has no effect on obstructive SA (OSA) in patients without history of heart failure (HF). In contrast, cardiac resynchronization therapy (CRT) does alleviate central SA/Cheyne-Stokes respiration (CSA), a breathing disorder present in $> 30\%$ of patients with stable HF and associated with a decreased survival rate.³⁻¹⁴

The aim of this study was to compare the effects of overnight overdrive ventricular pacing (OVP) versus overnight ventricular pacing at a low backup rate on SA in recipients of permanent pacemakers suffering from permanent atrial fibrillation (AF). The comparison was also made in separating the patients depending on whether they suffered from HF or not. Those patients were chosen since a high prevalence of SA has been observed in patients with permanent AF and in pacemaker recipients.^{15,16} Previous studies about cardiac pacing and SA included atrial pacing or CRT, but not right ventricular (RV) pacing alone.

BRIEF SUMMARY

Current Knowledge/Study Rationale: Cardiac pacing can alleviate central sleep apnea (SA) in patients with heart failure (HF). We examined whether overnight overdrive ventricular pacing (OVP) influenced SA in pacemaker recipients with permanent atrial fibrillation (AF).

Study Impact: The prevalence of SA, predominantly central, was high in our pacemaker recipients with permanent AF and, in those with HF, a single overnight OVP resulted in modest reduction in central events. Common programming of a nocturnal pacing rate decrement in pacemaker recipients might not be suitable to all the paced patients.

for ≥ 6 months. Patients were eligible for inclusion in the study if, for ≥ 6 months, they were (a) in stable general health, (b) in stable New York Heart Association HF functional class I-III, (c) on a stable medication regimen, and (d) not hospitalized. Eleven patients refused to participate in the study, and 8 were hospitalized or in unstable health within the previous 6 months. Ultimately, 43 patients were eligible and agreed to participate in the trial. Our institutional ethics committee approved the study protocol, and all the study participants granted their written informed consent. After the recording of a baseline electrocardiogram at rest, we excluded 2 patients from the study who were in sinus rhythm, and 3 patients who presented with AF and a ventricular rate > 75 bpm. The VVI pacing mode was verified with the pacemaker programmers.

METHODS

We screened 62 consecutive patients treated in our medical center who presented with permanent AF and were VVI paced

Table 1—Characteristics of the 28 study patients

Age, y	77.9 ± 7.6
Men	23 (82)
Body mass index, kg/m ²	27.6 ± 5.1
Medical history	
Systemic hypertension	14 (50)
Myocardial infarction	8 (29)
Myocardial revascularization	3 (11)
Heart failure decompensation	13 (46)
Stroke	6 (21)
NYHA heart failure functional classification	
Class I	2 (7)
Class II	14 (50)
Class III	12 (43)
Ambient drug therapy	
Angiotensin-converting enzyme inhibitor	15 (54)
Angiotensin II receptor antagonist	3 (11)
Spironolactone	5 (18)
Beta-adrenergic blocker	11 (39)
Amiodarone	7 (25)
Calcium antagonist	5 (18)
Furosemide	18 (64)
Nitrate	8 (29)
Digoxin	7 (25)
Echocardiography	
Left ventricular end-diastolic diameter, mm	58.6 ± 10.7
Interventricular septum thickness, mm	11.6 ± 1.9
Left ventricular ejection fraction, %	43 ± 18
Left atrial diameter, mm	51.9 ± 8.4
Cardiac pacing indications	
VVIR for atrial fibrillation and slow ventricular rate	14 (50)
DDDR for sinus node disease or atrioventricular block	12 (43)
Cardiac resynchronization therapy	2 (7)

Values are means ± SD or number (%) of observations. Heart failure decompensation = at least one episode of clinical hemodynamic decompensation. Myocardial revascularization = coronary artery bypass graft or percutaneous coronary intervention.

Overnight Pulse Finger Oximetry

After recording of the electrocardiogram, on the same day the 38 remaining patients underwent overnight home recording of pulse finger oximetry with a PalmSAT 2500 oximeter (Nonin Medical, Minneapolis, MN). For that recording, the pacemakers were programmed in VVI mode at a back-up rate of 40 bpm (BUV40), rate responsive function *off*, allowing ventricular pacing when the spontaneous heart rate was < 40 bpm. This allowed the detection of overnight O₂ desaturation events while the heart rate was the slowest, at the slowest acceptable back-up pacing rate. The recordings were scored with the automated analysis protocol of the Nonin software. A significant O₂ desaturation event was defined as ≥ 4% dip in O₂ for ≥ 10 sec immediately after the baseline arterial O₂ saturation signal.¹⁷ The mean hourly number of dips in O₂ defined the O₂ desaturation index, with ≥ 12 indicating a high probability of SA. We excluded 10 patients from the study (26%), who had < 12 dips/h, and included the 28 remaining patients (74%) with ≥ 12 dips/h, who completed the protocol. The cutoff of 12 dips/h was cho-

sen arbitrarily. The mean nocturnal heart rate measured during this recording was retained as the reference for the subsequent individual setting of OVP.

Study Population

The characteristics of the 28 patients are presented in **Table 1**. In the study, HF was defined by history of ≥ 1 episode of clinical cardiac decompensation corresponding to documented acute pulmonary edema treated with intravenous diuretics and/or nitrates. Thus, 13 patients were considered with HF, 7 suffering from ischemic cardiopathy, and 6 from idiopathic dilated, hypertrophic, or valvular cardiopathy. Recipients of dual chamber pacemakers were in sinus rhythm at the time of device implantation, which was reprogrammed to the VVI mode after the development of a permanent AF. Two patients were recipients of CRT-D because of a hemodynamic indication associating permanent AF with permanent low ventricular rate. These patients were equipped with a RV apical lead and an epicardial left ventricular (LV) lead via the coronary sinus. They were chronically paced in RV-VVI mode because of a non-functional LV lead. The other patients, paced for conventional bradyarrhythmia-related indications, had an RV lead implanted at the apex. Interrogation of the pacemakers before screening by finger pulse oximetry revealed a mean of 82% rate of ventricular pacing for the study population and a mean backup rate programmed at 62 bpm.

Nocturnal Ventilation Polygraphy

The 28 patients underwent, in random order, 2 consecutive nocturnal ventilation polygraphic examinations in our sleep laboratory, during BUV40, with the rate responsive function *off*, and during OVP, with the back-up pacing rate programmed to match the mean nocturnal heart rate observed during screening oximetry + 20 bpm, with the rate responsive function *on*.¹⁸ In 15 patients, BUV40 polygraphy and OVP polygraphy were performed on consecutive nights, and 13 patients underwent the same tests in the reverse order. The pacemakers were reprogrammed between 20:00 and 21:00 on the evening of each recording. The overnight sleep polygraphy signals was automatically acquired with an Embletta PDS system (Medcare Flaga, Reykjavik, Iceland) at 23:00 and ended at 06:00 the following morning. The recordings included (1) continuous airflow by a nasal cannula pressure transducer, (2) the sum of nasal and oral airflow via a thermistor, (3) rib cage and abdominal motion, using respiratory inductive plethysmograph sensor belts, (4) arterial O₂ saturation and heart rate by pulse finger oximetry, and (5) synchronized, single-channel electrocardiogram (**Figure 1**).

Interpretation of the Nocturnal Measurements

The same sleep specialist, unaware of the patient's identity, scored all recordings visually, using standard criteria.¹⁷ Apnea was defined as complete cessation of oro-nasal airflow ≥ 10 sec, confirmed by simultaneous nasal cannula and oro-nasal thermistor signals. Hypopnea was defined as a decrease ≥ 30% in inspiratory oro-nasal airflow amplitude below the surrounding baseline ≥ 10 sec, on at least the nasal cannula signal, accompanied by ≥ 4% decrease in O₂ saturation from the preceding stable baseline, in presence of thoraco-abdominal ventilatory efforts. In obstructive respiratory events, breathing efforts were

Figure 1—Nocturnal ventilation polygraphy. In this example, mixed apnea is documented, with 1 min 18 sec duration, associated with a marked dip in O₂ saturation from 98% to 73%

ECG trace shows atrial fibrillation with ventricular rate ranging from 56 to 40 bpm in this sequence, while the pacemaker is programmed in VVI mode at a backup rate of 40 bpm. See text for further explanations.

present, generally of greater amplitude during the event, and associated with out-of-phase rib cage and abdominal movements. Obstructive hypopnea was accompanied by distinct changes in the inspiratory flow pattern, such as prolonged inspiration with flattening of the upper airflow waveform, consistent with airflow limitation. In central respiratory events, breathing efforts were absent during apnea and weakened during hypopnea, associating an in-phase decrease in rib cage and abdominal movements with a proportional decrease in airflow amplitude. Cheyne-Stokes respiration was defined as a regular waxing and waning breathing pattern followed by central apnea or hypopnea in ≥ 3 consecutive respiratory cycles. In case of periodic breathing, apnea and hypopnea were scored as central apnea and central hypopnea, according to the definitions above. A mixed respiratory event was defined by either an initial central pattern followed by obstructive pattern of thoracic and abdomi-

nal movements, or by the absence of breathing efforts followed by in-phase thoraco-abdominal movements of increasing amplitude. Once scored, mixed respiratory events were classified as obstructive events. Obstructive and central nocturnal respiratory events could coexist in the same subject; therefore, SA was classified as central or obstructive when $\geq 50\%$ of the respiratory events were of central or obstructive origin, respectively. The apnea-hypopnea index (AHI) was calculated as the total number of apneas and hypopneas divided by the number of hours of nocturnal recording. SA was diagnosed when AHI was ≥ 15 , and severe SA when AHI was ≥ 30 . Results of the 2 polygraphies were compared in all patients and between the 2 subsets of patients without versus with HF.

Table 2—Measurements made during overnight BUV40 and OVP

	BUV40	OVP	p value
Recording duration, h	6.6 ± 0.2	6.7 ± 0.3	ns
Apnea-hypopnea index	35.4 ± 11.9	32.5 ± 15.5	ns
Central	23.9 ± 11.8	19.1 ± 12.7	p < 0.001
Obstructive	11.6 ± 13.1	13.5 ± 15.9	ns
Time in apnea-hypopnea, min	119 ± 47	102 ± 56	p < 0.001
Central sleep apnea	22 (79)	20 (71)	ns
Obstructive sleep apnea	6 (21)	8 (29)	ns
Apnea Index	17.0 ± 14.5	10.8 ± 11.9	p < 0.001
Central	9.0 ± 10.2	3.7 ± 6.3	p < 0.001
Obstructive	8.0 ± 5.7	7.2 ± 6.2	ns
Mean duration of apnea, s	28 ± 12	23 ± 11	p < 0.001
Time in apnea, min	62 ± 64	37 ± 51	p < 0.001
Hypopnea index	18.3 ± 11.2	21.6 ± 11.9	ns
Central	14.9 ± 10.6	15.4 ± 11.2	ns
Obstructive	3.4 ± 3.9	6.3 ± 5.5	p < 0.001
Mean duration of hypopnea, s	30 ± 6	28 ± 5	p < 0.02
Time in hypopnea, min	57 ± 33	64 ± 31	ns
Mean SpO ₂ , %	93 ± 2	93 ± 2	ns
O ₂ desaturation index	28.6 ± 11.1	25.8 ± 12.4	ns
Mean dip in SpO ₂ , %	7 ± 3	7 ± 3	ns
SpO ₂ < 90%, min	47 ± 53	47 ± 57	ns
Mean nocturnal heart rate, bpm	49 ± 8	71 ± 8	p < 0.0001
Percent ventricular pacing	36 ± 38	96 ± 6	p < 0.0001
Brain natriuretic peptide*, pg/mL	437 ± 313	397 ± 284	ns

Values are means ± SD, or numbers (%) of observations. *Normal range 36-65 pg/mL. Index, number of events per hour of nocturnal recording; BUV40, back up pacing rate programmed at 40 bpm; OVP, back up pacing rate programmed at mean nocturnal heart rate measured during the screening oximetry + 20 bpm; SpO₂, pulse oximeter O₂ saturation.

Measurements of Left Ventricular Function and Brain Natriuretic Peptide

A transthoracic echocardiogram was recorded, using Acuson-128 sonographic instrumentation (Siemens Medical Solutions USA, Inc., Malvern, PA) the evening before the first polygraphic recording and before pacemaker programming. Three measurements of LVEF were made according to the modified Simpson method, and averaged to mitigate the effects of the irregular spontaneous rhythm. Baseline plasma concentrations of brain natriuretic peptide (BNP) were not measured; nevertheless, they were measured after each nocturnal recording, upon awakening of the patient. At that time, the pacemaker memories, which were reset each evening, were interrogated, and the proportion of spontaneous and paced ventricular events was recorded. At the end of data acquisition, the pacemakers were returned to their pre-study settings.

Statistics

Statistical analysis consisted in comparison of means (Epi Info CDC). Student 2-tailed *t*-test was used to examine differences between paired quantitative variables. In the study group, difference between OVP and BUV40 values were established for each datum. The value given by [mean/(Std Dev/ $\sqrt{n}$)] was compared to those in Student tables for 27 degrees-of-freedom, and, matching in between 2 thresholds from Student tables determined p-value for the datum. It tested difference between mean and zero. Fisher exact test was used to compare cat-

egorical variables and suit to sample of small size. ANOVA, a parametric test for inequality of population means was used to examine differences in quantitative variables between patients without and those with HF. Each patient was compared to himself, and the mean of differences was analyzed between the 2 subgroups. A p-value < 0.05 was considered statistically significant.

RESULTS

The 74% prevalence of SA in our study population is consistent with that reported in paced patients or in patients with AF.^{15,16} We observed a high proportion of CSA, 79%, probably due to a high prevalence of HF and depressed LVEF in the study population.¹⁹ Severe SA was present on both nocturnal polygraphic recordings in 61% of our patients, compared with 67% of pacemaker recipients suffering from OSA in the study by Pepin et al.²⁰ Among our 13 patients with history of decompensated HF, 46% and 31% had severe SA during BUV40 and OVP, respectively, which is similar to the 36% prevalence previously reported in unpaced patients with HF and CSA.⁵

Table 2 compares the nocturnal observations made during BUV40 versus OVP in the 28 patients. During BUV40, a majority of patients had a highest density of spontaneous rhythm than paced, while pacing was permanent in 1 patient, and almost permanent ($\geq 90\%$ -99% $\leq$ of ventricular beats) in 5 patients. During OVP, 8 and 18 patients were, respectively, permanently

Table 3—Measurements made during both nocturnal recordings in patients without and with history of heart failure (HF) decompensation

	No history of HF decompensation n = 15		History of HF decompensation n = 13		p value	
	BUV40	OVP	BUV40	OVP	a	b
Apnea-hypopnea index	37.6 ± 11.0	39.0 ± 11.5	32.8 ± 12.9	24.9 ± 16.5	0.02	ns
Central	23.6 ± 12.4	21.5 ± 14.0	24.1 ± 11.6	16.2 ± 10.7	0.05	ns
Obstructive	14.0 ± 13.7	17.6 ± 16.5	8.8 ± 12.3	8.7 ± 14.3	ns	ns
Time in apnea-hypopnea, min	130 ± 52	122 ± 54	108 ± 41	79 ± 50	0.08	ns
Apnea index	19.8 ± 15.5	14.2 ± 12.9	13.9 ± 13.0	7.0 ± 9.6	ns	ns
Central	9.9 ± 11.1	5.0 ± 8.0	7.9 ± 9.3	2.1 ± 3.2	ns	ns
Obstructive	9.9 ± 10.7	9.2 ± 9.8	6.0 ± 8.7	4.8 ± 8.4	ns	ns
Hypopnea index	17.8 ± 12.8	24.8 ± 11.8	18.9 ± 9.3	17.9 ± 11.3	ns	ns
Central	13.7 ± 11.6	16.5 ± 12.3	16.1 ± 9.5	14.1 ± 10.2	0.07	ns
Obstructive	4.1 ± 8.9	8.4 ± 10.3	2.8 ± 5.0	3.8 ± 7.0	0.05	ns
Mean SpO ₂ , %	94 ± 1	93 ± 2	92 ± 2	92 ± 2	ns	ns
O ₂ desaturation index	28.9 ± 11.4	27.7 ± 7.3	28.3 ± 11.3	23.6 ± 16.6	ns	ns
SpO ₂ < 90%, min	26 ± 34	34 ± 39	71 ± 63	61 ± 72	ns	0.02
Mean nocturnal heart rate, bpm	49 ± 8	71 ± 8	48 ± 8	70 ± 8	ns	ns
% ventricular pacing	45 ± 42	98 ± 2	29 ± 32	94 ± 8	ns	ns
Brain natriuretic peptide*, pg/mL	446 ± 301	380 ± 252	426 ± 339	415 ± 326	ns	ns

Values are means ± SD. Indices represent number of events per hour of nocturnal recording. BUV40, back up pacing rate programmed at 40 bpm; OVP, back up pacing rate programmed at the mean nocturnal heart rate measured during the screening oximetry + 20 bpm; SpO₂, pulse oximeter O₂ saturation.

*Normal range 36–65 pg/mL. p values: (a) comparisons of magnitude of changes occurring between BUV40 and OVP; (b) comparisons of measurements made during BUV40.

and almost permanently paced, and 2 patients had < 90% of ventricular pacing. None of the patients have reported particular symptoms during BUV40 or OVP.

No significant difference was observed between the 15 patients without and the 13 patients with history of HF decompensation, comparing age (78.4 ± 6.5 versus 77.2 ± 8.9 y), sex (12 [80%] versus 11 [85%] males), body mass index (27.4 ± 4.6 versus 27.8 ± 5.8 kg/m²), and presence of central SA (10 [67%] versus 12 [92%] patients). In the patients without and those with history of HF decompensation, LVEF was 51% ± 17% versus 35% ± 15% (p = 0.01), respectively. We henceforth compared the changes observed between BUV40 and OVP, between these 2 subgroups of patients (**Table 3**). **Figure 2** shows the corresponding changes in AHI. Among the 13 patients with history of HF decompensation, LVEF was > 35% in 4 patients, including 2 with LVEF > 55%, 1 with LVEF = 50%, and 1 with LVEF = 43%. In these 4 patients, the absence of significant or severe cardiac contractility impairment did not prevent from AHI alleviation between BUV40 and OVP, since they had an AHI decrease ≥ 20%, and on average 39%.

DISCUSSION

In previous studies, a single night of fixed overdrive atrial pacing lowered AHI significantly in recipients of conventional dual chamber pacemakers or cardioverter defibrillators with HF and predominant CSA,^{1,21} whereas several months of dynamic overdrive atrial pacing had no effect on obstructive or mixed SA.^{22,23} Furthermore, in patients with HF, CRT might alleviate CSA, while leaving obstructive respiratory events, if present,

either unchanged or aggravated.²⁴ The majority of studies of CRT in patients with SA were performed without overdrive atrial pacing.^{13,14}

In our study population, AHI was similar during BUV40 and OVP, though the duration of time in apnea-hypopnea was significantly shortened during rapid pacing. This was due to a significant decrease in the severity and duration of central apnea, leading to significant decrease in central AHI and to an increase in hypopnea burden due essentially to obstructive events. In patients with history of HF decompensation, the decrease in AHI during OVP seemed mostly due to a decrease in apnea index, while the hypopnea index remained stable. In patients without history of HF decompensation, a decrease in apnea index combined with an increase in hypopnea index resulted in no significant change in AHI. That might be explained by the evolution of apnea toward hypopnea or by the development of new hypopnea events during OVP. Our observations are concordant with previous reports of a decrease in apneic events by cardiac pacing in patients with HF and predominant CSA.^{1,9–12,18,21} The impact of our experiment on apnea-related symptoms or on HF outcome has not been assessed. Patients with HF and CSA often have a paucity of symptoms related to central apnea. Therefore, a decrease in central AHI in a patient, though statistically significant, might not be expected to improve clinical symptoms. The focus of this study was to determine the influence of nocturnal heart rate modification on AHI.

In patients with HF and low LVEF, single chamber ventricular pacing and RV apical pacing can lower cardiac performance, mainly due to ventricular desynchronization.^{25–27} In those patients, it is suggested that dual-chamber pacing (with atrio-

Figure 2—Apnea-hypopnea index (AHI) during overnight BUV40 and OVP according to the absence versus presence of history of heart failure decompensation (HFD)

BUV40, back up pacing rate programmed at 40 bpm; OVP, back up pacing rate programmed at the mean nocturnal heart rate measured during the screening oximetry + 20 bpm. Box plot: upper and lower vertical bars are the maximum and minimum values of AHI, respectively; upper and lower horizontal boundaries of the box are the 75th and 25th percentiles, respectively; bold horizontal line inside the box indicates median AHI for the corresponding group.

ventricular synchronization) be combined with biventricular pacing. Recently, this was also proposed in patients with normal LVEF.²⁸ However, in patients with low permanent AF (with or without HF), few studies have been published about deleterious effects of RV pacing. Tops et al. reported detrimental effects of RV apical pacing after AV node ablation for permanent AF.²⁹ LV function deterioration was observed, with LV dilatation and LVEF decrease, possibly due to LV dyssynchrony after long-term RV pacing. This observation was performed on average 3.8 ± 1.7 years after the AV node ablation. The clinical consequences appeared modest, with tendency to NYHA functional class worsening, but without more hospitalizations for HF or related deaths reported. Orlov et al. observed beneficial effects of biventricular versus RV pacing in patients with HF 6 months after AV node ablation for rebel and permanent AF.³⁰ RV and not biventricular pacing had a negative impact on left atrium in increasing its volume while biventricular and not RV pacing improved LVEF. A decrease of interventricular dyssynchrony was observed with biventricular pacing. Moreover, superiority of biventricular pacing appeared in echographic measurements but not in functional and clinical HF parameters. In our study, in absence of ventricular resynchronization, the effects of overdrive pacing on SA may be simply related to an acceleration of the heart rate, which is a major compensatory mechanism

in the setting of HF. Javaheri et al. reported an alleviation of CSA by theophylline in patients with HF, which was attributed to a drug-induced acceleration of the heart rate.³¹ On the other hand, the potential effects of OVP may also explain the increase in AHI in a subset of patients, essentially those without HF. It may be the manifestation of deleterious effects of RV apical pacing which, in absence of HF, was not counterbalanced by the favorable effects of an increase in heart rate. We did not evaluate ventricular dyssynchrony upon OVP application on a single night.

High pacing rates are considered deleterious on myocardial performance, particularly in patients with HF.³²⁻³⁴ Nevertheless, Sinha et al. reported no adverse effects of long-term overdrive atrial pacing in patients with SA and HF.²² In our study, mean nocturnal heart rate during OVP was of 71 ± 8 bpm with $96\% \pm 6\%$ of ventricular pacing. This heart rate was very close to the threshold of 70 bpm recently highlighted in SHIFT study.^{35,36} It established better outcomes in patients with HF when heart rate, in sinus rhythm, was below 70 bpm. Before the protocol, our patients had a mean backup rate of 62 bpm with 82% of ventricular pacing. These data were not far from those recorded during OVP. One could consider that our patients at baseline were already with an OVP, while during BUV40, the proportion of ventricular pacing was of 36% with a mean heart rate of 49 bpm. We do not know if a difference would have been observed by comparing nocturnal recordings between pacemaker programming before the protocol and study OVP.

In our overall patient population, blood oxygenation did not change significantly between the two nocturnal recordings. Gabor et al. observed no change in blood O₂ saturation despite a clear alleviation of CSA by CRT,¹⁰ while Oldenburg et al. noted a mitigation of O₂ desaturation.¹¹ The duration of pulse oximeter O₂ saturation < 90% during BUV40 was significantly longer among our patients with history of HF decompensation than our patients without (Table 3), suggesting that patients with previous cardiac decompensation were more hypoxic at baseline than patients who never previously suffered an episode of acute HF. This did not seem strictly related to SA, since AHI was not highest among patients with the longest duration of pulse oximeter O₂ saturation < 90%. This is a noteworthy observation with respect to the pathophysiology of CSA in patients with HF, since hypoxia causes hyperventilation and hypocapnia, the main trigger of CSA.

No difference in BNP levels were observed in our study comparing measurements after BUV40 and OVP in all the patients, but also in the subgroups without versus with HF. Measurements of BNP have not been included in the majority of studies of CRT and sleep disordered breathing.^{9-12,14} Lüthje et al. observed a decrease in BNP after 3 months of CRT, of similar amplitude in patients with versus without CSA.¹³ In that study, BNP was unchanged by overnight overdrive atrial pacing. In two other studies of overdrive atrial pacing in patients with HF without CRT, neither BNP nor SA were changed in one study,³⁷ while BNP was not measured and SA was alleviated in the other.²¹

Limitations

A limitation of our study design was the absence of baseline recording of nocturnal ventilation polygraphy. Furthermore, in-

terpretation of nocturnal polygraphy was not performed blinded to the pacing mode, since heart rate and electrocardiogram were both visible on the recordings, nor did we examine the intraindividual variability of the AHI measurements.^{38,39}

The use of monitoring limited to respiratory and cardiac sensors may have resulted in less accurate indices of AHI. Medication was maybe not optimized for HF in some study patients, but they had been in stable health for at least six months. Finally, the impact of our observations is limited by the relatively small size of the entire population and its subgroups and by the modest changes in AHI.

CONCLUSIONS

A high prevalence of SA, predominantly central, was observed in our VVI-paced patients with permanent AF. In those with HF, defined by history of HF decompensation, a single overnight OVP could modestly alleviate CSA, despite the risk of decreased cardiac performance associated with RV apical pacing. Even if biventricular pacing might be more beneficial for patients such as in our study, we should keep in mind the ease of single chamber device implantation with RV apical lead. According to our findings, programming of a nocturnal pacing rate decrement that is generally suggested in pacemaker recipients might not be suitable to all the paced patients. Impact of our experiment on apnea-related symptoms or on HF outcome has not been assessed. A long-term protocol might demonstrate whether our results could be stable in time, considering that OVP would be applied intermittently, i.e., only during nighttime.

ABBREVIATIONS

AF, atrial fibrillation
AHI, apnea-hypopnea index
BNP, brain natriuretic peptide
BUV40, ventricular pacing at a backup rate of 40 bpm
CRT, cardiac resynchronization therapy
CSA, central sleep apnea/Cheyne-Stokes respiration
HF, heart failure
LV, left ventricular
LVEF, left ventricular ejection fraction
OSA, obstructive sleep apnea
OVP, overdrive ventricular pacing
RV, right ventricular
SA, sleep apnea

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