Clinical research

Atrial overdrive pacing compared to CPAP in patients with obstructive sleep apnoea syndrome

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Received 14 December 2004; revised 24 May 2005; accepted 26 May 2005; online publish-ahead-of-print 26 August 2005

Aims Obstructive sleep apnoea (OSA) is associated with oxygen desaturation, blood pressure increase, and neurohumoral activation, resulting in possible detrimental effects on the cardiovascular system. Continuous positive airway pressure (CPAP) is the therapy of choice for OSA. In a recent study, nocturnal atrial overdrive pacing (pacing) reduced the severity of sleep apnoea in pacemaker patients. We compared the effects of CPAP with those of pacing in patients with OSA but without pacemaker indication or clinical signs of heart failure.

Methods and results Ten patients with OSA on CPAP therapy were studied for three nights by polysomnography. During the nights that followed a night without any treatment (baseline), the patients were treated with CPAP or pacing in a random order. Pacing was performed with a temporary pacing lead. The pacing frequency was 15 b.p.m. higher than the baseline heart rate. The apnoea–hypopnoea index was 41.0 h\(^{-1}\) (12.0–66.6) at baseline and was significantly lower during CPAP [2.2 h\(^{-1}\) (0.3–12.4)] compared with pacing [39.1 h\(^{-1}\) (8.2–78.5)]. Furthermore, duration and quality of sleep were significantly improved during CPAP when compared with pacing.

Conclusion Nocturnal atrial overdrive pacing is no alternative therapeutic strategy to CPAP for the treatment of OSA in patients without clinical signs of heart failure and without conventional indication for antibradycardia pacing.

Key words Pacing; Continuous positive airway pressure; Sleep apnoea

Introduction

Obstructive sleep apnoea (OSA) is associated with arterial hypertension,\(^1\) worsening of heart failure,\(^2\) and cardiac rhythm abnormalities\(^3\) and is independently related to cardiac morbidity and mortality.\(^4\) The prevalence of sleep apnoea is high, with nearly 5% of women and 15% of men between 30 and 60 years being affected.\(^5\) The observed increase in the number of obese individuals will cause a further rise in the prevalence.\(^6\)

The standard treatment for OSA is continuous positive airway pressure (CPAP), which improves nocturnal ventilation, reduces excessive daytime sleepiness, and improves the quality of life.\(^7\) In patients with heart failure, CPAP increases left ventricular ejection fraction.\(^8\) However, CPAP causes considerable patient discomfort, and long-term compliance, which lies around 60–70%,\(^9,10\) depends highly on effective symptom relief.

The recent report of Garrigue et al.\(^11\) that nocturnal atrial overdrive pacing markedly reduced central and obstructive apnoea episodes in pacemaker patients was met with considerable enthusiasm because this might lead to a new and more convenient therapeutic concept. Two mechanisms by which pacing might exert its observed effect have been proposed.\(^12\) According to the first, overdrive pacing improves cardiac output and reduces pulmonary congestion with a consequent reduction of hyperventilation and central apnoea. The second hypothesis suggests that overdrive pacing counteracts nocturnal hypervagotonia and stabilizes respiration by acting on cardiac or sympathetic afferent neurons.

Neurohumoral markers [plasma and urinary norepinephrine, brain natriuretic peptide (BNP)]\(^13-15\) are elevated in OSA and associated with left ventricular function and prognosis in heart failure.\(^16,17\) The heart rate increase induced by overdrive pacing might affect these humoral parameters.

The population studied by Garrigue et al.\(^11\) was not representative for patients with OSA, as they had not sought medical care because of suspected sleep-related breathing disorders, and all had an indication for pacing due to bradycardia. Moreover, most of the patients had predominantly central but not obstructive apnoea. To further elucidate the effects of atrial overdrive pacing on sleep-disordered breathing and humoral parameters, we studied a characteristic sample of patients with OSA and compared the two therapeutic interventions, CPAP and nocturnal atrial overdrive pacing with a temporary external pacemaker, in a random cross-over design.

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Methods

Patient selection

Patients aged between 18 and 80 and with a body mass index >25 kg/m² were contacted via mail and telephone to participate in the study if they fulfilled the following criteria: a history of full-night polysomnography and manual analysis in our sleep laboratory because of daytime sleepiness (Epworth sleepiness scale more than 10 points) with the result of an apnoea–hypopnoea index (AHI) >15 h⁻¹ with >50% obstructive events and a subsequent CPAP treatment at least 3 months prior to the study. Exclusion criteria were cardiac valve disease or valvular replacement, patients with an indication for pacemaker implantation, decompensated heart failure, chronic atrial arrhythmias, immunosuppression, pregnancy, a life expectancy of <6 months, concurrent participation in another study, or non-compliance. The study complies with the Declaration of Helsinki and was approved by the local Ethics Committee, and written informed consent was obtained from each patient.

Protocol

At the beginning of the study, a detailed medical history was obtained and a thorough physical examination including electrocardiography (ECG), lung function, and echocardiography was performed. The patients underwent full-night polysomnography for three consecutive nights. The first night was without CPAP or pacing, and the data served as baseline. In the following nights, the patients were randomly assigned to either standard CPAP therapy or atrial overdrive pacing in a cross-over design. Randomization was accomplished by the use of 10 sealed envelopes, which were consecutively numbered. Five envelopes contained the word ‘CPAP’ and other five envelopes contained the word ‘pacing’ in a random order indicating the treatment method used during night 2.

For the CPAP night, the patients used their own masks and devices, whereas for the pacing night, a temporary pacing lead was inserted.

Polysomnography

Electroencephalogram, electrooculogram, electromyogram, and electrocardiogram were recorded as previously described.18 Airflow was recorded by nasal pressure, whereas thorax and abdominal wall motions were monitored by Respitrace, as described in detail subsequently. Arterial oxygen saturation (SaO₂) was measured transcutaneously by pulse oximetry (Healthdyne Technologies Inc., Marietta, OH, USA). The polysomnogram was analysed visually with a computer system (ALICE IV, Heinen und Löwenstein, Bad Ems, Germany). An apnoea was considered obstructive when nasal flow was absent in the presence of abdominal or thoracic movements and central when movements were absent as well. A hypopnoea was defined as a fall in nasal airflow >50% of baseline. Respiratory events were counted only when they were of at least 10 s duration. Sleep stages and arousal were evaluated according to standard criteria.19

Ventilation

Respiratory rate and tidal volume were registered by respiratory inductive plethysmography (Respitrace Systems, Ambulatory Monitoring Inc., NY, USA) calibrated in supine and standing positions using the least-squares method as described previously.20 End-tidal pCO₂ was monitored continuously by withdrawing expired gas from the nostrils (Datex Normocap, Helsinki, Finland). A 1 min period was evaluated once every hour during sleep stage 2 in a phase without apnoea or hypopnoea, and the data were averaged over the night.

Atrial pacing, Holter monitoring

A temporary bipolar atrial pacing lead (fixation with a screw, Model 6416, Medtronic Inc., Minneapolis, MN, USA) was inserted transvenously under sterile conditions. After puncture of the basilic or cephalic vein, the lead was advanced to the free wall of the right atrium and fixed with a screw at the tip of the lead. Lead contact was considered acceptable if the pacing threshold was ≤2 V at 0.5 ms with a temporary pacing (Model 5388, Medtronic Inc., Feucht, Germany). The pacing performance of the lead was verified by ECG monitoring. All patients were paced in an AAI mode. The next morning, the temporary pacing lead was removed and the patients were examined by echocardiography for the presence of pericardial effusion.

Humoral parameters

Urine collection for norepinephrine concentration determinations began after patients had voided prior to retiring and encompassed all urine passed during the night, including the first morning void on arising. Urine was collected in containers acidified with 4% HCl and stored at 4 °C prior to analysis. Norepinephrine was measured by high-performance liquid chromatography and normalized to urinary creatinine.

Each morning, blood samples for analysis of N-terminal pro-brain natriuretic peptide (NT-proBNP) were drawn in lithium-heparin tubes and immediately centrifuged for 10 min at 10 000 r.p.m. The supernatant was stored at −80 °C until analysis. NT-proBNP was determined by an electrochemoluminescence immunoassay (Elecsys pro-BNP sandwich immunoassay; Roche Diagnostics, Basel, Switzerland).

Statistical analysis

The primary endpoint was the AHI. Secondary endpoints were the apnoea index (AI), hypopnoea index (HI), the total sleep time (TST), light (S1 + S2), deep (S3 + S4), and rapid eye movement (REM) sleep stages in percentage of the TST, arousals index associated with respiratory events, respiratory rate, minute ventilation, partial pressure of carbon dioxide (pCO₂), mean oxygen saturation, minimum oxygen saturation, time of oxygen saturation <90%, the concentration of NT-proBNP in plasma, and norepinephrine in urine. Results for each variable studied were analysed with a standard approach for cross-over studies.21 The Wilcoxon rank-sum test was used to compare the sum of each patient’s measurements between the randomized arms to test for carry-over effect. If no significant carry-over effect was present, a Wilcoxon rank-sum test was used to compare the difference between CPAP and pacing measurement to test for confounding by systematic changes over time (period effect). If no significant period effect existed, the Wilcoxon signed-rank test was used for a paired comparison of treatments. If there was a significant period effect, the unpaired Wilcoxon rank-sum test was used on the differences between night 3 and night 2 measurements to test for a treatment effect. All results are shown as median (range). A P-value <0.05 was considered significant.

Results

Patients

A total of 107 patients were eligible to participate in the study. At the time of closure of the study, 65 patients have been contacted via mail and telephone. Of these, 12 have agreed to participate in the study and were admitted to our hospital. It was intended to include 20 patients in
the study. However, following a pre-defined interim analysis, the study was closed early, after 10 patients, by the Ethics Committee because of a highly significant difference in the primary endpoint. Thus, 10 patients completed the entire protocol of the study; there were no dropouts. Half of the patients were treated with CPAP prior to pacing, whereas the other half were treated in a reverse order. The patients were mostly obese and had normal left ventricular and pulmonary functions (Table 1). None of the patients had a history of heart failure. Diuretics were prescribed to one patient, beta-blockers to four, and ACE-Inhibitors/AT1-antagonists to five patients.

Heart rate
During the night with atrial pacing, effective stimulation was verified by Holter-ECG (Table 2, Figure 1). The difference in mean heart rate between the pacing and baseline nights was 14.5 b.p.m. (10–18). The minimum heart rate during the first night was 55.5 b.p.m. (43–65), 57.5 b.p.m. (43–73) during the CPAP night, and 63 b.p.m. (45–78) during the pacing night. The maximum heart rate during the first night was 87.5 b.p.m. (57–119), 95 b.p.m. (57–119) during the pacing night. The maximum heart rate during the first night was 55.5 b.p.m. (43–65), whereas the other half were treated in a reverse order. The patients were mostly obese and had normal left ventricular and pulmonary functions (Table 1). None of the patients had a history of heart failure. Diuretics were prescribed to one patient, beta-blockers to four, and ACE-Inhibitors/AT1-antagonists to five patients.

Respiratory events, ventilation, and sleep
During the first night, all patients had an AHI of >10 h⁻¹ (Figure 2, Table 2). Two patients had approximately equal numbers of central and obstructive apnoea events, with obstructive apnoea indexes (oAIs) of 2.5 and 4.9 h⁻¹, respectively, and central apnoea indexes (cAIs) of 2.5 and 4.4 h⁻¹, respectively. The predominant type of apnoea in the other eight patients was obstructive [oAI 7.0 h⁻¹ (2.5–30.0), cAI 1.2 h⁻¹ (0.0–7.9)]. The primary endpoint AHI was significantly higher during pacing when compared with CPAP (Figure 2, Table 2). The same was noted for the HI and AI, and also here the apnoea episodes were predominantly obstructive (Table 2). In line with this, the oxygen saturation was significantly higher during CPAP when compared with pacing (Table 3). Pacing also performed worse than CPAP in the two patients with approximately identical oAI and cAI. In these patients, the AHI at baseline was 33.6 and 17.9 h⁻¹, which remained nearly unchanged during pacing with 31.5 and 22.7 h⁻¹ and decreased during CPAP to 0.3 and 2.4 h⁻¹.

During CPAP therapy, the TST was significantly longer with a shift from light to deep sleep stages and REM sleep when compared with pacing (Table 4). In line with this, the arousal index was significantly lower during CPAP night than during pacing night (Table 4). As shown in Table 3, no significant difference was observed between pacing and CPAP therapies with regard to nocturnal ventilation, as reflected by the unchanged minute ventilation and pCO2.

Norepinephrine and NT-proBNP
At baseline, plasma NT-proBNP was not elevated; concentrations were significantly higher with pacing when compared with CPAP (Table 3). In eight patients, the NT-proBNP was higher during pacing night than during CPAP night, although the median was lower during pacing night for all patients (Table 3). The norepinephrine concentrations were not significantly different during the different treatment strategies (Table 3).

Period effect and carry-over effect
Statistical analysis revealed three significant period effects: S1 and S2 sleep stages in percentage of TST, minute ventilation, and arousals associated with a respiratory event. This means that the value of these three characteristics is influenced by whether the treatment is received in the second or in the third night. In our analyses, this was taken into account by using appropriate tests for these characteristics. No significant carry-over effects were revealed.

Discussion
In this first report on a randomized cross-over study comparing the acute effects of nocturnal atrial overdrive pacing with CPAP, the potential new therapy pacing performed significantly worse than the current therapeutic gold standard CPAP in improving the primary endpoint AHI as well as sleep stages and arousals. Another novel finding was that markers of neurohumoral activation were not affected by pacing.

The most important feature of our study, and its strength, is that it was designed to test whether pacing is effective in a characteristic population of OSA patients on CPAP therapy but without pacemaker indication or clinical signs of

<table>
<thead>
<tr>
<th>Table 1 Patient characteristics</th>
<th>Patients with pacing on night 2 (n = 5)</th>
<th>Patients with pacing on night 3 (n = 5)</th>
<th>All patients (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (Male/female)</td>
<td>4/1</td>
<td>5/0</td>
<td>9/1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>56 (55–65)</td>
<td>64 (50–69)</td>
<td>61 (50–69)</td>
</tr>
<tr>
<td>Left ventricular ejection fraction (%)</td>
<td>65 (40–66)</td>
<td>55 (36–65)</td>
<td>55 (36–66)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>34.8 (29.3–35.6)</td>
<td>29.6 (27.2–45.7)</td>
<td>33.0 (27.2–45.7)</td>
</tr>
<tr>
<td>Coronary artery disease (Number of patients)</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Arterial hypertension (Number of patients)</td>
<td>4</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>Diabetes mellitus (Number of patients)</td>
<td>1</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Vital capacity (L/min)</td>
<td>2.9 (2.7–4.5)</td>
<td>3.6 (1.9–4.1)</td>
<td>3.5 (1.9–4.5)</td>
</tr>
<tr>
<td>Forced expiratory volume in 1 s (L/s)</td>
<td>2.3 (2.1–3.6)</td>
<td>3.0 (1.4–3.5)</td>
<td>2.9 (1.4–3.6)</td>
</tr>
</tbody>
</table>
heart failure. The characteristic of OSA was the proof of predominately obstructive events during polysomnography associated with daytime sleepiness and thus an indication for CPAP therapy. Furthermore, the patients were overweight, which is one of the major risk factors for sleep apnoea. However, the age of our patient population was slightly higher than in other studies investigating OSA. Episodes of cardiac bradyarrhythmias can be expected in up to 20% of severe sleep apnoea patients; however, these bradycardiac episodes usually are reversible with CPAP therapy. Thus, OSA is no indication for pacemaker implantation. In line with this, none of our patients had pacemaker implanted in contrast to the patient population of the Garrigue study. In that study, patients were investigated with a permanent dual pacemaker that had been implanted because of symptomatic bradycardia. This and other differing patient characteristics might explain the discrepant results of our study in contrast to those of Garrigue et al., who reported a >50% reduction in the number of apnoea events during pacing.

Effects of pacing on sleep-disordered breathing

There are basically two interacting mechanisms that are responsible for nocturnal respiratory events: ventilatory...
Table 3  Nocturnal ventilation, CO₂ and SaO₂, humoral parameters

<table>
<thead>
<tr>
<th></th>
<th>Patients with pacing on night 2</th>
<th>Patients with pacing on night 3</th>
<th>All patients</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline CPAP Pacing Baseline CPAP Pacing Baseline CPAP Pacing</td>
<td>Baseline CPAP Pacing Baseline CPAP Pacing Baseline CPAP Pacing</td>
<td>Baseline CPAP Pacing Baseline CPAP Pacing Baseline CPAP Pacing</td>
<td>Baseline CPAP Pacing Baseline CPAP Pacing Baseline CPAP Pacing</td>
</tr>
<tr>
<td><strong>Respiratory rate (min⁻¹)</strong></td>
<td>17.0 (14.5–26.3) 15.4 (14.1–24.0) 16.3 (15.6–24.5)</td>
<td>15.6 (14.4–18.0) 16.1 (13.6–17.3) 16.3 (13.2–18.4)</td>
<td>16.0 (14.4–26.3) 16.1 (13.6–24.0) 16.3 (13.2–24.5)</td>
<td>0.375</td>
</tr>
<tr>
<td><strong>Minute ventilation (L/min)</strong></td>
<td>5.0 (3.9–7.1) 4.4 (4.3–7.9) 6.6 (6.2–9.8)</td>
<td>5.2 (3.6–6.3) 6.0 (4.1–6.4) 5.8 (3.7–8.1)</td>
<td>5.1 (3.6–7.1) 5.4 (4.1–7.9) 6.3 (3.7–9.8)</td>
<td>0.421</td>
</tr>
<tr>
<td><strong>pCO₂ (mmHg)</strong></td>
<td>40.0 (39.5–40.7) 38.3 (37.3–40.0) 39.4 (36.7–41.0)</td>
<td>39.3 (37.5–40.0) 40.0 (29.4–42.3) 39.2 (37.4–42.6)</td>
<td>39.9 (37.5–40.7) 38.7 (29.4–42.3) 39.3 (36.7–42.6)</td>
<td>0.496</td>
</tr>
<tr>
<td><strong>SaO₂ mean (%)</strong></td>
<td>90 (89–93) 93 (91–95) 91 (89–92)</td>
<td>93 (92–94) 94 (93–96) 92 (91–94)</td>
<td>92 (89–94) 94 (91–96) 92 (89–94)</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>SaO₂ min (%)</strong></td>
<td>68 (54–80) 86 (83–93) 71 (50–79)</td>
<td>78 (62–86) 89 (88–92) 76 (58–86)</td>
<td>75 (54–86) 88 (83–93) 74 (50–86)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>SaO₂ &lt;90% (%TST)</strong></td>
<td>37.2 (8.9–56.1) 5.9 (0.0–17.7) 36.4 (17.6–49.4)</td>
<td>7.1 (0.7–20.6) 0.3 (0.0–5.0) 17.4 (0.7–23.6)</td>
<td>20.4 (0.7–56.1) 0.3 (0.0–17.7) 22.1 (0.7–49.4)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>NT-proBNP (pg/mL)</strong></td>
<td>117.3 (115.5–226.6) 77.2 (9.7–202.2) 88.9 (18.0–337.3)</td>
<td>260.5 (19.3–526.2) 117.5 (9.5–220.1) 160.0 (16.8–341.7)</td>
<td>154.5 (115.5–526.2) 117.5 (9.5–220.1) 99.5 (16.8–341.7)</td>
<td>0.021</td>
</tr>
<tr>
<td><strong>Norepinephrine (nmol/mmol crea)</strong></td>
<td>23.0 (13.0–29.3) 19.3 (14.5–29.7) 24.0 (10.3–32.6)</td>
<td>15.1 (8.9–19.0) 14.0 (8.4–17.3) 13.2 (11.2–17.4)</td>
<td>17.3 (8.9–29.3) 15.9 (8.3–29.7) 16.0 (10.3–32.6)</td>
<td>0.547</td>
</tr>
</tbody>
</table>

PCO₂, end-tidal partial pressure of carbon dioxide; SaO₂ mean, mean oxygen saturation during the night; SaO₂ min, minimum oxygen saturation; SaO₂ < 90%, oxygen saturation below 90%; crea, creatinine; NT-proBNP, N-terminal pro-brain natriuretic peptide, measurement in blood samples at the end of the nights. Norepinephrine measured in overnight urine. P-value is given for all patients (CPAP vs. pacing). The P-value for minute ventilation is from a Wilcoxon rank-sum test on the differences (night 3 and night 2); all other P-values are from a paired Wilcoxon signed-rank test.
Table 4

<table>
<thead>
<tr>
<th>Patients with pacing on night 2</th>
<th>Patients with pacing on night 3</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TST (min)</strong></td>
<td><strong>Baseline CPAP</strong></td>
<td><strong>Pacing</strong></td>
</tr>
<tr>
<td>293</td>
<td>(211–382)</td>
<td>378</td>
</tr>
<tr>
<td><strong>S1 + S2 (%TST)</strong></td>
<td><strong>Baseline CPAP</strong></td>
<td><strong>Pacing</strong></td>
</tr>
<tr>
<td>94.9</td>
<td>(85.9–99.5)</td>
<td>85.1</td>
</tr>
<tr>
<td>88.1</td>
<td>(64.0–75.8)</td>
<td>79.3</td>
</tr>
<tr>
<td><strong>S3 + S4, sleep stages 3 and 4; arousal, arousal with respiratory event index.</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.2</td>
<td>(0.0–13.5)</td>
<td>4.7</td>
</tr>
<tr>
<td>0.037</td>
<td>(0.0–0.5)</td>
<td>0.2</td>
</tr>
<tr>
<td>0.008</td>
<td>(0.0–0.5)</td>
<td>0.004</td>
</tr>
<tr>
<td><strong>Arousal (h⁻¹)</strong></td>
<td><strong>Baseline CPAP</strong></td>
<td><strong>Pacing</strong></td>
</tr>
<tr>
<td>0.0</td>
<td>(0.0–0.4)</td>
<td>0.016</td>
</tr>
<tr>
<td>11.2</td>
<td>(7.5–17.5)</td>
<td>13.4</td>
</tr>
<tr>
<td>0.004</td>
<td>(0.0–0.4)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

P-values for S1 + S2 and for arousal are from a Wilcoxon rank-sum test on the differences (night 3 and night 2); all other P-values are from a paired Wilcoxon signed-rank test.

Control instability and upper airway anatomy and collapsibility.26 Purely obstructive apnoea is rather difficult to treat with drugs such as theophylline or serotonergic agents, which influence ventilatory control,27,28 but it responds excellently to mechanical therapy with CPAP. Central apnoea is more closely related to ventilatory control abnormalities and is amenable to treatment with drugs acting on ventilatory control.29

Two mechanisms have been hypothesized in the effort to explain the effects of nocturnal overdrive pacing on sleep-disordered breathing.11,12 The first of these suggests that pacing might counteract nocturnal hypervagotonia by influencing cardiac vagal or sympathetic afferent neurons.12 Indeed, pulmonary unmyelinated irritant receptors, such as J receptors, stimulate ventilation.29 However, whether cardiac afferents have an impact on ventilation is not known.11,27 Nevertheless, direct stimulation of the vagus nerve can aggravate OSA.30 The second hypothesis suggests that overdrive pacing might improve cardiac function, thus stabilizing ventilatory control11 as referred subsequently.

The patients studied by Garrigue et al.11 and those of our study differed clearly in the character of their apnoea events. The patients described in Garrigue’s report had an index of 12 central apnoea episodes per hour, whereas this index was only 2.7 h⁻¹ in our patients. Furthermore, our patients had more severe disordered breathing (AHI 41.0 vs. 27.0 h⁻¹). Therefore, we suggest that typical obstructive apnoea is not affected by overdrive pacing. However, central apnoea or hypopnoea, conditions that are more strongly influenced by ventilatory control mechanisms, might be affected by pacing.

Another difference between our study and that of Garrigue et al.11 was that our patients did not have nocturnal bradycardia. Our patients had a mean heart rate of 63 min⁻¹ during the baseline night compared to 51 min⁻¹ in those of Garrigue et al.11 The acute haemodynamic effect of pacing is frequency dependent. In 1871, Bowditch described the positive cardiac force–frequency relationship. Later, it was demonstrated that atrial pacing improved left ventricular contractility and diastolic filling.31 The effect of pacing depends on the basal heart rate. The same absolute increase in heart rate induced with pacing will yield a greater increase in cardiac output when the initial heart rate is lower than when it is higher.32 Thus, increasing heart rate via physiological pacing (AAI mode) increases stroke volume especially in bradycardic patients. The difference in nocturnal basal heart rate might thus contribute to the more pronounced effect of pacing in the study of Garrigue et al.11 Indeed, pacemaker implantation in six patients with pronounced bradycardia but normal ejection fraction was effective in alleviating Cheyne–Stokes type respiration in an uncontrolled case series.33

A third difference relates to the fact that a number of patients studied by Garrigue et al.11 had heart disease. In the patient population investigated in this study, three patients suffered from coronary artery disease; however, none of our patients had clinical signs of heart failure. As discussed previously, it was postulated that overdrive pacing might exert its effect on sleep-disordered breathing by improving cardiac function, thus reducing pulmonary congestion in patients with heart failure.27 Pulmonary congestion activates pulmonary J receptors, thereby inducing hyperventilation with hypocapnia. This destabilizes...
ventilatory control and predisposes to central sleep apnoea. The concept that left ventricular function is a key mechanism for the occurrence of central apnoea is further supported by recent data showing that the incidence of central apnoea in patients with heart failure is reduced by the haemodynamic improvement following cardiac resynchronization therapy. In our patients, who have OSA but no clinical evidence of heart failure, pulmonary congestion was unlikely. Thus, pacing could not improve pulmonary congestion in our patients. Accordingly, atrial overdrive pacing did not result in a significant change in minute ventilation or end-tidal CO₂.

As nocturnal pacing performed significantly worse than CPAP on sleep-disordered breathing in our patients, one can assume the same for sleep stages and arousals. However, temporary pacing did not seem to disturb sleep as reflected by the sleep quality during the pacing nights.

Our findings are corroborated by other studies recently published. Lu¨thje et al. report no significant effect of nocturnal atrial overdrive pacing on the AHI in OSA patients with pacemakers implanted because of bradycardia. Extending the period of nocturnal overdrive pacing to 1 week or to 1 month also did not show an improvement of sleep-related breathing disorders or sleep quality.

Neurohumoral activation

Sympathetic activity as measured by norepinephrine excretion or microneurography is increased in OSA and returns to normal with effective treatment. BNP is released primarily in response to ventricular myocyte stretching, as seen in congestive heart failure. BNP and NT-proBNP, the N-terminal portion of the high molecular weight BNP precursor, serve as prognostic markers in heart failure. The significantly higher NT-proBNP concentration during the pacing night compared with the CPAP night implies a more favourable effect of CPAP on left ventricular function. This is in line with the finding that CPAP therapy in patients with OSA can improve a reduced left ventricular systolic function. There was no significant difference in urinary norepinephrine concentrations between both treatment modalities, suggesting that there was no major negative impact on sympathetic tone.

Limitations

The primary limitation of this study was that it was not double-blinded. This approach was chosen to maximize patient safety: a double-blinded study would have required a fourth night with the pacing lead inserted but inactive. However, ventilatory, sleep, and biological markers were assessed by two observers blinded to subject and intervention. A second limitation was the use of calibrated respiratory thoracic inductance plethysmography. This method extrapolates qualitative measurements of chest wall motion to derive approximate quantitative measures of minute ventilation. It can detect changes in minute ventilation of ~15%. Thus, minor effects on ventilation cannot be ruled out. Cardiac output was not evaluated: evaluation of cardiac output during sleep is either inaccurate or disturbs sleep. Only the acute effect of atrial overdrive pacing during one night with a temporary pacing lead has been evaluated. Thus, we cannot exclude long-term improvements with continuous pacing. Furthermore, slight effects might be counteracted by pain and uneasiness of the patients because of the temporary pacing lead. However, as discussed previously, evaluation of the time and quality of sleep during the pacing night do not indicate a disturbed sleep.

Conclusion

Nocturnal atrial overdrive pacing is no alternative therapeutic strategy to CPAP for the treatment of OSA in patients without clinical signs of heart failure and without conventional indication for anti-bradycardia pacing.

Acknowledgements

Dr Lu¨thje and Dr Unterberg contributed equally to the study. We thank Mrs Köhler and Mr Gerritse for their statistical support. This investigator-initiated study was supported by Medtronic Inc., Minneapolis, MN, USA.

Conflicts of interest: C.U. has received a grant from Medtronic, which was unrestricted for performance of the study (16 000 € in 2003). S.A. has received a grant from Medtronic, which was unrestricted for performance of the study (16 000 € in 2003).

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