AJRCCM Articles in Press. Published on March 4, 2005 as doi:10.1164/rccm.200409-1258OC

Atrial overdrive pacing in sleep apnea patients with implanted pacemaker

Lars Lüthje, MD; Christina Unterberg-Buchwald MD; Dani Dajani; Dirk Vollmann, MD; Gerd Hasenfuß, MD; Stefan Andreas, MD

Department of Cardiology and Pneumology, Georg-August-Universität, Göttingen, Germany

Address for correspondence:

Prof. Dr. S. Andreas
Herzzentrum Göttingen
Abteilung Kardiologie und Pneumologie
Georg-August-Universität Göttingen Tel: +49 551 39-8921
Robert-Koch-Str. 40 Fax: +49 551 39-14370
37075 Göttingen E-Mail: sandreas@med.uni-goettingen.de

Support:

This investigator initiated study was supported by the Medtronic Inc., Minneapolis, USA

Running head: Pacing in sleep apnea

Descriptor number: 17

Word count: 2469

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

Abstract

Rationale: Atrial overdrive pacing markedly improved sleep disordered breathing in a recent study.

Objectives: Using a single blinded, randomized, crossover design, we aimed to reproduce these findings and investigate the possible underlying mechanisms.

Methods: Twenty ambulatory patients with an implanted pacemaker or cardioverter defibrillator were studied by polysomnography on three consecutive nights in a randomized single-blind crossover study in which devices were programmed for non-pacing, or for overdrive pacing at 7 or 15 beats per minute faster than the mean nocturnal heart rate. Ventilation (Respitrace) and biomarkers (urinary norepinephrine excretion, aminoterminal portion of the precursor of brain natriuretic peptide (NT-proBNP)) were also evaluated.

Measurements and Main Results: Neither the primary endpoint apnea-hypopnea index, nor the apnea index, oxygen desaturation, ventilation or biomarkers were affected by the nocturnal atrial overdrive pacing. A small, clinically insignificant rate-dependent reduction in the hypopnea index was evoked by pacing (non-pacing: 13.4 ± 1.4; pacing 7: 12.9 ± 1.4; pacing 15: 10.9 ± 1.0; p ANOVA < 0.01).

Conclusions: The lack of effect on the apnea-hypopnea index means that atrial overdrive pacing is inappropriate for treating sleep disordered breathing.

Word count: 183

Key words: sleep apnea, pacing, randomized trial

Introduction

Obstructive sleep apnea (OSA) has a high prevalence within the general population that will rise further given the obesity epidemic at hand [1]. OSA is associated with arterial hypertension and increased cardiovascular morbidity [2-4]. Continuous positive airway pressure (CPAP) is an effective therapy for OSA. However, CPAP therapy is often difficult to tolerate and patients frequently stop using it because of discomfort. The nasal mask interface may cause pressure sores, claustrophobia, nasal congestion, and other side effects that lead to suboptimal compliance [5-7].

The finding that atrial overdrive pacing reduces the number of central and obstructive sleep apnea episodes by about 50% [8] is tantalizing, as it might give rise to a new therapeutic concept [9]. Two key underlying mechanisms of the effect of atrial overdrive pacing in sleep apnea have been suggested: 1.) Overdrive pacing can improve cardiac output [10] as well as pulmonary congestion and thereby reduce hyperventilation and central apneas [11]. 2). Overdrive pacing counteracts nocturnal hypervagotonia by influencing cardiac vagal or sympathetic afferent neurons, thus affecting ventilation and stabilizing respiration [11]. However, these concepts have not been proven [9].

Biomarkers of neurohumoral activation, such as plasma and urinary norepinephrine as well as brain-type natriuretic peptide plasma concentration, are elevated in OSA [12-14] and are inversely correlated with left ventricular function and prognosis in patients with heart failure [15, 16]. It is possible that the increase in heart rate due to overdrive pacing impacts on systolic or diastolic left ventricular function and thus on these biomarkers.

Garrigue and colleagues performed atrial overdrive pacing with a rate that was arbitrarily set at 15 beats per minute faster than the mean nocturnal heart rate. It

remains to be investigated whether overdrive pacing at a lower rate has the same beneficial effect on sleep disordered breathing.

Using a single-blinded, randomized, crossover design, we investigated the effects of nocturnal atrial overdrive pacing on sleep disordered breathing, minute ventilation and biomarkers in patients with an implanted pacemaker (PM) or implanted cardioverter defibrillator (ICD). Overdrive pacing was performed with a rate of 7 as well as 15 beats per minute faster than the mean nocturnal heart rate. Some of the results of these studies have been previously reported in the form of abstracts [17, 18].

Methods (Word count: 500)

Patient selection

Patients in our out-patients' clinic for PMs and ICDs with stable sinus rhythm and a dual chamber device implanted were screened for sleep apnea with an ambulatory device (Somnocheck effort, Weinmann, Hamburg, Germany), regardless of any symptoms suggestive of sleep apnea. To evaluate the mean nocturnal heart rate by Holter ECG, the PM/ICD was programmed to 40 beats/min (DDD). Inclusion criterion was an apnea/hypopnea index (AHI) >15/h with associated oxygen desaturations >4%. Exclusion criteria were chronic atrial arrhythmias, myocardial infarction within one month of the study, decompensated heart failure, and age groups <18 or >75 years. Written informed consent was obtained from each patient, and the study was approved by the University of Göttingen Institutional Review Board.

Protocol

Patients underwent full-night polysomnography for three consecutive nights in a randomised single-blind crossover design. In the three nights, the PM/ICD was programmed either to a backup rate of 40 beats/min (non-pacing), or to an atrial overdrive pacing rate of 7 or 15 (pacing 7 or 15) beats higher than the mean nocturnal heart rate of the screening night. Before the first night an electrocardiogram, lung function tests, and echocardiography were performed. For further information see online data supplement.

Polysomnography

An electroencephalogram, electrooculogram, electromyogram and electrocardiogram were recorded as previously described [19]. Airflow was recorded by nasal pressure, while thorax and abdominal wall motion was monitored by Respitrace as detailed below. Arterial oxygen saturation (SaO_2) was measured transcutaneously by pulse oximetry (Healthdyne Technologies Inc., Marietta, USA). The polysomnogram was visually analysed with a computer system (ALICE IV, Heinen und Löwenstein, Bad Ems, Germany) as already described. An apnea was considered obstructive when nasal flow was absent in the presence of abdominal or thoracic movements, and central when movements were absent as well. Central hypopneas were defined as a 50% or greater reduction in tidal volume from the baseline value for at least 10 seconds with proportional in-phase reductions in rib cage and abdominal movements. Obstructive hypopneas were similarly defined except that out of phase thoracoabdominal motion had to be present [20]. Sleep stages and arousals were evaluated according to standard criteria [21, 22].

Ventilation, Holter monitoring, blood pressure, biomarker

Respiratory rate and tidal volume were registered by calibrated respiratory inductive plethysmography (Respitrace Systems, Ambulatory Monitoring Inc., New York, USA) as previously described [23]. Blood pressure was measured noninvasively by sphygmomanometry (Dinamap XL Monitor, model 9302, Johnson & Johnson Medical Inc., Tampa, USA) once every hour. Blood samples were taken each morning directly after waking. Urine was collected overnight. For details see online data supplement.

Statistical Analysis

Variables are given as mean ± SEM. Primary endpoint was the apnea/hypopnea index (AHI). Repeated measure analysis of variance (ANOVA) was used for comparison of the three nights. For the secondary endpoints (apnea index as well as hypopnea index) ANOVA with Bonferroni´s correction was applied. If ANOVA revealed significant differences, a paired t-test with Bonferroni´s correction as post hoc test was performed. Two-tailed tests were used and significance was recognized at a value of $p<0.05$.

Results

Subject characteristics

From May to December 2003 a total of 655 patients visited our PM and ICD out-patients clinic. Of these, 189 patients were excluded by the age criterion, and 215 patients because they had a single chamber device implanted. Of the remaining 251 patients, 130 gave written informed consent and fulfilled the remaining inclusion criteria. Suspected sleep apnea in the ambulatory measurement (AHI>15/h with

associated oxygen desaturations >4%) appeared in 28 cases. Of these, 8 patients failed an inclusion criterion or withdrew consent after screening.

Finally twenty predominately male and overweight patients were included in the study (Table 1). In ten patients PM and in ten ICD were implanted. Indications for implantation were ventricular tachycardia/fibrillation in 9, atrioventricular block in 7, sick sinus syndrome in 3 patients and prophylactic indication in 1 patient. An underlying heart disease was apparent in 13 patients, namely coronary artery disease in 10, dilated cardiomyopathy in two, and a Brugada syndrome in one patient. Diuretics were prescribed to 10, beta-blockers to 9, and ACE inhibitors/AT1-antagonists to 12 patients. Amiodarone was taken by 6, and digitalis by 2 patients.

Heart rate

In the pacing nights an effective stimulation with a significant increase in mean heart rate was revealed by the 24-h Holter monitoring (Table 2). Minimum heart rate in the non-pacing night was 50.0 ± 3.1 beats/min, with pacing 7 it was 54.5 ± 2.5 beats/min, and with pacing 15 it was 60.6 ± 2.7 beats/min ($p < 0.001$). Maximum heart rate with non-pacing was 66.2 ± 2.6 beats/min, increased to 72.7 ± 2.4 beats/min by pacing 7, and to 75.8 ± 2.5 beats/min during pacing 15 ($p < 0.01$). The percentage of atrial pacing was 10.8 ± 6.1% during non-pacing, it increased during pacing 7 to 87.7 ± 3.2% and during pacing 15 to 94.6 ± 1.5% ($p < 0.0001$).

Respiratory events

The patients suffered from moderate sleep apnea. The predominant type was obstructive (Table 1). The hypopneas were both central (central hypopnea index 8.2 ± 1.6/h) and obstructive (obstructive hypopnea index 5.6 ± 1.1/h). Central apneas

rarely occurred (central apnea index 1.8 ± 0.9/h), obstructive apneas were detected more frequently (obstructive apnea index 5.2 ± 0.8/h). Pacing did not result in a significant change of either the AHI (p ANOVA =0.07) or of the AI. There was a small but significant decrease of the hypopnoea index ($p<0.05$ following Bonferroni´s correction for multiple comparisons; figure 1 and table 2). The paired t-test (again with Bonferroni´s correction) revealed a significant difference only between baseline and pacing 15. When obstructive and central apneas as well as obstructive and central hypopneas were analyzed separately, no significant effects of pacing were seen.

Ventilation, sleep, biomarkers and blood pressure

As shown in table 2 pacing did not affect sleep, nocturnal ventilation or biomarkers. Similarly the mean nocturnal blood pressure showed no significant difference.

Discussion

In this randomized, single-blinded crossover study, nocturnal atrial overdrive pacing did not affect the primary endpoint apnea-hypopnea index nor did it improve oxygen desaturation. Nevertheless, there was a significant but minor and thus therapeutically not relevant reduction in the hypopnea index. Other novel findings were that higher pacing rates had a stronger effect on hypopneas as compared to lower rates; and ventilation as well as biomarkers were not affected by pacing.

Our results appear to differ from those in a previously published paper by Garrigue and colleagues, who described a reduction of over 50 percent in apneas, hypopneas and oxygen desaturations [11]. These discrepancies might be explained by the differences in patient characteristics. As compared to the study by Garrigue and

colleagues, our patients were slightly younger (63 versus 69 years), had a lower ejection fraction (47 versus 54%), and more of them had predominant obstructive sleep apnea (18 of 20 versus 7 of 15 patients) [11]. Body mass index as well as underlying heart disease cannot be compared, as these data were not given in the former study. It thus seems possible that the higher proportion of predominant obstructive apneas in our population might account for the differences. Moreover, in contrast to the Garrigue population, only ten of the twenty patients investigated in our study had an indication for device implantation for bradycardia. Accordingly, our patients had a higher mean nocturnal heart rate in the non-pacing night. As mentioned below, a low nocturnal heart rate might contribute to central apnea.

Effects of pacing on heart rate and hemodynamics

Our knowledge of the effects of pacing dates back to 1871, when Bowditch described the positive force-frequency relation in isolated hearts. Further work with animals and humans clearly revealed improvements in left ventricular contractility, and diastolic filling particularly following atrial pacing [24]. However, more recent work by ourselves and others suggests a low or even negative force-frequency relation with impaired left ventricular systolic and diastolic function and calcium-handling in older subjects as well as in patients with heart failure [24-26]. These findings were independent of the pacing site and can thus not be explained by pacing-induced ventricular desynchronisation. Of note is that there are no human studies evaluating the long-term effects of pacing-induced, slightly accelerated heart rates. It is known however, that increasing periods of ventricular pacing cause increased risk of heart failure, probably due to ventricular desynchronisation by right ventricular pacing [27]. In the study by Garrigue and colleagues the mean nocturnal heart rate was 51 beats/ minute as compared to 55 beats/ minute in our patient population. The acute

hemodynamic effect of pacing depends largely on the basal heart rate. The same absolute increase in heart rate with pacing will induce a higher increase in cardiac output if the basal heart rate is low as compared to a higher basal heart rate [10]. Thus the difference in nocturnal basal heart rate might contribute to the more pronounced effect of pacing in the study by Garrigue et al.. Indeed, pacemaker implantation in six patients with pronounced bradycardia but normal ejection fraction was effective in reducing mainly Cheyne-Stokes respiration in an uncontrolled case series [28].

Effects on central and obstructive events, and ventilation

When explaining the effects of nocturnal overdrive pacing on sleep disordered breathing, two key mechanisms linking overdrive pacing with ventilation were put forward [11]. 1.) Pacing might counteract nocturnal hypervagotonia by influencing cardiac vagal or sympathetic afferent neurons [11]. Indeed *pulmonary* vagal afferents to the medullary respiratory control center stimulate ventilation. However, whether cardiac afferents impact on ventilation is unknown [11]. 2.) Overdrive pacing might improve cardiac function, and thus pulmonary congestion might be ameliorated in patients with heart failure or bradycardia. In patients with heart failure, pulmonary congestion causes activation of pulmonary J receptors, thereby inducing hyperventilation with hypocapnia, thus destabilizing ventilatory control and favoring central sleep apnea [29]. However, in our patients we were unable to prove the hypothesis that overdrive pacing evokes a significant ventilatory response.

It was speculated that pacing - by impacting on cardiac function and thereby on the ventilatory control loop as discussed above [30] - might affect predominantly central hypopnea and apnea [9]. Recently published data supports this hypothesis [31]. In our patients central apneas only rarely occurred. Thus the effects of pacing on these

events could not be clarified. Central hypopneas were more common but their reduction following pacing did not reach statistical significance. Further studies using more elaborated tools to distinguish between obstructive and central events might verify the concept that pacing reduces mainly central respiratory events. This is of interest, since pacing is frequently applied in the aging population where central respiratory events are common [27].

Sleep

Garrigue and colleagues reported no change in total sleep time, with a clear reduction in the apnea-hypopnea index and accordingly in arousals due to disordered breathing [11]. Sleep stages and overall arousals were not reported. In our study, sleep stages as well as arousals were not affected by overdrive pacing, thus confirming that pacing *per se* has no negative effects on sleep.

Neurohumoral activation

In the present study, overdrive pacing did not influence urinary norepinephrine excretion or NT-proBNP concentration, suggesting that no major negative or positive effects on sympathetic activation or ventricular filling occurred. This is reassuring given the possibility of impaired ventricular function following tachycardia in heart failure or aged myocardium as discussed above [25, 26]. In accord with previous studies, NT-proBNP was increased in our patients as compared to 48 elderly healthy subjects investigated previously in our department (median 42 (range 10-118) pg/ml).

Limitations

Limitations include, first, the single-blinded study design. In mitigation, this approach was adopted so as to maximize patient safety. Also, even though the data were

obtained in a single-blinded fashion, quantification of ventilatory, sleep and biomarkers were made by two observers blinded to subject and intervention (LGCL, DD). Second we used calibrated respiratory inductance plethysmography. This method extrapolates semi-quantitative measures of chest wall movement to derive quantitative approximate measures of minute ventilation. In previous studies by others and by our group using the same method, changes in minute ventilation of about 15% were detected [23, 32]. Thus we cannot rule out minor effects of pacing on ventilation. More obtrusive methods, such as a tightly fitting face mask would have been necessary. Furthermore besides blood pressure and heart rate no hemodynamic data were obtained, thus the impact of pacing on hemodynamics has not thoroughly been investigated.

Clinically, the lack of effect on the apnea-hypopnea index and oxygen desaturations render atrial overdrive pacing inappropriate for treating sleep disordered breathing. Nevertheless, with regard to pathophysiology, the heart rate-dependent reduction in hypopneas sheds light on the complexity of the respiratory control mechanisms and mandates further investigation.

References

1. Young T, Peppard PE, Gottlieb DJ. Epidemiology of obstructive sleep apnea: a population health perspective. Am J Respir Crit Care Med 2002; **165**(9):1217-39.

2. Lattimore JD, Celermajer DS, Wilcox I. Obstructive sleep apnea and cardiovascular disease. J Am Coll Cardiol 2003; **41**(9):1429-37.

3. Imadojemu VA, Sinoway LI, Leuenberger UA. Vascular dysfunction in sleep apnea: a reversible link to cardiovascular disease? Am J Respir Crit Care Med 2004; **169**(3):328-9.

4. Peker Y, Hedner J, Norum J, Kraiczi H, Carlson J. Increased incidence of cardiovascular disease in middle-aged men with obstructive sleep apnea: a 7-year follow-up. Am J Respir Crit Care Med 2002; **166**(2):159-65.

5. Berry RB. Improving CPAP compliance - man more than machine. Sleep Med 2000; **1**(3):175-178.

6. Zozula R, Rosen R. Compliance with continuous positive airway pressure therapy: assessing and improving treatment outcomes. Curr Opin Pulm Med 2001; **7**(6):391-8.

7. Massie CA, McArdle N, Hart RW, Schmidt-Nowara WW, Lankford A, Hudgel DW, Gordon N, Douglas NJ. Comparison between automatic and fixed positive airway pressure therapy in the home. Am J Respir Crit Care Med 2003; **167**(1):20-3.

8. Garrigue S, Bordier P, Jais P, Shah DC, Hocini M, Raherison C, Tunon De Lara M, Haissaguerre M, Clementy J. Benefit of atrial pacing in sleep apnea syndrome. N Engl J Med 2002; **346**(6):404-12.

9. Gottlieb DJ. Cardiac pacing--a novel therapy for sleep apnea? N Engl J Med 2002; **346**(6):444-5.

10. Stein E, Damato AN, Kosowsky BD, Lau SH, Lister JW. The relation of heart rate to cardiovascular dynamics. Pacing by atrial electrodes. Circulation 1966; **33**(6):925-32.

11. Garrigue S, Bordier P, Barold SS, Clementy J. Sleep apnea: a new indication for cardiac pacing? Pacing Clin Electrophysiol 2004; **27**(2):204-11.

12. Carlson JT, Hedner J, Elam M, Ejnell H, Sellgren J, Wallin BG. Augmented resting sympathetic activity in awake patients with obstructive sleep apnea. Chest 1993; **103**(6):1763-8.

13. Somers VK, Dyken ME, Clary MP, Abboud FM. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995; **96**(4):1897-904.

14. Kita H, Ohi M, Chin K, Noguchi T, Otsuka N, Tsuboi T, Itoh H, Nakao K, Kuno K. The nocturnal secretion of cardiac natriuretic peptides during obstructive sleep apnoea and its response to therapy with nasal continuous positive airway pressure. J Sleep Res 1998; **7**(3):199-207.

15. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, Francis GS, Simon AB, Rector T. Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 1984; **311**(13):819-23.

16. Mark DB, Felker GM. B-type natriuretic peptide - a biomarker for all seasons? N Engl J Med 2004; **350**(7):718-20.

17. Luethje L, Unterberg-Buchwald C, Hagenah G, Vollmann D, Andreas S. Atrial overdrive pacing and sleep apnea syndrome. Eur Respir J 2004; **24**(Supplement 48):476s.

18. Luethje L, Unterberg C, Vollmann D, Hagenah G, Andreas S. Atrial overdrive pacing for the reduction of sleep apnea severity. Europace 2004; **6**(Supplement 1):118.

19. Andreas S, Clemens C, Sandholzer H, Figulla HR, Kreuzer H. Improvement of exercise capacity with treatment of Cheyne-Stokes respiration in patients with congestive heart failure. J Am Coll Cardiol 1996; **27**(6):1486-90.

20. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med 1999; **160**(4):1101-6.

21. Rechtschaffen A, Kales A. Manual of standardized terminology techniques and scoring system for sleep stages of human subjects. National Institute of Health publication No. 204 1968(No. 204).

22. EEG Arousals: scoring rules and examples. A preliminary report from the sleep disorders atlas task force of the American Sleep disorders association. Sleep 1992; **15**:173-84.

23. Heindl S, Lehnert M, Criee CP, Hasenfuss G, Andreas S. Marked sympathetic activation in patients with chronic respiratory failure. Am J Respir Crit Care Med 2001; **164**(4):597-601.

24. Feldman MD, Alderman JD, Aroesty JM, Royal HD, Ferguson JJ, Owen RM, Grossman W, McKay RG. Depression of systolic and diastolic myocardial

reserve during atrial pacing tachycardia in patients with dilated cardiomyopathy. J Clin Invest 1988; **82**(5):1661-9.

25. Hasenfuß G, Holubarsch C, Hermann HP, Astheimer K, Pieske B, Just H. Influence of the force-frequency relationship on haemodynamics and left ventricular function in patients with non-failing hearts and in patients with dilated cardiomyopathy. Eur Heart J 1994; **15**(2):164-70.

26. Lim CC, Apstein CS, Colucci WS, Liao R. Impaired cell shortening and relengthening with increased pacing frequency are intrinsic to the senescent mouse cardiomyocyte. J Mol Cell Cardiol 2000; **32**(11):2075-82.

27. Lamas GA, Lee KL, Sweeney MO, Silverman R, Leon A, Yee R, Marinchak RA, Flaker G, Schron E, Orav EJ, Hellkamp AS, Greer S, McAnulty J, Ellenbogen K, Ehlert F, Freedman RA, Estes NA, 3rd, Greenspon A, Goldman L. Ventricular pacing or dual-chamber pacing for sinus-node dysfunction. N Engl J Med 2002; **346**(24):1854-62.

28. Kato I, Shiomi T, Sasanabe R, Hasegawa R, Otake K, Banno K, Yamakawa H, Mizutani N, Kobayashi T. Effects of physiological cardiac pacing on sleep-

disordered breathing in patients with chronic bradyarrhythmias. Psychiatry Clin Neurosci 2001; **55**(3):257-8.

29. Bradley TD, Floras JS. Sleep apnea and heart failure: Part II: central sleep apnea. Circulation 2003; **107**(13):1822-6.

30. Khoo MC, Gottschalk A, Pack AI. Sleep-induced periodic breathing and apnea: a theoretical study. J Appl Physiol 1991; **70**(5):2014-24.

31. Abe H, Kitamura T, Oginosawa Y, Nakashima Y. Alleviation of central sleep apnea by ventricular pacing in a patient with an implanted cardioverter defibrillator. Pacing Clin Electrophysiol 2004; **27**(10):1447-8.

32. Xie A, Wong B, Phillipson EA, Slutsky AS, Bradley TD. Interaction of hyperventilation and arousal in the pathogenesis of idiopathic central sleep apnea. Am J Respir Crit Care Med 1994; **150**(2):489-95.

Figure legends

Figure 1: Effect of pacing on the apnea/hypopnea index (AHI), apnea index (AI) and hypopnea index (HI). P value (ANOVA) for HI revealed significance ($p < 0.05$). * p pacing 15 vs. non-pacing < 0.05. For further details see results.

Table 1: Subject characteristics		
Sex	**male/female**	19/1
Age (yr)		63.2 ± 1.7
Body mass index (kg/cm^2)		30.1 ± 0.8
Ejection fraction (%)		48.6 ± 3.2
Predominant type of SA	**obstructive/central**	18/2
Epworth sleepiness scale		8.4 ± 1.1

Table 2: Effect of atrial overdrive pacing

	non-pacing	pacing 7	pacing 15	p ANOVA
HR (/min)	55.3 ± 2.1	62.5 ± 2.1	71.1 ± 2.1	< 0.0001
BP (mmHg)	101.8 ± 2.1	103.9 ± 3.3	100.3 ± 2.4	n. s.
AHI (/h)	20.9 ± 2.1	19.5 ± 2.4	17.8 ± 1.9	n. s.
AI (/h)	7.6 ± 1.2	6.6 ± 1.3	6.9 ± 1.3	n. s.
HI (/h)	13.4 ± 1.4	12.9 ± 1.4	10.9 ± 1.0	<0.05
TST (min)	330.8 ± 20.0	351.3 ± 15.8	352.1 ± 12.9	n. s.
S1+S2 (%TST)	81.1 ± 2.1	79.1 ± 2.3	79.7 ± 1.7	n. s.
S3+S4 (%TST)	10.0 ± 4.6	9.8 ± 4.2	5.1 ± 1.6	n. s.
REM (%TST)	12.9 ± 1.6	15.1 ± 1.4	14.7 ± 1.4	n. s.
Arousal (/h)	13.7 ± 1.9	11.4 ± 1.9	13.4 ± 2.2	n. s.
RR (/min)	14.0 ± 0.4	13.9 ± 0.4	13.7 ± 0.5	n. s.
MV (l/min)	5.3 ± 0.4	5.0 ± 0.3	5.0 ± 0.3	n. s.
PCO_2 (mmHg)	39.0 ± 0.8	38.7 ± 0.8	39.0 ± 0.8	n. s.
SO_2 mean (%)	92.3 ± 0.5	91.9 ± 0.5	91.8 ± 0.5	n. s.
SO_2 min (%)	85.4 ± 1.0	83.1 ± 1.3	85.0 ± 1.4	n. s.
SO_2<90% (%TST)	8.9 ± 2.8	8.4 ± 1.7	9.7 ± 2.1	n. s.
NT-proBNP (pg/ml)	189 (16-1150)	162 (13-2888)	210 (12-3073)	n. s.
NE (nmol/mmol Crea)	25 (15-57)	28 (12-59)	25 (10-45)	n. s.

Non-pacing: no atrial overdrive pacing; pacing 7 and 15: atrial overdrive pacing with 7 or 15 beats > mean nocturnal heart rate; HR: heart rate; BP: mean nocturnal blood pressure; AHI: apnea/hypopnea index; AI: apnea index; HI: hypopnea index. TST: total sleep time; S1+S2: sleep stage 1 and 2; S3+S4: sleep stage 3 and 4; REM:

rapid eye movement sleep; Arousal: arousal with respiratory event index. RR: respiratory rate; MV: minute ventilation; pCO_2: endtidal partial pressure of carbon dioxide; SO_2 mean: mean oxygen saturation; SO_2 min: minimum oxygen saturation; SO_2<90%: oxygen saturation below 90%. NE: norepinephrine; Crea: creatinine. Data are expressed as mean ± SEM except NE and NT-proBNP (expressed as median (range)). For AI and HI the p following correction for multiple comparisons is given.

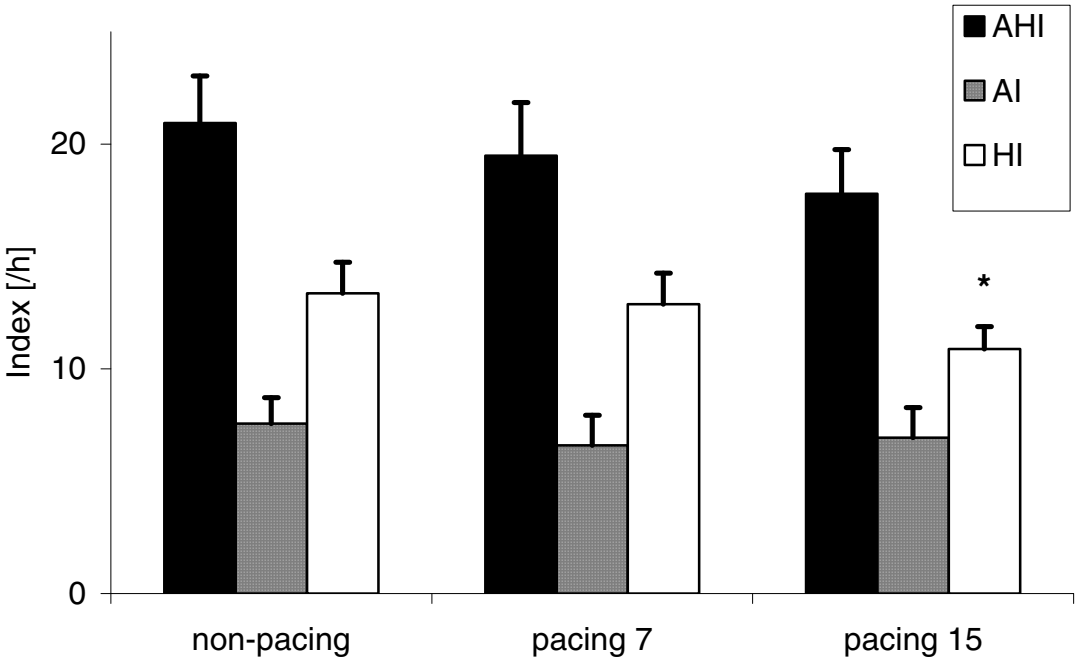

Figure 1

Atrial overdrive pacing in sleep apnea patients with implanted pacemaker

Lars Lüthje, MD; Christina Unterberg-Buchwald MD; Dani Dajani; Dirk Vollmann, MD; Gerd Hasenfuß, MD; Stefan Andreas, MD

Online Data Supplement

Methods

Protocol

To minimize ventricular pacing of the PM/ICD during the three nights, a step-by-step prolongation of the sensed and paced atrioventricular interval was performed till intrinsic ventricular complexes were detected.

Ventilation, Holter monitoring

Respiratory rate and tidal volume were registered by calibrated respiratory inductive plethysmography (Respitrace Systems, Ambulatory Monitoring Inc., New York, USA). The endtidal pCO_2 was monitored continuously by analysing expired gas from the nostrils (Datex Normocap, Helsinki, Finland). Evaluations were carried out for one minute every hour during sleep in a phase without apneas or hypopneas in sleep stage 2, and averaged over the night.

During the nights, Holter monitoring was performed (Lifecard CF, DelMar Reynolds Inc., Feucht, Germany). Analysis was done with a 12-second sliding window using Pathfinder 700 software (DelMar Reynolds Inc., Feucht, Germany).

Biomarkers

Blood samples were taken each morning directly after waking. CRP, fibrinogen, and NT-proBNP were determined from all samples. NT-proBNP was determined by an electrochemoluminiscence immunoassay (Elecsys pro BNP sandwich immunoassay; Roche Diagnostics, Basel, Switzerland). Urine was collected overnight and norepinephrine was measured by high-performance liquid chromatography and normalised to urinary creatinine.